Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende olaparib til behandling af 1. linje vedligeholdelses-behandling af avanceret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden med homolog rekombinations-defekt

Vers. 1.0

Bilagsoversigt

1. Medicinrådets sundhedsøkonomiske afrapportering vedr. olaparib i kombination med bevacizumab, version 1.0
2. Forhandlingsnotat fra Amgros vedr. olaparib i kombination med bevacizumab
3. Høringssvar fra ansøger, inkl. efterfølgende dialog
4. Medicinrådets vurdering vedr. olaparib i kombination med bevacizumab til 1. linje vedligeholdelsesbehandling af avanceret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden med homolog rekombinationsdefekt, version 1.0
5. Ansøgers endelige ansøgning
6. Ansøgers tekniske dokument til den sundhedsøkonomiske ansøgning
7. Medicinrådets protokol for vurdering vedr. olaparib i kombination med bevacizumab til 1. linje vedligeholdelsesbehandling af avanceret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden med homolog rekombinationsdefekt, version 1.0

Medicinrådet

Sundhedsøkonomisk afrapportering

Olaparib i kombination med bevacizumab

Avanceret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughulen

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.

Dokumentoplysninger	
Godkendelsesdato	23. juni 2021
Dokumentnummer	117408
Versionsnummer	1.0

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 23. juni 2021

Indholdsfortegnelse

1. Begreber og forkortelser

AIP	Apotekernes indkøbspris
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
SAIP	Sygehusapotekernes indkøbspriser
TTD	*Time-to-treatment discontinuation*

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser

Patienter med BRCA-mutation

I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for olaparib + bevacizumab ca. [redacted] DKK pr. patient sammenlignet med olaparib monoterapi. Når analysen er udført med apotekets indkøbspriser (AIP), er de inkrementelle omkostninger til sammenligning ca. 304.000 DKK pr. patient.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af olaparib + bevacizumab som mulig standardbehandling vil være ca. [redacted] DKK i år 5. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 3,8 mio. DKK i år 5.

HRD-positive patienter uden BRCA-mutation, der er kandidater til bevacizumab

I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for olaparib + bevacizumab ca. [redacted] DKK pr. patient sammenlignet med bevacizumab monoterapi. Når analysen er udført med apotekets indkøbspriser (AIP), er de inkrementelle omkostninger til sammenligning ca. 744.000 DKK pr. patient.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af olaparib + bevacizumab som mulig standardbehandling vil være ca. [redacted] DKK i år 5. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 20,9 mio. DKK i år 5.

HRD-positive patienter uden BRCA-mutation, der ikke er kandidater til bevacizumab

I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for olaparib + bevacizumab ca. [redacted] DKK pr. patient sammenlignet med ingen vedligeholdelsesbehandling. Når analysen er udført med apotekets indkøbspriser (AIP), er de inkrementelle omkostninger til sammenligning ca. 1.265.000 DKK pr. patient.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af olaparib + bevacizumab som mulig standardbehandling vil være ca. [redacted] DKK i år 5. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 47,0 mio. DKK i år 5.

For alle tre sammenligninger driver lægemiddelomkostningerne de inkrementelle omkostninger. For de HRD-positive patienter har omkostninger til test også en lidt indflydelse på de inkrementelle omkostninger.

3. Introduktion

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af olaparib i kombination med bevacizumab som mulig standardbehandling på danske hospitaler til

vedligeholdelsesbehandling af nydiagnosticeret high-grade kræft i æggestokkene, æggelederne eller primær bughulekræft med homolog rekombinationsdefekt (HRD).

Analysen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra AstraZeneca. Vi modtog ansøgningen den 12. februar 2021.

3.1 Patientpopulation

Kræft i æggestokkene, æggelederne og primær bughulekræft benævnes herefter samlet som kræft i æggestokkene.

Kræft i æggestokkene er den fjerde hyppigste kræftdødsårsag hos kvinder i Danmark. Der diagnosticeres omkring 450-550 nye tilfælde om året, og ved udgangen af 2016 levede 4697 kvinder med diagnosen [1,2].

Mutationer i Breast Cancer (BRCA) 1- eller 2-genet er en væsentlig arvelig risikofaktor for udviklingen af kræft i æggestokkene [3].

BRCA er involveret i homolog rekombination, som er en vital celleproces til reparation af DNA-skader [4,5]. Tumorer med BRCA-mutation vil oftest også have homolog rekombinationsdefekt (HRD), men HRD kan også forekomme i ikke-BRCA-muterede tumorer. Det anbefales i dag, at alle patienter udredes i forhold til BRCA-mutationsstatus [6], men der findes ingen nationale guidelines i forbindelse med udredning af HRD-status. Derfor vil det forventes, at en væsentlig gruppe af danske patienter uden påvist BRCA-mutation har tumorer, der udviser HRD.

Tilstedeværelsen af en patientgruppe uden BRCA-mutation men med HRD, gør det relevant at opdele den samlede patientgruppe. Ud fra de tidligere data på forekomsten af BRCA-mutation og HRD forventes det, at omkring 300 patienter i alt vil have avanceret high-grade kræft i æggestokkene, og omkring 60 af disse vil have en BRCA-mutation. Derudover forventes det, at omkring 100 vil have HRD-positive tumorer uden BRCA-mutation ud fra forekomsten rapporteret i de kliniske studier med MYRIAD myChoice CDx. De resterende 140 vil hverken have tumorer uden BRCA-mutation eller HRD.

Yderligere information om sygdomsområdet kan findes i Medicinrådets vurderingsrapport.

3.1.1 Komparator

Medicinrådet har vurderet den kliniske værdi af olaparib i kombination med bevacizumab på baggrund af følgende kliniske spørgsmål:

Klinisk spørgsmål 1:

Hvilken værdi har olaparib i kombination med bevacizumab sammenlignet med olaparib monoterapi som vedligeholdelsesbehandling for nydiagnosticerede patienter med avanceret BRCA-muteret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden, som responderer på platinbaseret kemoterapi (komplet eller partiel respons).

Klinisk spørgsmål 2:

Hvilken værdi har olaparib i kombination med bevacizumab sammenlignet med bevacizumab monoterapi for nydiagnosticerede patienter med avanceret ikke-BRCA-muteret, HRD-positiv high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden, som responderer på platinbaseret kemoterapi (komplet eller partiel respons) og kandiderer til bevacizumab?

Klinisk spørgsmål 3:

Hvilken værdi har olaparib i kombination med bevacizumab sammenlignet med placebo som vedligeholdelsesbehandling for nydiagnosticerede patienter med avanceret ikke-BRCA-muteret, HRD-positiv high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden, som responderer på platinbaseret kemoterapi (komplet eller partiel respons) og ikke kandiderer til bevacizumab?

4. Vurdering af den sundhedsøkonomiske analyse

I sin ansøgning har ansøger indsendt en sundhedsøkonomisk analyse, der består af en omkostningsanalyse og en budgetkonsekvensanalyse. I omkostningsanalysen estimeres de inkrementelle omkostninger pr. patient for olaparib i kombination med bevacizumab sammenlignet med hhv. olaparib monoterapi, bevacizumab monoterapi og ingen vedligeholdelsesbehandling til de tre kliniske spørgsmål. Medicinrådet vurderer nedenfor den sundhedsøkonomiske analyse, som ansøger har indsendt.

4.1 Antagelser og forudsætninger for model

Sammenligningen med alle tre komparatorer er lavet på baggrund af data fra PAOLA-1 og SOLO-1 [7,8]. PAOLA-1 er et fase III-studie, der undersøger effekten af olaparib i kombination med bevacizumab som vedligeholdelsesbehandling til kvinder med nydiagnosticeret avanceret ovariecancer. I studiet er der også en kontrolarm, hvor patienterne modtager bevacizumab + placebo.

Der er forskelle mellem patientpopulationerne i de to studier, men da olaparib monoterapi og ingen vedligeholdelsesbehandling ikke var inkluderet i PAOLA-1-studiet, anvendes SOLO-1-data for *time-to-treatment discontinuation* (TTD) i sammenligningen med olaparib monoterapi og ingen vedligeholdelsesbehandling.

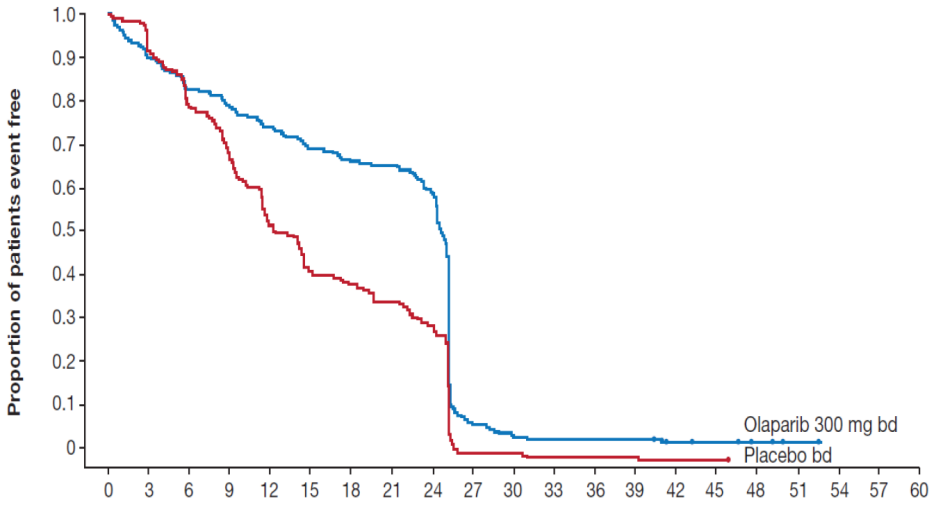
4.1.1 Modelbeskrivelse

Ansøger har indsendt en partitioned survival model til at estimere omkostningerne forbundet med behandlingen med olaparib i kombination med bevacizumab.

Behandlingsvarighed

Ansøger anvender TTD som mål for den gennemsnitlige behandlingslængde. Da olaparib gives til progression eller maksimalt 24 måneder, har alle patienterne afsluttet behandlingen, og det er derfor ikke nødvendigt at ekstrapolere Kaplan-Meier data for TTD. Bevacizumab gives indtil progression eller maksimalt 15 måneder, og der foreligger derfor også modne data for denne population, der kan anvendes direkte til at estimere den gennemsnitlige behandlingslængde for bevacizumab. I Figur 1, Figur 2 og Figur 3 er Kaplan-Meier kurverne for hhv. olaparib + bevacizumab, olaparib monoterapi og placebo og bevacizumab vist.

[redacted]



Figur 1. Kaplan-Meier kurve for TTD eller død for olaparib monoterapi og placebo

[redacted]

Medicinrådets vurdering af ansøgers modelantagelser

Medicinrådet accepterer ansøgers estimater for behandlingsvarighed. Estimaterne er præsenteret i Tabel 1.

Tabel 1. Gennemsnitlig tid i behandling

Population	Behandling	Behandlingsvarighed [år]
BRCA-positiv	Olaparib + bevacizumab	1,6
	Olaparib monoterapi	1,7
HRD-positiv, bevacizumabkandidater	Olaparib + bevacizumab	1,3
	Bevacizumab monoterapi	1,1
HRD-positiv, ikke kandidat til bevacizumab	Olaparib + bevacizumab	1,7

Medicinrådet accepterer ansøgers tilgang vedr. modelantagelser.

4.1.2 Analyseperspektiv

I overensstemmelse med metoderne har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en tidshorisont på 10 år. I ansøgers model er det muligt at vælge både en længere og kortere tidshorisont.

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

Medicinrådets vurdering af ansøgers analyseperspektiv
Medicinrådet vælger at ændre ansøgers analyse, så den har den længst mulige tidshorisont på 25 år, for at sikre at alle relevante omkostninger inkluderes i analysen.

Medicinrådet accepterer ansøgers valg vedr. analyseperspektiv, dog ændres tidshorisonten til at være 25 år i Medicinrådets hovedanalyse.

4.2 Omkostninger

I det følgende er ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af olaparib i kombination med bevacizumab sammenlignet med olaparib som monoterapi, bevacizumab som monoterapi og ingen vedligeholdelsesbehandling præsenteret. Ansøger har inkluderet lægemiddelomkostninger, hospitalsomkostninger, bivirkningsomkostninger og patientomkostninger.

4.2.1 Lægemiddelomkostninger

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

Bevacizumabdosis afhænger af patientens vægt, og ansøger estimerer den gennemsnitlige patients vægt ud fra PAOLA-1-studiet, hvor patienterne i gennemsnit vejede 63,3 kg. Bevacizumab kan både gives som 7,5 mg/kg og 15 mg/kg dosis. Ansøger antager, at 50 % af patienterne, der behandles med bevacizumab i første linje, vil modtage den høje dosis, og 50 % vil modtage den lave dosis. I efterfølgende behandlingslinjer antager ansøger, at alle patienter vil modtage den høje dosis på 15 mg/kg.

Medicinrådets vurdering af ansøgers antagelser vedr. lægemiddelomkostninger
Medicinrådet har udskiftet AIP med sygehusapotekets indkøbspris (SAIP), se Tabel 2.

Tabel 2. Anvendte lægemiddelpriser, SAIP, (marts 2021)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Betinget pris* [DKK]	Kilde
Olaparib	100 mg	56 stk.	[redacted]	[redacted]	Amgros
	150 mg	56 stk.	[redacted]	[redacted]	Amgros
Bevacizumab	25 mg/ml	4 ml	[redacted]		Amgros
	25 mg/ml	16 ml	[redacted]		Amgros

*AstraZeneca har tilbudt en pris betinget af at olaparib + bevacizumab bliver anbefalet til HRD-positive patienter uden BRCA-mutation.

Medicinrådet vælger at ændre ansøgers antagelse for bevacizumabdosis i efterfølgende linjer til at være tilsvarende dosis i første behandlingslinje, hvor 50 % af patienterne får den lave dosis, og 50 % af patienterne får den høje dosis.

Fagudvalget estimerer, at ca. 25 % af patienterne i behandling med olaparib vil modtage en lavere dosis (400 mg dagligt). På baggrund af dette, ændrer Medicinrådet den gennemsnitlige daglige dosis for olaparib fra 600 mg til 550 mg.

Medicinrådet accepterer ansøgers valg vedr. lægemiddelomkostninger, men ændrer bevacizumabdosis i efterfølgende behandlingslinjer, og den gennemsnitlige daglige dosis for olaparib.

4.2.2 Hospitalsomkostninger

Ansøger har inkluderet omkostninger til administration af lægemidlerne, monitorering af patienterne, mens de er i behandling, og omkostninger til behandlingsrelaterede bivirkninger. Derudover har ansøger inkluderet omkostninger til test af HRD-status i en følsomhedsanalyse.

Administrationsomkostninger

Ansøger har ikke inkluderet omkostninger i forbindelse med administration af olaparib, da dette er en oral behandling.

Ansøger har inkluderet administrationsomkostninger for bevacizumab og kemoterapi i form af DRG-takster. Her anvendes taksten 13MA98 til at taksere for administration af lægemidlerne.

Medicinrådets vurdering af ansøgers antagelser vedr. administrationsomkostninger
Medicinrådet accepterer ansøgers tilgang til estimering af administrationsomkostninger. Anvendte enhedsomkostninger kan ses i Tabel 3.

Tabel 3. Omkostninger til lægemiddeladministration

	Enhedsomkostning [DKK]	Kode	Kilde
Administration af kemoterapi	1.636	13MA98	DRG-2021
Administration af bevacizumab	1.636	13MA98	DRG-2021

Medicinrådet accepterer ansøgers tilgang vedr. administrationsomkostninger.

Monitoreringsomkostning

Ansøger har inkluderet monitoreringsomkostninger til behandling med olaparib, bevacizumab, kemoterapi og ingen vedligeholdelsesbehandling. Ansøger antager, at monitoreringen af disse patienter vil bestå af hospitalsbesøg, hvor der er besøg med kontakt til læge og sygeplejerske. Derudover vil patienterne også modtage CT-scanninger

og vaginal ultralyd. Ansøger har ikke inkluderet omkostninger til blodprøver, da de antager, at disse omkostninger vil være inkluderet i DRG-taksterne.

Ansøger estimerer, at behandling med olaparib i kombination med kemoterapi vil være forbundet med ét lægebesøg om måneden og besøg ved sygeplejerske hver 3. uge. Behandlingen med olaparib monoterapi vil kræve ét besøg ved både læge og sygeplejerske om måneden. Bevacizumab monoterapi vil kræve ét lægebesøg hver 3. måned og sygeplejerskebesøg hver 3. uge. Ingen vedligeholdelsesbehandling vil medføre besøg ved både læge og sygeplejerske hver 3. måned. Kemoterapi estimeres af ansøger at være forbundet med ét besøg ved både læge og sygeplejerske om måneden.

Ansøger estimerer, at alle behandlingsalternativerne vil være forbundet med CT-scanning hver 3. måned og vaginal ultralyd hver 5. måned.

Medicinrådets vurdering af ansøgers antagelser vedr. monitoreringsomkostninger
Medicinrådets fagudvalg er blevet konsulteret for at validere ansøgers estimater vedrørende monitorering af behandlingsalternativerne. Fagudvalget giver udtryk for, at vaginal ultralyd ikke anvendes i dansk klinisk praksis.

I Tabel 4 er frekvenserne for lægebesøg, sygeplejerskebesøg og CT-scanning i forbindelse med monitorering af de forskellige behandlingsalternativer vist.

Tabel 4. Frekvensen af undersøgelse i forbindelse med behandlingsmonitorering

	Olaparib + bevacizumab	Olaparib	Bevacizumab	Ingen vedligeholdelses-behandling	Kemoterapi
Lægebesøg	1	1	0,33	0,33	1
Sygeplejerskebesøg	1,45	1	1,45	0,33	1
CT-scanning	0,33	0,33	0,33	0,33	0,33

Medicinrådet accepterer ansøgers tilgang vedr. monitoreringsomkostninger, men ekskluderer omkostninger til vaginal ultralyd fra Medicinrådets hovedanalyse.

Bivirkningsomkostninger

Ansøger har inkluderet omkostninger til behandling af bivirkninger. Bivirkningsomkostninger inkluderes for de patienter der årligt er i aktiv behandling. Det gøres ved at multiplicere bivirkningsfrekvensen for en lægemiddelbehandling med den enhedsomkostning, ansøger antager, der vil være ved behandlingen af den pågældende bivirkning. Bivirkningsomkostningerne påregnes, når en behandling initieres.

Kun omkostninger til bivirkninger af grad tre eller mere med en frekvens på mindst 2 % i en af behandlingsarmene i PAOLA-1-studiet er inkluderet. For olaparib monoterapi og ingen vedligeholdelsesbehandling er bivirkningsfrekvenserne hentet fra SOLO-1-studiet.

Ansøger anvender DRG-2021 som enhedsomkostning forbundet med bivirkningerne. Lægemiddelbehandling af bivirkninger er ekskluderet, da ansøger antager, at dette vil have meget begrænset indflydelse på analysens resultat.

I sin model har ansøger inkluderet omkostninger til diarré, anæmi, hypertension, neutropeni, træthed og lymfopeni. Både neutropeni, træthed og lymfopeni, antager ansøger, vil være forbundet med et ekstra besøg ved en læge. Ved hypertension, antager ansøger, at halvdelen af patienterne vil blive indlagt. Anæmi, antager ansøger, vil medføre, at 80 % af patienterne får en blodtransfusion, og de resterende 20 % vil have ét ekstra ambulant besøg ved en sygeplejerske. Diarré, antager ansøger, vil medføre, at 70 % af patienterne vil have et ekstra besøg ved en læge, hvoraf 2 % vil være indlagt.

Medicinrådets vurdering af ansøgers antagelser vedr. bivirkningsomkostninger
Medicinrådet accepterer ansøgers tilgang til estimering af bivirkningsomkostninger. Medicinrådets fagudvalg er blevet konsulteret for at validere ansøgers tilgang til at estimere bivirkningsrelaterede omkostninger. Fagudvalget mener ikke, at hypertension vil medføre indlæggelse. Det vil i de fleste tilfælde ikke være behandlingskrævende, og kun i enkelte tilfælde vil patienten blive tilset af praktiserende læge. Fagudvalget mener ikke, at træthed og lymfopeni er behandlingskrævende bivirkninger. Fagudvalget vurderer, at behandling af anæmi vil kræve et ambulant besøg. Bivirkningsfrekvenser og anvendte takster kan ses i Tabel 5.

Tabel 5. Rapporterede bivirkningsfrekvenser ved behandling med olaparib, bevacizumab og ingen vedligeholdelsesbehandling

	Olaparib + bevacizumab [%]	Olaparib [%]	Bevacizumab [%]	Ingen vedlige-holdelses-behandling [%]	Enheds-omkostning [DKK]	Kilde
Anæmi	17,4	21,5	0,4	1,5	1.636	DRG 2021: 13MA98
Diarré	2,2	3,1	1,9	0	1.601	DRG 2021: 13MA98 og 06MA14
Hypertension	18,7	0	30,3	0	-	Ikke behandlings-krævende
Neutropeni	6,4	8,5	3,0	3,1	1.636	DRG 2021: 13MA98
Træthed	5,2	3,8	1,5	1,5	-	Ikke behandlings-krævende

	Olaparib + bevacizumab [%]	Olaparib [%]	Bevacizumab [%]	Ingen vedlige-holdelses-behandling [%]	Enheds-omkostning [DKK]	Kilde
Lymfopeni	5,9	0	1,1	0	-	Ikke behandlings-krævende

Medicinrådet accepterer ansøgers tilgang vedr. bivirkningsomkostninger, men ændrer omkostningerne forbundet med lymfopeni, træthed, hypertension og anæmi, så det tilsvarer fagudvalgets udsagn vedrørende behandling af disse bivirkninger.

Testomkostninger

Ansøger har ikke inkluderet omkostninger til BRCA- og HRD-test, da de argumenterer, at disse tests udføres forud for behandlingen med olaparib og ikke i forbindelse med den. Omkostningerne til de to tests er undersøgt i følsomhedsanalyser, hvor de antager, at både BRCA- og HRD-test vil koste 7.000 DKK.

Medicinrådets vurdering af ansøgers antagelser vedr. testomkostninger

Medicinrådet accepterer ikke ansøgers tilgang til testomkostninger. På nuværende tidspunkt testes der ikke rutinemæssigt for HRD hos patienter, der ikke er BRCA-muterede, men dette vil være en forudsætning for ibrugtagning af olaparib. Medicinrådet vælger derfor at inkludere testomkostninger til ikke-BRCA-muterede patienter, der behandles med olaparib i kombination med bevacizumab, i Medicinrådets hovedanalyse.

Omkostningen for en HRD-test finder Medicinrådet for lav. I stedet for et estimat på 7.000 DKK anvendes en omkostning på 24.711 DKK pr. test. Det er listeprisen på HRD-testen, myChoice test, fra Myriad Genetics. Estimatet er omregnet fra dollars til danske kroner ved anvendelse af den gennemsnitlige valutakurs for 2021.

Fagudvalget vurderer, at der årligt er 240 ikke BRCA-muterede patienter, der enten er HRD-positive eller HRD-negative. Det er således i ovenstående population, at man skal identificere de patienter, som kan være kandidater til behandling med olaparib. Hvis olaparib i kombination med bevacizumab anbefales til HRD-positive ikke-BRCA-muterede patienter, vil 240 patienter (både HRD-positive og HRD-negative ikke-BRCA-muterede patienter) skulle testes for at finde de 100 HRD-positive ikke-BRCA-muterede, som vil være kandidater til olaparib i kombination med bevacizumab. Dermed bliver de samlede årlige testomkostninger 5.930.753 DKK, hvilket betyder, at den gennemsnitlige testomkostning er 59.308 DKK pr. HRD-positiv ikke BRCA-muterede patient.

Der er konkrete tiltag i gang på Rigshospitalet for at kunne udbyde testen lokalt, hvilket vil medføre en pris på ca. [redacted] DKK. Det forventes, at testen vil være implementeret på Rigshospitalet i løbet af 2021. Derfor vælger Medicinrådet også at udarbejde følsomhedsanalyser, hvor den forventerede danske pris anvendes. Dermed bliver den

gennemsnitlige testomkostning ca. [redacted] DKK pr. HRD-positiv patient uden BRCA-mutation.

Medicinrådet accepterer ikke ansøgers tilgang vedr. testomkostninger og vælger at inkludere omkostninger til HRD-test for ikke-BRCA-muterede patienter. Medicinrådet anvender en enhedsomkostning på 24.711 DKK pr. HRD-test i sin hovedanalyse og en gennemsnitlig omkostning på 59.308 DKK pr. HRD-positiv ikke-BRCA-muteret patient.

4.2.3 Efterfølgende behandling

Tid til efterfølgende behandling

Ansøger har i analysen også inkluderet omkostninger til efterfølgende behandlinger. Tiden til den efterfølgende behandling afhænger af, hvilken type efterfølgende behandling der gives.

Ansøger har inkluderet muligheden for at patienter kan modtage sekventiel behandling med PARP-hæmmere. Da dette er modstridende med dansk klinisk praksis, er dette dog ikke inkluderet i hovedanalysen.

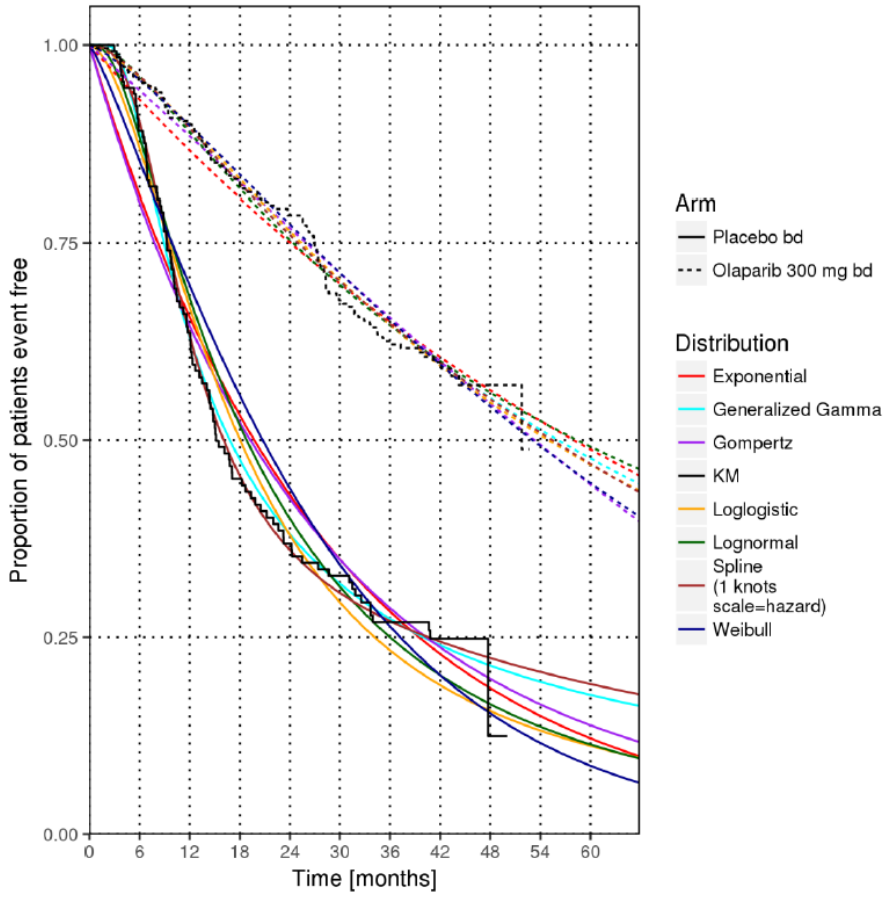
Tiden til efterfølgende behandling med kemoterapi er baseret på *time to first subsequent therapy* og *time to second subsequent therapy* fra SOLO-1-studiet. Andelen af patienter, der modtager forskellige behandlingstyper, er også baseret på SOLO-1-studiet.

Population	Behandling	Gennemsnitlig tid [år]
Time to first subsequent therapy SOLO-1	Olaparib	8,7
	Placebo	2,7
Time to second subsequent therapy SOLO-1	Olaparib	9,8
	Placebo	4,6
Time to first subsequent therapy PAOLA-1	Olaparib + bevacizumab	3,7
	Bevacizumab	2,2
Time to second subsequent therapy PAOLA-1	Olaparib + bevacizumab	3,2
	Bevacizumab	2,7

Ansøger har ekstrapoleret tid til første og anden efterfølgende behandling for at finde den gennemsnitlige tid. I Figur 4 er ekstrapoleringerne for tid til første efterfølgende behandling for olaparib monoterapi og ingen vedligeholdelsesbehandling vist, hvor

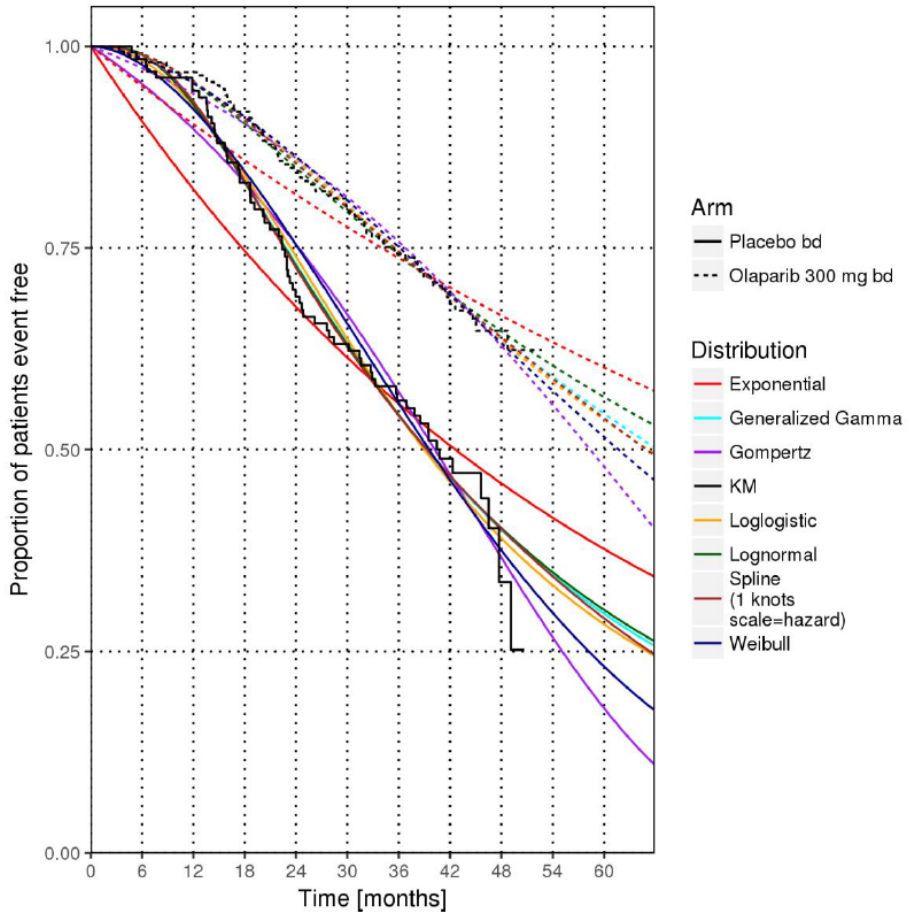
ansøger vælger at bruge den log-logistiske funktion. I Figur 5 er tiden til anden efterfølgende behandling vist, hvor ansøger vælger at anvende log-normal funktionen.

Figure 16. Parametric distributions for time to first subsequent therapy vs KM data.



Figur 2. Ekstrapoleringer af tid til første efterfølgende behandling for olaparib monoterapi og ingen vedligeholdelsesbehandling

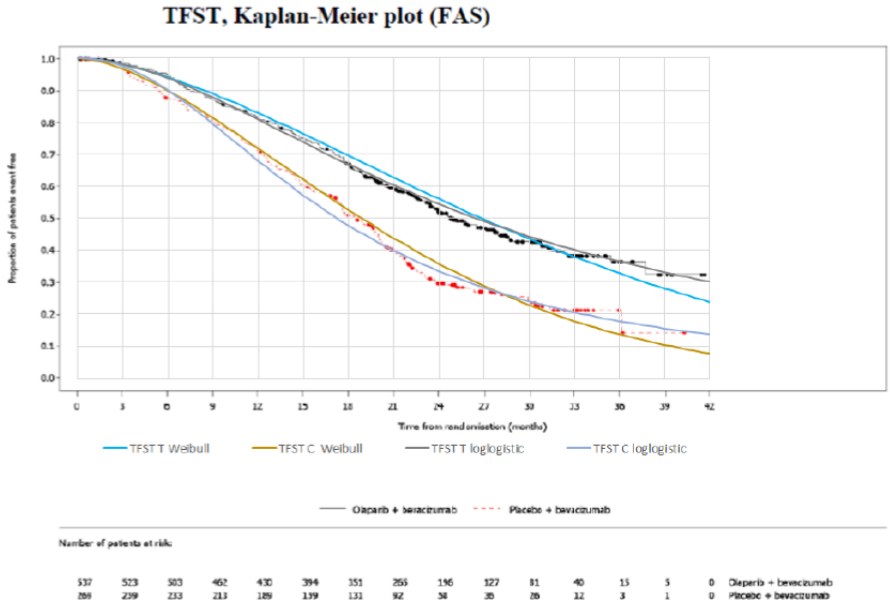
Figure 20. Parametric distributions for time to second subsequent therapy vs KM data.



Figur 3. Ekstrapoleringer af tid til anden efterfølgende behandling for olaparib monoterapi og ingen vedligeholdelsesbehandling

I Figur 6 er ekstrapoleringerne for tiden til første efterfølgende behandling for olaparib + bevacizumab og bevacizumab monoterapi vist, hvor ansøger vælger at bruge Weibull-funktion. I Figur 7 er tiden til anden efterfølgende behandling vist, hvor ansøger vælger at anvende log-logistisk funktionen.

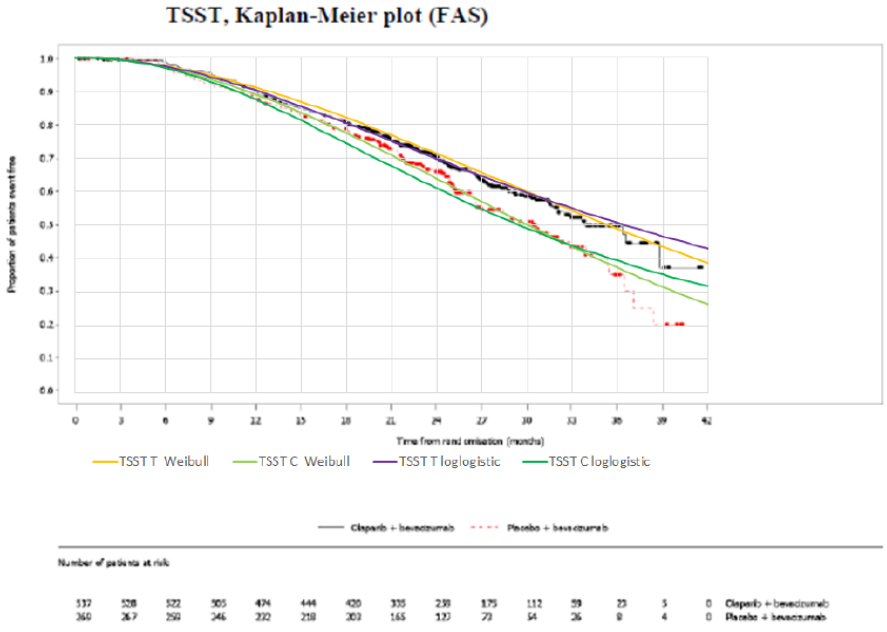
Figure 17. Time to first subsequent therapy in PAOLA-1. KM data and loglogistic and Weibull distributions fitted to the KM data.



TFST: Time to first subsequent therapy; T: Treatment arm, i.e. olaparib + bevacizumab; C: Control arm, i.e. bevacizumab

Figur 4. Ekstrapoleringer af tid til første efterfølgende behandling for olaparib + bevacizumab og bevacizumab monoterapi

Figure 22. Time to second subsequent therapy in PAOLA-1. KM data and loglogistic and Weibull distributions fitted to the KM data.



TSST: Time to second subsequent therapy; T: Treatment arm, i.e. olaparib + bevacizumab; C: Control arm, i.e. bevacizumab

Figur 5. Ekstrapoleringer af tid til anden efterfølgende behandling for olaparib + bevacizumab og bevacizumab monoterapi

Varigheden af den efterfølgende behandling er baseret på gennemsnitligt antal behandlingslinjer fra SOLO-1-studiet. Ansøger antager, at varigheden af al efterfølgende behandling vil forekomme inden for 10 år. Det vil sige, at de vælger at renormalisere deres data, således at sandsynligheden for at være i behandling hver måned i det ujusterede data bliver divideret med den samlede (kumulative) sandsynlighed for at blive behandlet inden for 10 år. Derved bliver sandsynligheden for at modtage efterfølgende behandling inden for 10 år lig med 100 %. Ansøger angiver, at dette fra deres synspunkt vil være mere plausibelt, uden yderligere argumentation.

Ansøger antager, at patienterne behandles med doxorubicin, carboplatin, paclitaxel, docetaxel og cisplatin i de efterfølgende linjer med kemoterapi

Ansøger argumenterer, at da tiden til progression er længere for både olaparib + bevacizumab i PAOLA-1 og olaparib monoterapi i SOLO-1, er det plausibelt at antage, at en andel af patienterne aldrig vil have relaps. I 1. linje har behandlingen kurativ intention, og en stor del af patienterne i SOLO-1 og PAOLA-1 havde ikke tilbageværende sygdom efter operation. På baggrund af dette antager ansøger at patienter i gennemsnit gennemgår tre behandlingslinjer af efterfølgende kemoterapi efter olaparib + bevacizumab og fire linjer efterfølgende kemoterapi efter bevacizumab eller ingen vedligeholdelsesbehandling.

Bevacizumab anvendes som efterfølgende behandling efter olaparib monoterapi. Behandlingen med bevacizumab som efterfølgende behandling baserer ansøger også på tid til første efterfølgende behandling fra SOLO-1-studiet. Den gennemsnitlige behandlingslængde for bevacizumab i efterfølgende behandlingslinjer baserer ansøger på studiet OCEANS[9], hvor det antages at være 11,7 måneder. OCEANS-studiet er et randomiseret fase III-studie, der sammenligner bevacizumab + kemoterapi med kemoterapi + placebo.

Medicinrådets vurdering af ansøgers antagelser vedr. efterfølgende behandling
Medicinrådet accepterer ansøgers tilgang til estimering af omkostninger til efterfølgende behandling. Fagudvalget har dog kommenteret på ansøgers valg af kemoterapi i de efterfølgende ligner, som de ikke mener afspejler dansk klinisk praksis. Medicinrådet vælger dog, at acceptere ansøgers tilgang, da forskellen mellem de kemoterapier ansøger har anvendt og de kemoterapier som fagudvalget angiver at være dansk klinisk praksis, afviger minimalt i pris.

Ansøger har ekstrapoleret data for at estimere, hvornår patienter gennemsnitligt påbegynder første efterfølgende behandlingslinje, og hvornår de gennemsnitligt påbegynder anden efterfølgende behandlingslinje. Der ligger ikke data til grund for yderligere efterfølgende behandlinger, og derfor vælger Medicinrådet at ekskludere omkostninger til efterfølgende behandlinger efter anden efterfølgende behandlingslinje.

Medicinrådet har udskriftet AIP for lægemiddelpriser til efterfølgende behandling med SAIP, se Tabel 6. Lægemiddelpriserne for olaparib og bevacizumab kan ses i Tabel 2.

Tabel 6. Anvendte lægemiddelpriser for efterfølgende behandling, SAIP (marts 2021)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Paclitaxel	6 mg/ml	50 ml	[redacted]	Amgros
Docetaxel	20 mg/ml	4 ml	[redacted]	Amgros
Doxorubicin	2 mg/ml	25 ml	[redacted]	Amgros
	2 mg/ml	10 ml	[redacted]	Amgros
Cisplatin	1 mg/ml	50 ml	[redacted]	Amgros
Carboplatin	10 mg/ml	45 ml	[redacted]	Amgros
Cyclophosphamid	50 mg	100 stk.	[redacted]	Amgros

Anvendte doser og behandlingsvarigheder af efterfølgende behandling kan ses i Tabel 7.

Tabel 7. Anvendte doser og behandlingsvarigheder for efterfølgende behandling

Lægemiddel	Doser	Behandlingsvarighed	Kilde
Gemcitabin	1000 mg/m^2	6 cyklusser á 21 dage	SPC'et for gemicitabin
Paclitaxel	175 mg/m^2	6 cyklusser á 21 dage	SPC'et for paclitaxel
Docetaxel	100 mg/m^2	6 cyklusser á 21 dage	SPC'et for docetaxel
Doxorubicin	30 mg/m^2	6 cyklusser á 28 dage	SPC'et for doxorubicin
Cisplatin	100 mg/m^2	6 cyklusser á 21 dage	SPC'et for cisplatin
Carboplatin	AUC (5mg/mL/min)	6 cyklusser á 21 dage	SPC'et for carboplatin
Cyclophosphamid	50 mg	6 cyklusser á 28 dage	SPC'et for cyclophosphamid

Medicinrådet accepterer ansøgers tilgang vedr. efterfølgende behandling, ekskluderer efterfølgende behandlingslinjer efter anden efterfølgende behandlingslinje.

4.2.4 Patientomkostninger

Patientomkostninger er estimeret på baggrund af monitoreringsbesøg på hospitalet og inkluderer patientens effektive tid på hospitalet, ventetid og transporttid.

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

Medicinrådets vurdering af ansøgers antagelser vedr. patientomkostninger
Medicinrådet accepterer ansøgers estimerede patienttid, som kan ses i Tabel 8.

Tabel 8. Estimat af effektiv patienttid

	Patienttid [minutter]
Konsultation (læge eller sygeplejerske)	20
CT-scanning	30

Medicinrådet accepterer ansøgers tilgang til estimering af patientomkostninger. I Tabel 9 er estimater for patienternes ressourceforbrug vist.

Tabel 9. Estimerede patientomkostninger pr. måned

	Olaparib + bevacizumab	Olaparib	Bevacizumab	Ingen vedligeholdelses-behandling	Kemoterapi
Antal besøg pr. måned	2,78	2,33	1,98	1,00	2,33
Patienttid, besøg [timer]	0,93	0,93	0,86	0,49	0,93
Patienttid, omkostning [DKK]	201	167	154	88	167
Transporttid [timer]	4,67	4,67	4,22	2,01	4,67
Transport, omkostning [DKK]	557	467	422	201	467

Medicinrådet accepterer ansøgers tilgang vedr. patientomkostninger.

4.3 Følsomhedsanalyser

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

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

Tabel 10. Følsomhedsanalyser og beskrivelse

Følsomhedsanalyse	Beskrivelse
Diskonteringsrente	Diskonteringsrenten varieres med +/- 1%

Følsomhedsanalyse	Beskrivelse
Lægemiddelpris for olaparib	Prisen for olaparib varieres med +/- 20%
Lægemiddelpris for bevacizumab	Prisen for bevacizumab varieres med +/- 20%
Monitoreringsomkostninger	Monitoreringsomkostningerne varieres med +/- 20%
Administrationsomkostninger	Administrationsomkostningerne varieres med +/- 20%
Patient- og transporttidsomkostninger	Patient- og transporttidsomkostninger varieres med +/- 20%
Bivirkningsomkostninger	Bivirkningsomkostninger varieres med +/- 20%
Efterfølgende behandling	Alt efterfølgende behandling ekskluderes fra analysen
Tidshorisont	Analysens tidshorisont ændres til 5 år
Valg af efterfølgende behandling	Andelen af patienter der modtager efterfølgende bevacizumab i olaparib monoterapiarmen varieres
Tid til efterfølgende behandling	Tid til efterfølgende behandling baseres på PAOLA-1 studiet i stedet for SOLO-1 studiet
Spild	Der inkluderes deling af hætteglas i analysen

Medicinrådets vurdering af ansøgers valg af følsomhedsanalyser
Ansøger har baseret deres analyse på en kortere tidshorisont end den Medicinrådet har valgt at anvende. Derfor vil de udførte følsomhedsanalyser ikke være udført på baggrund af den ønskede tidshorisont. På baggrund af dette vælger Medicinrådet ikke at præsentere resultaterne af ansøgers følsomhedsanalyse, men udfører i stedet egne analyser, hvor HRD-test-omkostninger ekskluderes fra analysen. Derudover udførers en følsomhedsanalyse baseret på Medicinrådets hovedanalyse, hvor den betingede pris for olaparib anvendes.

Medicinrådet vælger ikke at præsentere ansøgers følsomhedsanalyser, men udfører i stedet egen følsomhedsanalyse hvor testomkostninger til HRD-status ekskluderes og en hvor den betingede lægemiddelpris for olaparib anvendes.

4.4 Opsummering af basisantagelser

I Tabel 11 opsummeres basisantagelserne i henholdsvis ansøgers og Medicinrådets hovedanalyse.

Tabel 11. Basisantagelser for ansøgers og Medicinrådets hovedanalyse

Basisantagelser	Ansøger	Medicinrådet
Tidshorisont	10 år	25 år
Diskonteringsrate	3,5 %	3,5 %
Inkluderede omkostninger	Lægemiddelomkostninger Hospitalsomkostninger Efterfølgende behandling Patientomkostninger	Lægemiddelomkostninger Hospitalsomkostninger Efterfølgende behandling Patientomkostninger Testomkostninger
Dosering		
Olaparib:	600 mg dagligt	550 mg dagligt
Bevacizumab:	1. linje: 50 % får 7,5 mg/kg 50 % får 15 mg/kg 2. linje: 100 % får 15 mg/kg	1. linje: 50 % får 7,5 mg/kg 50 % får 15 mg/kg 2. linje: 50 % får 7,5 mg/kg 50 % får 15 mg/kg
Behandlingslinje	**Intervention:** 1. linjebehandling Tre efterfølgende behandlingslinjer **Komparatorer:** 1. linjebehandling Fire efterfølgende behandlingslinjer	**Intervention:** 1. linjebehandling To efterfølgende behandlingslinjer **Komparatorer:** 1. linjebehandling To efterfølgende behandlingslinjer
Tid til første efterfølgende behandling, valgte funktion til ekstrapolering:		
Olaparib + bevacizumab	Weibull	Weibull
Olaparib monoterapi	Log-logistisk	Log-logistisk
Bevacizumab monoterapi	Weibull	Weibull
Ingen vedligeholdelsesbehandling	Log-logistisk	Log-logistisk

Basisantagelser	Ansøger	Medicinrådet
Tid til anden efterfølgende behandling, valgte funktion til ekstrapolering:		
Olaparib + bevacizumab	Log-logistisk	Log-logistisk
Olaparib monoterapi	Log-normal	Log-normal
Bevacizumab monoterapi	Log-logistisk	Log-logistisk
Ingen vedligeholdelsesbehandling	Log-normal	Log-normal
Inkludering af spild	Nej	Nej

5. Resultater

5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse med undtagelse af de ændringer, der fremgår af Tabel 11.

BRCA-muterede patienter

Den gennemsnitlige inkrementelle omkostning pr. patient bliver [redacted] DKK i Medicinrådets hovedanalyse.

Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient ca. 304.000 DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 12.

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

	Olaparib + bevacizumab	Olaparib monoterapi	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	351.598	293.368	58.230
Efterfølgende behandling	[redacted]	[redacted]	[redacted]
Patientomkostninger	67.394	45.852	21.542
Totale omkostninger	[redacted]	[redacted]	[redacted]

HRD-positive ikke-BRCA-muterede patienter, der er kandidater til bevacizumab

Den gennemsnitlige inkrementelle omkostning pr. patient bliver [redacted] DKK i Medicinrådets hovedanalyse.

Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient ca. 744.000 DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 13.

Tabel 13. Resultatet af Medicinrådets hovedanalyse ved sammenligning med bevacizumab monoterapi, DKK, diskonterede tal

	Olaparib + bevacizumab	Bevacizumab monoterapi	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	264.625	180.351	84.274
Efterfølgende behandling	[redacted]	[redacted]	[redacted]
Patientomkostninger	64.079	32.661	31.417
Totale omkostninger	[redacted]	[redacted]	[redacted]

HRD-positive ikke-BRCA-muterede patienter, der ikke er kandidater til bevacizumab

Den gennemsnitlige inkrementelle omkostning pr. patient bliver [redacted] DKK i Medicinrådets hovedanalyse.

Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient 1.265.000 DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 14.

Tabel 14. Resultatet af Medicinrådets hovedanalyse ved sammenligning med ingen vedligeholdelsesbehandling, DKK, diskonterede tal

	Olaparib + bevacizumab	Ingen vedligeholdelses-behandling	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	278.579	160.719	117.860
Efterfølgende behandling	[redacted]	[redacted]	[redacted]
Patientomkostninger	68.159	34.589	33.570
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 15.

Tabel 15. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalysen, DKK

Scenarie	Inkrementelle omkostninger
Resultatet af hovedanalysen (HRD-positive, bevacizumab-kandidater)	[redacted]
HRD-testomkostninger ekskluderes	[redacted]
HRD-testomkostninger fra Rigshospitalet	[redacted]
Resultatet af hovedanalysen (HRD-positive, bevacizumab-kandidater)	[redacted]
HRD-testomkostninger ekskluderes	[redacted]
HRD-testomkostninger fra Rigshospitalet	[redacted]

6. Budgetkonsekvenser

Budgetkonsekvenserne pr. år er baseret på antagelsen om, at olaparib i kombination med bevacizumab vil blive anbefalet som mulig standardbehandling. Man ser derfor på to scenarier:

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

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

6.1 Ansøgers estimat af patientantal og markedsandel

BRCA-muterede patienter

Ansøger har antaget, at der vil være ca. 55 patienter med BRCA-mutation om året, der ved anbefaling vil være kandidater til behandling med olaparib i kombination med bevacizumab.

Hvis olaparib i kombination med bevacizumab anbefales, forventer ansøger, at behandlingen vil have et stigende markedsoptag fra 20 % i år 1 til 50 % i år 5. Markedsandelene, forventer ansøger, vil komme fra bevacizumab monoterapi og olaparib monoterapi. De patienter, der i dag modtager ingen vedligeholdelsesbehandling, forventer ansøger, fortsat vil modtage denne behandling ved en anbefaling.

Ikke-BRCA-muterede HRD-positive patienter, der er kandidater til bevacizumab

Ansøger har antaget, at der vil være ca. 45 patienter uden BRCA-mutation, der er HRD-positive, som er kandidater til bevacizumab om året, der ved anbefaling vil være kandidater til behandling med olaparib i kombination med bevacizumab.

Hvis olaparib i kombination med bevacizumab anbefales, forventer ansøger, at behandlingen vil have et stigende markedsoptag fra 20 % i år 1 til 75 % i år 5. Markedsandelene, forventer ansøger, vil komme fra bevacizumab monoterapi. De patienter, der i dag modtager ingen vedligeholdelsesbehandling, forventer ansøger, fortsat vil modtage denne behandling ved en anbefaling.

Ikke-BRCA-muterede HRD-positive patienter, der ikke er kandidater til bevacizumab

Ansøger har antaget, at der vil være ca. 32 patienter uden BRCA-mutation om året, der er HRD-positive, som ikke er kandidater til bevacizumab, der ved anbefaling vil være kandidater til behandling med olaparib i kombination med bevacizumab.

Hvis olaparib i kombination med bevacizumab anbefales, forventer ansøger, at behandlingen vil have et stigende markedsoptag fra 20 % i år 1 til 60 % i år 5. Markedsandelene, forventer ansøger, vil komme fra de patienter, der i dag ingen vedligeholdelsesbehandling modtager.

Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse

Fagudvalget er blevet konsulteret i forhold til patientantal og markedsoptag, hvis olaparib i kombination med bevacizumab anbefales som mulig standardbehandling, og hvis ikke olaparib i kombination med bevacizumab anbefales. Fagudvalget forventer, at ca. 60 patienter vil have BRCA-mutation, mens ca. 100 ikke vil have BRCA-mutation men vil være HRD-positive.

Fagudvalget forventer, at færre BRCA-muterede patienter vil modtage olaparib i kombination med bevacizumab ved en anbefaling, end hvad ansøger estimerer. Fagudvalget mener, at 30 % vil være mere realistisk.

Fagudvalget mener, at flere HRD-positive ikke-BRCA-muterede patienter vil starte på behandlingen med olaparib i kombination med bevacizumab, hvis det anbefales. De forventer, at der vil være et markedsoptag på 60 % i første år og 80 % i år 5.

Forventet patientantal og markedsoptag baseret på fagudvalgets estimater kan ses i Tabel 16, Tabel 17 og Tabel 18.

Tabel 16. Medicinrådets estimat af antal nye patienter pr. år for BRCA-muterede patienter

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Olaparib + bevacizumab	12	18	18	18	18
Olaparib	45	39	39	39	39
Ingen vedligeholdelses-behandling	3	3	3	3	3
Bevacizumab	0	0	0	0	0
			Anbefales ikke		
Olaparib + bevacizumab	0	0	0	0	0
Olaparib	54	54	54	54	54
Ingen vedligeholdelses-behandling	3	3	3	3	3
Bevacizumab	3	3	3	3	3

Tabel 17. Medicinrådets estimat af antal nye patienter pr. år for HRD-positive ikke-BRCA-muterede patienter (bevacizumab kandidater)

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Olaparib + bevacizumab	22	26	30	30	30
Ingen vedligeholdelses-behandling	6	4	4	4	4
Bevacizumab monoterapi	7	6	2	2	2
Olaparib monoterapi	2	2	2	2	2
			Anbefales ikke		

	År 1	År 2	År 3	År 4	År 5
Olaparib + bevacizumab	0	0	0	0	0
Ingen vedligeholdelses-behandling	28	28	28	28	28
Bevacizumab monoterapi	7	7	7	7	7
Olaparib monoterapi	2	2	2	2	2

Tabel 18. Medicinrådets estimat af antal nye patienter pr. år for HRD-positive ikke-BRCA-muterede patienter (ikke-bevacizumab-kandidater)

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Olaparib + bevacizumab	38	44	50	50	50
Ingen vedligeholdelses-behandling	25	19	13	13	13
			Anbefales ikke		
Olaparib + bevacizumab	0	0	0	0	0
Ingen vedligeholdelses-behandling	63	63	63	63	63

Medicinrådet har udført sin egen budgetkonsekvensanalyse, hvor patientantallet er ændret til 60 patienter der er BRCA-muterede, og 100 patienter uden BRCA-mutation, der er HRD-positive pr. år.

6.2 Medicinrådets budgetkonsekvensanalyse

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

- 60 patienter med BRCA-mutation

- 37 patienter uden BRCA-mutation, der er HRD-positive og kandidater til bevacizumab
- 63 patienter uden BRCA-mutation, der er HRD-positive og ikke er kandidater til bevacizumab

BRCA-muterede patienter

Medicinrådet estimerer, at anvendelse af olaparib i kombination med bevacizumab vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Resultatet er præsenteret i Tabel 19.

Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 3,8 mio. DKK i år 5.

Tabel 19. Medicinrådets analyse af totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal

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

Ikke-BRCA-muterede HRD-positive patienter, der er kandidater til bevacizumab

Medicinrådet estimerer, at anvendelse af olaparib i kombination med bevacizumab vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Resultatet er præsenteret i Tabel 20.

Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 20,9 mio. DKK i år 5.

Tabel 20. Medicinrådets analyse af totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal

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

Ikke-BRCA-muterede HRD-positive patienter, der ikke er kandidater til bevacizumab

Medicinrådet estimerer, at anvendelse af olaparib i kombination med bevacizumab vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Resultatet er præsenteret i Tabel 21.

Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 47,0 mio. DKK i år 5.

Tabel 21. Medicinrådets analyse af totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal

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

7. Diskussion

Behandling med olaparib i kombination med bevacizumab til patienter med BRCA-mutation er forbundet med inkrementelle omkostninger på ca. [redacted] DKK sammenlignet med behandling med olaparib monoterapi. Behandling med olaparib i kombination med bevacizumab til HRD-positive patienter uden BRCA-mutation, som er kandidater til bevacizumab, er forbundet med inkrementelle omkostninger på ca. [redacted] DKK sammenlignet med behandling med bevacizumab monoterapi. Behandling med olaparib i kombination med bevacizumab til HRD-positive patienter uden BRCA-mutation, der ikke er kandidater til bevacizumab, er forbundet med inkrementelle omkostninger på ca. [redacted] DKK sammenlignet med behandling med ingen vedligeholdelsesbehandling.

De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne for olaparib.

På nuværende tidspunkt testes der ikke rutinemæssigt for HRD hos patienter uden BRCA-mutation, men dette vil være en forudsætning for ibrugtagning af olaparib i kombination med bevacizumab til patienter der er HRD-positive uden BRCA-mutation. Omkostningerne pr. patient ved indførelse af HRD-testen udgør ca. 60.000 DKK, da testen på nuværende tidspunkt kun udbydes i USA.

8. Referencer

1. Mosgaard BJ, Pedersen LK, Bjørn SF, Christiansen T, Markauskas A, Lund B et al. Retningslinier for visitation, diagnostik, behandling og opfølgning af epitelial ovarie-, tuba- og primaer peritonealcancer samt borderline tumorer 5. udgave 2016.

2. NORDCAN - Association of the Nordic Cancer Registry. Kræftstatistik: Nøgletal og figurer. 2017.

3. Bolton KL, Chenevix-Trench G, Goh C, Sadetzki S, Ramus SJ, Karlan BY, et al. Association between BRCA1 and BRCA2 Mutations and Survival in Women with Invasive Epithelial Ovarian Cancer. JAMA - J Am Med Assoc [internet]. 2012 [citeret 23. marts 2021];307(4):382–90. Tilgængelig fra: https://pubmed.ncbi.nlm.nih.gov/22274685/

4. Hoppe MM, Sundar R, Tan DSP, Jeyasekharan AD. Biomarkers for homologous recombination deficiency in cancer [internet]. Bd. 110, Journal of the National Cancer Institute. Oxford University Press; 2018 [citeret 23. marts 2021]. s. 704–13. Tilgængelig fra: https://pubmed.ncbi.nlm.nih.gov/29788099/

5. Pellegrino B, Mateo J, Serra V, Balmaña J. Controversies in oncology: Are genomic tests quantifying homologous recombination repair deficiency (HRD) useful for treatment decision making? [internet]. Bd. 4, ESMO Open. BMJ Publishing Group; 2019 [citeret 23. marts 2021]. Tilgængelig fra: https://pubmed.ncbi.nlm.nih.gov/31231558/

6. Forslag til national guideline for genetisk udredning af patienter med ovariecancer [internet]. [citeret 23. marts 2021]. Tilgængelig fra: http://dgcg.dk/images/Grupper/Ovariecancergruppen/Retningslinier2016/nye_filer/Kap_5.pdf

7. Ray-Coquard I, Pautier P, Pignata S, Pérol D, González-Martín A, Berger R, et al. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. N Engl J Med [internet]. 2019 [citeret 11. marts 2021];381(25):2416–28. Tilgængelig fra: http://www.nejm.org/doi/10.1056/NEJMoa1911361

8. Moore K, Colombo N, Scambia G, Kim B-G, Oaknin A, Friedlander M, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med [internet]. 2018 [citeret 11. marts 2021];379(26):2495–505. Tilgængelig fra: https://pubmed.ncbi.nlm.nih.gov/30345884/

9. Aghajanian C, Blank S V., Goff BA, Judson PL, Teneriello MG, Husain A, et al. OCEANS: A randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol [internet]. 2012 [citeret 8. april 2021];30(17):2039–45. Tilgængelig fra: /pmc/articles/PMC3646321/

9. Bilag

9.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient med BRCA-mutation ca. [redacted] DKK over en tidshorisont på 10 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 22.

Tabel 22. Resultatet af ansøgers hovedanalyse for patienter med BRCA-mutation, DKK, diskonterede tal

	Olaparib + bevacizumab	Olaparib monoterapi	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	131.042	242.243	70.799
Efterfølgende behandling	[redacted]	[redacted]	[redacted]
Patientomkostninger	42.742	37.078	5.664
Totale omkostninger	[redacted]	[redacted]	[redacted]

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient, der er HRD-positiv uden BRCA-mutation, som er kandidat til bevacizumab, ca. [redacted] DKK over en tidshorisont på 10 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 23.

Tabel 23. Resultatet af ansøgers hovedanalyse for HRD-positive patienter, der er kandidater til bevacizumab, DKK, diskonterede tal

	Olaparib + bevacizumab	Bevacizumab monoterapi	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	227.000	207.005	19.995
Efterfølgende behandling	[redacted]	[redacted]	[redacted]
Patientomkostninger	39.427	33.499	5.928
Totale omkostninger	[redacted]	[redacted]	[redacted]

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient, der er HRD-positiv uden BRCA-mutation, som ikke er kandidat til bevacizumab, ca. [redacted] DKK over en tidshorisont på 10 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 24.

Tabel 24. Resultatet af ansøgers hovedanalyse for HRD-positive patienter uden BRCA-mutation, der ikke er kandidater til bevacizumab, DKK, diskonterede tal

	Olaparib + bevacizumab	Ingen vedligeholdelses-behandling	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	243.443	201.814	41.629
Efterfølgende behandling	[redacted]	[redacted]	[redacted]
Patientomkostninger	43.507	35.426	8.081
Totale omkostninger	[redacted]	[redacted]	[redacted]

9.2 Resultatet af ansøgers budgetkonsekvensanalyse

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

Med de ovenstående antagelser om patientantal og markedsandel estimerer ansøger, at anvendelse af olaparib + bevacizumab vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5 for patienter med BRCA-mutation. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 25.

Tabel 25. Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal

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

For patienter, der er HRD-positive uden BRCA-mutation, og som er kandidater til bevacizumab, vil anvendelse af olaparib + bevacizumab resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5 for patienter med BRCA-mutation. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 26.

Tabel 26. Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

For patienter der er HRD-positive uden BRCA-mutation, og som ikke er kandidater til bevacizumab vil anvendelse af olaparib + bevacizumab resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5 for patienter med BRCA-mutation. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 26.

Tabel 27. Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal

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

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

Forhandlingsnotat

Dato for behandling i Medicinrådet	23.06.2021
Leverandør	Astra Zeneca
Lægemiddel	Olaparib (Lynparza)
Ansøgt indikation	Olaparib i kombination med bevacizumab til 1. linje vedligeholdelsesbehandling af avanceret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden med homolog recombinationsdefekt.

Forhandlingsresultat

Amgros har opnået følgende betinget pris på olaparib på betingelse af en godkendelse af **klinisk spørgsmål 2 og 3**:

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP	Nuværende SAIP	Betinget pris SAIP	Rabatprocent ift. AIP
Olaparib	100 mg	56 stk.	18219,87	[redacted]	[redacted]	[redacted]
Olaparib	150 mg	56 stk.	18219,87	[redacted]	[redacted]	[redacted]

[redacted]

Vurdering af forhandlingsresultatet

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

- Leverandøren ser at de kliniske vurderinger giver en fordel for patienterne som indtil nu ikke har haft nogen tilgængelige behandlinger.

[redacted]

Konklusion

Det er Amgros vurdering at vi på nuværende tidspunkt har fået den bedst mulige pris.

[redacted]

Relation til markedet

Der er i dag en behandlingsvejledning til behandling af patienter med BRCA-mutation i både 1. og 2. linje. Der er ingen behandlingsvejledning til patienter uden BRCA-mutation.

Følgende skema viser priserne for et års behandling i rene lægemiddelpriser for hhv. olaparib og niraparib. Priserne er udregnet med SAIP.

Lægemiddel	Daglig dosis	Tabletter pr dag	Årspris beregnet med betinget pris (DKK)	Årspris beregnet med nuværende rabat (DKK)
Niraparib	100 mg daglig	1 x 100 mg	[redacted]	[redacted]
Niraparib	200 mg daglig	2 x 100 mg	[redacted]	[redacted]
Niraparib	300 mg daglig	3 x 100 mg	[redacted]	[redacted]
Olaparib*	400 mg daglig	4 x 100 mg	[redacted]	[redacted]
Olaparib*	500 mg daglig	2 x 150 mg 2 x 100 mg	[redacted]	[redacted]
Olaparib*	600 mg daglig	4 x 150 mg	[redacted]	[redacted]

*Olaparib er til denne indikation i kombination med bevacizumab. Prisen for et års behandling i rene lægemiddelpriser er her hhv. 30.298 DKK for 7 mg/kg og 60.597 DKK for 15 mg/kg.

**Udregnet på baggrund af den betingede pris som GSK har tilbudt Amgros i prisforhandling på niraparib i juni 2021.

Status fra andre lande

Norge: Kombinationen med olaparib og bevacizumab til samme indikationer er under evaluering[1].

[1] Olaparib (Lynparza) - Indikasjon VII (nyemetoder.no)

Fra: Hans Christian Cederberg Helms
Sendt: 26. april 2021 20:56
Til: Clausen, Søren <Soren.Clausen@astrazeneca.com>
Cc: Ekman, Mattias <Mattias.Ekman@astrazeneca.com>; Hansen, Jesper <Jesper.Hansen@astrazeneca.com>
Emne: SV: PAOLA vurderingsrapporten

Kære Søren

Mange tak for høringssvar vedr. udkast til klinisk vurdering og sundhedsøkonomisk afrapportering for olaparib i kombination med bevacizumab.
Vi har diskuteret svaret vedr. den sundhedsøkonomiske afrapportering, og finder ikke anledning til at ændre i denne. Afrapporteringen følger fagudvalgets vurderinger af de sundhedsøkonomiske antagelser og følger Medicinrådets metodevejledning for omkostningsanalyser ift. at omkostninger til diagnostiske tests medtages i de økonomiske analyser. Afrapporteringen indeholder en følsomhedsanalyse, uden omkostninger for HRD-testen, som kan afspejle de samlede omkostninger i en situation, hvor testomkostningen er væsentlig lavere end den angivne listepris.

Jeres høringssvar vil indgå i den videre sagsbehandling, og høringssvaret vil blive offentliggjort sammen med den endelige anbefaling.

Mvh

Hans Christian Cederberg Helms
Sundhedsvidenskabelig specialkonsulent
Cand.pharm., ph.d.
hce@medicinraadet.dk
+45 21 34 08 76

Medicinrådet
Dampfærgevej 27-29, 3. th.
2100 København Ø
+45 70 10 36 00
medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Medicinrådet

Fra: Clausen, Søren <Soren.Clausen@astrazeneca.com>
Sendt: 26. april 2021 09:48
Til: Hans Christian Cederberg Helms <HCE@medicinraadet.dk>
Cc: Ekman, Mattias <Mattias.Ekman@astrazeneca.com>; Hansen, Jesper <Jesper.Hansen@astrazeneca.com>
Emne: PAOLA vurderingsrapporten

Kære Hans Christian,

Tak for udkastet til merværdi for olaparib + bevacizumab på baggrund af PAOLA ansøgningen.

Til den kliniske del har vi ikke kommentarer til vurderingen. Vi finder at evalueringen er i tråd med de kliniske resultater for kombinationen vs. de valgte komparatorer.

I den sundhedsøkonomiske afrapportering sættes prisen til HRD testning til DKK 24.711(listepris). Vi vurderer at denne pris ikke vil være gældende i en længere periode. I Danmark arbejdes for tiden på flere løsninger for lokal test for genomisk instabilitet, hvoraf implementering af et Myriad Satellit Laboratorium forhandles mellem Myriad og Rigshospitalet, og forventes igangsat 2. halvår 2021. Dette laboratorium vil kunne teste prøver fra Danmark generelt, og løsningen forventes at reducere omkostningerne fra ~4.000$ ved Myriad MyChoice HRD test i Salt Lake City til ~1.000$ ved Myriad HRD score udført på Rigshospitalet. Udgifterne til HRD inkluderer test for BRCA.

Med venlig hilsen

Søren

Søren Clausen
Market Access Head

AstraZeneca A/S
Nordic Marketing Company | Denmark | Market Access Department
World Trade Center Ballerup
Borupvang 3, DK-2750 Ballerup, Denmark
T: +45 43666462 M: +45 23615584
soren.clausen@astrazeneca.com

Medicinrådet

Medicinrådets vurdering vedrørende olaparib i kombination med bevacizumab til 1. linje vedligeholdelsesbehandling af avanceret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden med homolog rekombinationsdefekt

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	
Godkendelsesdato	28. april 2021
Dokumentnummer	113721
Versionsnummer	1.0

Indholdsfortegnelse

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 28. april 2021

1. Medicinrådets konklusion

Medicinrådet har vurderet olaparib i kombination med bevacizumab i patientpopulationer opdelt efter BRCA-mutationsstatus.

For patienter med BRCA-mutation kan den samlede værdi af olaparib i kombination med bevacizumab sammenlignet med olaparib alene ikke kategoriseres. Medicinrådet vurderer, at olaparib i kombination med bevacizumab samlet set ikke har bedre effekt og er forbundet med flere bivirkninger end olaparib alene.

For HRD-positive patienter uden BRCA-mutation medfører olaparib i kombination med bevacizumab en lille merværdi sammenlignet med henholdsvis bevacizumab alene og placebo. Denne merværdi kan ikke overføres til 2. linjebehandling, da effekten af kombinationsbehandlingen kun er undersøgt i nydiagnosticerede patienter.

Vurderingerne er baseret på evidens af meget lav kvalitet. Medicinrådet bemærker, at der ikke foreligger modne data til at vurdere effekten af olaparib i kombination med bevacizumab på overlevelsen.

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

BRCA	To specifikke gener involveret i homolog rekombination *(Breast cancer gene*)
CI:	Konfidensinterval
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EPAR:	*European Public Assessment Report*
FDA	*U.S. Food and Drug Administration*
GRADE:	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HGSC	High-grade serøst karcinom *(High grade serous carcinoma)*
HR:	*Hazard ratio*
HRD	Homolog rekombinationsdefekt (*Homologues recombination deficiency)*
HRD-negativ	Patienter med intakt homolog rekombination I tumorvævet
HRD-positiv	Patienter med defekt homolog rekombination i tumorvævet
ITT:	*Intention-to-treat*
OR:	*Odds ratio*
OS	Samlet overlevelse (*Overall survival*)
PAIC	*Population adjusted indirect comparison*
PARP	Poly-ADP-ribose-polymerase
PARPi	Poly-ADP-ribose-polymerasehæmmer (*Poly-ADP-ribose-polymerase inhibitor*)
PFS	Progressionsfri overlevelse (*Progression free survival*)
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 olaparib i kombination med bevacizumab til 1. linje vedligeholdelsesbehandling af avanceret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden med homolog rekombinationsdefekt er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra AstraZeneca. Medicinrådet modtog ansøgningen den 12. februar 2021. En del af det indsendte data som ligger til grund for fagudvalgets vurdering af olaparib i kombination med bevacizumab, er fortroligt. Ansøger har tilkendegivet, at den fortrolige data for patienterne inddelt efter progressionsrisiko forventes at kunne offentliggøres indenfor den nærmeste fremtid.

De kliniske spørgsmål er:

1. Hvilken værdi har olaparib i kombination med bevacizumab sammenlignet med olaparib monoterapi som vedligeholdelsesbehandling for nydiagnosticerede patienter med avanceret BRCA-muteret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden, som responderer på platinbaseret kemoterapi (komplet eller partiel respons)?
2. Hvilken værdi har olaparib i kombination med bevacizumab sammenlignet med bevacizumab monoterapi som vedligeholdelsesbehandling for nydiagnosticerede patienter med avanceret ikke-BRCA-muteret, HRD-positiv high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden, som responderer på platinbaseret kemoterapi (komplet eller partiel respons) og kandiderer til bevacizumab?
3. Hvilken værdi har olaparib i kombination med bevacizumab sammenlignet med placebo som vedligeholdelsesbehandling for nydiagnosticerede patienter med avanceret ikke-BRCA-muteret, HRD-positiv high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden, som responderer på platinbaseret kemoterapi (komplet eller partiel respons) og ikke kandiderer til bevacizumab?

Se endvidere Figur 3-1 for en skitsering af de kliniske spørgsmål.

3.1 Kræft i æggestokkene, æggelederne eller primær bughulekræft

Kræft i æggestokkene, æggelederne og primær bughulekræft benævnes herefter samlet som kræft i æggestokkene.

Kræft i æggestokkene er den fjerde hyppigste kræftdødsårsag hos kvinder i Danmark. Der diagnosticeres omkring 450-550 nye tilfælde om året, og ved udgangen af 2016 levede 4697 kvinder med sygdommen. [1,2]. Kræft i æggestokkene udgør i alt 2,8 % af alle kræfttilfælde hos kvinder, og livstidsrisikoen for at udvikle sygdommen er ca. 2 %. Median alder for diagnosen er 63 år, og overlevelsen er afhængig af alder ved diagnosen

samt sygdomsstadiet (FIGO-stadium, herfra blot benævnt stadium). 5-års overlevelsesrater for stadium I, II, III og IV er henholdsvis 93, 76, 41 og 23 % med faldende respektive værdier ved stigende alder på diagnosetidspunktet [3,4]. Tidlige stadier af sygdommen er ofte asymptomatiske på grund af æggestokkenes frie beliggenhed i det lille bækken. Således har ca. 70-80 % af patienter med kræft i æggestokkene på diagnosetidspunktet lokal spredning eller avanceret sygdom (stadium II-IV) [1], hvilket er kraftigt medvirkende til en samlet 5-års overlevelse på ca. 40-50 [2,4].

Kræft i æggestokkene er overordnet set en heterogen gruppe. Dog er omkring 90 % af tilfældene af epitelial type (karcinomer), og størstedelen af disse er af typen high-grade serøst karcinom (HGSC) (268-307 patienter per år fra 2016-2019 svarende til ca. 55 % af alle tilfælde) [4].

Mutationer i *Breast Cancer* (BRCA) 1- eller 2-genet er en væsentlig arvelig risikofaktor for udviklingen af kræft i æggestokkene. Forekomsten er ca. 15-20 % med en højere forekomst hos patienter med HGSC [5-7]. BRCA-mutationer kan være både arvelige eller somatiske. I dansk klinisk praksis behandles disse på samme måde, hvorved BRCA-mutationer i denne protokol bruges som fællesbetegnelse for begge typer. Patienter med BRCA-mutation har generelt en bedre prognose, da mutationerne medfører et signifikant bedre respons på både platinbaseret kemoterapi og hæmmere af Poly-ADP-Ribose-Polymerase (PARPi) [8-10].

BRCA er involveret i homolog rekombination, som er en vital celleproces til reparation af DNA-skader [9,11]. Tumorer med BRCA-mutation vil oftest også have homolog rekombinationsdefekt (HRD), men HRD kan også forekomme i ikke-BRCA-muterede tumorer. Flere studier har dokumenteret HRD i op mod 40 % af platinsensitive tumorer i æggestokkene uden BRCA-mutation, hvorved gruppen med HRD er op mod dobbelt så stor som gruppen med BRCA-mutation [6,10,12-14]. I studierne var HRD defineret som enten BRCA-mutation eller en genomisk ustabilitetsscore over 42 målt vha. MYRIAD myChoice CDx. Dette er en kompleks molekylærbiologisk analyse, der kombinerer genomic scar assays, hhv. '*Telomeric Allelic Imbalance*', '*Loss Of Heterozygosity*' og '*Large Scale Transition*' med en samlet tærskelværdi på 42 til bestemmelse af HRD-positivitet.

Det anbefales i dag, at alle patienter udredes i forhold til BRCA-mutationsstatus [15], men der findes ingen nationale guidelines i forbindelse med udredning af HRD-status. Derfor vil det forventes, at en væsentlig gruppe af danske patienter uden påvist BRCA-mutation har tumorer, der udviser HRD. *U.S. Food and Drug Administration* (FDA) har i 2020 godkendt et *companion diagnostics* til at identificere HRD i high-grade kræft i æggestokkene [16]. Denne diagnostiske metode er anvendt i flere kliniske forsøg med PARPi i Danmark, heriblandt på Herlev Hospital, Odense Universitetshospital, Rigshospitalet og Aarhus Universitetshospital, hvor mere end 100 patienter er blevet testet [10,13,17].

Tilstedeværelsen af en HRD-positiv patientgruppe uden BRCA-mutation gør det relevant at dele patientpopulationen op i to subpopulationer af forskellig forventet størrelse, ud fra en antagelse om samlet 300 nydiagnosticerede patienter med HGSC om året:

- Patienter med BRCA-mutation: Ca. 60 patienter om året.
- HRD-positive patienter uden BRCA-mutation: Ca. 100 patienter om året.
- HRD-negative patienter uden BRCA-mutation: Ca. 140 patienter om året. Disse er ikke omfattet af EMA-indikationen for olaparib i kombination med bevacizumab.

3.2 Olaparib og bevacizumab

Olaparib og bevacizumab er godkendt af Europakommisionen som kombinationsbehandling til 1. linje vedligeholdelsesbehandling af patienter med avanceret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden, som responderer på platinbaseret kemoterapi (komplet eller partielt respons), og hvor der er konstateret homolog rekombinationsdefekt (HRD) i en tumorprøve defineret som enten BRCA-mutation eller genomisk ustabilitet.

Olaparib er i forvejen indikeret som monoterapi til 2. linje vedligeholdelsesbehandling af patienter med recidiverende platinsensitiv high-grade kræft i æggestokkene af stadium III eller IV og til 1. linje vedligeholdelsesbehandling af patienter med platinsensitiv high-grade kræft i æggestokkene af stadium III eller IV i patienter med mutation i BRCA1/2 [18]. Olaparib som monoterapi er anbefalet til både 1. og 2. linje vedligeholdelsesbehandling i Medicinrådets behandlingsvejledning vedrørende lægemidler til BRCA-muteret, platinsensitiv high-grade kræft i æggestokkene med en standarddosering på 600 mg dagligt i 2 år eller indtil progression eller uacceptabel toksicitet [19].

Olaparib tilhører gruppen af selektive PARPi, der hæmmer aktivering af enzymerne, PARP-1, -2 og -3 [18]. PARP indgår i cellens DNA-reparationsrespons, hvor de faciliterer reparation af enkeltstrengsbrud på DNA'et. Hæmning af denne proces resulterer i yderligere brud på DNA'et kaldet DNA-dobbeltstrengsbrud. Disse brud repareres normalt via homolog rekombination, men i celler med HRD (som er tilfældet i BRCA-mutationer) vil dobbeltstrengsbrud akkumulere og medføre celledød i tumoren [20].

Bevacizumab er et monoklonalt antistof, der hæmmer angiogenesen via binding til *vascular endothelial growth factor* (VEGF). Dette hæmmer dannelsen af nye blodkar i tumoren og normaliserer de eksisterende blodkar, hvorved tumorvæksten hæmmes [21]. Bevacizumab er indikeret til kombinationsbehandling med carboplatin og paclitaxel i 1. eller 2. linje af kræft i æggestokkene af stadium III eller IV. Derudover er det indikeret i kombination med paclitaxel, topotecan eller pegyleret liposomal doxorubicin til platinresistent – recidiverende kræft i æggestokkene, hvor der ikke tidligere er anvendt VEGF-hæmmere, og hvor patienter ikke har gennemgået mere end to tidligere kemoterapilinjer.

I dansk klinisk praksis stilles yderligere krav til patientens sygdom for at anvende bevacizumab (se afsnit 3.3). Ved behandling gives enten 7,5 eller 15 mg/kg hver 3. uge indtil sygdomsprogression.

Der kan være en potentiel synergistisk effekt ved at kombinere olaparib og bevacizumab eller anden VEGF-hæmmer. Dette er observeret i et fase II-klinisk studie, hvor patienterne modtog enten olaparib monoterapi eller olaparib i kombination med cediranib (en VEGF-receptorinhibitor) [22]. Her sås en signifikant øget progressionsfri overlevelse (PFS) og generel overlevelse (OS) ved kombinationsbehandlingen overfor olaparib alene i subpopulationen uden BRCA-mutationer, hvorimod der ikke sås nogen signifikante forskelle i populationen med BRCA-mutation.

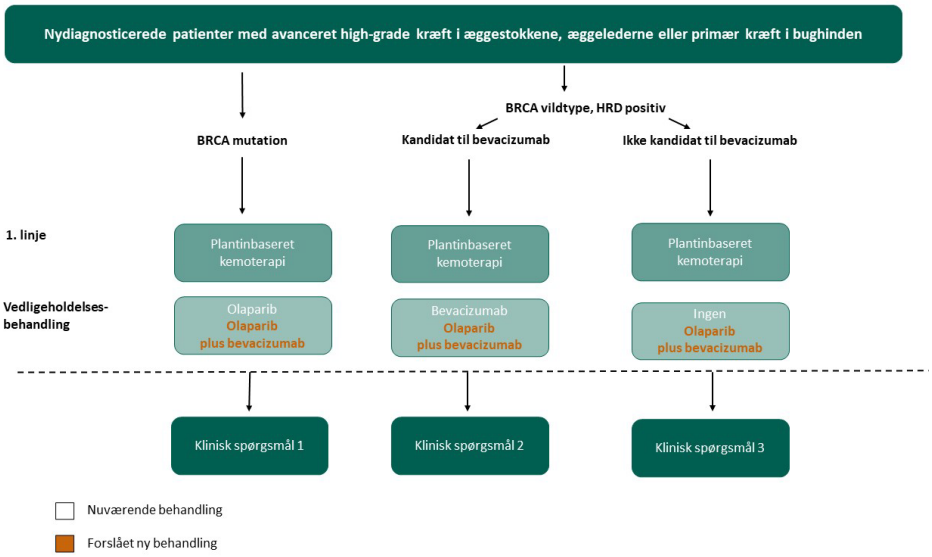
3.3 Nuværende behandling

Det overordnede mål for behandlingen af kræft i æggestokkene er helbredelse, alternativt at forlænge overlevelsen og/eller at øge livskvaliteten. Den primære behandling er kirurgisk, hvor målet er at fjerne alt synligt kræftvæv (makroradikal operation) samt korrekt stadieinddeling [1,23]. Dette opnås for ca. 70 % af patienter med stadium III eller IV enten primært eller efter indledende kemoterapi [4]. Efterfølgende behandling afhænger af patientens sygdomsstadie, operationsresultat og sundhedsmæssige status. I klinisk praksis skelnes der mellem patienter, hvor der er efterladt mindre end eller mere end eller lig med 1 cm tumorvæv efter operation. Patienter i stadium IIB-IV uden makroskopisk tumorvæv efter operation (< 1 cm) behandles som standard med adjuverende platinbaseret kombinationskemoterapi bestående af carboplatin og paclitaxel. Behandlingen gives i 6 serier, med mindre der opstår progression eller uacceptabel toksicitet [24]. Patienter med BRCA-mutation, som responderer på kemoterapi, tilbydes vedligeholdelsesbehandling med olaparib, som beskrevet i afsnit 3.2. Patienter uden BRCA-mutation tilbydes ikke yderligere vedligeholdelsesbehandling.

Patienter i stadium III med efterladt makroskopisk tumorvæv efter operation (≥ 1 cm) samt patienter i stadium IV og inoperable patienter behandles som standard også med carboplatin og paclitaxel. Patienter med BRCA-mutation tilbydes vedligeholdelsesbehandling med olaparib som beskrevet ovenfor, hvorimod patienter uden BRCA-mutation kan tilbydes behandling med bevacizumab i kombination med og/eller efter kemoterapien [19].

Størstedelen af patienterne (60-80 %) responderer på 1. linjebehandlingen, men omkring 80 % af disse vil opleve tilbagefald inden for 2-3 år efter afsluttet kemoterapi [1]. Disse patienter har generelt dårligere prognose end nydiagnosticerede patienter og vil typisk opleve kortere progressionsfri overlevelse (PFS) efter gentagne kemoterapilinjer [25].

Det nuværende behandlingsforløb, samt hvorledes olaparib i kombination med bevacizumab placeres i forhold til dette i de tre kliniske spørgsmål er skitseret nedenfor.



Figur 3-1: Olaparib i kombination med bevacizumabs indplacering som vedligeholdelsesbehandling efter den nuværende 1. linjebehandling med platinbaseret kemoterapi af kræft i æggestokkene. EMA-indikationen for olaparib i kombination med bevacizumab dækker alle patienter med nydiagnosticeret kræft i æggestokkene, der responderer på platinbaseret kemoterapi og har diagnosticeret HRD, men den samlede patientpopulation er i denne vurderingsrapport opdelt for at belyse effekterne i de forskellige subgrupper.

4. Metode

Medicinrådets protokol for vurdering af olaparib i kombination med bevacizumab til 1. linje vedligeholdelsesbehandling af avanceret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden med homolog rekombinationsdefekt beskriver sammen med *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, hvordan Medicinrådet vil vurdere lægemidlets værdi for patienterne.

5. Resultater

5.1 Klinisk spørgsmål 1

Klinisk spørgsmål 1 er:

- Hvilken værdi har olaparib i kombination med bevacizumab sammenlignet med olaparib monoterapi som vedligeholdelsesbehandling for nydiagnosticerede patienter med avanceret BRCA-muteret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden, som responderer på platinbaseret kemoterapi (komplet eller partiel respons)?

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. Der blev ikke identificeret nogen direkte sammenligning af olaparib i kombination med bevacizumab og olaparib monoterapi. Ansøger har udvalgt 3 fuldtekstartikler, der tilsammen beskriver data fra 2 fase III-kliniske studier. Disse er anført i tabellen nedenfor.

Tabel 5-1. Oversigt over studier

Publikationer	Klinisk forsøg	NCT-nummer	Population	Intervention overfor komparator	Median opfølgningstid for primært endepunkt
Rai-Coquard et al. 2019 [26] EPAR [27]	PAOLA-1	NCT02477644	Patienter med nydiagnosticeret kræft i æggestokkene. Populationen indeholder både BRCA-muterede og BRCA-vildtype samt HRD-positive og HRD-negative patienter bestemt ud fra Myriad Mychoice-test.	Olaparib i kombination med bevacizumab overfor bevacizumab	22,7 måneder (intervention) og 24 måneder (komparator)
Moore et al. 2018 [28] DiSilvestro et al. 2020 [29] EPAR [18]	SOLO-1	NCT01844986	BRCA-muterede patienter med ny-diagnosticeret kræft i æggestokkene.	Olaparib overfor placebo	41 måneder

PAOLA-1 sammenligner olaparib i kombination med bevacizumab med bevacizumab som vedligeholdelsesbehandling efter respons på platinbaseret kemoterapi for patienter med nydiagnosticeret kræft i æggestokkene uagtet BRCA-status. SOLO-1 sammenligner olaparib med placebo som vedligeholdelsesbehandling efter respons på platinbaseret kemoterapi for patienter med nydiagnosticeret kræft i æggestokkene med BRCA-mutation. De to kliniske studier er begge multicenter fase III randomiserede, dobbeltblindede kliniske studier, hvor patienterne er randomiseret 2:1 til hhv. interventionsarm og komparatorarm. Randomiseringerne var stratificerede for respons på platinbaseret kemoterapi og BRCA-mutationsstatus (kun PAOLA-1). SOLO-1-studiet omfatter udelukkende patienter med BRCA-mutation, mens PAOLA-1 omfatter patienter både med og uden BRCA-mutation (BRCA-vildtype). Patienterne uden BRCA-mutation blev yderligere inddelt i HRD-positive og HRD-negative patienter bestemt ud fra MYRIAD myChoice-test. Det primære endepunkt i begge studier var PFS defineret som tid fra

randomisering indtil objektiv radiologisk progression ifølge RECIST-kriterierne eller død. I begge studier er kontrol- og interventionsarmene velbalancerede i forhold til baselinekarakteristika.

En fuldtekstartikel rapporterer data fra PAOLA-1-studiet (Ray-Coquard et al. [26]). Alle relevante data findes i denne artikel samt EMAs opdaterede EPAR omhandlende olaparib i kombination med bevacizumab [27].

To fuldtekstartikler rapporterer data fra SOLO-1-studiet. Alle relevante data til denne vurdering findes dog i Moore et al. [28], hvorimod DiSilvestro et al. rapporterer subgruppeanalyser fra SOLO-1, som ikke er relevante i denne vurdering [29]. Desuden suppleres med data fra EMAs EPAR omhandlende olaparib [18].

Ved klinisk spørgsmål 1 anvendes interventionsarmen (olaparib i kombination med bevacizumab) i PAOLA-1-studiet som intervention, mens interventionsarmen (olaparib) i SOLO-1 anvendes som komparator. I PAOLA-1 anvendes kun data for subpopulationen af patienter med påvist BRCA-mutation. Denne subpopulation udgør i alt 157 ud af 537 patienter i interventionsarmen. I PAOLA-1 og SOLO-1 indgår der forskellige komparatorer (henholdsvis bevacizumab og placebo), og resultaterne kan derfor ikke standardiseres overfor samme komparator. Derfor er komparatorarmene ikke relevante til at besvare klinisk spørgsmål 1, og de fremgår ikke i oversigten over baselinekarakteristika.

Tabel 5-2. Baselinekarakteristika for patienter i PAOLA-1-studiet med BRCA-mutation, der modtager olaparib i kombination med bevacizumab og patienterne i SOLO-1, der modtager olaparib.

		PAOLA-1 – olaparib + bevacizumab, BRCA-mutation [26] **N = 157**	**SOLO-1 – olaparib** [28] **N = 260**
Alder, median (rækkevidde)		57 (37-77)	53 (29-82)
ECOG PS	0	115 (73 %)	200 (77 %)
	1	39 (25 %)	60 (23 %)
	Kendes ikke	3 (2 %)	0 (0 %)
Primær tumorlokation	Æggestokkene	135 (86 %)	220 (85 %)
	Æggelederne	15 (10 %)	22 (8 %)
	Bughulen	7 (4 %)	15 (6 %) *
Histologi	High-grade serøst karcinom	150 (95 %)	246 (95 %)

	Endometroid	4 (3 %)	9 (3 %)
	Anden	3 (2 %)	5 (2 %)
FIGO-stadium	III	113 (71 %)	220 (85 %)
	IV	43 (28 %)	40 (15 %)
Operationsstatus	Primært opereret – makroradikal operation	55 (35 %)	123 (47 %)
	Primært opereret – resttumor	32 (20 %)	37 (14 %)
	Interval opereret – makroradikal operation	50 (32 %)	76 (29 %)
	Interval opereret – resttumor	15 (10 %)	18 (7 %)
	Ikke-opereret	5 (3 %)	4 (2 %)
Resultat af 1. linje kemoterapi	Ingen synlig restsygdom	92 (59 %)	
	Komplet respons	35 (22 %)	213 (82 %) **
	Partiel respons	30 (19 %)	47 (18 %)

* I SOLO-1-studiet angives primærlokation som ukendt i 1 tilfælde. ** I SOLO-1 indeholder kategorien komplet respons også ingen synlig restsygdom.

Overordnet er baselinekarakteristika sammenlignelige mellem de to studiearme. De væsentligste forskelle i baselinekarakteristika er andelen af patienter med kræft i stadium IV samt andelen af patienter med restsygdom efter operation. Fagudvalget vurderer, at populationerne afspejler populationen i dansk klinisk praksis.

5.1.2 Databehandling og analyse

Da SOLO-1 og PAOLA-1 har forskellige komparatorer og forskelle i baselinekarakteristika, kan der ikke udføres en formel indirekte sammenligning. Ansøger har derfor foretaget en deskriptiv sammenligning med udgangspunkt i interventionsarmene i henholdsvis PAOLA-1 og SOLO-1 for effektmålene samlet overlevelse (OS), bivirkninger og livskvalitet. For PFS har ansøger indsendt en analyse, hvori der udføres en indirekte sammenligning

af PFS mellem behandlingsarmene i studierne baseret på individuelle patientdata efter justering for forskelle i baselinekarakteristika (*population adjusted indirect comparison,* PAIC). Denne analyse er publiceret som et abstract og præsenteret til *Society of Gynecologic Oncology-2020 annual meeting* [30]*,* men er ikke peer reviewed.

Medicinrådet er enige i ansøgers tilgang. Medicinrådet vurderer, at PAIC-analysen er korrekt udført og giver et mere retvisende billede af behandlingernes effekt på PFS end en deskriptiv sammenligning. For de resterende effektmål foretager fagudvalget en deskriptiv sammenligning af interventionsarmene fra subpopulationen med BRCA-mutation fra PAOLA-1 og SOLO-1. Da komparatorerne i studierne er forskellige, anvendes komparatorarmene ikke i den deskriptive gennemgang.

Som en del af effektmålet, bivirkninger, efterspurgte fagudvalget i protokollen andelen af patienter, der stopper behandlingen pga. bivirkninger *(adverse drug reactions)*, samt andelen af patienter, der oplever minimum en bivirkning af grad 3-4. Ansøger har ikke indsendt disse data, og de er ikke publiceret, hverken i de kliniske studier eller i den opdaterede EPAR. I stedet har ansøger indsendt data for uønskede hændelser *(adverse events)* til at belyse effektmålene. Fagudvalget tager udgangspunkt i dette samt bivirkningsprofilerne publiceret i EPAR ved gennemgangen [27].

Uønskede hændelser og livskvalitet er ikke opgivet specifikt for subpopulationen med BRCA-mutation i PAOLA-1. Derfor anvendes data for den samlede intention-to-treat (ITT) -population (n = 537) til vurderingen af disse effektmål. Fagudvalget vurderer, at der ikke er grund til at antage, at profilen for uønskede hændelser eller livskvalitet er væsentlig forskellig mellem den samlede ITT-population og subpopulationen med BRCA-mutation.

5.1.3 Evidensens kvalitet

Da vurderingen af olaparib i kombination med bevacizumab er baseret på en deskriptiv sammenligning med olaparib, 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 både PAOLA-1 og SOLO-1 er forbundet med lav risiko for bias (bilag 1). Den samlede evidenskvalitet er dog meget lav, da vurderingen af de fleste effektmål er foretaget vha. deskriptive sammenligninger. Dette betyder, at nye studier med høj sandsynlighed kan ændre konklusionen.

5.1.4 Effektestimater og kategorier

I tabellen herunder fremgår effektestimaterne fra interventionsarmene i PAOLA-1 (olaparib i kombination med bevacizumab) og SOLO-1 (olaparib), som anvendes til en deskriptiv sammenligning. Derudover fremgår effektestimaterne og de absolutte og relative effektforskelle fra ansøgers PAIC-analyse af PFS (markeret med gråt), som anvendes til en indirekte statistisk sammenligning.

Tabel 5-3. Resultater for klinisk spørgsmål 1

Effektmål	Målenhed (MKRF)	Vigtighed	Effektestimater fra studierne		PAIC- olaparib + bevacizumab vs. olaparib*			Aggregeret værdi for effektmålet
			Olaparib + bevacizumab (PAOLA-1)	Olaparib (SOLO-1)	Estimater		Forskel (95 % CI)	
					Olaparib + bevacizumab	Olaparib		
Samlet overlevelse (OS)	Median OS (3 måneder)	Kritisk	Ikke nået	Ikke nået	Ikke angivet		Ikke angivet	Kan ikke kategoriseres
	OS-rate ved 60 måneder (5 %-point)		Ikke angivet	Ikke angivet				
Progressionsfri overlevelse (PFS)	Median PFS (6 måneder)	Kritisk	Ikke nået	Ikke nået	Ikke nået		Ikke angivet	Ingen dokumenteret merværdi
	PFS-rate ved 24 måneder (10 %-point)		76 %	74 %	82 % (76; 89 %)	73 % (68; 79 %)	9 %-point HR = 0,71 (0,45; 1,09)	
Bivirkninger**	Andel af patienter, som ophører behandling pga. bivirkninger (5 %-point) ***	Kritisk	20,4 %	11,5 %	Ikke angivet		Ikke angivet	Kan ikke kategoriseres
	Andel af patienter, der oplever en eller flere bivirkninger af grad 3-4 (10 %-point) ***		57,6 %	39 %	Ikke angivet		Ikke angivet	
	Kvalitativ gennemgang							

Effektmål	Målenhed (MKRF)	Vigtighed	Effektestimater fra studierne		PAIC- olaparib + bevacizumab vs. olaparib*			Aggregeret værdi for effektmålet
			Olaparib + bevacizumab (PAOLA-1)	Olaparib (SOLO-1)	Estimater		Forskel (95 % CI)	
					Olaparib + bevacizumab	Olaparib		
Livskvalitet**	Andel af patienter, der ikke viser statistisk signifikant forværring i livskvalitet (10 %-point)	Vigtigt	Ikke angivet	Ikke angivet	Ikke angivet		Kan ikke kategoriseres	Kan ikke kategoriseres

Konklusion	
Samlet kategori for lægemidlets værdi	Kan ikke kategoriseres. Fagudvalget vurderer, at data ikke tyder på en bedre behandlingseffekt ved kombinationsbehandlingen, men derimod at den er forbundet med flere bivirkninger end olaparib monoterapi.
Kvalitet af den samlede evidens	Meget lav.

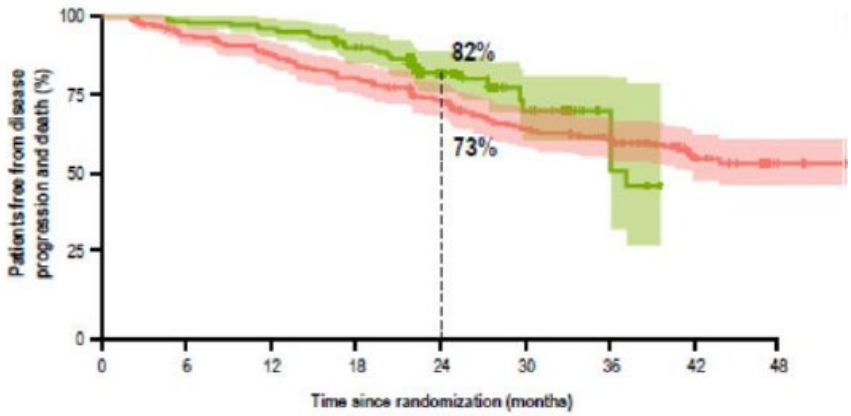
* Data stammer fra en populationsjusteret indirekte sammenligning (PAIC) mellem PAOLA-1 og SOLO-1 og kan derfor anvendes til en kategorisering. ** Data stammer fra den samlede ITT-population i PAOLA-1 og SOLO-1.
*** Effektmålet er opgjort ud fra uønskede hændelser i stedet for bivirkninger, da kvantitative bivirkningsdata ikke var tilgængelige. CI = konfidensinterval, HR = Hazard Ratio.

Samlet overlevelse (OS)
Som beskrevet i protokollen er effektmålet samlet overlevelse kritisk for vurderingen af lægemidlets værdi for patienterne. Data for samlet overlevelse er umodne for både olaparib i kombination med bevacizumab fra PAOLA-1 og olaparib fra SOLO-1 (henholdsvis 19,6 % og 21 % af patienterne er døde). Median overlevelse er ikke nået for hverken olaparib i kombination med bevacizumab eller for olaparib, og der findes ikke data for OS-rate ved 5 år, da der ikke er tilstrækkelig opfølgning.
[redacted] Til sammenligning var OS-raten i SOLO-1 ved 4 år 75,2 % for olaparib og 74,8 % ved placebo, hvilket gav en HR på 0,95 (0,60 ; 1,54) [18].

Effekten på overlevelse af olaparib i kombination med bevacizumab overfor olaparib kan ikke kategoriseres. Fagudvalget kan på dette datagrundlag ikke vurdere, om der er forskelle i effekten mellem olaparib i kombination med bevacizumab og olaparib.

Progressionsfri overlevelse (PFS)
Effektmålet progressionsfri overlevelse anvendes som surrogat for OS, når OS-data ikke er modne. Desuden afspejler PFS ved vedligeholdelsesbehandling tiden til næste linje med platinbaseret kemoterapi, hvilket er en kritisk patientrelateret parameter. PFS vurderes derfor som et kritisk effektmål.

Nedenfor ses Kaplan-Meier-kurven for PFS for olaparib i kombination med bevacizumab og olaparib monoterapi fra ansøgers PAIC-analyse.



Figur 5-1. Kaplan-Meier plot baseret på ansøgers PAIC-analyse af PFS. Kurven viser forløbet for subgruppen af patienter med BRCA-mutation behandlet med olaparib i kombination med bevacizumab fra PAOLA-1-studiet (grøn) samt forløbet for patienterne behandlet med olaparib i SOLO-1-studiet (rød). Den stiplede linje viser PFS-raten ved 24 måneder [30].

Median PFS er ikke nået for hverken olaparib i kombination med bevacizumab eller olaparib. PFS-raten ved 24 måneder var henholdsvis 82 % (76 ; 89 %) og 73 % (68 ; 79 %) for olaparib i kombination med bevacizumab og olaparib. Den absolutte forskel var 9 %-point, hvilket ikke repræsenterer en klinisk relevant forskel. HR var 0,71 (0,45 ; 1,09), hvorved den relative forskel kategoriseres som ingen dokumenteret merværdi.

Forskellene mellem olaparib i kombination med bevacizumab og olaparib monoterapi mindskes yderligere, hvis der i stedet foretages en deskriptiv sammenligning mellem PFS-raterne i PAOLA-1 (76 %) og SOLO-1 (74 %).

Fagudvalget vurderer, at olaparib i kombination med bevacizumab ikke har nogen dokumenteret merværdi på PFS overfor olaparib monoterapi.

Bivirkninger
Forbedret OS med mindst mulig toksicitet er det optimale mål for kræftbehandling. Fagudvalget anser derfor bivirkninger som et kritisk effektmål. Fagudvalget ønskede effektmålet opgjort på baggrund af opgørelser over bivirkninger *(adverse reactions)*. Dette var dog ikke muligt, og effektmålet vurderes i stedet samlet ud fra behandlingsophør på grund af uønskede hændelser *(adverse events)*, andelen af patienter, der oplever minimum 1 uønsket hændelse af grad 3-4, samt en deskriptiv gennemgang af bivirkningerne. Opgørelserne omkring uønskede hændelser og bivirkninger fra PAOLA-1 baseres på ITT-populationen, der modtog olaparib i kombination med bevacizumab uagtet BRCA-status. Det er ikke muligt at justere sammenligningen ved brug af komparatorarmene i PAOLA-1 og SOLO-1, da bevacizumab (PAOLA-1) må antages at medføre betydelig flere uønskede hændelser end placebo (SOLO-1).

Behandlingsophør grundet bivirkninger:
Samlet set ophørte 20,4 % af patienterne behandling grundet uønskede hændelser ved olaparib i kombination med bevacizumab i PAOLA-1 mod 11,5 % ved olaparib i SOLO-1. Dette medfører en forskel på 8,9 %-point, hvilket afspejler en klinisk relevant forskel. Dette er dog baseret på en deskriptiv sammenligning, og forskelle mellem studierne medfører, at der er stor usikkerhed forbundet med sammenligningen af resultaterne. Værdien kan ikke kategoriseres. Fagudvalget vurderer dog, at væsentlig flere patienter ophører behandlingen med olaparib i kombination med bevacizumab pga. uønskede hændelser, men studieforskelle vedr. registrering af årsager til behandlingsophør vanskeliggør vurderingen.

Bivirkninger af grad 3-4:
Andelen af patienter, der oplevede minimum en uønsket hændelse af grad 3-4, var 57,6 % ved olaparib i kombination med bevacizumab i PAOLA-1 mod 39 % ved olaparib i SOLO-1. Dette medfører en forskel på 18,6 %-point, hvilket afspejler en klinisk relevant forskel. Dette er baseret på en deskriptiv sammenligning, og værdien kan derved ikke kategoriseres. I EPAR for olaparib er der udført en samlet opgørelse af uønskede hændelser ved behandling med olaparib alene baseret på en række lignende studier, hvor olaparib administreres i samme dosis [27]. Denne samlede opgørelse indeholder data fra 1585 patienter på tværs af 15 kliniske studier (inklusive SOLO-1) og viser, at 41,6

% af patienterne oplevede minimum en uønsket hændelse af grad 3-4. Dette indikerer, at det observerede niveau af grad 3-4 uønskede hændelser i SOLO-1 er konsistent med, hvad der generelt ses for behandling med olaparib. Derfor vurderer fagudvalget, at olaparib i kombination med bevacizumab er forbundet med flere uønskede hændelser af grad 3-4 end olaparib monoterapi.

Kvalitativ gennemgang af bivirkningerne:
Detaljerede profiler for bivirkninger *(adverse drug reactions)* for både intervention og komparator er angivet i EPAR for olaparib i kombination med bevacizumab [27].
De alvorligste bivirkninger (grad ≥ 3), som forekommer hos mindst 2 % af patienterne, er anæmi (17,4 %), hypertension (19 %), neutropeni (6,4 %), lymfopeni (7,1 %), træthed (5,2 %), leukopeni (2 %), trombocytopeni (2 %), opkastning (2,4 %) og diarré (2,2 %). Bivirkningsprofilen er som forventet ved behandling med olaparib i kombination med bevacizumab, hvor hypertension (grad ≥ 3) er en kendt bivirkning ved bevacizumab, mens de andre nævnte bivirkninger er kendte med sammenlignelig frekvens ved olaparib monoterapi. Således observeres de samme bivirkninger, fraset hypertension, ved olaparibbehandling: anæmi (16 %), neutropeni (6 %), træthed (13,9 %), leukopeni (3 %), trombocytopeni (2 %) og opkastning (2 %) [18]. Fagudvalget vurderer, at bivirkningsprofilen for olaparib i kombination med bevacizumab er som forventet ud fra de to lægemidlers kendte bivirkningsprofiler. Bivirkningerne er generelt håndterbare i klinikken. Fagudvalget bemærker dog, at det ikke er muligt at dosisjustere behandlingen med bevacizumab.

Den samlede værdi for effektmålet bivirkninger kan ikke kategoriseres. Fagudvalget vurderer, at der samlet set er væsentlig flere bivirkninger for olaparib i kombination med bevacizumab end for olaparib monoterapi. Bivirkningerne for begge behandlinger er dog kendte og håndterbare i klinikken.

Livskvalitet
Ændring i livskvalitet er et patientrelevant effektmål, som kan give indblik i, hvordan lægemidlernes fordele og ulemper samlet set påvirker patienten. På baggrund af dette betragter fagudvalget livskvalitet som et vigtigt effektmål. I protokollen efterspurgte fagudvalget en opgørelse af andelen af patienter, der ikke viser en statistisk signifikant forværring i livskvalitet ift. baseline. Dette er ikke opgivet. I stedet har ansøger opgivet ændringer i den samlede middelværdi i forhold til baselinemålingen over et forløb på 24 måneder. Data fra PAOLA-1 er opgjort ved hjælp af det generelle spørgeskema for kræft, EORTC QLQ-C30, samt det ovariecancerspecifikke, EORTC QLQ-OV28, som efterspurgt af fagudvalget. Data fra SOLO-1 er opgjort ved hjælp af det ovariecancerspecifikke FACT-O-spørgeskema, hvilket resulterer i en TOI-score som mål for den samlede livskvalitet. Dette vanskeliggør en sammenligning mellem studierne, og effekten vedr. livskvalitet kan derved ikke kategoriseres.

Fagudvalget vurderer dog, at hverken olaparib i kombination med bevacizumab eller olaparib som monoterapi medfører nogen signifikant ændring i patienternes livskvalitet ud fra de anvendte måleinstrumenter. Dette understøttes af, at middelændringen over 24 måneder fra baselinescoren for olaparib i kombination med bevacizumab var 0,13 (-1,2 ; 1,27) ud fra en baselinescore på 68,6 (ved EORTC QLQ-C30), mens der tilsvarende

sås en gennemsnitsændring på 0,30 (−0,717 ; 1,318) ud fra en baselinescore på 73,6 for olaparib (ved FACT-O-TOI).

5.1.5 Fagudvalgets konklusion

Den samlede værdi af olaparib i kombination med bevacizumab overfor olaparib som monoterapi som vedligeholdelsesbehandling til nydiagnosticerede patienter med avanceret BRCA-muteret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden, som responderer på platinbaseret kemoterapi, kan ikke kategoriseres.

Fagudvalget vurderer, at data ikke tyder på en bedre behandlingseffekt ved kombinationsbehandlingen, men at den derimod er forbundet med flere bivirkninger end olaparib monoterapi.

Fagudvalget mener derfor *ikke*, at olaparib i kombination med bevacizumab er et ligeværdigt alternativ til olaparib monoterapi til behandling af patienter med BRCA-muteret kræft i æggestokkene.

5.2 Klinisk spørgsmål 2

Klinisk spørgsmål 2 er:

- Hvilken værdi har olaparib i kombination med bevacizumab sammenlignet med bevacizumab monoterapi som vedligeholdelsesbehandling for nydiagnosticerede patienter med avanceret ikke-BRCA-muteret, HRD-positiv high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden, som responderer på platinbaseret kemoterapi (komplet eller partiel respons) og kandiderer til bevacizumab?

5.2.1 Litteratur

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

Ansøger har søgt litteratur med søgestrengen fra protokollen og har fundet 7 fuldtekstartikler, der beskriver data fra 3 kliniske studier. PAOLA-1 indeholder en direkte sammenligning af olaparib i kombination med bevacizumab og bevacizumab monoterapi, der kan anvendes til at besvare det kliniske spørgsmål. De andre to kliniske studier, GOG-0218 og ICON7 indeholder ikke en direkte sammenligning. Derfor baseres vurderingen udelukkende på PAOLA-1 (se Tabel 5-1), og GOG-0218 og ICON7 beskrives ikke yderligere her.

Baselinekarakteristika for den samlede ITT-population i PAOLA-1 er vist i den nedenstående tabel.

Tabel 5-4. Udvalgte baselinekarakteristika for intention-to-treat-populationen i PAOLA-1

PAOLA-1, samlet population [26]		**Olaparib + bevacizumab, N = 537**	**Placebo + bevacizumab N = 269**
Alder, median (rækkevidde)		61 (32–87)	61 (32–87)
ECOG PS	0	378 (70,4 %)	378 (70,4 %)
	1	153 (28,5 %)	153 (28,5 %)
	Kendes ikke	6 (1,1 %)	6 (1,1 %)
Primær tumorlokation	Æggestokkene	456 (84,9 %)	456 (84,9 %)
	Æggelederne	39 (7,3 %)	39 (7,3 %)
	Bughulen	42 (7,8 %)	42 (7,8 %)
Histologi	High-grade serøst karcinom	519 (96,6 %)	519 (96,6 %)
	Endometrioid	12 (2,2 %)	12 (2,2 %)
	Anden	6 (1,2 %)	6 (1,2 %)
FIGO-stadium	III	378 (70,4 %)	378 (70,4 %)
	IV	159 (29,6 %)	159 (29,6 %)
Operationsstatus	Primært opereret – makroradikal operation	160 (29,8 %)	85 (31,6 %)
	Primært opereret – resttumor	111 (20,7 %)	53 (19,7 %)
	Interval opereret – makroradikal operation	163 (30,4 %)	75 (27,9 %)
	Interval opereret – resttumor	65 (12,1 %)	35 (13,0 %)
	Ikke opereret	38 (7,1 %)	21 (7,8 %)

Resultat af 1. linje kemoterapi	Ingen synlig restsygdom	290 (54,0 %)	141 (52,4 %)
	Komplet respons	106 (19,7 %)	53 (19,7 %)
	Partiel respons	141 (26,3 %)	75 (27,9 %)
Andel med BRCA-vildtype og HRD	Samlet	97 (18,1 %)	55 (20,4 %)
	Heraf høj risiko for progression	64 (11,9 %)	37 (13,8 %)
	Heraf lav risiko for progression	33 (6,2 %)	18 (6,6 %)

Overordnet er der ikke er nogen betydende forskelle i baselinekarakteristika mellem de to studiearme.

5.2.2 Databehandling og analyse

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

Interventions- og kontrolarmene i PAOLA-1 var designet til at undersøge forskellene mellem kombinationsbehandling med olaparib og bevacizumab og placebo + bevacizumab, hvorved dette studie er velegnet til at besvare det kliniske spørgsmål. Til besvarelsen af det kliniske spørgsmål har ansøger anvendt publicerede data fra den HRD-positive subpopulation uden BRCA-mutation (n = 97 og 55 i hhv. interventions- og komparatorarmen). Subgruppen kan dog inddeles yderligere i to grupper med henholdsvis høj risiko og lav risiko for progression. Gruppen af patienter med høj risiko for progression består af patienter med:

- Stadie III-sygdom og restsygdom efter primæroperation
- Stadie III-sygdom og intervalkirurgi uanset operationsresultat
- Stadie IV-sygdom.

Denne subgruppe stemmer tilnærmelsesvis overens med de patienter, der er kandidater til bevacizumabbehandling i dansk klinisk praksis, hvorved den er mere repræsentativ for populationen defineret i det kliniske spørgsmål. Subgruppen indeholder 64 patienter i interventionsarmen og 37 patienter i komparatorarmen.

Data på subgruppen af patienter med høj risiko for progression er ikke publiceret. Ansøger har derfor indsendt fortrolige '*data on file*' for PFS, andelen af patienter med minimum en uønsket hændelse af grad 3-4 samt andelen, der ophører med behandlingen pga. uønskede hændelser for subgruppen med høj risiko for progression. Medicinrådet vurderer, at de fortrolige data giver et mere retvisende billede af interventionens effekt overfor komparator end de publicerede data fra den samlede

HRD-positive subgruppe uden BRCA-mutation. Derfor lægges de fortrolige data til grund for vurderingen af effektmålene PFS og uønskede hændelser, jf. Medicinrådets principper for anvendelse af upublicerede data. Ansøger har ikke indsendt data for effektmålene OS eller livskvalitet fra højrisiko subgruppen. Fagudvalget har i stedet anvendt OS-data fra den samlede HRD-positive subgruppe uden BRCA-mutation uagtet progressionsrisiko, dog kun til perspektivering. Den samlede ITT-population bruges til at vurdere livskvalitet, hvilket Medicinrådet accepterer, da der ikke forventes at være forskel på livskvalitet på subpopulationsniveau.

5.2.3 Evidensens kvalitet

Medicinrådet har anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Nedenfor følger en beskrivelse af vurderingen af de væsentligste domæner for hvert klinisk spørgsmål. Den fuldstændige GRADE-vurdering og begrundelserne er samlet i en GRADE-profil (bilag 2).

For alle effektmål er der nedgraderet for inkonsistens, da der kun er ét studie. For OS er der ikke angivet data for den relevante subgruppe, og evidensens kvalitet kan derved ikke vurderes. For PFS er der bl.a. nedgraderet 2 niveauer for unøjagtighed, da de relative og absolutte værdier indikerer forskellige konklusioner, og da *Optimal information size*-kriteriet ikke er opfyldt. For bivirkninger er der nedgraderet et niveau for indirekthed, da effektmålet er opgjort på baggrund af uønskede hændelser i stedet for bivirkninger og et niveau for unøjagtighed, da konfidensintervallet indeholder både positive og negative konklusioner. For livskvalitet er evidenskvaliteten lav. Den samlede evidenskvalitet bestemmes af PFS og bivirkninger som de kritiske effektmål med lavest evidenskvalitet.

Evidensens kvalitet er meget lav, hvilket betyder, at nye studier eller længere opfølgningstid med høj sandsynlighed kan ændre konklusionen.

Medicinrådet har vurderet studierne ved Cochrane risk of bias tool 2.0. Overordnet er det vurderet, at risikoen for bias ved PAOLA-1 er lav.

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

5.2.4 Effektestimater og kategorier

I tabellen herunder fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 2.

Tabel 5-5. Resultater for klinisk spørgsmål 2

Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Samlet overlevelse (OS)*	Median OS (3 måneder)	Kritisk	Ikke angivet	Kan ikke kategoriseres	Ikke angivet	Kan ikke kategoriseres	Kan ikke kategoriseres
	OS-rate ved 60 måneder (5 %-point)		Ikke angivet	Kan ikke kategoriseres			
Progressionsfri overlevelse (PFS)	Median PFS (6 måneder)	Kritisk	[redacted]	Kan ikke kategoriseres	[redacted]	Moderat merværdi	Moderat merværdi
	PFS-rate ved 24 måneder (10 %-point)		[redacted]	Kan ikke kategoriseres			
Bivirkninger	Andel af patienter, som ophører behandling pga. bivirkninger*** (5 %-point)	Kritisk	[redacted]	Negativ værdi	[redacted]	Negativ værdi	Negativ værdi
	Andel af patienter, der oplever en eller flere bivirkninger af grad 3-4*** (10 %-point)		[redacted]	Kan ikke kategoriseres	[redacted]	Kan ikke kategoriseres	
	Kvalitativ gennemgang						

Livskvalitet**	Andel af patienter, der ikke viser statistisk signifikant forværring i livskvalitet	Vigtigt	0,59 (-1,40 ; 2,57)****	Ingen dokumenteret merværdi	Ikke angivet	Kan ikke kategoriseres	Ingen dokumenteret merværdi

Konklusion	
Samlet kategori for lægemidlets værdi	Lille merværdi
Kvalitet af den samlede evidens	Meget lav

* OS-data stammer fra den samlede HRD-positive population uden BRCA-mutation uagtet risiko for progression. Dette bruges kun perspektiverende og er ikke indsat i skemaet. ** Data stammer fra den samlede ITT-population. *** Effektmålet er opgjort ud fra uønskede hændelser i stedet for bivirkninger, da kvantitative bivirkningsdata ikke var tilgængelige. **** Effektmålet er opgjort som gennemsnitlig ændring i forhold til baselinemålinger på hele populationen, da data ikke var tilgængeligt på enkeltpatientniveau. CI = konfidensinterval, HR = Hazard Ratio, RR = relativ risiko.

Samlet overlevelse (OS)
Der er ikke indsendt data for den relevante subpopulation. Effekten på OS kan derfor ikke kategoriseres.

Fagudvalget anvender data fra den samlede HRD-positive population uden BRCA-mutation til perspektivering. Ved data cut-off, september 2019, var 27 ud af 97 patienter (28 %) i interventionsarmen døde, hvilket var tilfældet for 16 ud af 55 patienter (29 %) i komparatorarmen efter median opfølgningstid på 30-33 måneder [27].

[redacted].

Fagudvalget kan på dette datagrundlag ikke vurdere om behandling med olaparib i kombination med bevacizumab adskiller sig fra behandling med olaparib monoterapi.

Progressionsfri overlevelse (PFS)
PFS er rapporteret for den samlede population af HRD-positive uden BRCA-mutation [26,27]. I interventionsarmen var der 43 events ud af 97 patienter (44 %) overfor 40 events ud af 55 patienter (73 %) i komparatorarmen. Median PFS var henholdsvis 28,1 måneder og 16,6 måneder i interventions- og komparatorarmen, og PFS-raten ved 24 måneder var henholdsvis ca. 55 % og 25 %. Samlet HR var 0,43 (0,28 ; 0,66). Disse data stammer dog fra den samlede population, der indeholder både gruppen med høj og lav risiko for progression.

PFS for populationen med høj risiko for progression er vist i nedenstående figur.

[redacted]

[redacted]

[redacted] Da høj-risikopopulation bedst reflekterer populationen defineret i det kliniske spørgsmål, anvendes disse data til kategoriseringen af effekten overfor komparator.

[redacted]

Fagudvalget vurderer, at olaparib i kombination med bevacizumab aggregeret har en moderat merværdi for PFS [redacted]. Det er velkendt i klinisk praksis og dokumenteret i kliniske studier [31,32], at bevacizumab har

en effekt på median PFS i denne patientgruppe, men at effekten aftager over tid og nærmer sig placebo efter 1,5-2 års opfølgning, hvorved en forbedring af andelen af patienter, der er langtidsprogressionsfri, er vigtig.

Bivirkninger

Opgørelserne omkring uønskede hændelser baseres på hele populationen af patienter i højrisikogruppen uagtet BRCA-status og HRD-status.

Behandlingsophør grundet bivirkninger:

[redacted]

Bivirkninger af grad 3-4:

[redacted]

[redacted]

[redacted]

[redacted]

Kvalitativ gennemgang af bivirkningerne:
Ansøger har ikke indsendt en samlet opgørelse over bivirkninger for høj-risikopopulationen. I stedet tager fagudvalget udgangspunkt i bivirkningsprofilen for den samlede ITT-population. For en gennemgang af bivirkningsprofilen olaparib i kombination med bevacizumab henvises til gennemgangen i klinisk spørgsmål 1 (afsnit 5.1.4).

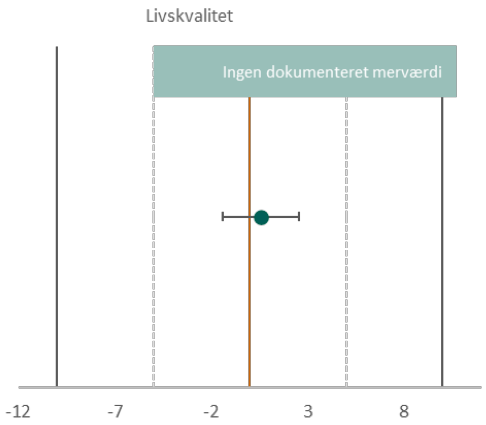
For bevacizumab var hypertension klart den hyppigste bivirkning af grad ≥ 3 (30 %). Andre bivirkninger var neutropeni (3 %), diarré (2 %), opkast (2 %), mavesmerter (2 %) og intestinal obstruktion (2 %). Proteinuri, lungeembolisme og intestinal perforation, som er bivirkninger med særlig opmærksomhed ved bevacizumabbehandling, var alle meget sjældne i studiet (< 1 % - 1 %). Dog er disse hyppigere observeret (omkring 2 % for hver) i andre studier af bevacizumab til kræft i æggestokkene [33]. Tromboembolier af grad 3-4 optræder i ca. 3 % af patienterne, hvilket medfører behandlingsstop.

Samlet set vurderer fagudvalget, at olaparib i kombination med bevacizumab har en negativ værdi for effektmålet bivirkninger. Dette skyldes hovedsageligt den markant højere frekvens af patienter, der ophører med behandlingen pga. uønskede hændelser.

Bivirkningerne er generelt håndterbare i klinikken, og bivirkningsprofilen for kombinationsbehandlingen afviger ikke fra de enkelte lægemidlers kendte bivirkningsprofiler.

Livskvalitet
Livskvalitet er angivet for den samlede ITT-population. Fagudvalget vurderer, at dette kan anvendes, da det ikke forventes, at interventionens indflydelse på livskvalitet vil variere med BRCA- eller HRD-status.

Ligesom ved klinisk spørgsmål 1 er ændringer i livskvalitet angivet som den samlede middelværdi over et forløb på 24 måneder fratrukket middelværdien ved baselinemålingen. Fagudvalget vurderer, at dette kan lægges til grund for en kategorisering af effekten, og betragter en ændring på 10 point som klinisk relevant. Den absolutte forskel i udviklingen mellem intervention og komparator er vist i figuren nedenfor.



Figur 5-2. Punktestimat og 95 % konfidensinterval for den absolutte forskel for livskvalitet. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Udviklingen i livskvalitetsmålingerne over 2 år var meget begrænset i begge behandlingsarme med en gennemsnitlig forskel fra baseline på 0,13 (1,02 ; 1,27) for olaparib i kombination med bevacizumab (baselinemåling = 68,64) og -0,46 (-2,08 ; 1,16) for bevacizumab (baselinemåling = 67,14). Dette giver en samlet absolut forskel på 0,59 (-1,4 ; 2,57). På baggrund af den absolutte forskel kategoriseres den foreløbige værdi som ingen dokumenteret effekt. Ansøger har ikke angivet et relativt effektmål. Merværdien baseret på den relative forskel kan derfor ikke kategoriseres. Der er dog ingen signifikant forskel mellem udviklingen i interventions- og komparatorarmen. Fagudvalget vurderer derfor, at der aggregeret ikke er nogen dokumenteret merværdi for livskvalitet ved behandling med olaparib i kombination med bevacizumab overfor bevacizumab alene. Derudover bemærker fagudvalget, at de tilgængelige data indikerer, at vedligeholdelsesbehandling med olaparib i kombination med bevacizumab ikke påvirker patienternes livskvalitet.

5.2.5 Fagudvalgets konklusion

Fagudvalget vurderer, at olaparib i kombination med bevacizumab til patienter med HRD-positiv kræft i æggestokkene uden BRCA-mutation, som kandiderer til bevacizumabbehandling, giver en lille merværdi sammenlignet med bevacizumab. Evidensens kvalitet er meget lav.

Fagudvalget lægger vægt på, at betydeligt flere patienter var progressionsfri efter 2 år, hvilket repræsenterer en langsigtet værdi for patienterne, som almindeligvis ikke opnås med behandling med bevacizumab alene. Det markant højere antal patienter der ophører behandlingen grundet uønskede hændelser vægter negativt i vurderingen, men derudover er bivirkningsprofilen for kombinationsbehandlingen generelt velkendt og håndterbar.

5.3 Klinisk spørgsmål 3

Klinisk spørgsmål 3 er:

- Hvilken værdi har olaparib i kombination med bevacizumab sammenlignet med placebo som vedligeholdelsesbehandling for nydiagnosticerede patienter med avanceret ikke-BRCA-muteret, HRD-positiv high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden, som responderer på platinbaseret kemoterapi (komplet eller partiel respons) og ikke kandiderer til bevacizumab?

5.3.1 Litteratur

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

Litteraturen til besvarelse af klinisk spørgsmål 3 er den samme som for klinisk spørgsmål 1. Derfor henvises til afsnit 5.1.1 for yderligere detaljer omkring studier og inkluderede artikler.

5.3.2 Databehandling og analyse

Til besvarelse af det kliniske spørgsmål anvendes data for interventionen (olaparib i kombination med bevacizumab) fra den HRD-positive subpopulation uden BRCA-mutation (n = 97 og 55 i hhv. interventions- og komparatorarmen) fra PAOLA-1-studiet jf. afsnit 5.2.2 samt data for komparator (placebo) fra SOLO-1-studiet. Medicinrådet fremhæver følgende:

For effektmålene OS og PFS ligger en kvantitativ opgørelse fra PAOLA-1 til grund for kategoriseringen. Interventions- og kontrolarmene i PAOLA-1 var designet til at undersøge forskellene mellem kombinationsbehandling med olaparib og bevacizumab og placebo + bevacizumab, hvorimod komparatoren i klinisk spørgsmål 3 er placebo. Ansøger argumenterer for, at PAOLA-1-studiets komparatorarm kan anvendes til en direkte sammenligning, selvom komparatorarmen indeholder bevacizumab. Dette skyldes:

- at det tidligere er vist, at bevacizumab har begrænset effekt på OS og PFS i patienter med stadie III-kræft uden restsygdom efter operation [32].
- at en eventuel effekt af bevacizumab på PFS eller OS vil overestimere komparatorarmen ift. placebo, hvorved effektestimatet for interventionen bliver konservativt.

Medicinrådet kan tilslutte sig argumenterne og vurderer, at en direkte sammenligning ud fra interventions- og kontrolarm i PAOLA-1 giver en mere retvisende besvarelse af det kliniske spørgsmål end en deskriptiv sammenligning mellem interventionsarmen i PAOLA-1 og kontrolarmen i SOLO-1, da patienterne i SOLO-1 har BRCA-mutation.

For effektmålene bivirkninger og livskvalitet ligger en deskriptiv sammenligning af ITT-populationen fra PAOLA-1-studiet og kontrolarmen fra SOLO-1 (placebo) til grund for kategoriseringen. Dette skyldes, at kontrolarmen fra PAOLA-1 (placebo + bevacizumab) ikke kan anvendes som komparator for disse effektmål, da en negativ effekt af bevacizumab på disse sandsynligvis vil medføre, at en eventuel negativ effekt af kombinationsbehandlingen overfor placebo underestimeres. Fagudvalget bemærker, at populationen i SOLO-1 har BRCA-mutation, men at dette ikke forventes at påvirke effektmålene, bivirkninger og livskvalitet.

Ansøger har anvendt data fra subgruppen af HRD-positive patienter uden BRCA-mutation og med lav risiko for progression, jf. afsnit 5.2.2. Denne gruppe består af patienter med stadie III-sygdom og ingen synlig restsygdom efter primær operation og udgør 33 patienter i interventionsarmen og 18 patienter i komparatorarmen. Her har ansøger indsendt '*data on file*' for PFS, andelen af patienter med minimum en uønsket hændelse af grad 3-4 samt andelen, der ophører med behandlingen pga. uønskede hændelser for denne subgruppe. Medicinrådet vurderer, at denne subgruppe stemmer bedre overens med populationen defineret i det kliniske spørgsmål. Subgruppen indeholder dog for få patienter til at give tilstrækkeligt solide estimater til en kategorisering. Derfor bliver disse subgruppedata kun anvendt til en perspektivering.

5.3.3 Evidensens kvalitet

Medicinrådet har anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Nedenfor følger en beskrivelse af vurderingen af de væsentligste domæner for hvert klinisk spørgsmål. Den fuldstændige GRADE-vurdering og begrundelserne er samlet i en GRADE-profil (bilag 2).

For alle effektmål er der nedgraderet for inkonsistens, da der kun er ét studie. For OS er der ikke angivet data for den relevante subgruppe, og evidensens kvalitet kan derved ikke vurderes. For PFS er der nedgraderet ét niveau for indirekthed, da effektmålet er opgjort overfor bevacizumab i stedet for placebo, og da data stammer fra en population, der indeholder patienter, der ville være kandidater til bevacizumab i dansk klinisk praksis. For bivirkninger og livskvalitet er der ikke et grundlag for en statistisk sammenligning, og evidensens kvalitet kan derved ikke kategoriseres. Den samlede evidenskvalitet bestemmes af PFS, da det er det eneste kritiske effektmål, der kan kategoriseres.

Evidensens kvalitet vedr. PFS er lav, hvilket betyder, at nye studier med moderat sandsynlighed kan ændre konklusionen. Samlet set kategoriseres evidendens kvalitet dog som meget lav, da der ikke foreligger kategoriserbare data for overlevelse, bivirkninger og livskvalitet.

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

5.3.4 Effektestimater og kategorier

I tabellen herunder fremgår effektestimaterne fra interventionsarmen i PAOLA-1 (olaparib i kombination med bevacizumab) og komparatorarmen i SOLO-1 (placebo), som anvendes til en deskriptiv sammenligning for effektmålene bivirkninger og livskvalitet. Derudover fremgår de absolutte og relative effektforskelle fra PAOLA-1 (markeret gråt), som anvendes til en direkte sammenligning, samt den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 3.

Tabel 5-6. Resultater for klinisk spørgsmål 3

Effektmål	Målenhed (MKRF)	Vigtighed	Effektestimater fra studierne		Direkte sammenligning fra PAOLA-1		Aggregeret værdi for effektmålet
			Olaparib + bevacizumab (PAOLA-1)	Placebo (SOLO-1)	Absolut forskel (95 % CI)	Relativ forskel (95 % CI)	
Samlet overlevelse (OS)*	Median OS (3 måneder)	Kritisk	Ikke nået	Ikke nået	Ikke nået	Ikke angivet	Kan ikke kategoriseres
	OS-rate ved 60 måneder (5 %-point)		Ikke angivet	Ikke angivet	Ikke angivet	Ikke angivet	
Progressionsfri overlevelse (PFS)*	Median PFS (6 måneder)	Kritisk	Ikke relevant	Ikke relevant	11,5 måneder	HR: 0,43 (0,28 ; 0,66)	Stor merværdi
	PFS-rate ved 24 måneder (10 %-point)		Ikke relevant	Ikke relevant	30 %-point		
Bivirkninger**	Andel af patienter, som ophører behandling pga. bivirkninger (5 %-point) ***	Kritisk	20,4 %	2,3 %	Ikke relevant	Ikke relevant	Kan ikke kategoriseres
	Andel af patienter, der oplever en eller flere bivirkninger af grad 3-4 (10 %-point) ***		57,6 %	18 %	Ikke relevant	Ikke relevant	
	Kvalitativ gennemgang						

Livskvalitet**	Andel af patienter, der ikke viser statistisk signifikant forværring i livskvalitet (10 %-point)	Vigtigt	Ikke angivet	Kan ikke kategoriseres	Ikke relevant	Ikke relevant	Kan ikke kategoriseres

Konklusion	
Samlet kategori for lægemidlets værdi	Lille merværdi
Kvalitet af den samlede evidens	Meget lav

* Data stammer fra en kvantitativ sammenligning fra PAOLA-1 og fra den samlede HRD-positive population uden BRCA-mutation. ** Data for interventionen stammer fra den samlede ITT-population fra PAOLA-1, mens data for komparator stammer fra kontrolarmen (placebo) i SOLO-1. *** Effektmålet er opgjort ud fra uønskede hændelser i stedet for bivirkninger, da kvantitative bivirkningsdata ikke var tilgængelige. CI = konfidensinterval, HR = Hazard Ratio.

Samlet overlevelse (OS)
Ansøger har ikke indsendt data specifikt for denne patientpopulation, men i stedet for den samlede HRD-positive population uden BRCA-mutation. Se afsnit 5.2.4 for en gennemgang.

Samlet set kan effekten på OS ikke kategoriseres pga. manglende data for den relevante population samt generelt manglende modenhed af data. Fagudvalget kan på dette datagrundlag ikke vurdere, om behandling med olaparib i kombination med bevacizumab adskiller sig fra placebo.

Progressionsfri overlevelse (PFS)
PFS er rapporteret for den samlede population af HRD-positive uden BRCA-mutation [26,27]. I interventionsarmen var der 43 events ud af 97 patienter (44 %) overfor 40 events ud af 55 patienter (73 %) i komparatorarmen. Median PFS var henholdsvis 28,1 måneder og 16,6 måneder i interventions- og komparatorarmen, og PFS-raten ved 24 måneder var henholdsvis ca. 55 % og 25 %. Dette giver absolutte effektestimater på 11,5 måneder for median PFS og ca. 30 %-point for PFS-raten, hvilket i begge tilfælde klart overstiger de mindste klinisk relevante forskelle. Samlet HR var 0,43 (0,28 ; 0,66), hvorved den relative effekt karakteriseres som stor merværdi. Disse data er dog ikke fuldstændig repræsentative for den population, som er defineret i det kliniske spørgsmål, da den samlede HRD-positive population uden BRCA-mutation indeholder både patienter med høj og lav risiko for progression, jf. afsnit 5.2.2, dvs. både bevacizumab-kandidater og ikke-bevacizumab-kandidater ifølge dansk klinisk praksis.

Ansøger har desuden indsendt data fra en subgruppeanalyse indeholdende patienter med lav risiko for progression, som stemmer bedre overens med den efterspurgte population. Jf. afsnit 5.3.2 kan data anvendes til at perspektivere effekterne fra den samlede gruppe.

PFS for denne population er vist i nedenstående figur.

Figur 5-3.

Samlet vurderer fagudvalget, at olaparib i kombination med bevacizumab giver en stor merværdi overfor placebo for effektmålet, PFS. Dette bygger på data fra den samlede HRD-positive population uden BRCA-mutation.

Bivirkninger

Opgørelserne omkring bivirkninger baseres på den samlede ITT-population uagtet HRD- og BRCA-status. De kvantitative opgørelser for olaparib i kombination med bevacizumab kan dog ikke sammenlignes direkte med kontrolarmen i PAOLA1-studiet, da patienterne

her behandles med bevacizumab, hvilket forventes at påvirke andelen af bivirkninger betragteligt [32,34]. For at få en mere retvisende komparator udføres i stedet en deskriptiv sammenligning med kontrolarmen fra SOLO1-studiet, hvor patienterne modtager placebo i vedligeholdelsesfasen.

Behandlingsophør grundet bivirkninger:
Samlet set ophørte 20,4 % af patienterne behandling grundet uønskede hændelser ved olaparib i kombination med bevacizumab. Ved placebobehandling i SOLO-1 ophørte 2,3 % af patienterne behandling grundet uønskede hændelser. En deskriptiv sammenligning af de to giver en forskel på 18,1 %-point. Effekten kan ikke kategoriseres, da det er en deskriptiv sammenligning, men fagudvalget bemærker, at den absolutte forskel mellem de to grupper er væsentlig.

Bivirkninger af grad 3-4:
Andelen af patienter, der oplevede minimum en uønsket hændelse af grad 3-4, var 57,6 % ved olaparib i kombination med bevacizumab. Den tilsvarende andel i kontrolarmen i SOLO1-studiet var 18 %. En deskriptiv sammenligning af de to giver en forskel på 37,6 %-point. Effekten kan ikke kategoriseres, men fagudvalget bemærker, at der umiddelbart er væsentlig flere uønskede hændelser af grad 3-4 forbundet med olaparib i kombination med bevacizumab end med placebo, hvilket må forventes, når en aktiv behandling sammenlignes med placebo.

Kvalitativ gennemgang af bivirkningerne:
For en gennemgang af bivirkningsprofilen for olaparib i kombination med bevacizumab henvises til gennemgangen i klinisk spørgsmål 1.

Værdien af olaparib i kombination med bevacizumab kan ikke kategoriseres, da vurderingen baseres på en deskriptiv sammenligning. Fagudvalget vurderer dog, at der er væsentlig flere patienter, der ophører behandlingen pga. uønskede hændelser, og at der samlet set opleves væsentlig flere uønskede hændelser ved olaparib i kombination med bevacizumab. Ved klinisk spørgsmål 2 kategoriserede fagudvalget effekten for bivirkninger som negativ. I denne sammenligning vil fagudvalget forvente en større forskel mellem intervention og komparator, da klinisk spørgsmål 2 indeholdt en aktiv komparator (bevacizumab). Derfor tillægger fagudvalget effektmålet negativ værdi i den samlede vurdering, selvom effektmålet ikke kan kategoriseres ud fra Medicinrådets metoder på grund af en deskriptiv sammenligning. Fagudvalget bemærker dog, at bivirkningerne forbundet med behandling med olaparib i kombination med bevacizumab er velkendte og håndterbare.

Livskvalitet
Som ved klinisk spørgsmål 1 er der ikke en tilgængelig direkte sammenligning af livskvalitet mellem intervention og komparator. I stedet foretages en deskriptiv sammenligning af data for olaparib i kombination med bevacizumab fra PAOLA-1 og placeboarmen i SOLO-1. Af samme årsager som ved klinisk spørgsmål 1 kan effekten ikke kategoriseres.

Middelændringen over 24 måneder fra baselinescoren for olaparib i kombination med bevacizumab var 0,13 (-1,2 ; 1,27) ud fra en baselinescore på 68,6 i PAOLA-1, mens der tilsvarende sås en gennemsnitsændring på 3,3 (1,84 ; 4,76) ud fra en baselinescore på 75 for placebo i SOLO-1. Fagudvalget vurderer dermed, at hverken olaparib i kombination med bevacizumab eller placebo medfører nogen signifikant ændring i patienternes livskvalitet ud fra de anvendte målemetoder.

5.3.5 Fagudvalgets konklusion

Fagudvalget vurderer, at olaparib i kombination med bevacizumab til patienter med HRD-positiv kræft i æggestokkene uden BRCA-mutation, og som ikke kandiderer til bevacizumabbehandling giver en lille merværdi sammenlignet med placebo. Evidensens kvalitet er meget lav.

Fagudvalget finder, at der er en stor merværdi for effektmålet, PFS, hvor både median PFS og PFS-raten ved 24 måneder er markant forbedret sammenlignet med placebo. Den øgede grad af behandlingsophør grundet uønskede hændelser samt den øgede forekomst af uønskede hændelser af grad 3-4 medfører en negativ værdi. Fagudvalget er samlet set positive i forhold til effekten af behandlingen. Fagudvalget vurderer dog ikke, at en samlet moderat merværdi kan godtgøres, da der på det nuværende datagrundlag ikke findes dokumentation for, at kombinationsbehandlingen forbedrer den samlede overlevelse på sigt eller patienternes livskvalitet i behandlingsforløbet.

6. Andre overvejelser

PFS2

Fagudvalget efterspurgte i protokollen en opgørelse for PFS2, defineret som tid fra randomisering indtil anden objektiv radiologisk progression ifølge RECIST-kriterierne eller død. Formålet med dette effektmål er at vurdere effekten af 1. linje vedligeholdelsesbehandlingen på længere sigt i det tilfælde, hvor OS-data ikke er modne. Data for ITT-populationen i PAOLA-1 ved database cut-off i marts 2019 er publiceret i Ray-Coquard et al. 2019 [26]. Disse er dog meget umodne (6 % for intervention og 20 % for komparator), og ITT-populationen er ikke velegnet til at estimere effekten i patienter med BRCA-mutation og/eller HRD. Ansøger har derfor indsendt '*data on file*' fra et senere opfølgningspunkt (marts 2020) over subpopulationerne, HRD-positiv inklusive BRCA-mutation og HRD-positiv uden BRCA-mutation. Fagudvalget har taget udgangspunkt i disse data i det følgende afsnit.

[redacted]

[redacted] Fagudvalget vurderer, at effekten af vedligeholdelsesbehandlingen i 1. linje stadig er relevant på længere sigt, selvom forskellene mellem intervention og komparator mindskes. Størstedelen (ca. 95 %) af patienterne med første progression i begge arme modtog en ny behandlingslinje efter progression, hovedsageligt platinbaseret kemoterapi (92 % for intervention og 88 % for komparator). Andelen, der modtog PARPi i 2. linje, afveg mellem interventions- (10,7 %) og komparatorarmen (30,4 %). Dette, samt de generelt umodne data, kan have medvirket til de mindskede forskelle i forhold til 1. linjebehandlingen.

Diagnose af HRD
EMAs indikation for olaparib i kombination med bevacizumab kræver, at patienterne er HRD-positive, defineret som enten BRCA-mutation (somatisk eller arvelig) eller genomisk ustabilitet. Definitionen af genomisk ustabilitet er uklar, men i de fleste studier defineres dette ved hjælp af MYRIAD myChoice-testen (se endvidere afsnit 3.1). Denne test er godkendt af FDA som *companion diagnostics* til identifikation af HRD-positive patienter.

Diagnose vha. MYRIAD myChoice vil for nuværende kræve, at en tumorprøve sendes til virksomheden i USA for analysen. Fagudvalget vurderer, at dette vil være praktisk muligt, men at det vil medføre omkostninger for diagnosen. Samtidig bemærker fagudvalget, at alle nydiagnosticerede patienter med avanceret kræft i æggestokkene, der ikke har en BRCA-mutation, bør undersøges for HRD, hvis olaparib i kombination med bevacizumab anbefales.

Ansøger har opstillet tre muligheder for at facilitere en mere effektiv diagnose:

- Facilitere opsætning af lokalt Myriad satellitlaboratorium, der kan udføre Genomisk Instability Score (GIS)-analyse og i samarbejde med Myriad kan bestemme patienternes HRD-score.
- På Nordisk plan supportere udvikling af lokal HRD-test, der valideres mod Myriad MyChoice-test. Dette projekt pågår med deltagelse af danske laboratorier.
- På Nordisk plan at støtte forskningsprojekter, der dels sikrer et datagrundlag for yderligere klinisk validering af de udviklede lokale test men også genererer *Real-World data* på subgrupper af patienter defineret på baggrund af HRD-status.

Fagudvalget vurderer, at alle tre scenarier vil medføre en lettere og hurtigere diagnose, men at alle tre vil tage tid at implementere. Derved er det mest sandsynlige scenarie for nuværende, at tumorprøver skal sendes til USA til diagnose via. MYRIAD myChoice-testen. Fagudvalget bemærker dog, at der er konkrete tiltag i gang på Rigshospitalet for at kunne udføre MYRIAD myChoice testen lokalt. Det forventes, at testen vil være implementeret på Rigshospitalet i løbet af 2021.

Påvirkning af efterfølgende behandlingslinjer og vurderingens relation til eventuel 2. linjebehandling
Indførslen af olaparib i kombination med bevacizumab til alle HRD-positive patienter, der responderer på platinbaseret kemoterapi, vil medføre ændringer i behandlingsmulighederne i 2. linje for patienter med BRCA-mutation, da hverken

olaparib eller bevacizumab anvendes sekventielt i dansk klinisk praksis. Derved vil patienter, der har modtaget kombinationsbehandlingen i 1. linje, ikke kunne behandles med bevacizumab i 2. linje, som ellers er muligt ved nuværende praksis. Der vil ikke være nogen ændringer i forhold til mulighed for behandling med PARPi i efterfølgende behandlingslinjer, da disse kun er anbefalet til patienter med BRCA-mutation, som allerede får tilbudt olaparib i 1. linje.

I tilfælde af at olaparib i kombination med bevacizumab bliver anbefalet til HRD-positive patienter uden BRCA-mutation, vil der opstå situationer, hvor patienter med nydiagnosticeret kræft i æggestokkene vil kunne få tilbudt kombinationsbehandlingen, mens patienter, der tidligere er progredieret efter 1. linjebehandling, ikke vil få tilbudt dette.

Medicinrådet besluttede på rådsmødet den 9. december 2020, at fagudvalget i forbindelse med vurderingen af olaparib i kombination med bevacizumab til 1. linje vedligeholdelsesbehandling skulle vurdere konsekvensen for 2. linjebehandlingen til patienter med uhelbredelig kræft i æggestokkene uden BRCA-mutation.

Der findes ingen kliniske studier, der dokumenterer effekten af vedligeholdelse med kombinationsbehandlingen efter senere platinbaserede behandlingslinjer. Den dokumenterede effekt på PFS ved 1. linjebehandling kan ikke umiddelbart overføres til 2. linjebehandling. Derimod vurderer fagudvalget, at bivirkningshyppigheden og graden vil være sammenlignelig mellem 1. og 2. linje.
Fagudvalget vurderer, at kombinationsbehandlingen i tilfælde af en anbefaling kun bør anvendes som vedligeholdelsesbehandling efter 1. linje kemoterapi. Dette skyldes, at bivirkningerne er af betydende størrelse og frekvensen af behandlingsophør er høj ved kombinationsbehandlingen, hvorimod effekten ikke er dokumenteret.

7. Relation til behandlingsvejledning

Fagudvalget mener ikke, at olaparib i kombination med bevacizumab kan ligestilles med olaparib i Medicinrådets behandlingsvejledning for BRCA-muteret kræft i æggestokkene. Ved en eventuel anbefaling af kombinationsbehandlingen til BRCA-muterede patienter, vurderer fagudvalget, at olaparib i kombination med bevacizumab skal indplaceres efter olaparib monoterapi i Medicinrådets behandlingsvejledning vedrørende lægemidler til BRCA-muteret kræft i æggestokkene, æggelederne eller primær kræft i bughinden.

Til patienter med avanceret ikke-BRCA-muteret, HRD-positiv high-grade kræft i æggestokkene findes der ikke en behandlingsvejledning.

8. Referencer

1. Mosgaard BJ, Pedersen LK, Bjørn SF, Christiansen T, Markauskas A, Lund B, et al. Retningslinier for visitation, diagnostik, behandling og opfølgning af epitelial ovarie-, tuba- og primær peritonealcancer samt borderline tumorer. Kapitel 1: Introduktion. 2016;(5):1–9.
2. NORDCAN - Association of the Nordic Cancer Registries. Kræftstatistik: Nøgletal og figurer Danmark – Æggestok, æggeleder mv. 2019.
3. NORDCAN - Association of the Nordic Cancer Registries. Æggestok, æggeleder mv. 5-års aldersspecifik relativ overlevelse, diagnoseår 2012-2016. 2017.
4. Dansk Gynækologisk Cancer Database. Landsdækkende klinisk database for gynækologisk kræft. National Årsrapport 2017/2018 og 2018/2019. 2019.
5. Bolton KL, Chenevix-Trench G, Goh C, Sadetzki S, Ramus SJ, Karlan BY, et al. Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer. JAMA. 2012;307(4):382–90.
6. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature. 2011;474(7353):609–15.
7. Zhang S, Royer R, Li S, McLaughlin JR, Rosen B, Risch HA, et al. Frequencies of BRCA1 and BRCA2 mutations among 1,342 unselected patients with invasive ovarian cancer. Gynecol Oncol. 2011;121(2):353–7.
8. Huang Y. Association of BRCA1/2 mutations with ovarian cancer prognosis: An updated meta-analysis. Medicine (Baltimore). 2018;97(2):e9380.
9. Hoppe MM, Sundar R, Tan DSP, Jeyasekharan AD. Biomarkers for homologous recombination deficiency in cancer. J Natl Cancer Inst. 2018;110(7):704–13.
10. Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med. 2016;375(22):2154–64.
11. Pellegrino B, Mateo J, Serra V, Balmaña J. Controversies in oncology: are genomic tests quantifying homologous recombination repair deficiency (HRD) useful for treatment decision making? ESMO open. 2019;4(2):e000480.
12. Mirza MR, Coleman RL, González-Martín A, Moore KN, Colombo N, Ray-Coquard I, et al. The forefront of ovarian cancer therapy: update on PARP inhibitors. Ann Oncol. 2020;31(9):1148–59.
13. Mirza MR, Åvall Lundqvist E, Birrer MJ, dePont Christensen R, Nyvang GB, Malander S, et al. Niraparib plus bevacizumab versus niraparib alone for platinum-sensitive recurrent ovarian cancer (NSGO-AVANOVA2/ENGOT-ov24): a randomised, phase 2, superiority trial. Lancet Oncol. 2019;20(10):1409–19.
14. Takaya H, Nakai H, Takamatsu S, Mandai M, Matsumura N. Homologous recombination deficiency status-based classification of high-grade serous ovarian carcinoma. Sci Rep. 2020;10(1):1–8.
15. Charlotte Lautrup, Uffe Birk Jensen, Anders Bojesen, Mads Thomassen, Thomas van Overeem Hansen, Anne-Marie Gerdes, Jan Blaakær, Henrik Roed, Ulla Peen, Karina Dahl Steffensen, Bente Lund, Lotte Nedergaard Thomsen EH. Forslag til national guideline for genetisk udredning af patienter med ovariecancer . 2018. 1–4 sider.
16. MYRIAD ONCOLOGY. MYRIAD myChoice CDx [internet]. [citeret 20. august 2020]. Tilgængelig fra: https://myriad-oncology.com/mychoice-cdx/
17. Coleman RL, Fleming GF, Brady MF, Swisher EM, Steffensen KD, Friedlander M, et al. Veliparib with first-line chemotherapy and as maintenance therapy in ovarian cancer. N Engl J Med. 2019;381(25):2403–15.
18. European Medicines Agency EMA. EPAR - Assessment report - Lynparza. 2019.
19. Medicinrådet. Medicinrådets behandlingsvejledning vedrørende lægemidler til BRCA-muteret kræft i æggestokkene, ægge-lederne eller primær kræft i

bughinden. 2020.
20. O'Connor MJ. Targeting the DNA Damage Response in Cancer. Mol Cell. 2015;60(4):547–60.
21. European Medicines Agency EMA. EPAR - Assessment report - Avastin. 2017.
22. Liu JF, Barry WT, Birrer M, Lee JM, Buckanovich RJ, Fleming GF, et al. Overall survival and updated progression-free survival outcomes in a randomized phase II study of combination cediranib and olaparib versus olaparib in relapsed platinum-sensitive ovarian cancer. Ann Oncol. 2019;30(4):551–7.
23. Mosgaard BJ, Pedersen LK, Bjørn SF, Christiansen T, Markauskas A, Lund B, et al. Retningslinier for visitation, diagnostik, behandling og opfølgning af epitelial ovarie-, tuba- og primær peritonealcancer samt borderline tumorer. Kapitel 3: Kirurgisk behandling af epitheliale ovarietumorer. 2019;(6):1–19.
24. Mosgaard BJ, Pedersen LK, Bjørn SF, Christiansen T, Markauskas A, Lund B, et al. Retningslinier for visitation, diagnostik, behandling og opfølgning af epitelial ovarie-, tuba- og primær peritonealcancer samt borderline tumorer. Kapitel 5: Ikke-kirurgisk behandling af epiteliale tumorer. 2019;(6):1–36.
25. Hanker LC, Loibl S, Burchardi N, Pfisterer J, Meier W, Pujade-Lauraine E, et al. The impact of second to sixth line therapy on survival of relapsed ovarian cancer after primary taxane/platinum-based therapy. Ann Oncol. 2012;23(10):2605–12.
26. Ray-Coquard I, Pautier P, Pignata S, Pérol D, González-Martín A, Berger R, et al. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. N Engl J Med. 2019;381(25):2416–28.
27. European Medicines Agency Committee for Medicinal Products For Human Use (CHMP). Assessment report - Lynparza - EMA/523504/2020. 2020;31(September).
28. Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2018;379(26):2495–505.
29. DiSilvestro P, Colombo N, Scambia G, Kim B-G, Oaknin A, Friedlander M, et al. Efficacy of Maintenance Olaparib for Patients With Newly Diagnosed Advanced Ovarian Cancer With a BRCA Mutation: Subgroup Analysis Findings From the SOLO1 Trial. J Clin Oncol. 2020;38(30):3528–37.
30. Vergote IB, Moore KN, Hettle R, Rhodes K, Ouwens M, Ray-Coquard I. Population adjusted indirect comparison of the SOLO1 and PAOLA-1/ENGOT-ov25 studies of olaparib with or without bevacizumab, bev alone and placebo in the maintenance treatment of women with newly diagnosed stage III/IV ovarian cancer with BRCA mutation. Gynecol Oncol. 2020;159:19–20.
31. Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, et al. Incorporation of Bevacizumab in the Primary Treatment of Ovarian Cancer for the Gynecologic Oncology Group*. Seattle Cancer Care Alliance, Seattle (BEG Minneap (MB); Harvard Med Sch Massachusetts Gen-eral Hosp Bost (MJB. 2011;26(29):2473–83.
32. Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, et al. A Phase 3 Trial of Bevacizumab in Ovarian Cancer. N Engl J Med. 2011;365(26):2484–96.
33. European Medicines Agency. Avastin SmPC. 2021.
34. Phippen NT, Secord AA, Wolf S, Samsa G, Davidson B, Abernethy AP, et al. Quality of life is significantly associated with survival in women with advanced epithelial ovarian cancer: An ancillary data analysis of the NRG Oncology/Gynecologic Oncology Group (GOG-0218) study. Gynecol Oncol. 2017;147(1):98–103.

9. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende kræft i æggestokkene og livmoderkærft

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Trine Jakobi Nøttrup *Overlæge*	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Anya Eidhammer *Ledende overlæge*	Region Nordjylland
Jacob Christian Lindegaard *Overlæge, Dr.med.*	Region Midtjylland
Trine Lembrecht Jørgensen *Afdelingslæge*	Region Syddanmark
Dejan Labudovic *Afdelingslæge*	Region Sjælland
Kristine Madsen *Afdelingslæge*	Region Hovedstaden
Trine Zeeberg Iversen *Afdelingslæge*	Dansk Selskab for Klinisk Onkologi
Henrik Horwitz *Afdelingslæge*	Dansk Selskab for Klinisk Farmakologi
Henrik Kjer *Klinisk farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Birthe Lemley *Patient/patientrepræsentant*	Danske Patienter
Dorte Blou *Patient/patientrepræsentant*	Danske Patienter

Medicinrådets sekretariat
Medicinrådet
Dampfærgevej 27-29, 3.th.
2100 København Ø
+45 70 10 36 00
medicinraadet@medicinraadet.dk

10. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	28. april 2021	Godkendt af Medicinrådet

11. Bilag

Bilag 1: Cochrane – risiko for bias

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

Tabel 11-1. Vurdering af risiko for bias - Ray-Coquard et al., 2020, PAOLA-1, NCT02477644

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Allokering til behandling eller placebo var randomiseret i en ratio 2:1. Randomiseringen blev udført centralt via et *interactive web or voice response system.* Baselinekarakteristika i de to arme er sammenlignelige.
Effekt af tildeling til intervention	**Lav**	Allokering til behandling eller placebo var dobbelt-blindet.
Manglende data for effektmål	**Lav**	Transparent og begrænset frafald. Effektivitetsanalyser er baseret på *intention-to-treat*-data, mens frafald i analyserne af livskvalitet er transparent og udgør mindre end 10 % af den samlede population.
Risiko for bias ved indsamlingen af data	**Lav**	Effektmålene vurderes ikke at være påvirket pga. blinding.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Protokollen er offentlig tilgængelig. De primære effektmål, der beskrives i protokollen, er rapporteret i studiet. *Overall survival* er I protokollen beskrevet som et sekundært effektmål, men data vurderes i artiklen at være umodne.
Overordnet risiko for bias	**Lav**	

Tabel 11-2. Vurdering af risiko for bias - K. Moore, 2018, SOLO1, NCT01844986

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiseringsprocessen	**Lav**	Allokering til behandling eller placebo var randomiseret i en ratio 2:1. Randomiseringen blev udført centralt via et *interactive web or voice response system.*
Effekt af tildeling til intervention	**Lav**	Allokering til behandling eller placebo var dobbelt-blindet.
Manglende data for effektmål	**Lav**	Transparent og begrænset frafald. Effektivitetsanalyser er baseret på *intention-to-treat*-data, mens sikkerhedsanalyser er baseret på alle patienter, som har modtaget mindst én behandling. Frafald i livskvalitetsanalyserne er transparent og udgør mindre end 20 % af den samlede population.
Risiko for bias ved indsamlingen af data	**Lav**	Effektmålene vurderes ikke at være påvirket på grund af blinding.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Protokol er offentlig tilgængelig. De primære og sekundære effektmål, der beskrives i protokollen, er rapporteret i studiet.
Overordnet risiko for bias	**Lav**	

Bilag 2: GRADE

Klinisk spørgsmål 2 – olaparib i kombination med bevacizumab sammenlignet med bevacizumab til behandling af kræft i æggestokkene ved patienter uden BRCA-mutation, HRD-positiv.

Tabel 11-3. GRADE evidensprofil for klinisk spørgsmål 2

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Olaparib + bevacizumab	Bevacizumab	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
Overlevelse (median), follow up: median 39 måneder												
1	RCT	Ikke alvorlig	Alvorlig [a]	Kan ikke kategoriseres [b]	Kan ikke kategoriseres [b]	Ingen	[redacted]	[redacted]	Ikke angivet	Ikke angivet	Kan ikke kategoriseres [b]	Kritisk
Overlevelse (OS-rate ved 5 år), follow up: median 39												
1	RCT	Ikke alvorlig	Alvorlig [a]	Kan ikke kategoriseres [b]	Kan ikke kategoriseres [b]	Ingen	[redacted]	[redacted]	Ikke angivet	Ikke angivet	Kan ikke kategoriseres [b]	Kritisk
Progressionsfri overlevelse (median), follow up: 22,7 måneder (olaparib + bevacizumab) og 24,0 måneder (bevacizumab)												
1	RCT	Ikke alvorlig	Alvorlig [a]	Ikke alvorlig	Meget alvorlig [c]	Ingen	[redacted]	[redacted]	[redacted]	[redacted]	⨁◯◯◯ MEGET LAV	Kritisk
Progressionsfri overlevelse (PFS-rate ved 2 år), follow up: 22,7 måneder (olaparib + bevacizumab) og 24,0 måneder (bevacizumab)												

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Olaparib + bevacizumab	Bevacizumab	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
1	RCT	Ikke alvorlig	Alvorlig [a]	Ikke alvorlig	Alvorlig [d]	Ingen	[redacted]	[redacted]	[redacted]	[redacted]	⨁⨁◯◯ LAV	Kritisk
Uønskede hændelser, Behandlingsophør(%-point)												
1	RCT	Ikke alvorlig	Alvorlig [a]	Alvorlig [e]	Ikke-alvorlig	Ingen	[redacted]	[redacted]	[redacted]	[redacted]	⨁⨁◯◯ LAV	Kritisk
Uønskede hændelser, Andel der oplever grad 3-4 bivirkninger (%-point)												
1	RCT	Ikke alvorlig	Alvorlig [a]	Alvorlig [e]	Alvorlig [f]	Ingen	[redacted]	[redacted]	[redacted]	[redacted]	⨁◯◯◯ MEGET LAV	Kritisk
Livskvalitet, Andel der oplever signifikant forværring (%-point), follow up: 2 år												
1	RCT	Ikke alvorlig	Alvorlig [a]	Alvorlig [g]	Ikke-alvorlig		446	229	Ikke angivet	0,59 (-1.40 ; 2.57)	⨁⨁◯◯ LAV	Vigtig
Kvalitet af den samlede evidens	MEGET LAV [h]											

[a] Der er nedgraderet ét niveau, da der kun var ét studie.

[b] Effektmålet kan ikke kategoriseres, da data ikke stammer fra den rigtige population. Dette kan have stor betydning for effektmålet, og derfor indgår data ikke til en kategorisering men udelukkende til perspektivering.

[c] Der er nedgraderet to niveauer, da de relative og absolutte værdier indikerer forskellige konklusioner, og da Optimal information size-kriteriet ikke er opfyldt.

[d] Der er nedgraderet ét niveau, da Optimal information size-kriteriet ikke er opfyldt.

[e] Der er nedgraderet ét niveau, da effektmålet er opgjort på baggrund af uønskede hændelser i stedet for bivirkninger, som defineret i protokollen.

[f] Der er nedgraderet ét niveau, da konfidensintervallet indeholder både positive og negative konklusionener.

[g] Der er nedgraderet ét niveau, da data er angivet som et andet effektmål end efterspurgt (gennemsnitlig livskvalitet i stedet for andelen af patienter, der oplever et signifikant fald i livskvaliteten).

[h] Den samlede evidenskvalitet er vurderet ud fra den laveste kvalitet af de kritiske effektmål.

Klinisk spørgsmål 3 – olaparib i kombination med bevacizumab sammenlignet med placebo til behandling af kræft i æggestokkene ved patienter uden BRCA-mutation, HRD-positiv.

Tabel 11-4. GRADE evidensprofil for klinisk spørgsmål 3

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Olaparib + bevacizumab	Bevacizumab	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
Overlevelse (median)												
1	RCT	Ikke alvorlig	Alvorlig [a]	Kan ikke kategoriseres [b]	Kan ikke kategoriseres [b]	Ingen	[redacted]	[redacted]	Ikke angivet	Ikke angivet	Kan ikke kategoriseres [b]	Kritisk
Overlevelse (OS-rate ved 5 år)												
1	RCT	Ikke alvorlig	Alvorlig [a]	Kan ikke kategoriseres [b]	Kan ikke kategoriseres [b]	Ingen	[redacted]	[redacted]	Ikke angivet	Ikke angivet	Kan ikke kategoriseres [b]	Kritisk
Progressionsfri overlevelse (median)												
1	RCT	Ikke alvorlig	Alvorlig [a]	Alvorlig [c]	Ikke alvorlig	Ingen	43/97	40/55	HR: 0,43 (0,28; 0,66)	11,5 måneder	⊕⊕◯◯ LAV	Kritisk
Progressionsfri overlevelse (24 måneder)												

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Olaparib + bevacizumab	Bevacizumab	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
1	RCT	Ikke alvorlig	Alvorlig [a]	Alvorlig [c]	Ikke alvorlig	Ingen	43/97	40/55	HR: 0,43 (0,28; 0,66)	30 %-point	⨁⨁◯◯ LAV	Kritisk
Uønskede hændelser, Behandlingsophør(%-point)												
Kan ikke kategoriseres [d]										[redacted]	Kan ikke kategoriseres [c]	Kritisk
Uønskede hændelser, Andel der oplever grad 3-4 bivirkninger (%-point)												
Kan ikke kategoriseres [d]											Kan ikke kategoriseres [c]	Kritisk
Livskvalitet												
Kan ikke kategoriseres [d]											Kan ikke kategoriseres [c]	Vigtig

[a] Der er nedgraderet ét niveau, da der kun var ét studie.

[b] Effektmålet kan ikke kategoriseres, da data ikke stammer fra den rigtige population. Dette kan have stor betydning for effektmålet, og derfor indgår data ikke til en kategorisering men udelukkende til perspektivering

[c] Der er nedgraderet ét niveau, da data stammer fra en anden komparator og en anden population end efterspurgt.

d Da vurderingen af effektmålet er baseret på en deskriptiv sammenligning kan GRADE ikke anvendes til at vurdere kvaliteten af evidensen.

Application for the assessment of clinically added value of Lynparza (olaparib) in combination with bevacizumab for maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a *BRCA1/2* mutation and/or genomic instability.

Contents

1 Basic information

Table 1. Contact information

Name	Søren Clausen
Title	Market Access Head
Area of responsibility	Reimbursement and negotiations
Phone	23615584
E-mail	soren.clausen@astrazeneca.com
Name	Jesper Hansen
Title	Therapeutic Area Lead Women´s Cancer
Area of responsibility	Medical ovarian cancer
Phone	+4525970199
E-mail	Jesper.hansen@astrazeneca.com
Name	Mette Skovbro
Title	Medical Affairs Manager Women's cancer
Area of responsibility	Ovarian and breast cancer
Phone	+4522869886
E-mail	mette.skovbro@astrazeneca.com

Table 2. Overview of the pharmaceutical

Proprietary name	Lynparza
Generic name	Olaparib
Marketing authorization holder in Denmark	AstraZeneca AB
ATC code	L01XX46
Pharmacotherapeutic group	poly [ADP-ribose] polymerase inhibitors (PARPi),
Active substance(s)	Olaparib
Pharmaceutical form(s)	Tablets 150 mg and 100 mg
Mechanism of action	Olaparib is an oral potent inhibitor of PARP1, PARP2, and PARP3. These PARP enzymes are required for the efficient repair of DNA single-strand breaks. During the repair process, after chromatin modification, PARP auto-modifies itself and dissociates from the DNA to facilitate access for base excision repair (BER) enzymes. Olaparib, when bound to the active site of DNA-associated PARP, prevents dissociation from DNA, blocking repair of the single-strand break
Dosage regimen	2 tablets twice daily.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	**EMA approval 04.11.2020**: Maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based

	chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a *BRCA1/2* mutation and/or genomic instability.
Other approved therapeutic indications	**Ovarian cancer**: • Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed *BRCA*-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy *(capsule formulation)* • Lynparza™ as monotherapy for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) *BRCA1/2*-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy. *(tablet formulation)* • Monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy *(tablet formulation)* **Breast cancer**: • Monotherapy for the treatment of adult patients with germline *BRCA1/2*-mutations, who have HER2 negative locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments. Patients with hormone receptor (HR)-positive breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy. *(tablet formulation)* **Adenocarcinoma of the pancreas:** • Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with germline *BRCA1/2*-mutations who have metastatic adenocarcinoma of the pancreas and have not progressed after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen. *(tablet formulation)* **Prostate cancer**: • Lynparza is indicated as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and *BRCA1/*2-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent *(tablet formulation)*
Will dispensing be restricted to hospitals?	Yes. Labelled BEGR

Combination therapy and/or co-medication	No
Packaging – types, sizes/number of units, and concentrations	56 tablets
Orphan drug designation	No. Was orphan until March 2018

2 Abbreviations

Abbreviations	
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BARD1	BRCA1-associated ring domain 1 (gene)
BICR	Blinded independent central review
BRCA	Breast cancer susceptibility gene
BRCA1	Breast cancer susceptibility gene 1
BRCA2	Breast cancer susceptibility gene 2
BRCAm	Breast cancer susceptibility gene mutation (germline and/or somatic)
CA-125	Cancer antigen-125
CI	Confidence interval
CP	Carboplatin plus paclitaxel
CPB15+	Carboplatin, paclitaxel, bevacizumab (15 mg/kg for cycles 2 to 22
CPP	Carboplatin, paclitaxel, placebo
CR	Complete response
CR (objective)	Complete objective response (RECIST)
CSR	Clinical study report
DCO	Data cut-off
DCR	Disease control rate; percentage of patients with a best objective response of complete response, partial response, or stable disease ≥24 weeks following randomisation
DOR	Duration of response
EMA	European Medicines Agency
ENGOT	European Network of Gynaecological Oncological Trials
EOC	Epithelial ovarian cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer life questionnaire 30

Abbreviations	
EORTC QLQ-OV28	European Organisation for Research and Treatment of Cancer life questionnaire-ovarian cancer module 28
EoT	End of treatment
EQ-5D-5L	European Profile of Quality of Life (EuroQoL) 5 dimensions, 5 level
ESMO	European Society for Medical Oncology
EuroQoL	European Profile of Quality of Life
FACT	Functional Assessment of Cancer Therapy
FACT-O	Functional Assessment of Cancer Therapy – Ovarian
FAS	Full analysis set
gBRCA	Germline (mutation in) breast cancer susceptibility gene
HGEC	High-grade endometroid carcinoma
HGSC	High-grade serous carcinoma
HGSOC	High-grade serous ovarian cancer
HR	Hazard ratio
HRD	Homologous recombination deficiency
HRQoL	Health-related quality of life
HRR	Homologous recombination repair
ITC	Indirect treatment comparison
ITT	Intent-to-treat
LGEC	Low-grade endometroid carcinoma
LGSC	Low-grade serous carcinoma
NS	Not significant
OC	Ovarian cancer
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PARP	Poly (ADP-ribose) polymerase
PARPi	Poly (ADP-ribose) polymerase inhibitor
PFS	Progression-free survival
PFS2	Time to second progression or death
PPS	Post-progression survival
PR	Partial response
PRO	Patient-reported outcome
PRR	Platinum resistant/refractory
PS	Performance status
PSR	Platinum-sensitive recurrent
QoL	Quality of life

Abbreviations	
RCT	Randomised clinical trial
RECIST	Response Evaluation Criteria in Solid Tumours
RR	Relative Risk
SAE	Serious adverse event
SAS	Safety analysis set
sBRCA	Somatic (mutation in) breast cancer susceptibility gene
SD	Standard deviation
SE	Standard error
SST	Second subsequent therapy
TDT	Time to discontinuation of treatment
TFST	Time to first subsequent therapy or death
TNM	Tumour (T), Node (N), Metastasis (M)
TSST	Time from randomisation to second subsequent therapy or death
TTP	Time to progression
VUS	Variants of unknown significance
Wt	Wild-type

3 Executive Summary (dansk)

This section contains data that are to be considered confidential. It is marked with [redacted]

Ifølge NORDCAN, diagnosticeres der årligt (2012-2016) 550 nye tilfælde ovarie cancer. Prævalens ved udgangen af 2016 er opgjort til cirka 4700. Ovariecancer har høj dødelighed blandt andet fordi sygdommen oftest opdages i sene stadier (III-IV). Der er desuden høj frekvens af tilbagefald (ca. 80 % af patienterne)[1, 2]. Som for andre kræftformer er overlevelsen afhængig af sygdomsstadiet på diagnosepunktet. Den samlede 5-årsoverlevelse er ca. 40 % men 87 % i stadium I og 15 % i stadium IV. Omkring 90 % af alle tilfælde af kræft i æggestokkene er af epitelial type (karcinomer) svarende til ca. 500 nye patienter om året, hvoraf ca. 80% skønnes at være af high-grade histologi (~400 patienter). Ifølge data fra DGCGs årsrapport vil omkring ca. 70% af patienter være i sygdomsstadie III/IV på diagnosetidspunktet [3]. Med baggrund i ovenstående skønnes det for denne ansøgning derfor at **ca. 270** stadium III/IV high-grade epitial ovarie cancer patienter diagnosticeres årligt i Danmark.

Den primære behandling af ovariecancer er kirurgisk, hvor målet er korrekt stadieinddeling og radikal operation. Stadie og udfaldet af operation er afgørende for efterfølgende medicinsk behandling idet patienter tilbydes tillæg af bevacizumab til standard platinbaseret kemoterapi efterfulgt af vedligeholdelse behandling med bevacizumab baseret på følgende kriterier:

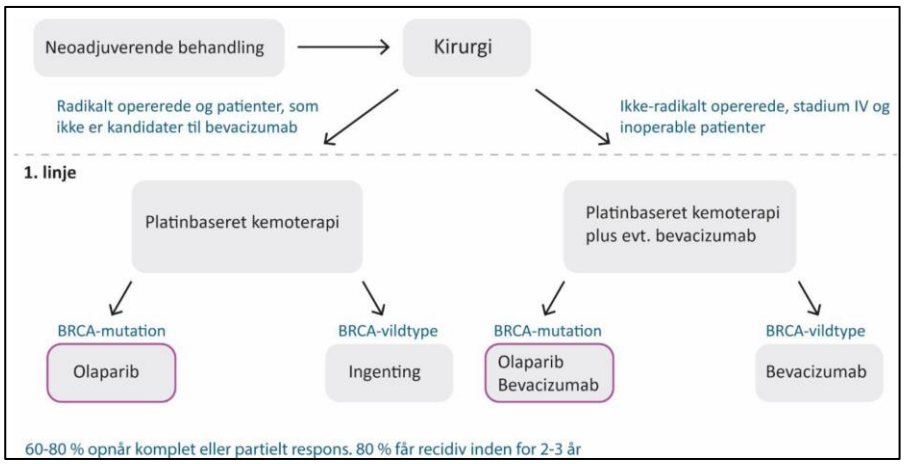
- Alle stadie IV patienter
- Stadie III patienter, primært opererede, ÷ makroradikal operation

- Stadie III patienter, interval opereret efter Neo-adjuverende kemoterapi, ÷ makroradikal operation
- Ikke opererede patienter

Medicinrådets behandlingsvejledning vedr. lægemidler til BRCAm kræft i æggestokkene godkendt 24. april 2020 skelner i sin anbefaling af ny-diagnosticerede patienter med avanceret BRCA-muteret high-grade epitelial kræft i æggestokkene, æggelederne eller primær kræft i bughinden (1. linje vedligeholdelsesbehandling) mellem patienter som er eller kunne være kandidater til bevacizumab.

Patienter uden påvist BRCA-mutation behandles med platinbaseret kemoterapi enten som monoterapi eller i kombination og/eller efterfulgt af vedligeholdelsesbehandling med bevacizumab jævnfør ovenstående kriterier [4].

Figur 1. Behandlingsalgoritme for kræft i æggestokkene med BRCAm



Source: Medicinrådet behandlingsvejledning [4].

Nedenfor følger et estimat af patientfordelingen i undergrupper af stadium III/IV high-grade epitial ovarie cancer patienter.

Ifølge data fra DGCGs database præsenteret i årsrapporten fra 2017-2019 modtager nedenstående procentdel kun onkologisk behandling i årene 18/19; 17/18 og 16/17

- ÷ kirurgi
  - ✓ 15.5%; 19.6%; 16.5%

Blandt de patienter der opereres er der følgende fordeling i timing af kirurgi

- Primært opererede
  - ✓ ~62%
- Interval opererede
  - ✓ ~38%

Andel af stadie IIIC/IV patienter der opnår **makroradikal operation** fordelt ift timing af operation i årene 18/19; 17/18 og 16/17 :

- Primært opererede

- ✓ 83.6%; 76.9%; 81.5%

- Interval opererede
  - ✓ 62.6%; 67.3%; 62.5%

Ligeledes opgøres andelen af stadie IV patienter som følger:

- Stadie IV
  - ✓ 18.3%; 22.3%; 19.2%

Baseret på ovenstående data estimeres nedenstående fordeling stadium III/IV high-grade epitial ovarie cancer patienter per undergrupper (absolutte tal) med andel af de estimerede 270* patienter i %.

Table 3. Patients per mutation status

Mutations status	Ikke omfattet af kriterier for bevacizumab behandling	Omfattet af kriterier for bevacizumab behandling
BRCAm	22 (8%)	30 (11%)
BRCAwt	86 (32%)	122 (45%)

* *3 – 4 % af patienterne får ikke aktiv behandling og derfor er summen i tabellen kun 260 patienter*

Forudsætningerne for beregningerne er baseret på data fra DGCG:

- ~ 19% af patienterne er BRCAm
- andelen af patienter der opnår makroradikal operation (Stadium IIIC/IV) er repræsentativ for stadium III patienter
- andelen af stadium IV patienter estimeres til at udgøre 29% af den samlede stadium III/IV population

Med baggrund i de kliniske spørgsmål i protokollen og tidligere fremhævede estimater over patientantal vurderer AstraZeneca følgende for patientantal i undergrupper af stadium III/IV high-grade epitial ovarie cancer :

- HRD+ exBRCAm: ~76 patienter årligt (bestemt ved test for genomisk instabilitet) vil være nye kandidater for olaparib baseret kombinationsbehandling:
  - ✓ 44 patienter være omfattet af de nuværende kriterier for bevacizumab behandling (~58%)
  - ✓ 32 patienter vil pt ikke modtage vedligeholdelse behandling med hverken bevacizumab eller olaparib

- BRCAm: ~54 patienter årligt (bestemt ved test for BRCAm status) allerede værende kandidater for olaparib behandling kan have gavn af kombinationsbehandling med bevacizumab:
  - ✓ 32 patienter vil være omfattet af de nuværende kriterier for bevacizumab behandling

- ✓ 22 patienter vil pt ikke modtage bevacizumab behandling

Figur 2. Patientantal HRD baseret på DGCG databasen [1].

Status	÷ bevacizumab behandling	+ bevacizumab behandling
BRCAm	22 (8%)	32 (11%)
	54 (19%)	
HRD+ exBRCAm	32 (11%)	44 (16%)
HRD÷/ukendt	59 (21%)	82 (29%)

Medicinrådets protokol for vurdering af olaparib i kombination med bevacizumab til 1. linje vedligeholdelsesbehandling af avanceret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden med homlog recombinationsdefekt indeholder tre overordnede kliniske spørgsmål:

Klinisk spørgsmål 1:

- Patientpopulation omfatter den totale gruppe af BRCAm patienter jvf figur 2 da olaparib defineres som standard behandling for denne gruppe

Klinisk spørgsmål 2:

- Patientpopulationen omfatter gruppen af HRD+ extBRCAm der møder kriterierne for bevacizumab behandling. Spørgsmålet bliver i ansøgning besvaret med subgruppe data fra PAOLA-1 studiet. Kriterierne for denne "higher-risk"subgruppe er ikke 100% identiske med kriterierne defineret i denne protokol, da patienter med stadium III der modtager sekundær kirurgi uden efterfølgende residual tumor er inkluderet i data analysen. Dette modsvarer ikke klinisk praksis i Danmark

Klinisk spørgsmål 3:

- Patientpopulationen omfatter gruppen af HRD+ extBRCAm der ikke møder kriterierne for bevacizumab behandling. Jvf ovenstående er patienter med stadium III der modtager sekundær kirurgi uden efterfølgende residual tumor ikke inkluderet i datasættet, der danner grundlag for denne ansøgning.

Data fra PAOLA-1 studiet sammenholdt med indirekte sammenligninger med data fra SOLO-1 for at belyse **klinisk spørgsmål 1** viser følgende:

- **OS** fra PAOLA-1 studiet er endnu ikke modne, hvorfor dette effektmål er vanskeligt at adressere i ansøgning. En trend mod forbedret overlevelse for den samlede HRD+ population med en observeret HR på 0.55 (95% CI 0.33, 0.92), og en HR på 0.66 (95% CI 0.37, 1.21) i subgruppen af tBRCAm patienter.

- **PFS data. Klinisk spørgsmål 1 (naiv sammenligning for tillæg af bevacizumab til olaparib):**

    - PAOLA-1 studiet var ikke designet til at vurdere effekten af tillæg af bevacizumab til olaparib, hvorfor dette adresseres med naive sammenligninger og PAIC med data fra SOLO-1.
    - Median PFS (BRCAm subgruppe) i PAOLA-1 studiet er ustabil grundet få events hvorfor mulighed for bedømmelse af effektmål (Δ 6 måneder) er begrænset

    - For PFS rate ved 2 år blev der på baggrund af naive sammenligninger af higher-risk og lower-risk population fundet følgende:

        - 15 procentpoints forbedring af 2-års PFS rate for lower-risk population indikerende potentiel synergistisk effekt. Dette understøttet af en HR på 0,11 (0,03-0,31) observeret for denne population i PAOLA-1

        - 7 procentpoints forbedring af 1-års PFS rate i higher-risk population mens 2-års PFS rate ikke viste forbedring potentielt foreslående en additiv effekt ved kombinationsbehandlingen

- **PFS data. Klinisk spørgsmål 1 (Patient Adjusted Indirect Comparison):**

    - 9 procentpoints forbedring af 2-års PFS rate for en PAIC baseret på justering ift SOLO-1 baseline karakteristika

Klinisk spørgsmål 2:

- [redacted]
- 4.9 måneders forbedring af median PFS i kombinationsarmen versus bevacizumab mono
- Data indikerer at effekten af tillæg olaparib for denne higher-risk poulation er additiv, og at den reelle effekt af tillæg af olaparib bedst belyses ved forbedring i PFS-rate ved 2 år.

Klinisk spørgsmål 3:

- [redacted]

Bivirkningsprofil af olaparib plus bevacizumab behandling gældende for alle 3 spørgsmål:

- Overordnet er den observerede bivirkningsprofil for kombinationen af olaparib og bevacizumab bedømt til at være konsistent med den kendte bivirkningsprofil for de to behandlinger når givet som monoterapi

- Data fra subgruppe undersøgelser af PAOLA-1 datasættet foreslår ingen forskelle i bivirkningsprofil mellem de enkelte subgrupper defineret af de kliniske spørgsmål

- En øgning i andelen af patienter som oplever Grad ≥3 bivirkninger fra 49.6% i bevacizumab armen til 56% i kombinationsarmen foreslår ikke klinik relevant forskel på de to behandlinger ved tillæg af olaparib til bevacizumab (klinisk spørgsmål 2). Det må forventes at kombinationsbehandlingen

sammenlignet med placebo øger denne forskel jvf. data fra ICON-7, hvorfor den forskelle vil forventes potentielt at være klinisk relevant (klinisk spørgsmål 3). En naiv sammenligning af tillæg af bevacizumab til olaparib (SOLO-1 vs PAOLA-1 sammenligning) kan foreslår en klinisk relevant gruppe af patienter der oplever Grad ≥3 bivirkninger

- Ophør af behandlingen grundet TEAE var rapporteret højere i PAOLA-1 (20%) end i SOLO-1 (12%). I Da ophør af behandling grundet "Patient decision" relateret til bivirkninger blev rapporteret forskelligt i SOLO-1 (8%) mod 1% i PAOLA-1 vurderes der ikke at være forskel i andelen af patienter der ophører behandlingen ved tillæg af bevacizumab. Tillæg af olaparib til bevacizumab øger andelen af patienter der ophører behandling og vurderes at være klinisk relevant (klinisk spørgsmål 2 & 3)

Livskvalitet gældende for alle 3 spørgsmål:

- Der fandtes ingen klinisk eller statistisk relevant forskel i livskvalitet mellem behandlingsarmene i PAOLA-1 studiet

Konklusion:

Påvisning af mutation i BRCA genet har vist sig ikke kun at være en prognostisk faktor.

Overlevelsesdata fra SOLO-2 studiet præsenteret på ASCO 2020 demonstrerede en klinisk relevant forskel i overlevelse med en ~13 måneders forbedring af median OS (51.7 vs 38.8 måneder). I SOLO-2 studiet modtog 38% af de placebo behandlede patienter efterfølgende PARPi behandling mod 10% i den aktive arm. I en rank-preserving structural failure time (RPSFT) model, hvor SOLO-2 resultaterne justeredes for efterfølgende PARPi i placebo armen, fandtes overlevelsesgevinsten at være ~16 måneder (51.7 vs 35.4 måneder) [5].

Dette understøttes i data fra SOLO-1 studiet, som har medført at behandlingsvejledningen (Medicinrådet) for BRCAm patienter anbefaler at 2 års vedligeholdelses behandling med olaparib anvendes til 90% af populationen. Denne beslutning understøttes nu af follow-up data fra SOLO-1 studiet præsenteret på ESMO 2020. Efter 5 års follow-up demonstreres en median PFS på 56,0 måneder ved 2 års behandling med olaparib sammenholdt med en median PFS i kontrolarmen (placebo) på 13,8 måneder givende en behandlingsgevinst på ~3,5 år med en HR på 0,33 (95% CI 0.25–0.43) [6].

At selektere patienter på baggrund af denne genetiske information har vist sig afgørende for behandlingsresultatet for disse patienter og dermed også for introduktionen af *Personlig Medicin* i behandling af ovarie cancer.

Resultaterne fra PAOLA-1 demonstrerer tillige, at patienter med homolog recombinationsdefekt har en klinisk relevant behandlings gevinst ved tillæg af olaparib til behandling med bevacizumab. For populationen af patienter værende HRD+ men ikke tBRCAm, og dermed ikke omfattet af nuværende behandlingsvejledning, fandtes en forbedring i median PFS ~12 måneder med 26 procentpoints forbedring af 2-års PFS rate.

PAOLA-1 studiet er ikke designet til at adressere klinisk spørgsmål 1. Derved beror analysen af data på indirekte sammenligninger mellem SOLO-1 og PAOLA-1 studiet. Denne analyse begrænses af kortere follow-up i PAOLA-1 studiet. Naive sammenligninger mellem higher-risk og lower-risk BRCAm populationer i de to studier kunne indikere en synergistisk effekt i lower-risk populationen på baggrund af en forbedring i PFS rate ved 2 år på 15 procentpoint og en HR på 0.11(95% CI 0,03-0,31).

PAOLA-1 studiet demonstrerede tillige, at der ikke var signifikant behandlingsmæssig gevinst ved tillæg af olaparib til bevacizumab for gruppen af patienter værende HRD negative eller unknown (HR 0.92 95% CI 0.72, 1.17). Dette understreger behovet for nødvendigheden af at selektere de rigtige patienter til den rigtige behandling.

I PAOLA-1 studiet udnyttede man Myriads MyChoice test til at bestemme patienternes homolog recombinations-defekt status. Denne test har været anvendt i en række studier i 2. linje samt andre 1. linje studier, med varierende resultat i forhold til at prædiktere effekt af PARPi. To faktorer relevante for PALOA-1 studiet kan diskuteres som mulige årsager til at man i PAOLA-1 studiet fandt at Myriads MyChoice test klart prædikterer behandlingsresultat.

- Patientpopulationen i PAOLA-1 studiet var ikke præ-selekteret på baggrund af respons til platinholdig kemoterapi

- Tillæg af olaparib var bedømt mod en aktiv komparator bevacizumab

AstraZeneca finder det for nærværende ikke muligt at præcisere den diskussion, men kan konkludere at Myriad MyChoice testen i PAOLA-1 studiet prædikterer effekten af tillæg af olaparib til bevacizumab.

AstraZeneca arbejder for nærværende på 3 projekter, der skal sikre lokal adgang til test for homolog recombinations-defekt:

- Facilitere opsætning af lokalt Myriad satellitlaboratorium, der kan udføre Genomis Instability Score (GIS) analyse og i samarbejde med Myriad kan bestemme patienternes HRD score. BRCA test udføres efter gældende standarder i Danmark

- På Nordisk plan supportere udvikling af lokal HRD test, der valideres mod Myriad MyChoice test. Dette projekt er pågår med deltagelse af danske laboratorier

- På Nordisk plan at støtte forskningsprojekter, der dels sikre et datagrundlag for yderligere klinisk validering af de udviklede lokale test, men også genererer Real World data på subgrupper af patienter defineret på baggrund af GIS (HRD status). Dette projekt forhandles i øjeblikket

4 Literature search

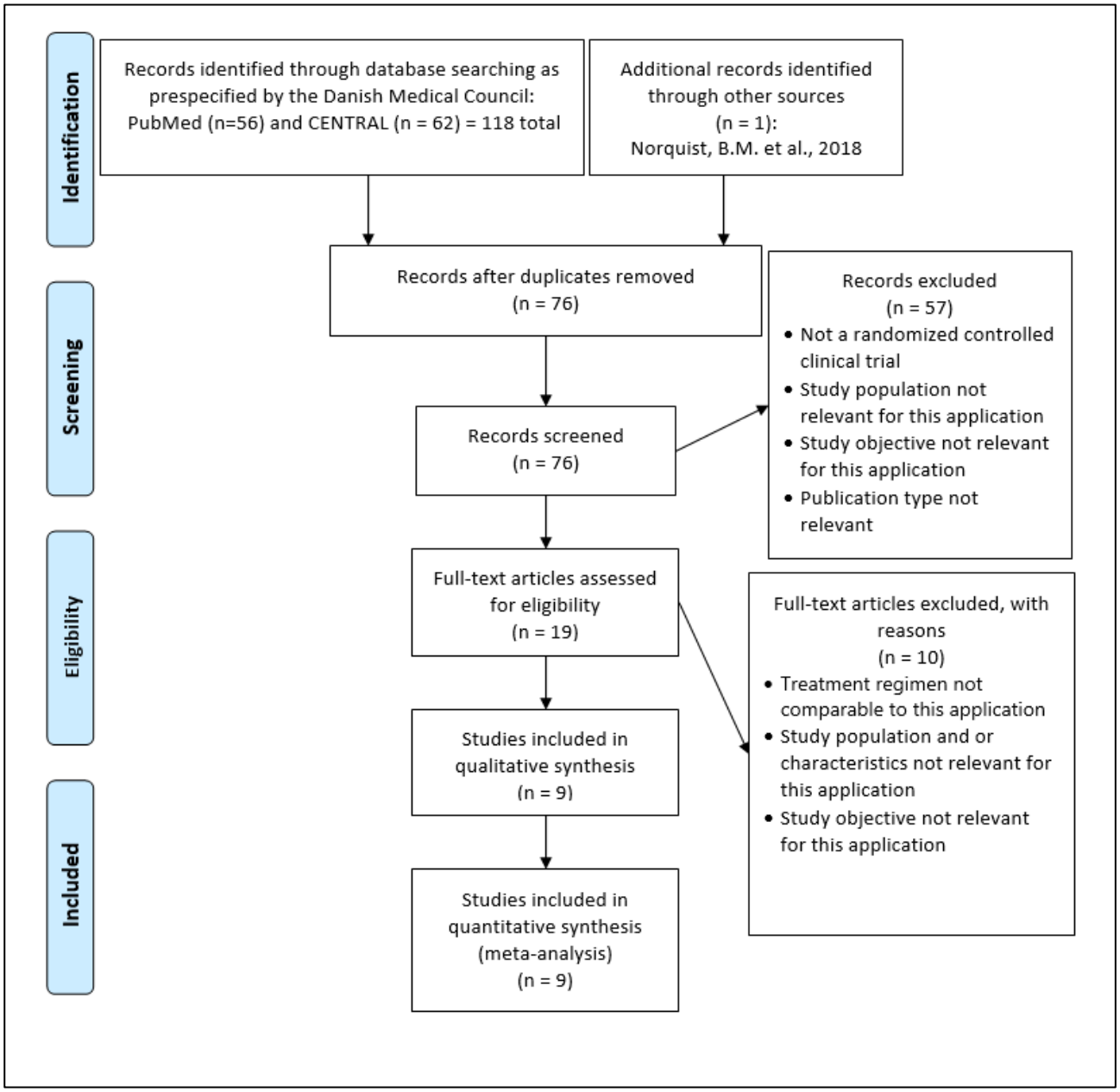
We received the following search guide from Medicinrådet:

Table 4. Search guide Medicinrådet

Sæt	Søgetermer	Kommentarer
1	Ovarian Neoplasms[mh]	Termer for population
2	(ovary[ti] OR ovari*[ti]) AND (cancer[ti] OR carcinoma*[ti] OR neoplasm*[ti] OR tumor*[ti] OR tumour*[ti])	
3	Fallopian Tube Neoplasms[mh]	
4	(fallopian tube*[ti] OR tubal[ti] OR oviduct[ti] OR tuba[ti]) AND (cancer[ti] OR carcinoma*[ti] OR neoplasm*[ti] OR tumor*[ti] OR tumour*[ti])	
5	Peritoneal Neoplasms[mh]	
6	(peritoneal[ti] OR peritoneum[ti] OR serous surface papillary[ti] OR extra-ovarian serous[ti] OR primary serous papillary[ti]) AND (cancer[ti] OR carcinoma*[ti] OR neoplasm*[ti] OR tumor*[ti] OR tumour*[ti])	
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	
8	newly diagnosed[tiab]	
9	1L[tiab] OR firstline[tiab] OR first-line[tiab] OR frontline[tiab] OR front-line[tiab] OR primary treatment[tiab] OR primary therapy[tiab]	
10	#7 AND (#8 OR #9)	
11	olaparib[nm] OR olaparib[tiab] OR Lynparza*[tiab] OR Bevacizumab[mh] OR bevacizumab[tiab] OR Avastin*[tiab] OR Mvasi*[tiab] OR HRD[tiab] OR homologous recombination[tiab]	Termer for lægemidler og HRD defekt
12	#10 AND #11	Kombination population og lægemidler
13	Randomized Controlled Trial[pt] OR Controlled Clinical Trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR Clinical Trials as Topic[mh:noexp] OR randomly[tiab] OR trial[ti]	Filter til identifikation af randomiserede forsøg
14	#12 AND #13	
15	Animals[mh] NOT Humans[mh]	Eksklusion af dyr og irrelevante pub.typer
16	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR case report[ti]	
17	Review[pt] OR Systematic Review[pt] OR Meta-Analysis[pt] OR review[ti] OR meta-analys*[ti]	
18	#15 OR #16 OR #17	
19	**#14 NOT #18**	**Resultater til screening - alle kliniske spørgsmål**

The literature search and included/excluded studies are described in details in a separate document enclosed with the application. The search revealed 12 full publications that can be used in answering the 3 clinical questions plus supplementary questions. The Prisma diagram is shown in figure 3.

Figure 3. Prisma diagram



4.1 Relevant studies

Table 5. Relevant studies/publications

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
1)Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. K. Moore, N. et al. N Engl J Med 2018; 379:2495-2505 [7] 2)DiSilvestro, P., et al. (2020). "Efficacy of Maintenance Olaparib for Patients With Newly Diagnosed Advanced Ovarian Cancer With a BRCA Mutation: Subgroup Analysis Findings From the SOLO1 Trial." J Clin Oncol **38**(30): 3528-3537' [8]	SOLO-1	NCT01844986	Enrolment between August 2013 and May 17th 2016. Subgroup update 2020 by Di Silvestro et al. 2020 [8]	Overall survival, progression free survival, Discontinuations, AE grade 3 or more and HQoL.
Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer Ray-Coquard I, et al. *N Engl J Med* 2019;381:2416–28 [3]	PAOLA-1	NCT02477644	Inclusion between July 2015 and September 2017	Overall survival, progression free survival, Discontinuations, AE grade 3 or more and HQoL
1)Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med.* 2011;365(26):2473-2483 [9] 2) Mutations in Homologous Recombination Genes and Outcomes in Ovarian Carcinoma Patients in GOG 218: An NRG Oncology/Gynecologic Oncology Group Study. Norquist BM, Brady MF,	GOG-0218 a phase III, randomized trial of bevacizumab in women with newly diagnosed ovarian, fallopian tube, or primary peritoneal carcinoma.	NCT00262847	October 2005 to June 2009. Bevacizumab 15 mg/kg The trial included 1,873 patients OS update by Tewari et al. 2019 [12] HRR mutation outcome, Norquist et al. 2018 [10] PRO update, Monk 2013 [11]	Overall Survival. Progression Free Survival, AE grade 3 and more

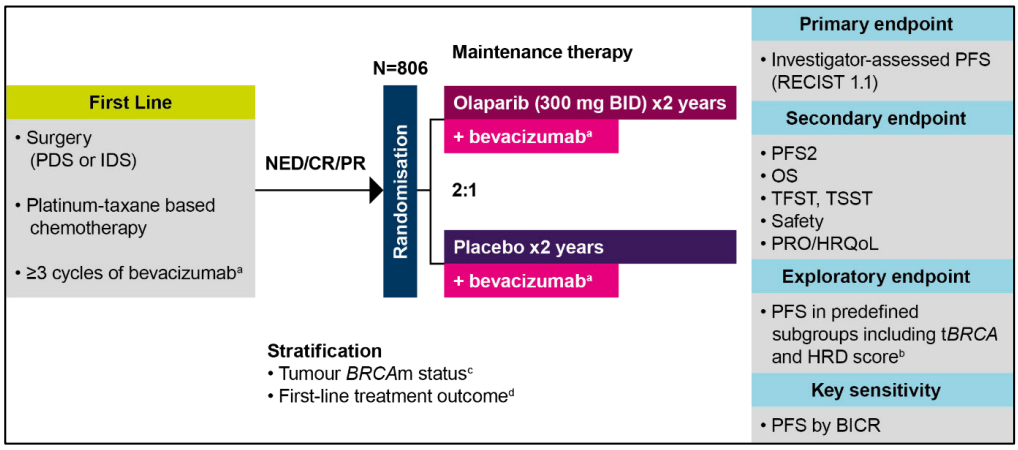
Harrell MI, et al. Clin Cancer Res. 2018 [10] 3) Patient reported outcomes of a randomized, placebo-controlled trial of bevacizumab in the front-line treatment of ovarian cancer: a Gynecologic Oncology Group Study. Monk BJ, Huang HQ, Burger RA, et al. Gynecol Oncol. 2013 [11]				
1) A phase III trial in Ovarian Cancer. Timothy J. Perren, et al. N Engl J Med 2011; 365:2484-2496 [13] 2) Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial.. Oza AM, Cook AD, Pfisterer J, et al. Lancet Oncol. 2015 [14]	ICON7	ISRCTN91273375.	December 2006 to February 2009. 1528 patients randomized. Bevacizumab: 7.5 mg per kilogram of body weight, given concurrently every 3 weeks OS update by Oza et al. 2015 [14]	Overall survival, progression free survival, Grade 3 AEs

4.2 Main characteristics of included studies

4.2.1 PAOLA-1

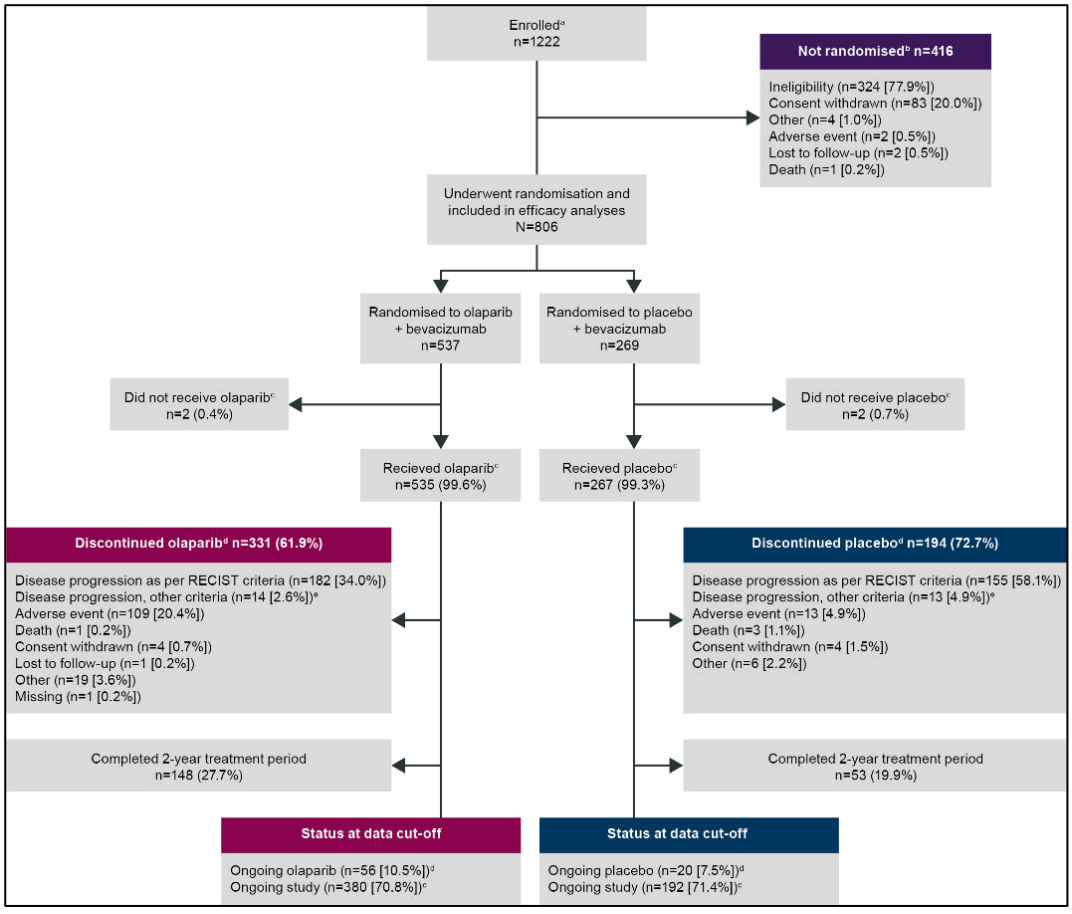
The PAOLA-1 study demonstrates that olaparib in combination with bevacizumab has a positive benefit-risk profile for the maintenance treatment of patients with newly diagnosed AOC which is in response to 1L chemotherapy consisting of platinum-taxane and bevacizumab. PAOLA-1 met its primary objective, demonstrating a statistically significant and clinically meaningful improvement in PFS for olaparib + bevacizumab (median 22.1 months) over placebo + bevacizumab (median 16.6 months) in the ITT population. This PFS benefit was seen across subgroups, including HRD+ patients, as well as by stratification factors (including 1L treatment outcome [NED, CR and PR] and t*BRCA* status) and pre-defined clinical characteristics. Based on KM estimates, 46% of olaparib + bevacizumab-treated patients remained progression-free at 24 months, compared to 27.7% of placebo + bevacizumab-treated patients in the ITT population [3]. Design and patient disposition are shown below(figure 4,5).

FIGURE 4. DESIGN OF THE PAOLA-1 TRIAL



SOURCE: RAY-COQUARD ET AL. 2019, ESMO CONGRESS PRESENTATION [15, 16].

FIGURE 5. PATIENT DISPOSITION (ALL PATIENTS)



Source: *AstraZeneca Data on File [17].*

PAOLA-1 is a Phase III double-blind, placebo-controlled, multicentre randomised controlled trial (RCT) (NCT02477644) examining the clinical benefit of adding olaparib to 1L maintenance therapy in patients with

newly diagnosed AOC with or without *BRCA*m, which is in response to platinum-based chemotherapy with bevacizumab [18].

Olaparib or placebo treatment continued for 24 months. As per marketing authorisation, bevacizumab was administered for up to 15 months, including the period pre-randomisation in combination with platinum-based chemotherapy.

The **primary endpoint** was PFS, assessed by investigators. **Secondary endpoints** include OS, TFST and PFS2.

PAOLA-1 randomised 806 patients to the two treatment arms (2:1 olaparib + bevacizumab, placebo + bevacizumab), stratified by 1L treatment outcome and tumour BRCA (tBRCA) status [16, 19]. Patient demographics and baseline characteristics, including t*BRCA* status, were well balanced between treatment arms. After randomisation, HRD status was determined using the Myriad myChoice® HRD plus test.

The median duration of follow-up was 22.7 months for the olaparib + bevacizumab arm and 24.0 months in the placebo + bevacizumab arm [3].

In this application we refer to first DCO which is March 2019 and second DCO is March 2020.

Generalisability of PAOLA-1:

PAOLA-1 was a robust, double-blinded, randomised placebo-controlled trial that was conducted to a high standard. Patients included in the study were representative of the broader AOC population, including by tumour stage and grade, and were unselected by biomarker status or 1L surgical outcome.

Given the population in PAOLA-1 is representative of the real-word AOC population, it is anticipated that similar gains in PFS as were captured in the PAOLA-1 study will be observed in clinical practice when olaparib is added to bevacizumab for 1L maintenance therapy in AOC.

As a non-investigational study treatment, bevacizumab was administered according to its marketing authorisation, making this regimen generalisable to a number of different settings.

The PFS benefit observed in PAOLA-1 is unprecedented for a population of women who have not been selected by surgical outcome or biomarker status. As a high proportion of AOC patients relapse and eventually become resistant to platinum-based chemotherapy, this significant increase in patients remaining progression-free highlights the capacity of olaparib to maintain patients free of relapse long-term and postpone further rounds of chemotherapy. No clinically meaningful differences in HRQoL were observed between patients in the olaparib + bevacizumab arm compared with the placebo + bevacizumab arm. This demonstrates that olaparib added to bevacizumab does not have a detrimental effect on HRQoL compared to placebo + bevacizumab. Finally, the safety outcomes were consistent with the known safety profiles of olaparib and bevacizumab and no new safety signals were identified.

The number of important protocol deviations in PAOLA-1 was low (6.0%) and the treatment arms were well balanced with respect to the percentage of patients with important protocol deviations and early censoring [3]. These are therefore unlikely to have influenced the study conclusions. In addition, PFS was assessed both by investigators and by BICR, as a sensitivity analysis. The degree of discordance between investigator and BICR assessments of disease progression reported in this study (18%) was favorable in comparison to that observed in previous ovarian cancer clinical trials [20-22]. This demonstrates the robustness of the study conclusions.

In PAOLA-1, patient demographics and baseline characteristics, were well balanced between the study arms. Patients included in the study were representative of the broader AOC population: patient characteristics for the ITT population were reflective of those typically seen in the overall patient population targeted by the PAOLA-1 trial, including tumour stage and grade. Patients in the PAOLA-1 trial were accordingly unselected by mutation status or surgical outcome. The majority of patients were FIGO Stage IIIC and had HGS histology, as expected for patients with newly diagnosed advanced epithelial ovarian cancer; 30% of patients overall were Stage IV [3]. The generalisability of PAOLA-1 is further enhanced through use of the licensed dose of bevacizumab, with a similar treatment duration to that observed in clinical practice [23], and the fact that the population falls within that of the bevacizumab regulatory label; identification of relevant patients for this regimen can therefore be based on standard clinical practice.

4.2.2 SOLO-1

SOLO1 is a Phase III, randomised, double-blind, placebo-controlled, multicentre study to assess the efficacy of olaparib as maintenance monotherapy in newly diagnosed advanced OC patients (including patients with primary peritoneal and/or fallopian tube cancer) with BRCA mutations (documented mutation in *BRCA*1 or *BRCA*2) that were predicted to be loss of function mutations (known or predicted to be detrimental/lead to loss of function) who were in response following platinum-based chemotherapy. Study treatment continued until investigator-assessed objective radiological disease progression (RECIST version 1.1 criteria), provided patients were experiencing benefit and did not meet other discontinuation criteria. Patients with no evidence of disease at two years stopped treatment. Patients who continued to have evidence of disease that remained stable (i.e., not progressed) at 2 years could continue to receive study treatment if, in the opinion of the investigator, it was in the patient's best interest. However, if at 2 years the patient had no evidence of disease (NED), study treatment was discontinued.
The primary objective of SOLO1 was to determine the efficacy by PFS (objective radiological disease progression as per RECIST 1.1 as assessed by the investigator) of olaparib compared with placebo in newly diagnosed BRCAm advanced OC patients who were in clinical CR or PR following first-line platinum-based chemotherapy.

The secondary objectives of SOLO1 were:

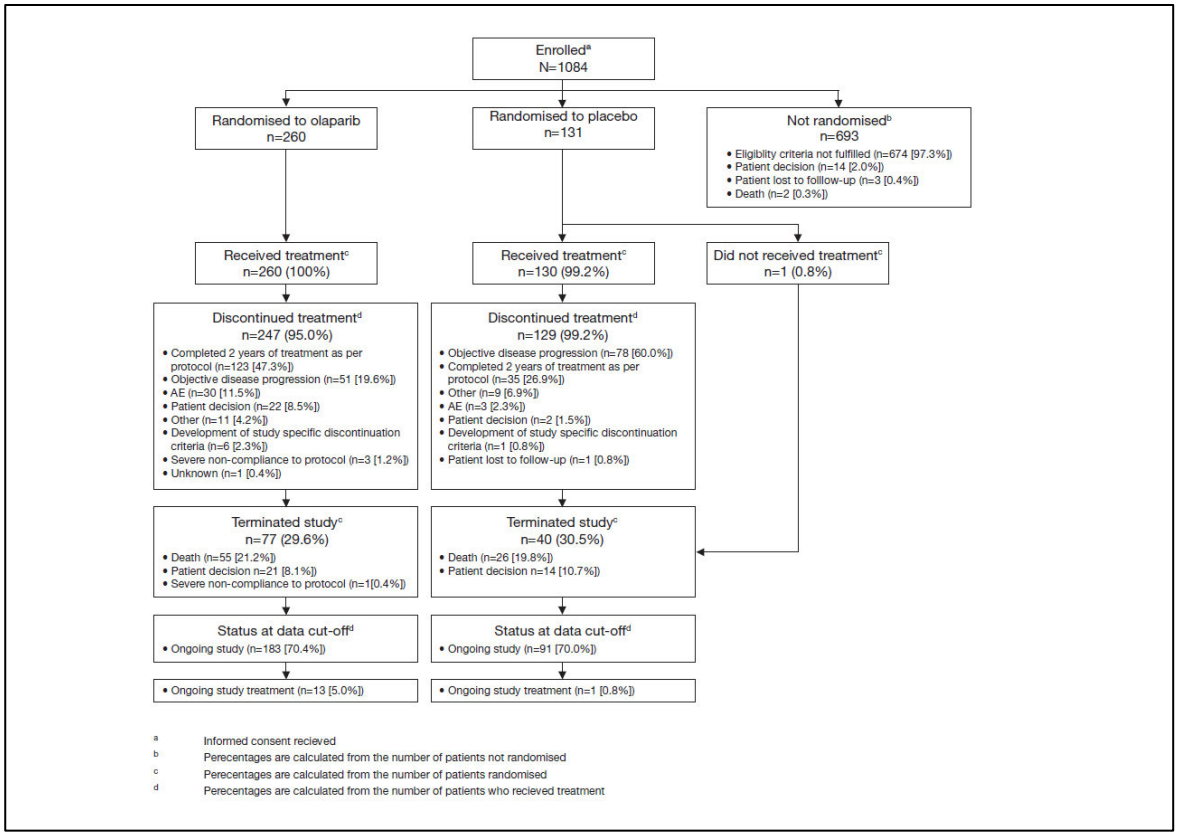
- Comparison of olaparib with placebo by assessment of OS, time to earliest progression by RECIST or cancer antigen-125 (CA-125), or death, and time from randomisation to second progression (PFS2)
- Comparison of olaparib with placebo by TFST, TSST and time to discontinuation of treatment (TDT)
- Effect of olaparib on Health-related quality of life (HRQoL) as measured by the Trial Outcome Index (TOI), of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O)

In total, 1084 patients were enrolled into the study, but 693 patients were not randomised as they did not meet the eligibility criteria [7] . Of the 391 patients randomised into the study, all patients received their allocated treatment except one patient who received no treatment in the placebo arm due to withdrawal (figure 6) [7].

A SOLO-1 update at ESMO 2020 showed that after 5 years on olaparib treamtment, 48.3% patients had no disease progression and were still living with stable disease vs 20.5% of those who received placebo. The results showed that the women treated with olaparib for 2 years following standard treatment had 56

progression free months, compared with 13.8 months for the individuals receiving standard treatment only referring to the placebo arm of the SOLO-1 study [24].

Figure 6. SOLO1 patient disposition



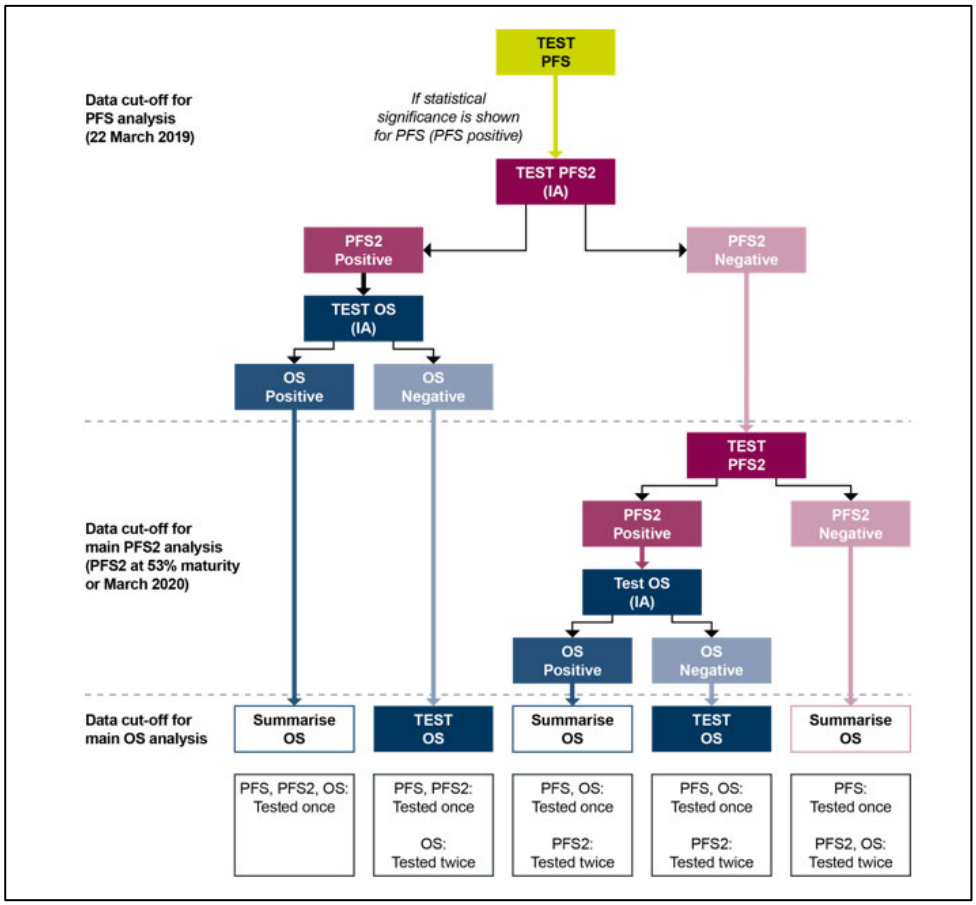
Source: AstraZeneca Data on File [17].

For full patient characteristics see SOLO-1 in Table A2. Also for details on ICON-7 and GOG-218 studies.

4.2.3 Data cut off(DCO) in PAOLA study

In the PAOLA study data was based on DCO March 2019. In the application we also show data from the DCO in March 2020. Median follow up for PFS DCO March 2019 is 22.7 m in (olaparib + o) and 24.0 m (placebo + olaparib). At DCO2 median follow-up was 36.4 m and 38.7 m

Figure 7. Hierarchical testing strategy employed and DCOs in PAOLA-1



Source: *AstraZeneca Data on File [17].*

5 Background information on bevacizumab and high and low risk patient definitions

In 2012, bevacizumab, in combination with carboplatin and paclitaxel, and continued as maintenance therapy, was approved by the National Board of Health for the first-line treatment of advanced ovarian cancer patients who have increased risk profile being defined as:

- FIGO Stage III ovarian cancer, with residual disease following primary debulking surgery, OR
- FIGO Stage III ovarian cancer, with residual disease following NACT and Interval debulking surgery, OR
- FIGO Stage IV disease, OR
- Inoperable FIGO Stage III/IV

The approved dosage and schedule were 15 mg/kg q3w starting from cycle 2 continuing for a total of 15 months and were based on results from two large randomized phase III trials assessing the efficacy and

safety of bevacizumab (in combination with carboplatin and paclitaxel, followed by a maintenance period with bevacizumab) for newly diagnosed patients with ovarian, primary peritoneal or fallopian tube cancer.

- The GOG-218 trial assessed patients with newly diagnosed stage III (incompletely resectable) or stage IV epithelial ovarian cancer who had undergone debulking surgery. Patients received one of three treatments
    - Bevacizumab treatment concurrent to Chemotherapy – no maintenance (15 mg/kg bevacizumab added in cycles 2 through 6 plus carboplatin and paclitaxel)
    - Bevacizumab treatment concurrent to Chemotherapy – followed by Bevacizumab maintenance **(15 mg/kg bevacizumab added in cycles 2 through 22** plus carboplatin and paclitaxel cycle 1 through 6)
    - Placebo (carboplatin and paclitaxel alone) [9]
- The ICON-7 trial assessed the addition of bevacizumab **(7.5 mg/kg for 18 cycles)** to carboplatin and paclitaxel, followed by bevacizumab maintenance therapy for 12 additional cycles or until disease progression. In ICON7 a predefined patient group (n=465) - characterized as FIGO stage III with >1cm residual tumor and stage IV – had special interest due to increased risk for progression hence impacting prognosis [13]

In both trials, result demonstrated that Bevacizumab treatment concurrent to Chemotherapy – followed by Bevacizumab maintenance significantly extended PFS in the ITT population:

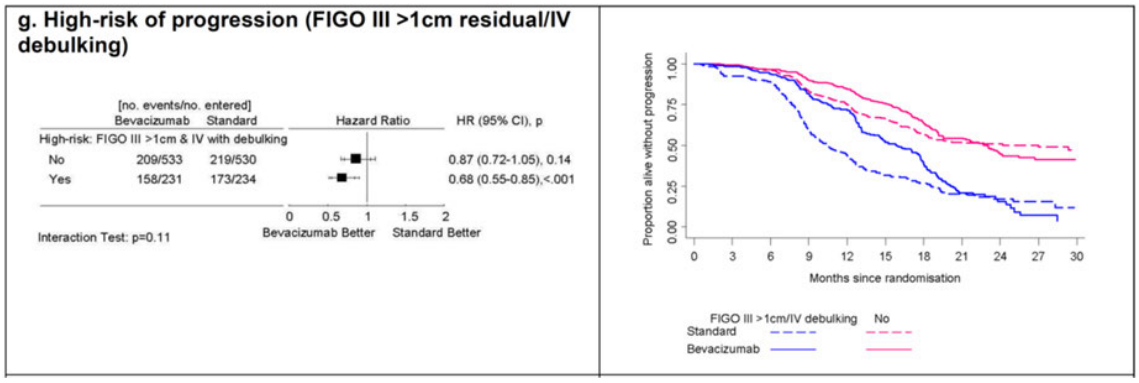
- GOG-218: 14.1 months vs 10.3 months; HR 0.72; 95% CI, 0.625, 0.824; p<0.001 [9]
- ICON-7: 19.0 months vs 17.3 months; HR 0.81; 95% CI, 0.70, 0.94; p=0.004 [13]

Results for the pre-defined High-risk subgroup suggested a greater treatment benefit when adding bevacizumab (figure 8).

- ICON-7 (high-risk): 15.9 months vs 10.5 months; HR 0.68; 95% CI, 0.55, 0.85; p<0.001

A post-hoc OS analysis further demonstrated a median overall survival gain of 7.8 months (36.6 months vs 28.8 months) in the pre-defined high-risk group (HR=0.64; p=0.002). In an update analysis of OS data from ICON-7, the survival advantage were 4.8 months (39.3 months vs 34.5 months), whereas no survival advantages where seen in the ITT population [14].

Figure 8. OS high risk subgroup adding bevacizumab



Source: Oza, A. M., et al., 2015 [14].

Based on the above results and recommendation from National Board of Health, the DGCG Ovarian Cancer Group has stated that they consider 7.5 mg/kg and 15 mg/kg equivalent and recommends a treatment length for a total of 15 months [25].. Based on feedback from various departments in Denmark it is Applicants view that variation exist with regards to chosen dosage at individual oncology departments in Denmark.

Globally and within Europe, the interpretation of the result from GOG-218 and ICON-7 has led to significant variation in current bevacizumab treatment patterns. Not only reflecting variation in terms of recommended dosage and schedule, but also the population(s) being candidates for 1L bevacizumab treatment.

In the PAOLA-1 study sponsored by ARCAGY Research, bevacizumab was **not** considered an "investigational" treatment **but** considered an active comparator reflecting clinical practice in countries (e.g. in France), where "higher-risk" restrictions haven't been implied on bevacizumab utilization.

This leads to two considerations for this applications:

1. Data from subgroup analysis of the PAOLA-1 dataset, where the ITT population were split in a **higher-risk** patient population (FIGO stage III disease with upfront surgery and residual disease or NACT, or FIGO stage IV disease) and **lower-risk** patient population (FIGO stage III disease with upfront surgery and complete resection) were presented at IGCS 2020. These subgroup analysis constitute the data base for addressing Clinical question 2 and 3 hence raising the question of potential concordance between the above definition of subpopulation, and the definition of the population defined in clinical question 2 and 3?

2. In the PAOLA-1 study, the subgroup of patients being defined as having a lower-risk of progression, received an active comparator, which is not defined as standard of care in Denmark, thereby raising two questions related to efficacy and toxicity

    a) Does data from ICON7 suggest that placebo performs better than bevacizumab in the population not being defined as high-risk in this study?

    b) Toxicity: Will potential additional toxicity - as a consequence of combination treatment - be underestimated when comparing against an active comparator not currently applicable in clinical practice in Denmark?

With regards to 1:

According to Nordcan approximately 550 patients are diagnosed with ovarian cancer annually in Denmark [2] with ~90% being of epithelial origin [26]. Data from DGCG database estimates that ~80% of the epithelial carcinomas are high-grade with ~68% being stage III-IV, hence estimated that a total population of 269 Stage III-IV high-grade epithelial OC patients are diagnosed annually in Denmark.

Based on current Bevacizumab eligibility criteria and data for surgical outcome in DGCG database [27] AstraZeneca estimate that ~54% of the overall population of newly diagnosed high-grade epithelial Stage III-IV Ovarian Cancer patients currently meet the eligible criteria for bevacizumab treatment in Denmark (assuming other eligibility criteria are met and treatment is considered appropriate by the treating clinician) (table 6).

Table 6: Estimation of proportion of ovarian cancer patients being eligible for bevacizumab treatment in Denmark

	N	% OF STAGE III-IV HIGH-GRADE EPITHELIAL OC*	ELIGIBILITY TO BEVACIZUMAB
STAGE IV	73	27	**146 of 269 (~54%) meets current eligibility criteria**
INOPERABLE	32	12	
STAGE III, NACT + IDS, RESIDUAL	22	8	
STAGE III, PDS, RESIDUAL	19	7	
STAGE III, NACT + IDS, NO RESIDUAL DISEASE	38	14	**116 of 269 (~43%) do not meet current eligibility criteria**
STAGE III, PDS, NO RESIDUAL DISEASE	78	29	
NO TREATMENT	8	3	**3% receives no treatment**

**According to NORDCAN total* [2].

Discrepancy exist between the "higher-risk and lower-risk" definition in PAOLA-1 subgroup analysis and the population criteria for clinical question 2 & 3, when it comes to the subgroup of patients being defined as Stage III patients with no residual disease following Interval Debulking Surgery.

This specific group of patients constitute 20% (n=161) of the ITT population in PAOLA-1 with the HRD+ ex tBRCAm constituting 19% of the ITT population. It is estimated that this subgroup account for 14% of a Real-World population in Denmark.

For the overall HRD+ positive group excluding tBRCAm in PAOLA-1 the following benefit of adding olaparib to bevacizumab were observed:

- HR 0.43 (95% CI 0.28-0.66)
- 11.5 months improvement in mPFS (28.1m vs 16.6m)
- 26 percent point improvement in landmark PFS at 24 months (52% vs 26%)

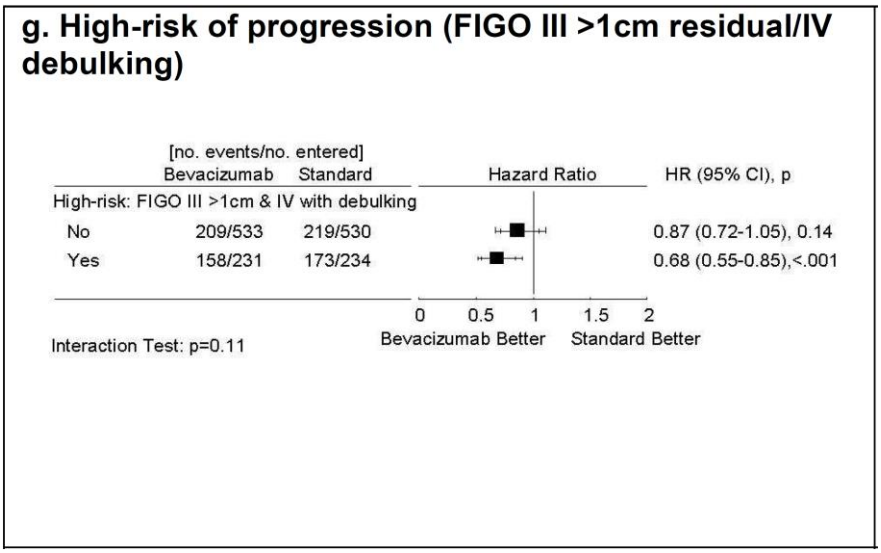
For this application specific analysis of the subgroup of Stage III patients with no residual disease following Interval Debulking Surgery have not been performed. It is therefore not possible for applicant to assess to which extent the result discussed for clinical question 2 & 3 would have been affected by relocating this specific subgroup to the defined **"lower risk"** subgroup.

With regards to 2:

A HR of 0,87 (0,72 – 1,05) p=0,14 for the non-high-risk patients in ICON7 (figure 9) suggests no detrimental effect of the addition of bevacizumab **(7.5 mg/kg for 18 cycles)** to carboplatin and paclitaxel, followed by bevacizumab maintenance therapy compared to placebo.

In the opinion of AstraZeneca these data support that the efficacy signal observed for the lower-risk segment in PAOLA haven't been enhanced by an underperforming control arm, hence justifiable to utilize the observed data from PAOLA-1 to assess clinical question 3 with regards to efficacy.

Figure 9. Low risk ICON7

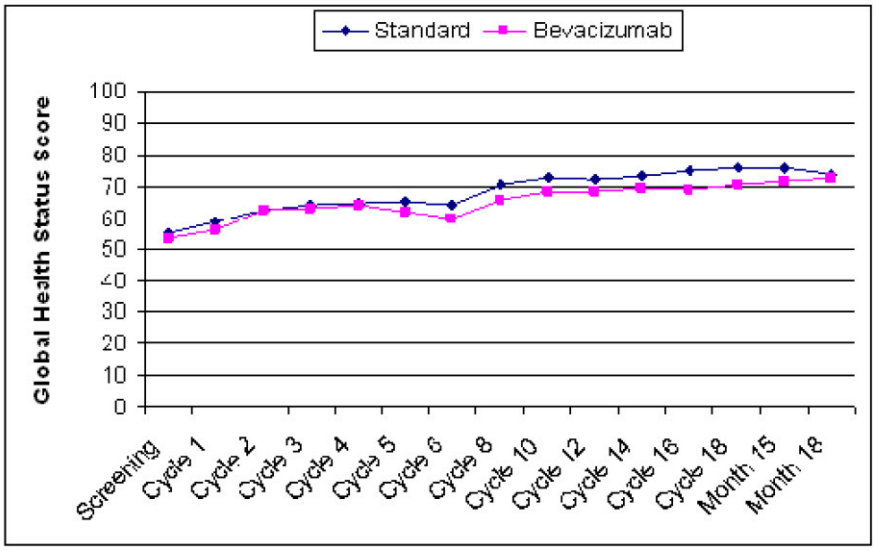


Source: Perren, T. J., et al. , 2011, supplementary appendix [13].

In ICON 7, adverse events of grade 3 or higher were reported in 56% of women in the standard-therapy group and in 66% of the women in the bevacizumab group.

Both treatment groups in ICON7 showed improvement in global quality of life over time; although differences between the two groups were consistently present, these were small and not considered to be clinically significant (i.e., there was less than a 10-point difference).

Figure 10. HQoL bevacizumab vs placebo



Source: Perren, T. J., et al. , 2011, supplementary appendix [13]

AstraZeneca finds it likely that the observed toxicity signal in PAOLA-1 underestimates the actual difference if the combination of olaparib + bevacizumab were to be compared with placebo as relevant for clinical question 3.

6 Questions 1. Olaparib plus bevacizumab vs. olaparib in BRCAm

6.1 OS vs olaparib in the BRCAm population

This section contains data that are to be considered confidential. It is marked with [redacted]

6.1.1 Comparative analyses median OS and OS rate at 5 years

There are no olaparib monotherapy arm in the PAOLO-1 study and a patient adjusted indirect comparison (PAIC) has been conducted with the SOLO1 study based on PFS, but not OS due to immature data as described below.

SOLO-1 BRCAm population:

At the time of the DCO (17 May 2018), the survival follow-up showed that 70.4% of patients in the olaparib arm and 69.5% of patients in the placebo arm were alive [7]. The interim OS data were however immature (82/391 events, 21.0% maturity) and showed no significant difference between the groups (HR 0.95; 95% CI 0.60, 1.53; *P*=0.8903) with median OS not reached in either group [28]. The HR suggested no OS detriment for patients in the olaparib arm. Final OS analysis will be conducted at approximately 60% maturity (approximately 206 events) and is expected to be in 2023 +/- 2 years.

PAOLA-1 HRD+ population

OS data(DCO March 2019) in the HRD+ patients of the ITT population as relevant for this application had reached 16.3% maturity at the first DCO, with a greater proportion of deaths occurring in the placebo plus bevacizumab arm. Median OS was not reached with either arm. As for the SOLO-1 study, next OS analysis for PAOLA-1 will be conducted at 60 % maturity.

In the **HRD+** population at the first DCO March 2019 the HR was 0.55(table 7) but the median OS was not reached.

TABLE 7. OS FOR THE **HRD+** POPULATION AT THE FIRST DCO MARCH 22ND 2019

	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
OS (16.3% mature)		
Events, n (%)	35 (13.7)	28 (21.2)
Median follow-up (IQR), months	27.7 (22.9, 32.3)	26.4 (23.3, 31.3)
Median OS[a] (95% CI), months	Not reached (Not reached, Not reached)	Not reached (Not reached, Not reached)
HR[b] (95% CI; p [2-sided][c])	0.55 (0.33, 0.92; 0.0189)	

The March 2020 DCO OS update in the HRD+ and BRCAm population are show below(figure 11,12). Median follow-up is 39 and 38.7 months

Source: AstraZeneca data on file [29].

Source: AstraZeneca data on file [29].

EPAR:

The ITT interim OS follow-up analysis is considered extremely immature (209 events; 25.9% mature) with a similar proportion of patients in the olaparib/bevacizumab arm and in the placebo/bevacizumab arm (70.8% vs 71.4% respectively). The median OS was 39.4 months in the olaparib/bevacizumab arm and was not reached in the placebo/bevacizumab arm with a HR of 1.01 (95% CI 0.76, 1.36, *p*=0.9270). At the DCO of 30 September 2019, the updated OS analysis shows a HR of 0.94 (95% CI 0.73 to 1.21) in the ITT population. In the tBRCAm subgroup based on test result at randomisation, the OS HR point estimate was reported as 0.66 (95% CI 0.37 to 1.21), while in non-tBRCAm subgroup it was 1.02 (95% CI 0.77 to 1.36). In line with analysis in these prospectively defined subgroups(DCO 30 September 2019), exploratory subgroups by mutation status determined retrospectively by Myriad test showed an OS HR point estimate of 0.61 (95% CI 0.34 to 1.09) in the Myriad tBRCAm subgroup while it was 1.04 (95% CI 0.77 to 1.4) in the non-tBRCAm subgroup [30].

6.1.2 Conclusion median OS and OS rate at 5 years vs. olaparib BRCAm

Both PAOLA1 and SOLO1 show immature OS data and we can currently not draw any conclusion around the OS benefit of adding bevacizumab to BRCAm patients with high-grade, platins sensitive OC. In the BRCAm population as included in the HRD+ group of the PAOLA1 study there is a separation of the curves but as stated no conclusion can be made based on immature data when compared with olaparib monotherapy (SOLO1).

Source: AstraZeneca data on file [29]

In the BRCAm population the combination of olaparib plus bevacizumab cannot show 4 month or 5% difference in survival rate vs olaparib monotherapy due to lack of maturity of the data in both populations.

6.2 PFS vs olaparib in BRCAm

6.2.1 Comparative analyses median PFS and PFS rate at 2 years

The effect of combining olaparib with bevacizumab in women with tBRCAm was substantial (HR 0.31; 95% CI 0.20 to 0.47]), and consistent with the relative effect for olaparib versus placebo seen in SOLO-1 (HR 0.30; 95% CI 0.23 to 0.41). This despite the improvement in the outcomes of the control group in PAOLA-1 likely due to the addition of bevacizumab or to differences in patient selection between the studies.

A naïve comparison of the result from PAOLA-1 and SOLO-1 with data split according to "higher-risk" and "lower-risk" definition reveals that for PFS rate at 24 months a 15 percent point differences in favour of addition of bevacizumab to olaparib excist compared to no difference when adding bevacizumab to placebo. In addition, the subgroup data reveal a HR of 0,11 (0,03-0,31) in the PAOLA-1 subset versus a HR of 0,33 (0,20-0,52) in the SOLO-1 subset all in all suggesting a potential synergistic effect of adding bevacizumab to olaparib.

For the higher risk subgroups identical HR were observed and with a maximal numerical difference of 7% percent point observed at 12 months this could suggest that an additive effect is seen whit the addition of bevacizumab to olaparib (table 8,9)

Table 8. PFS rate PAOLA-1 vs SOLO1

Naïve Comparison – SOLO-1 and PAOLA-1			
12 Months	PFS rate (%)	PFS rate (%)	Δ PFS
SOLO-1	88	51	37
PAOLA-1	94	76	18
Δ PFS	6	25	
24 Months			Δ PFS
SOLO-1	74	35	39
PAOLA-1	76	39	37
Δ PFS	2	4	

Table 9. PFS rate higher-risk and lower-risk subgroup

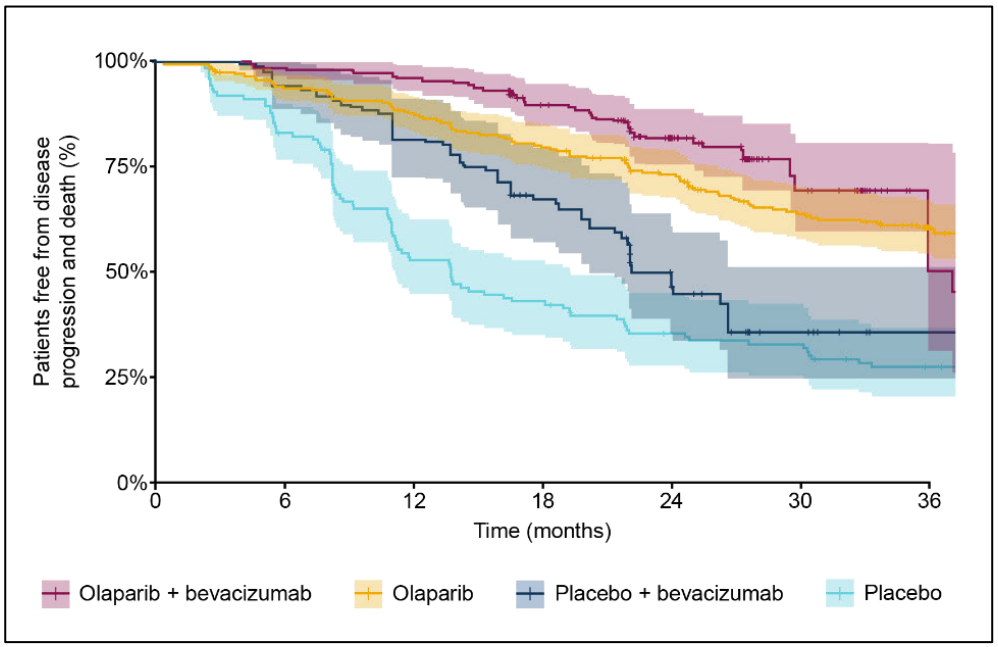
Naïve Comparison – SOLO-1 and PAOLA-1 Lower risk segment				**Naïve Comparison – SOLO-1 and PAOLA-1 Higher risk segment**			
HR	SOLO-1	0,33 (0,20-0,52)		HR	SOLO-1	0,34 (0,24-0,48)	
	PAOLA-1	0,11 (0,03-0,31)			PAOLA-1	0,37 (0,23-0,59)	
12 Months	PFS rate (%)	PFS rate (%)	Δ PFS	12 Months	PFS rate (%)	PFS rate (%)	Δ PFS
SOLO-1	92	66	26	SOLO-1	85	40	42
PAOLA-1	98	83	15	PAOLA-1	92	72	20
Δ PFS	6	17		Δ PFS	7	32	
24 Months			Δ PFS	24 Months			Δ PFS
SOLO-1	81	45	36	SOLO-1	68	26	42
PAOLA-1	96	44	52	PAOLA-1	68	37	31
Δ PFS	15	-1		Δ PFS	0	11	

An unanchored indirect comparison(PAIC) was performed on the endpoint of radiological PFS (RECIST version 1.1) according to study investigator using individual patient data (IPD) from the SOLO-1 (olaparib versus placebo) phase III trial pooled with IPD from the tBRCAm subset of the PAOLA-1 phase III trial. The analysis was performed on the SOLO-1 data and the subset of patients in PAOLA-1 that had confirmed tBRCA mutations, using local test results as per the eCRF for patient selection.

Kaplan-Meier curves (figure 14,15) were constructed for each treatment arm and supplemented with PFS probability estimates at specified time points (1, 2 and 3 years) after baseline. The main analysis included the fitting of Cox proportional hazards models to estimate HR for comparison of PFS between arms of PAOLA-1 and SOLO-1. This PAIC analysis required adjustment for imbalances between arms in effect modifiers and prognostic factors at baseline. We refer to these baseline characteristics as matching variables throughout.

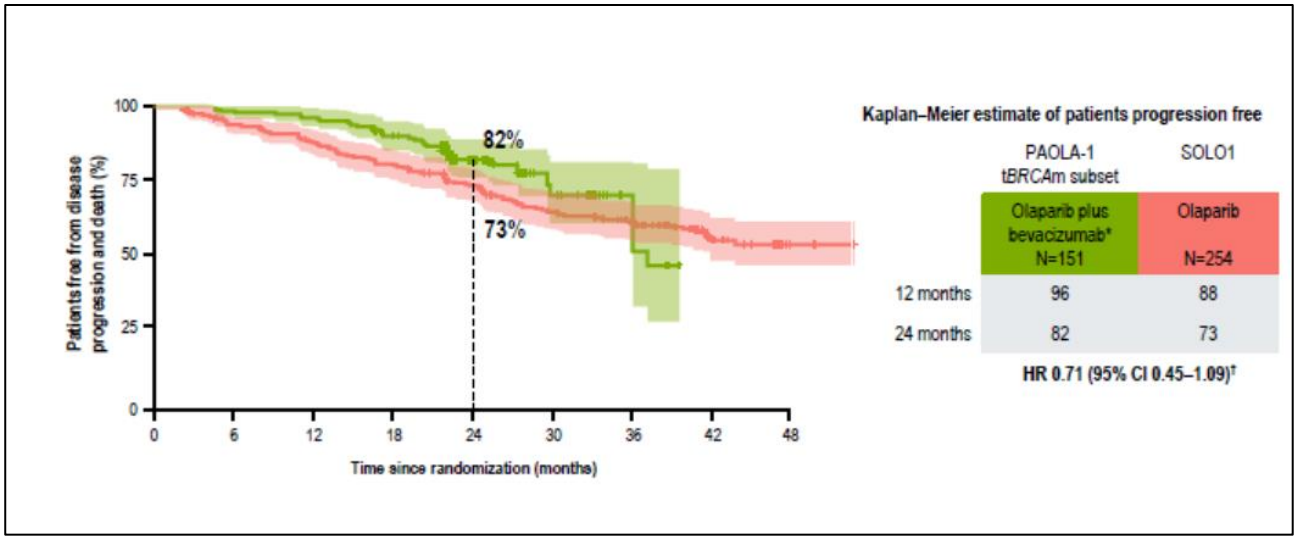
The weighted PAOLA-1 t*BRCA*m cohort had comparable baseline data to SOLO-1. The addition of bevacizumab to olaparib was associated with a clinically meaningful improvement in PFS vs olaparib monotherapy (HR 0.71; 95% CI 0.45, 1.09). A comparison of bevacizumab and olaparib monotherapies suggested that olaparib alone was significantly more efficacious than bevacizumab alone (HR 0.48; 95% CI 0.35, 0.75)

FIGURE 14. PFS FOR OLAPARIB + BEVACIZUMAB, OLAPARIB, BEVACIZUMAB AND PLACEBO IN TBRCAM PATIENTS



Kaplan-Meier curves of PFS from the MAIC analysis of the PAOLA-1 and SOLO-1 trials. PAOLA-1 tBRCA subgroup is weighted, SOLO-1 is unweighted.
Source: *AstraZeneca Data on File* [17].

FIGURE 15. PFS FOR OLAPARIB + BEVACIZUMAB VS OLAPARIB IN TBRCAM PATIENTS



Kaplan-Meier curves of PFS from the MAIC analysis of the PAOLA-1 and SOLO-1 trials. PAOLA-1 tBRCA subgroup is weighted, SOLO-1 is unweighted.
Source: *AstraZeneca Data on File* [17].

The ITC was presented at SGO, 2020 [31]. The full report can be submitted to Medicinrådet on request.

The results of the PAIC provide important insights on the potential role of olaparib and bevacizumab in the maintenance treatment of women with tBRCAm newly diagnosed ovarian cancer. The analysis suggests that treatment with olaparib, either in combination with bevacizumab or as a monotherapy, would yield superior efficacy on PFS to bevacizumab alone or placebo (SOLO-1) in women with tBRCAm newly

diagnosed ovarian cancer. Thus, supporting the position of olaparib as the standard of care in this treatment setting. Secondly, the analysis suggests that the combination of olaparib plus bevacizumab has the potential to improve on the efficacy of olaparib alone, with the effect of bevacizumab appearing to be additive to that of olaparib. The combination regimen may therefore be suitable in cases where maximal treatment benefit is being sought, and where other aspects involved in treatment selection including tolerability, and the convenience of regular bevacizumab infusions have been considered.

EPAR:

Based on Kaplan-Meier estimates, the proportion of patients that were progression free at 12 and 24 months were 89% and 66% for olaparib/bevacizumab versus 71% and 29% for placebo/bevacizumab.

6.2.2 Conclusion median PFS and PFS rate at 2 years BRCAm vs. olaparib

In descending order, the landmark probability for PFS at 24 months was 82% for olaparib plus bevacizumab, 73% for olaparib, 50% for bevacizumab and 36% for placebo. The addition of bevacizumab to olaparib was associated with a numerical improvement in PFS versus olaparib alone (HR 0.71; 95% CI 0.45, 1.09). (table 10). Throughout the majority of study follow-up, there was consistent separation in the KM curves favoring the combination regimen. The estimated relative effect of bevacizumab plus placebo versus placebo alone (HR 0.65; 0.43, 0.95) was relatively consistent with the relative effect of olaparib plus bevacizumab versus olaparib alone (HR 0.71; 95% CI 0.45, 1.09).

TABLE 10. RESULTS OF THE POPULATION ADJUSTED INDIRECT COMPARISON BRCAM

Regimen 1	Regimen 2	Kaplan-Meier estimate of PFS [95% Confidence interval]						Hazard Ratio for regimen 1 versus regimen 2 [95% confidence interval] **
		at 12 months for regimen 1	at 12 months for regimen 2	at 24 months for regimen 1	at 24 months for regimen 2	at 36 months for regimen 1	at 36 months for regimen 2	
Olaparib plus bevacizumab*	Olaparib	96% [0.93% to 0.99%]	88% [84% to 92%]	82% [76% to 89%]	73% [68% to 79%]	70% [60% to 81%]	61% [55% to 67%]	0.71 [0.45 to 1.09]
Olaparib	Bevacizumab plus placebo*	88% [84% to 92%]	81% [73% to 91%]	73% [68% to 79%]	50% [39% to 64%]	61% [55% to 67%]	36% [25% to 52%]	0.48 [0.30 to 0.75]
Bevacizumab plus placebo*	Placebo	81% [73% to 91%]	53% [45% to 63%]	50% [39% to 64%]	36% [28% to 45%]	36% [25% to 52%]	28% [21% to 37%]	0.65 [0.43 to 0.95]

** results based on weighted outcomes after matching tumour location status, ECOG status, FIGO stage, type of surgery (interval versus initial), residual disease status after surgery (yes or no), response to first-line treatment and age to SOLO1; ** confidence intervals generated via bootstrapping*

The PAIC analysis suggests that the combination of olaparib plus bevacizumab has the potential to improve the efficacy of olaparib alone and effect appears to be additive. Overall a HR of 0.71 (CI 0.45,1.09) and a PFS difference at 24 month of 9% suggest an additive effect of bevacizumab in BRCAm ovarian cancer patients. At 36 months the difference stays at 9 %. The target from Medicinrådet is 10 % so a “borderline” met target.

A combination of olaparib plus bevacizumab could be relevant in cases where maximal treatment effect is aimed for with respect for tolerability and convenience of regular bevacizumab infusion. This is also supported by Vergote et al at the SGO presentation, 2020 [31].

6.3 SAE grade 3 or more and discontinuations vs olaparib in BRCAm

6.3.1 Comparative SAE grade ≥ 3 and discontinuations vs. olaparib BRCAm

Medicinrådet has asked for drug(olaparib + bevacizumab/olaparib) related adverse events. In PAOLA and SOLO1 adverse reactions are listed as AEs and SAEs. There are no specific data on the BRCAm population, but it is not expected that SAE is different in the BRCAm population vs. the HRD+ population.

Median total duration of exposure to study treatment for t*BRCA*m patients was longer for olaparib (23.3 months) than for placebo (19.4 months) in SOLO-1, consistent with results for the Safety Analysis Set (SAS) . In non-t*BRCA*m patients, median total duration of exposure was similar for olaparib (14.8 months) and placebo (14.0 months) [19].

Grade ≥3 AEs

In order to evaluate the toxicity impact of the addition of bevacizumab to olaparib a narrative comparison with data from the SOLO-1 study is undertaken to further evaluate the impact of treating with the combination of olaparib and bevacizumab

Since a similar frequency of AEs, grade ≥3 AEs, SAEs, deaths, dose interruptions, dose reductions and discontinuations was observed in the HRD+ population as compared to the overall population in the PAOLA-1 study, the assessment will utilize data from the overall population in addition to safety data from SOLO-1.

In the PAOLA-1 study, a similar level of AEs was observed in both study arms (table 11). Although grade ≥3 AEs occurred in a greater proportion of patients in the olaparib plus bevacizumab arm, the difference was minimal vs the placebo plus bevacizumab arm (57.6% vs 50.9%, respectively).

However a naïve comparison with data from SOLO-1 reveals a higher frequency of grade ≥3 AEs in the olaparib + bevacizumab arm in PAOLA-1 versus olaparib arm in SOLO-1 (57.6% vs 39%, respectively). The absolute difference observed in this naïve comparison is above the threshold defined by Medicinrådet.

Table 11. SAE grade 3 or more naïve comparison PAOLA vs SOLO1

	PAOLA-1		SOLO-1	
	Olaparib + bevacizumab (N=535)	Placebo + bevacizumab (N=267)	Olaparib (N=260)	Placebo (N=130)
All grade AEs, n (%)	531 (99.3)	256 (95.9)	256 (98%)	120 (92%)
Grade ≥3 AEs, n (%)	308 (57.6)	136 (50.9)	102 (39%)	24 (18%)
SAEs, n (%)	167 (31.2)	83 (31.1)	54 (21%)	16 (12.%)
Deaths, n (%)	1 (0.2)	4 (1.4)	0	0
Dose interruptions due to AEs, n (%)	291 (54.4)	65 (24.3)	135 (52%)	22 (17%)
Dose reductions due to AEs, n (%)	220 (41.1)	20 (7.5)	74 (28%)	4 (3%)
Discontinuations due to AEs, n (%)	109 (20.4)	15 (5.6)	30 (11.5%)	3 (2.3%)

Source: AstraZeneca Data on File, Ray-Coquard I et al.; Moore K et al [19]

The safety profile of olaparib in combination with bevacizumab was generally consistent with previous trials of each drug and the addition of olaparib did not impact on bevacizumab tolerability. However the naïve comparison could suggest a higher cumulative toxicity profile related to the combination when compared with olaparib monotherapy

AEs of special interest for bevacizumab treatment, all of which are known Adverse Drug Reactions (ADRs), are shown in Table 12.

Attention needs to be drawn to hypertension which is known to be an ADR related to bevacizumab. Grade ≥ 3 hypertension was reported in 30.3% of patients in the placebo + bevacizumab arm, compared with 18.7% of patients in the olaparib + bevacizumab arm. This may imply that olaparib has the potential to be protective against bevacizumab-related hypertension.

Table 12. ADRs of special interest for bevacizumab treatment

Bevacizumab ADRs in either treatment arm in PAOLA-1[a]	PAOLA-1			
	Olaparib + bevacizumab (N=535)[b]		Placebo + bevacizumab (N=267)[b]	
	All grades	Grade 3/4	All grades	Grade 3/4
Patients with any AE	531 (99.3)	308 (57.6)	256 (95.9)	136 (50.9)
Hypertension	245 (45.8)	100 (18.7)	160 (59.9)	81 (30.3)
Haemorrhage	52 (9.7)	3 (0.6)	28 (10.5)	2 (0.7)
Proteinuria	31 (5.8)	5 (0.9)	41 (15.4)	1 (0.4)
Venous thromboembolic events	17 (3.2)	8 (1.5)	4 (1.5)	1 (0.4)
Arterial thromboembolic events	9 (1.7)	3 (0.6)	8 (3.0)	7 (2.6)
Wound healing complications	3 (0.6)	1 (0.2)	5 (1.9)	1 (0.4)
GI perforations, abscesses and fistulae	2 (0.4)	2 (0.4)	2 (0.7)	2 (0.7)
Non-GI fistulae or abscess	2 (0.4)	1 (0.2)	2 (0.7)	1 (0.4)
Congestive heart failure	1 (0.2)	1 (0.2)	0	0
PRES	0	0	1 (1.4)	0

Footnotes: [a]Includes multiple MedDRA preferred terms. [b] Patients with multiple events in a category are only counted once in that category. Patients with events in more than one category were counted once in each of those categories. CTCAE Version 4.0, MedDRA Version 22.0. Source: AstraZeneca Data on File (PAOLA-1 CSR) [19].

Dose interruptions of olaparib or placebo due to AEs occurred in a higher proportion of patients in the olaparib + bevacizumab arm (54.4%) compared to the placebo + bevacizumab arm (24.3%), but a level similar to the observed in the active arm of SOLO-1. The majority of these interruptions occurred in the combination phase, and AEs leading to olaparib treatment interruptions were consistent with the known safety profile of olaparib.

Dose reductions and treatment discontinuations followed a similar trend, however a higher frequency of discontinuations due to AEs were observed when compared to the active arm in SOLO-1 (20,4% vs 11,5% respectively). However important differences in study conduct between SOLO-1 and PAOLA-1 is highlighted in table 13. Patient deciding to discontinue due to AEs were reported as TEAE unlike in SOLO-1, where it was reported as patient decision. In PAOLA-1 21% discontinue due to TEAE and patient decision, which is at the same level as observed in SOLO-1 (20%). Please also see section below from EPAR which compares against a 300 mg olaparib pool.

Table 13. Reason for discontinuation of treatment

Reason for discontinuation other than disease progress or completion of protocol defined therapy at 2 years, n (%)	PAOLA-1		SOLO-1	
	Olaparib (N=537)	Placebo (N=269)	Olaparib (N=260)	Placebo (N=130)
TEAE	109 (20)	13 (5)	30 (12)	3 (2)
Patient decision	4 (1)	4 (2)	22 (8)	2 (2)
Other	19 (4)	6 (2)	11 (4)	9 (7)

Ray-Coquard I et al.; Moore K et al. [3, 7].

EPAR:

Overall, the safety profile of olaparib in combination with bevacizumab is considered to be consistent with the known safety profiles of the treatments when given as monotherapies.
The incidence and severity of the ADR identified with olaparib monotherapy treatment (300 mg bd pool data) and identified with olaparib plus bevacizumab in PAOLA-1 were compared. Several ADRs had similar incidences with olaparib monotherapy as when combined with bevacizumab. However, some ADRs had different incidences with the monotherapy than when combined (table 19).
The frequency was lower with combination treatment (common) than observed with monotherapy (very common) for the following ADR: thrombocytopenia, decreased appetite, dizziness, dysgeusia, cough, and dyspnoea (all grade). The frequency was higher with combination treatment (very common) than observed with monotherapy (common) for lymphopenia (all grade).
Although some differences of incidence have been noted, the larger patient exposure (n=2351) in the olaparib therapeutic dose pool provides the most robust estimates of the ADR frequencies for olaparib. A separate ADR table for the combination treatment olaparib plus bevacizumab is not warranted. The statement in section 4.8 of the SmPC "When Lynparza is used in combination with bevacizumab, the safety profile is generally consistent with that of the individual therapies" is considered sufficient. For overlapping toxicities, no notable increase in severity of events has been observed.
The majority of AEs were reported in the combination treatment of olaparib plus bevacizumab and mostly within the first 3 months of treatment [30, 32].

6.3.2 Conclusion SAE grade 3 or more and discontinuations vs. olaparib BRCAm

Conclusion AE ≥ 3 in the HRD population in PAOLA

Medicinrådet has asked for drug(olaparib + bevacizumab/olaparib) related adverse events. In PAOLA and SOLO1 adverse reactions are listed as AEs and SAEs. The same is the case for discontinuations. In the HRD+ population, a similar level of AEs was observed in both study arms. Although grade ≥3 AEs occurred in a greater proportion of patients in the olaparib plus bevacizumab arm, the difference of 5,9% or RR of 1.1 was minimal vs the placebo plus bevacizumab arm (56.5% vs 49.6%, respectively).

	Groups	AE of CTCAE 3 or more	No CTCAE 3 or more	Total patients	Risk Ratio	Relative RR
	Olaparib	144	111	255	0,56471	1,103
	placebo	65	62	127	0,511811024	
AE	95 % CI	LN(RR)+/-1,96*SQRT((((n1-x1)/x1)/n1) + ((n2-x2)/x2)/n2))	exp af log	95 % CI	interpretation	
((n1-x1)/x1)/n1	0,003022876	0,300	**1,34919714**	**0,90; 1,35**	**inkl. 1 = ikke sig. Relativ risiko**	
((n2-x2)/x2)/n2	0,0075106	-0,103	**0,902297886**	NA	NA	

Calculated by AstraZeneca

Conclusion AE ≥ 3 in the BRCAm population vs. olaparib

The PAIC/NMA do not compare AEs ≥ 3 vs. olaparib alone. A narrative comparison with SOLO1(BRCAm) reveals that AEs grade ≥ 3 in PAOLA were higher than in SOLO1(BRCAm) 57.6% vs 39%. The safety profile of olaparib in combination with bevacizumab was generally consistent with previous trials of each drug and the addition of olaparib did not impact on bevacizumab tolerability, however it is expected to observe a higher frequency of grade ≥ 3 due to additive toxicity.

Conclusion AE ≥ 3 in the BRCAm population vs. olaparib

The PAIC/NMA do not compare AEs ≥ 3 vs. olaparib alone. A narrative comparison with SOLO1(BRCAm) reveals that AEs grade ≥ 3 in PAOLA were higher than in SOLO1(BRCAm) 57.6% vs 39%. The safety profile of olaparib in combination with bevacizumab was generally consistent with previous trials of each drug and the addition of olaparib did not impact on bevacizumab tolerability, however it is expected to observe a higher frequency of grade ≥ 3 due to additive toxicity.

Conclusion discontinuations HRD+ population in PAOLA

For the direct comparison of the combination vs placebo + bevacizumab a 12,5% negative difference and a RR of 2.99 (see below).

	Groups	Discontinuations	Continued	Total patients	Risk Ratio	Relative RR
	Olaparib	48	207	255	0,18824	2,988
	placebo	8	119	127	0,062992126	
AE	95 % CI	LN(RR)+/-1,96*SQRT((((n1-x1)/x1)/n1) + ((n2-x2)/x2)/n2))	exp af log	95 % CI	interpretation	
((n1-x1)/x1)/n1	0,016911765	1,812	**6,124284099**	**1,46; 6,12**	**inkl. 1 = ikke sig. Relativ risiko**	
((n2-x2)/x2)/n2	0,117125984	0,377	**1,458056163**	NA	NA	

Calculated by AstraZeneca

Conclusion discontinuations in the BRCAm population vs. olaparib

The PAIC/NMA do not include discontinuation due AEs. A narrative comparison with SOLO1(BRCAm) show that discontinuations in PAOLA(HRD+) was numerical higher than in PAOLA 18.8 % vs. 11.5 %. When compared with other Phase III studies in the olaparib clinical development programme, the olaparib

discontinuation rate in PAOLA-1 due to AEs, patient decision and other causes unrelated to disease progression (combined) was similar to the rates reported in other studies [7].

6.3.3 Qualitative overview of side effects vs. olaparib

Medicinrådet has asked for drug(olaparib + bevacizumab) related adverse events. In adverse reactions are listed as AEs and SAEs.

Below in table 14 are listed the most common side effect in the PAOLA Study

Table 14. Most common AEs, overall study duration PAOLA

AEs[a]	n (%) of patients with AEs[b]			
	Olaparib + bevacizumab (N=535)		Placebo + bevacizumab (N=267)	
	All grades	Grade ≥3	All grades	Grade ≥3
Nausea	285 (53.3)	13 (2.4)	58 (21.7)	2 (0.7)
Fatigue or asthenia	283 (52.9)	28 (5.2)	86 (32.2)	4 (1.5)
Hypertension	245 (45.8)	100 (18.7)	160 (59.9)	81 (30.3)
Anaemia	219 (40.9)	93 (17.4)	27 (10.1)	1 (0.4)
Lymphopenia	120 (22.4)	37 (6.9)	24 (9.0)	3 (1.1)
Vomiting	117 (21.9)	9 (1.7)	29 (10.9)	5 (1.9)
Arthralgia	116 (21.7)	3 (0.6)	64 (24.0)	4 (1.5)
Abdominal pain	103 (19.3)	8 (1.5)	53 (19.9)	5 (1.9)
Diarrhoea	98 (18.3)	12 (2.2)	45 (16.9)	5 (1.9)
Leukopenia	87 (16.3)	9 (1.7)	26 (9.7)	3 (1.1)
Urinary tract infection	79 (14.8)	1 (0.2)	27 (10.1)	1 (0.4)
Headache	73 (13.6)	2 (0.4)	36 (13.5)	2 (0.7)
Neutropenia[c]	97 (18.1)	34 (6.4)	42 (15.7)	8 (3.0)
Constipation	53 (9.9)	0	28 (10.5)	1 (0.4)
Proteinuria	31 (5.8)	5 (0.9)	40 (15.0)	1 (0.4)

Footnotes: *[a]Preferred term, MedDRA Version 22.0. [b]Includes AEs with an onset date on or after the date of first dose and up to and including 30 days following the date of last dose of olaparib or placebo. Sorted by decreasing order of frequency in the olaparib + bevacizumab arm and then by order of frequency in the placebo + bevacizumab arm [c]The preferred terms agranulocytosis, febrile neutropenia, granulocyte count decreased, granulocytopenia, neutropenia, neutropenic infection, neutropenic sepsis and neutrophil count decreased are included under the grouped term neutropenia.* ***Source:*** *AstraZeneca Data on File (PAOLA-1 CSR) [19] .*

SOLO1

Medicinrådet has asked for drug(olaparib) related adverse events. In SOLO1 adverse reactions are listed as AEs and SAEs.

AEs of grade ≥3 were reported in 39.2% of patients receiving olaparib and 18.5% of patients receiving placebo (table 15). Of the grade ≥3 AEs the most commonly observed were blood and lymphatic system disorders, gastrointestinal disorders, investigations and general disorders and administration-site conditions. Anaemia and neutropenia were the only AEs of grade ≥3 reported in ≥5% of patients. AEs of grade ≥3 were typically known adverse drug reactions for olaparib *[7, 17].*

TABLE 15: AEs GRADE ≥3 BY SYSTEM ORGAN CLASS AND PREFERRED TERM (>1 PATIENT IN THE OLAPARIB ARM) SOLO1

System organ class	Number of patients (%)[a]	
	Olaparib 300 mg BID (n=260)	Placebo (n=130)
Patients with AE of grade ≥3[b]	102 (39.2%)	24 (18.5%)
Blood and lymphatic system disorders	63 (24.2%)	8 (6.2%)
Anaemia[c]	56 (21.5%)	2 (1.5%)
Neutropenia[d]	22 (8.5%)	6 (4.6%)
Leukopenia	4 (1.5%)	0
Lymphopenia	2 (0.8%)	1 (0.8%)
Thrombocytopenia[e]	2 (0.8%)	2 (1.5%)
Gastrointestinal disorders	17 (6.5%)	3 (2.3%)
Diarrhoea	8 (3.1%)	0
Abdominal pain	4 (1.5)	1 (0.8%)
Nausea	2 (0.8%)	0
Small intestinal obstruction	2 (0.8%)	1 (0.8%)
Investigations	12 (4.6%)	4 (3.1%)
Neutrophil count decreased	7 (2.7%)	2 (1.5%)
White blood cell count decreased	4 (1.5%)	0
Lymphocyte count decreased	2 (0.8%)	0
General disorders and administration-site conditions	11 (4.2%)	2 (1.5%)
Asthenia	5 (1.9%)	0
Fatigue	5 (1.9%)	2 (1.5%)
Infections and infestations	8 (3.1%)	4 (3.1%)
Urinary tract infection	2 (0.8%)	0
Respiratory, thoracic and mediastinal disorders	5 (1.9%)	0
Pulmonary embolism	2 (0.8%)	0
Musculoskeletal and connective tissue disorders	2 (0.8%)	0
Rotator cuff syndrome	2 (0.8%)	0
Renal and urinary disorders	2 (0.8%)	0
Urinary incontinence	2 (0.8%)	0

[a]Number (%) of patients with AEs ≥grade 3 or higher, sorted by frequency in the olaparib arm for system organ class and for preferred term. [b]Patients with multiple AEs ≥grade 3 or higher are counted once for each preferred term. [c]Includes anaemia, anaemia macrocytic, erythropenia, haematocrit decreased, haemoglobin decreased, normochromic anaemia, normochromic normocytic anaemia, normocytic anaemia and red blood cell decreased; [d]Includes agranulocytosis, febrile neutropenia, granulocyte count decreased, granulocytopenia, idiopathic neutropenia, neutropenia, neutropenic infection, neutropenic sepsis and neutrophil count decreased; [e]Includes platelet count decreased, platelet production decreased, plateletcrit decreased and thrombocytopenia. Includes AEs with an onset date on or after the date of first dose and up to and including 30 days following the date of last dose of olaparib/placebo. Source: [33]

Table 16. Summary of SAEs

SAEs[a]	Olaparib + bevacizumab (N=535)	Placebo + bevacizumab (N=267)
Patients with any SAE n, (%)	167 (31.2)	83 (31.1)
Vascular disorders	56 (10.5)	35 (13.1)
Hypertension	48 (9.0)	35 (13.1)
Blood and lymphatic system disorders	40 (7.5)	4 (1.5)
Anaemia	34 (6.4)	1 (0.4)
Gastrointestinal disorders	31 (5.8)	19 (7.1)
Ileus	3 (0.6)	3 (1.1)
Intestinal obstruction	8 (1.5)	2 (0.7)
Subileus	8 (1.5)	3 (1.1)
Cardiac disorders	4 (0.7)	7 (2.6)
Myocardial infarction	0	4 (1.5)

Footnotes: *[a]Preferred term, MedDRA Version 22.0. SAEs for overall study duration, includes SAEs affecting >1% of patients in either treatment arm. Patients with multiple SAEs are counted once for each system organ class/preferred term.* ***Source:*** *AstraZeneca Data on File (PAOLA-1 CSR), Ray-Coquard I et al. [3, 7].*

AEs of special interest for olaparib

AEs of special interest for olaparib, which are AEs considered to be potential risks associated with olaparib treatment, are summarised in table 15. Myelodysplastic syndrome (MDS), acute myeloid leukaemia (AML) and new primary malignancies were considered AEs of special interest in PAOLA-1 as they may be related to agents that affect DNA repair, including chemotherapy. Pneumonitis is also an AE of special interest and has been observed in previous trials of olaparib.

Incidence of MDS/AML in olaparib plus bevacizumab treated patients was low and in line with previously reported frequencies. A causal relationship between olaparib treatment and the development or acceleration of MDS/AML has not been established.

New primary malignancies were reported in six patients (1.1%) of the olaparib plus bevacizumab arm and three patients (1.1%) in the placebo plus bevacizumab arm.

All events of pneumonitis (2 patients), interstitial lung disease (3 patients) and bronchiolitis (1 patient) occurred in the olaparib plus bevacizumab arm.

Table 17. AEs of special interest for olaparib

AEs	Olaparib + bevacizumab (N=535)	Placebo + bevacizumab (N=267)
MDS/AML/AA, n (%)	6 (1.1)	1 (0.4)
New primary malignancies	7 (1.3)	3 (1.1)
Acute lymphocytic leukaemia	1	0
Breast cancer	2	2
Lung cancer	1	0
Myeloma	1	0
Pancreatic cancer	1	0
Thyroid cancer	0	1
Squamous skin cancer	1	0
Pneumonitis/ILD, n (%)	6 (1.1)	0

Source: *Ray-Coquard et al., 2019 [15, 16].*

AEs of special interest for bevacizumab

AEs of special interest for bevacizumab treatment, all of which are known ADRs, are shown in Table 18. Patients receiving olaparib plus bevacizumab had a similar or lower incidence of bevacizumab ADRs than patients receiving placebo plus bevacizumab. In particular, Grade ≥3 hypertension was reported in 30.3% of patients in the placebo plus bevacizumab arm, compared with 18.7% of patients in the olaparib plus bevacizumab arm; accordingly, use of antihypertensive drugs was lower in the olaparib plus bevacizumab arm (26.4%) than the placebo plus bevacizumab arm (40.9%). This may imply that olaparib has the potential to be protective against bevacizumab-related hypertension.

Table 18. Bevacizumab AEs in either treatment arm

Medical concept[a]	Olaparib + bevacizumab (N=535)[b]		Placebo + bevacizumab (N=267)[b]	
	All grades	Grade 3/4	All grades	Grade 3/4
Patients with any AE	531 (99.3)	308 (57.6)	256 (95.9)	136 (50.9)
Hypertension	245 (45.8)	100 (18.7)	160 (59.9)	81 (30.3)
Haemorrhage	52 (9.7)	3 (0.6)	28 (10.5)	2 (0.7)
Proteinuria	31 (5.8)	5 (0.9)	41 (15.4)	1 (0.4)
Venous thromboembolic events	17 (3.2)	8 (1.5)	4 (1.5)	1 (0.4)
Arterial thromboembolic events	9 (1.7)	3 (0.6)	8 (3.0)	7 (2.6)
Wound healing complications	3 (0.6)	1 (0.2)	5 (1.9)	1 (0.4)
GI perforations, abscesses and fistulae	2 (0.4)	2 (0.4)	2 (0.7)	2 (0.7)
Non-GI fistulae or abscess	2 (0.4)	1 (0.2)	2 (0.7)	1 (0.4)
Congestive heart failure	1 (0.2)	1 (0.2)	0	0
PRES	0	0	1 (1.4)	0

Footnotes: *[a]Includes multiple MedDRA preferred terms. [b] Patients with multiple events in a category are only counted once in that category. Patients with events in more than one category were counted once in each of those categories. CTCAE Version 4.0, MedDRA Version 22.0.* ***Source:*** *AstraZeneca Data on File (PAOLA-1 CSR) [19].*

In the EPAR there is a comparison of PAOLA-1 vs. a 300 mg olaparib pool that can be used to describe AEs and SAEs related to olaparib and bevacizumab (table 19).

Table 19. AE and SAE vs a 300 mg olaparib pool

System organ class Preferred term	Number (%) of patients		
	PAOLA-1 SAS, overall study duration		Olaparib 300 mg bd pool (N=1585)
	Olaparib/ bevacizumab N=535	Placebo/ bevacizumab N=267	
Patients with any SAE	**167 (31.2)**	**83 (31.1)**	**365 (23.0)**
Vascular disorders	**56 (10.5)**	**35 (13.1)**	**13 (0.8)**
Hypertension	48 (9.0)	35 (13.1)	0
Blood and lymphatic system disorders	**40 (7.5)**	**4 (1.5)**	**110 (6.9)**
Anaemia	34 (6.4)	1 (0.4)	89 (5.6)
Gastrointestinal disorders	**31 (5.8)**	**19 (7.1)**	**66 (4.2)**
Subileus	8 (1.5)	3 (1.1)	1 (0.1)
Intestinal obstruction	8 (1.5)	2 (0.7)	6 (0.4)
Ileus	3 (0.6)	3 (1.1)	5 (0.3)
Cardiac disorders	**4 (0.7)**	**7 (2.6)**	**14 (0.9)**
Myocardial infarction	0	4 (1.5)	1 (0.1)

6.4 HQoL vs olaparib in BRCAm

6.4.1 Comparative analyses HQoL vs. olaparib BRCAm

PAOLA

PROs for HRQoL were gathered using the EORTC Quality of Life Questionnaire Core 30 (QLQ-C30) and the ovarian cancer specific module (QLQ-OV28), every 12 weeks for two years from first study drug administration. Change from baseline in EORTC QLQ-C30 GHS was regarded as the key analysis of the PROs; this was analyzed using a mixed model for repeated measures (MMRM) analysis of the change from baseline (defined as prior to first dose) in QLQ-C30 global health status (GHS) for each visit.

EORTC QLQ-C30 baseline scores were generally high and similar in both arms (68.64 in the olaparib plus bevacizumab arm and 67.14 in the placebo + bevacizumab arm) and remained stable across the 24-month treatment period. No clinically meaningful difference in HRQoL was observed between the treatment arms over the 24-month treatment period or across individual timepoints. Adjusted mean change (table 20) from baseline over 24 months was 0.13 points for the olaparib + bevacizumab arm and -0.46 points for the placebo + bevacizumab arm, with the threshold for a meaningful difference being a 10 point change. Similar results were observed for the physical and role functioning scales of the QLQ-C30. A transient worsening in the mean nausea/vomiting score for patients in the olaparib + bevacizumab arm was observed at 12 weeks, and an improvement in mean social functioning score for patients in the placebo + bevacizumab arm was observed at 96 weeks. Otherwise, there were no clinically meaningful changes from baseline in any QLQ-C30 functioning or symptom subscales at any timepoint on treatment over 24 months. This demonstrates that treatment with the combination of olaparib + bevacizumab does not have a detrimental effect on the HRQoL of advanced ovarian cancerpatients. As EORTC QLQ-C30 baseline scores were generally high (>10 points higher than the ovarian cancer stage III/IV reference value of 56.3, and approximately three points lower than the general population reference value of 71.2) , patients undergoing treatment with olaparib + bevacizumab have a generally high HRQoL, which is not meaningfully different from that of the general population. The high baseline score for patients in the PAOLA-1 trial may however have led to a ceiling effect in which meaningful increases in HRQoL were not possible.

TABLE 20. CHANGE FROM BASELINE IN QLQ-C30 GHS/QOL SCORE, MMRM, ITT POPULATION

	Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)
Average over 24 months		
n	446	229
Adjusted mean	0.13	-0.46
95% CI	-1.02, 1.27	-2.08, 1.16
Estimated difference	0.59	
95% CI	-1.40, 2.57	
p value[a]	0.5626	

Footnotes: *Baseline was defined as the last evaluable assessment prior to dosing with study treatment. The analysis was performed using an MMRM analysis of the change from baseline QLQ-C30 QoL score for all post-baseline visits (up to study treatment discontinuation) with treatment, visit and treatment by visit interaction included as explanator variables and the baseline QLQ-C30 QoL score included as a covariate along with the baseline QLQ-C30 QoL score by visit interaction. Treatment, visit and treatment by visit interaction were fixed effects in the model, patient was included as a random effect. [a]Not adjusted for multiplicity.* ***Source:*** *AstraZeneca Data on File (PAOLA-1 CSR) [19].*

As with EORTC QLQ-C30, QLQ-OV28 baselines scores were similar in both treatment arms, and subscale scores remained stable or improved over the treatment period. Clinical meaningful improvements from baseline on single item subscales including peripheral neuropathy, attitudes towards disease/treatment and body image, were observed at multiple timepoints over 24 months. The proportions of patients who improved, had no change, or worsened from baseline in subscale scores were generally similar across timepoints for both treatment arms. Treatment with both olaparib + bevacizumab and bevacizumab + placebo therefore aided in sustaining a higher QoL than was experienced by patients immediately following 1L chemotherapy. Combined with the improvements in PFS observed in the olaparib-treatment patients, these data suggest that patients were maintained in a higher QoL state for a longer period of time, with the detrimental effects of further chemotherapy being delayed [19].

EQ-5D-5L

The EuroQoL five dimensions five level (EQ-5D-5L) index is a standardized measure of health status applicable to a wide range of health conditions and treatments. It provides a simple descriptive profile and single index value for health status that can be used in both clinical and economic evaluations. The EQ-5D-5L outputs a health state referred to by a five-digit code, allowing for a total of 3,125 health states. These data were converted into a weighted health state index. In addition, respondents also assessed their health on a visual analogue scale (VAS), ranging from 0 (worst imaginable health to 100 (best imaginable health).

EQ-5D-5L data did not demonstrate meaningful deterioration for patients in the olaparib + bevacizumab arm relative to patients in the placebo + bevacizumab arm, as measured by the weighted health state index score or the VAS.

Overall, results from EORTC QLQ-C30, QLQ-OV28, EQ-5D-5L indicated that addition of olaparib to bevacizumab does not result in a deterioration in patient HRQoL. Given that treatment with olaparib + bevacizumab results in a significant PFS gain, it is important that this is not accompanied by a detrimental impact in HRQoL. Patients treated with olaparib in addition to bevacizumab can therefore expect benefits of a longer PFS, with the detrimental impact of subsequent chemotherapy consequently being delayed, without a decrease in QoL [19].

SOLO1

Patient-reported HRQoL was assessed using the FACT-O questionnaire, while patient health status was measured through the EQ-5D-5L questionnaire. The FACT-O is composed of several subscales: physical, social/family, emotional, and functional well-being scales, as well as the additional concerns scale consisting of specific ovarian cancer symptoms. The primary HRQoL analysis in SOLO1 was the TOI, change from baseline over the first 24 months in the TOI score, an established single targeted index derived from the FACT-O questionnaire. The TOI targets the most relevant symptoms and functional and physical well-being that can be directly related to symptoms and AEs. The TOI is composed of the following scales of the FACT-O: physical and functional well-being and additional concerns.

Baseline scores for the TOI and FACT-O were high with no differences between treatment arms for all patients. Mean TOI scores at baseline were 73.6 and 75.0 for patients in the olaparib and placebo arms, respectively.

Over 24 months, patients in the olaparib arm remained stable with no detrimental effect, whereas, patients in the placebo arm showed small but not clinically relevant improvements. The estimated difference between the arms was significant, but not clinically meaningful because as TOI scores range from 0 to 100, a clinically meaningful difference is defined as ±10 points, and the observed between-group difference in the change in TOI score was <10 points [28].

The adjusted mean change from baseline in TOI score over 24 months for patients in the olaparib arm was 0.30 (95% CI −0.717, 1.318) and 3.30 (95% CI 1.839, 4.758) for patients in the placebo arm. The estimated difference in treatment arms was -3.00 (95% CI −4.779, −1.216; *P*=0.001). The observation of no clinically meaningful worsening in TOI of olaparib relative to placebo in HRQoL was supported by a sensitivity analysis using area under the curve (AUC) over all visits. This analysis found that up to 24 months there were no statistically significant or clinically relevant differences between the treatment arms (estimated difference −2.05; 95% CI −5.596, 1.501; *P*=0.2573).

The primary measure of HRQoL, the FACT-O TOI score, did not decrease and there was no clinically significant deterioration in TOI of olaparib relative to placebo or baseline in HRQoL

EPAR:

Table 21: Change from baseline in QLQ-C30 global health status/QoL score, MMRM (FAS) (DCO 22 March 2019)

	Olaparib/bevacizumab (N=537)	Placebo/bevacizumab (N=269)
Average over 24 months		
n	446	229
Adjusted mean	0.13	-0.46
Standard error	0.583	0.824
95% CI	-1.020, 1.271	-2.078, 1.159
Estimated difference	0.59	
95% CI for difference	-1.399, 2.570	
p-value[a]	0.5626	

The EPAR do not compare to olaparib monotherpy

6.4.2 Conclusion HQoL vs. olaparib BRCAm

PAOLA

QoL data for the specific population of the HRD+ including BRCAm ovarian cancer patients are not available. These patient are however not expected to have a significant different QoL values compared to the ITT population of PAOLA-1. Adjusted mean change in the ITT population from baseline over 24 months was 0.13 points for the olaparib plus bevacizumab arm and -0.46 points for the placebo + bevacizumab arm, with the threshold from Medicinrådet for a meaningful difference being a 10 point change. The target

set by Medicinrådet/Fagudvalget is 10 points could not be met by the combination of olaparib and bevacizumab in the HRD+, non-BRCAm population.

SOLO1 olaparib BRCAm

The clincal question refers to a comparison vs. olaparib alone. We have not been able to indirect compare tha HQoL data from PAOLA(ITT) vs. the olaparib(BRCAm) monotherapy arm in SOLO1. We are however able to conclude that is not likely that the combination can deliver a 10% positive difference vs. the olaparib single arm in SOLO1.

7 Questions 2. Olaparib plus bevacizumab vs bevacizumab HRD+ non-BRCAm(Higher Risk)

This section contains data that are to be considered confidential. It is marked with [redacted]

Population:

Patients with advanced non-BRCA mutated, HRD+ High-Grade Ovarian Cancer. Newly diagnosed patients evaluated to be candidates for bevacizumab being defined with following characteristic

- Stage III patients with residual disease ≥1cm
- Stage IV patients
- Inoperable patients

The discordance between higher-risk population in the PAOLA-1 dataset and the population criteria set by Medicinrådet for Clinical Question 2 was discussed in section 5. For the analysis of the HRD+ ex tBRCAm higher risk population, the Myriad dataset for higher risk patients with positive HRD status (42 cut-off, excluding tBRCAm) are utilized (data on file). A total of 101 subjects meets the criteria with 64 being treated with olaparib plus bevacizumab and 37 being treated with placebo plus bevacizumab.

7.1 OS vs bevacizumab HRD+ non-BRCAm population

7.1.1 Comparative analyses median OS/OS rate at 5 years vs. bevacizumab HRD+ non-BRCAm

The addition of olaparib to bevacizumab maintenance reduced the overall risk of death by 45% versus placebo and bevacizumab in the HRD-positive group (HR=0.55; 95% CI: 0.33, 0.92). Median OS was not reached in either arm.

Although these data are immature (13.7% maturity in the olaparib plus bevacizumab arm, and 21.2% maturity in the placebo plus bevacizumab arm), they clearly indicate a compelling OS advantage in favour of olaparib plus bevacizumab, that is sustained throughout the study period (table 7)

[redacted]

EPAR:

Not specified for the patient group. Please section 5 for ITT and HRD+ population

7.1.2 Conclusion median OS and OS rate at 5 years vs. bevacizumab HRD+ non-BRCAm

The data can currently not meet the targets set my Medicinrådet/Fagudvalet. OS data for the specific subgroup of HRD+ ex tBRCAm higher risk patients are currently not available, hence more mature data needed in order to assess potential improvement in OS.

7.2 PFS vs. bevacizumab HRD+ non-BRCAm

7.2.1 Comparative analyses m PFS and PFS rate 2 years vs. bevacizumab HRD+ non-BRCAm

PFS Kaplan-Meier plot (FAS) for the subgroup of patients being HRD+ ex tBRCAm with a higher-risk profile are shown in figure 17. [redacted]

[redacted]

Source: AstraZeneca. Data on file [29].

An improvement in median PFS of 4.9 months was demonstrated (20.3 months vs 15.4 months) which did not meet the predefined criteria of 6 months set by Medicinrådet.

[redacted]

As previously discussed for the BRCAm segment, the data for this higher-risk subgroup could suggest an additive effect of the combination of olaparib plus bevacizumab, hence suggesting that the increased difference in %-point observed from Landmark at 6 months to Landmark at 24 months reflects maintained long-term benefit of olaparib treatment as previously observed in SOLO-1.

[redacted]

Source: AstraZeneca. Data on file [29].

EPAR:

Data for the specific HRD+ non-BRCAm is not mentioned in the EPAR

7.2.2 Conclusion median PFS and PFS rate at 2 years vs. bevacizumab HRD+ non-BRCAm

An improvement in median PFS of 4.9 months were demonstrated (20.3 months vs 15.4 months) which did not meet the predefined criteria of 6 months set by Medicinrådet.

[redacted]

As previously discussed for the BRCAm segment, the data for this higher-risk subgroup could suggest an additive effect of the combination of olaparib plus bevacizumab, hence suggesting that the increased difference in %-point observed from Landmark at 6 months to Landmark at 24 months reflects maintained long-term benefit of olaparib treatment as previously observed in SOLO-1.

7.3 SAE grade 3 and discontinuations vs bevacizumab in higher-risk patients

7.3.1 Comparative SAE grad 3 or more and discontinuations vs. bevacizumab

Medicinrådet has asked for drug(olaparib + bevacizumab) related adverse events. In PAOLA and SOLO1 adverse reactions are listed as AEs and SAEs. The same is the case for discontinuations

Data from the safety analysis set for the higher-risk population (n=592) reveals no significant difference between the safety analysis set for the ITT population and this subgroup in terms AEs, Any AE of CTCAE Grade ≥3 or any AE Leading to discontinuation of intervention(table 23).

AstraZeneca refer to section 6.3.3 for more detailed discussion of safety signal, but conclude that more patients are expected to discontinue treatment (> 10 %-point) with the combination of olaparib and bevacizumab versus bevacizumab.

[redacted]

Source: AstraZeneca. Data on file [29].

EPAR:

Not specified for this patient group.

7.3.2 Conclusion SAE grade 3 + and discontinuations vs. bevacizumab higher-risk

Conclusion SAE grade 3 or more

[redacted]

Calculated by AstraZeneca

Conclusion discontinuations

Calculated by AstraZeneca

Fagudvalget/Medicinrådet had set a target of 10 % for SAE and 5 % for discontinuations to prove the benefit of the combination. Olaparib + bevacizumab did not meet these targets in the higher risk population that are candidates for bevacizumab

7.4 HQoL vs olaparib in HRD+ non-BRCAm higher-risk

7.4.1 Comparative analyses HQoL vs. bevacizumab HRD+ non-BRCAm

Data for the HRD+ non-BRCAm higher risk specific population is not available. Please see section 5.4 for data from the ITT population

EPAR:

Data for the specific HRD+ non-BRCAm is not mentioned in the EPAR.

7.4.2 Conclusion HQoL vs. bevacizumab higher-risk.

QoL data for the specific population of HRD+, non-BRCA OC patients are not available. These patient are however not expected to have a significant different QoL values compared to ITT population

Adjusted mean change in the ITT population from baseline over 24 months was 0.13 points for the olaparib + bevacizumab arm and -0.46 points for the placebo + bevacizumab arm, with the threshold for a meaningful difference being a 10 point change. The target set by Medicinrådet/Fagudvalget is 10 points and this could not be met by the combination of olaparib and bevacizumab in the HRD+, non-BRCAm population

8 Questions 3. olaparib plus bevacizumab vs placebo in HRD+ nonBRCAm(lower-risk)

Population: Newly diagnosed patients not evaluated to be candidates for bevacizumab being defined with following characteristic

- **Stage III patients with no residual disease (<1cm)**

This section contains data that are to be considered confidential. It is marked with [redacted]

8.1 OS vs placebo in HRD+ non-BRCAm

8.1.1 Comparative analyses median OS and OS rate at 5 years

See section 7.1.1

The addition of olaparib to bevacizumab maintenance reduced the overall risk of death by 45% versus placebo and bevacizumab in the HRD-positive group (HR=0.55; 95% CI: 0.33, 0.92). Median OS was not reached in either arm.

EPAR:

Not mentioned for this specific group of patients.

8.1.2 Conclusion median OS and OS rate at 5 years vs. placebo HRD+ non-BRCAm

OS data is not available for the HRD+, non-BRCA patient lower-risk population. The absolute target of 4 months in mOS and 5 %(points) in OS rate vs bevacizumab cannot be met due to immature data.

8.2 PFS vs vs. placebo HRD+ non-BRCAm not candidates for bevecizumab

8.2.1 Comparative analyses median PFS and PFS rate at 2 years vs. placebo HRD+ non-BRCAm

PFS Kaplan-Meier plot for the subgroup of patients being HRD+ ex tBRCAm with a lower-isk profile are shown in figure 18. [redacted]

[redacted]

Source: AstraZeneca. Data on file [29].

EPAR:

Not specified for the patient group.

8.2.2 Conclusion median PFS and PFS rate at 2 years vs. placebo HRD+ non-BRCAm

[redacted]

A highly significant improvement [redacted]

As previously discussed for the BRCAm segment, the data for this lower-risk subgroup could potential suggest a synergistic effect of the combination of olaparib plus bevacizumab. Subgroup analysis from SOLO-1 revealed at relative risk reduction of 68% (HR=0.32; 95% CI: 0.20, 0.51) for the lower-risk population[8],

with an even more pronounced relative risk reduction of 81% for this subgroup in the PAOLA-1 study supporting arguments for a synergistic effect being observed.

8.3 SAE grade 3 or more and discontinuations vs placebo lower-risk

8.3.1 Comparative SAE grade 3 or more and discontinuations vs. placebo lower-risk

Medicinrådet has asked for drug(olaparib + bevacizumab) related adverse events. In PAOLA and SOLO1 adverse reactions are listed as AEs and SAEs. The same is the case for discontinuations.

Data from the safety analysis set for the lower risk population (n=210) reveals no significant difference between the safety analysis set for the ITT population and this subgroup in terms AEs, Any AE of CTCAE Grade ≥3 or Any AE Leading to discontinuation of intervention.

In assessing the added toxicity related to the potential introduction of the combination of olaparib + bevacizumab for a lower-risk population, a narrative comparison versus the control arm in SOLO-1 is undertaken. This to mimic the current clinical condition being observation for this patient group

Table 11 in section 6.3.1 reveals that grade 3 AEs is reported at a significant higher frequency when comparing active olaparib + bevacizumab vs observation[placebo in SOLO-1] (57.6% vs 18%).

In addition this naïve comparison reveals a higher proportion of patients discontinuing in the olaparib + bevacizumab versus observation[placebo in SOLO-1] (20,4% vs 2,3%).

For both variables a clinical relevant difference are suggested by this naïve comparison. AstraZeneca fully acknowledge the importance of this naïve comparison in assessing the overall risk/benefit profile of olaparib + bevacizumab in clinical question 3.

AstraZeneca refer to section 6.3.3 for more detailed discussion of safety signal, but do not expect variation in terms of AE profile for lower risk HRD+ subgroup versus the overall PAOLA-1 population.

EPAR:

This group of patients is not directly mentioned in the EPAR

8.3.2 Conclusion SAE grade 3 or more and discontinuations vs. placebo lower-risk.

SAE grade 3 or more

Calculated by AstraZeneca

Discontinuations:

Calculated by AstraZeneca

8.4 HQoL vs olaparib in lower-risk.

8.4.1 Comparative analyses HQoL vs. placebo lower-risk.

Data for the specific HRD+ non-BRCAm is not available.

EPAR:

Data for the specific HRD+ non-BRCAm is not mentioned in the EPAR. Please see section 6.4 for data from the ITT population.

8.4.2 Conclusion HQoL vs. placebo non-BRCAm

QoL for the specific population of HRD+, non-BRCA OC patients not candidates to bevacizumab is not available. These patient are however not expected to have a significant different QoL values compared to ITT population

Adjusted mean change in the ITT population from baseline over 24 months was 0.13 points for the olaparib + bevacizumab arm and -0.46 points for the placebo + bevacizumab arm, with the threshold for a meaningful difference being a 10 point change. The target set by Medicinrådet/Fagudvalget is 10 points and this could not be met by the combination of olaparib and bevacizumab in the HRD+, non-BRCAm population.

8.5 PFS2 and subsequent therapies

An interim PFS2 analysis was to be performed at the time of the PFS1 analysis. Final PFS2 analysis was planned to be performed when the PFS2 data were approximately 53% mature (approximately 411 events) OR after a maximum duration of 1 year following the PFS1 analysis, whichever occurred first.

At the time of the first DCO, the PFS2 data in the overall population were 39,1 % mature and 27,9% in the HRD+ group. Median PFS2 in the ITT population was 32.3 months in the olaparib + bevacizumab arm and 30.1 months in the placebo + bevacizumab arm and a point estimate of HR favoured the olaparib + bevacizumab arm.

In the HRD+ population median PFS2 was not reached in the olaparib + bevacizumab arm and was 34.6 months in the placebo + bevacizumab arm and a point estimate of HR favoured the olaparib + bevacizumab arm.

TABLE 26. SUMMARY OF SECONDARY ENDPOINTS FOR THE OVERALL POPULATION AT THE FIRST DCO

	Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)
PFS2 (39.1% mature)		
Events, n, (%)	196 (36.5)	119 (44.2)
Median follow-up (IQR), months	24.0 (19.8–28.3)	24.8 (21.6–28.2)
Median PFS2[a] (95% CI), months	32.3 (29.2, 39.8)	30.1 (25.7, 32.6)
HR[b] (95% CI; p [2-sided][c])	0.86 (0.69, 1.09; 0.2097)	

AstraZeneca Data on File (PAOLA-1 CSR Ray-Coquard I et al.; [3, 7]

TABLE 27. SUMMARY OF SECONDARY ENDPOINTS FOR THE HRD+ POPULATION AT THE FIRST DCO

	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
PFS2 (27.9% mature)		
Events, n, (%)	60 (23.5)	48 (36.4)
Median follow-up (IQR), months	24.4 (21.8, 30.6)	25.2 (22.1, 30.4)
Median PFS2[a] (95% CI), months	Not reached (Not reached, Not reached)	34.6 (27.9, Not reached)
HR[b] (95% CI; p [2-sided][c])	0.60 (0.41, 0.89; 0.0100)	

AstraZeneca Data on File (PAOLA-1 CSR) [19].

Data for PFS2 is available for the 2nd March 2020 DCO and is shown below in figure 19.

Source: AstraZeneca Data on File (PAOLA-1 CSR) [19].

Of patients who received any subsequent therapy, PARP inhibitors were received by 49 (16.4%) of the 298 olaparib/bevacizumab-treated patients and 83 (43.0%) of the 193 placebo/bevacizumab-treated patients (DCO Sept 2019). Out of the 36 patients in the olaparib/bevacizumab arm who received a subsequent PARPi treatment, 34 patients receive it as maintenance treatment and 2 patients as a first subsequent treatment (DCO 22 March 2019)

Source: AstraZeneca. Data on file [29].

Source: AstraZeneca. Data on file [29].

EPAR:

Table 30. PFS2 in the ITT population

	Olaparib/bevacizumab (N=537)	Placebo/bevacizumab (N=269)
n (%) of events[a]	196 (36.5)	119 (44.2)
Treatment effect		
Median PFS2 (95% CI), months[b]	32.3 (29.2, 39.8)	30.1 (25.7, 32.6)
HR[c]	0.86	
95% CI[c]	0.69, 1.09	
2-sided p-value[d]	0.2097	
Second progression free at 6 months (%)[b]	98.3	97.3
Second progression free at 12 months (%)[b]	88.7	86.7
Second progression free at 18 months (%)[b]	79.0	80.1
Second progression free at 24 months (%)[b]	67.0	64.6
Median (IQR) follow-up for second progression-free survival (months)[e]	24.0 (19.8, 28.3)	24.8 (21.6, 28.2)

Subsequent therapies

PAOLA population:

Overall, at the time of the DCO for the PFS analysis, 181 (67.3%) patients in the placebo/bevacizumab arm had started a first subsequent therapy compared with 261 (48.6%) patients in the olaparib/bevacizumab arm, in keeping with the higher proportion of patients progressing on placebo/bevacizumab arm. The majority of these patients received subsequent therapy after progression (95.4% [249/261] of patients in the olaparib/bevacizumab arm and 95.0% [172/181] of patients in the placebo/bevacizumab arm). A similar proportion of patients in the olaparib/bevacizumab and placebo/bevacizumab arms (4.8% vs 6.3%, respectively) received no further therapy after they progressed.
The most commonly reported subsequent treatments included chemotherapy (carboplatin, pegylated liposomal doxorubicin, paclitaxel, gemcitabine) and PARP inhibitors, which is consistent with clinical practice. Out of the patients who received subsequent anticancer treatment, the most common regimen was platinum-based chemotherapy (241/261 [92.3%] for olaparib/bevacizumab-treated patients vs 160/181 [88.4%] for placebo/bevacizumab-treated patients; table 31).

Subsequent PARP inhibitors were received by 36 (13.8%) of the 261 olaparib/bevacizumab treated patients who received a subsequent therapy, and 65 (35.9%) of the 181 placebo/bevacizumab-treated patients who received a subsequent therapy (Table 31 and Table 32). PARP inhibitors were received as the first subsequent therapy in 28 (10.7%) of the 261 patients in the olaparib/bevacizumab arm and 55 (30.4%) of the 181 patients in the placebo/bevacizumab arm potentially the PFS2 results.

Currently no data exist on re-challenge with PARPi, however the question is being addressed in the OReO trial currently enrolling at three sites in Denmark. For a HRD+ population data from PAOLA-1 and SOLO-1 support the finding that more patients will be candidate for PARPi treatment if treatment are advanced into 1st line. As highlighted by the control arms ~15-20% of will experience a platinum resistant relapse hence not being candidates for subsequent PARPi treatment. In addition, the percentage of patients not

responding to 2nd line platinum based chemotherapy would also be denied the potential opportunity of PARPi treatment.
The MITO16B - MaNGO OV2B - ENGOT OV17 trial demonstrated that re-challenge with bevacizumab in 2nd line PSR Ovarian Cancer is a viable solution meeting the primary endpoint with a HR of 0.51 (0.41-0.65). As of today, however currently not approved for treatment in Denmark. It is therefore speculative whether that would be an alternative options for the new group of patients who potentially would be treated with bevacizumab in 1st line.

Table 31. Subsequent cancer therapies

Category type[a]	Number (%) of patients		
	Olaparib/ bevacizumab (N=537)	Placebo/ bevacizumab (N=269)	Total (N=806)
Total	261 (48.6)	181 (67.3)	442 (54.8)
Platinum chemotherapy	241 (44.9)	160 (59.5)	401 (49.8)
Carboplatin	241 (44.9)	160 (59.5)	401 (49.8)
Other platinum	16 (3.0)	11 (4.1)	27 (3.3)
Non-platinum cytotoxic drug	253 (47.1)	175 (65.1)	428 (53.1)
Pegylated liposomal doxorubicin	204 (38.0)	144 (53.5)	348 (43.2)
Paclitaxel	102 (19.0)	55 (20.4)	157 (19.5)
Gemcitabine	91 (16.9)	64 (23.8)	155 (19.2)
Topoisomerase inhibitor	34 (6.3)	15 (5.6)	49 (6.1)
Trabectedin	17 (3.2)	10 (3.7)	27 (3.3)
Cyclophosphamide	7 (1.3)	7 (2.6)	14 (1.7)
Alkylating agent	7 (1.3)	3 (1.1)	10 (1.2)
Docetaxel	6 (1.1)	1 (0.4)	7 (0.9)
5-Fluorouracil	1 (0.2)	1 (0.4)	2 (0.2)
Anthracycline	2 (0.4)	0	2 (0.2)
Doxorubicin	1 (0.2)	1 (0.4)	2 (0.2)
Antimetabolite	0	1 (0.4)	1 (0.1)
Azatidine	1 (0.2)	0	1 (0.1)
Trabectedin analogue	0	1 (0.4)	1 (0.1)
Other	15 (2.8)	11 (4.1)	26 (3.2)
Other	15 (2.8)	11 (4.1)	26 (3.2)
Targeted therapy	96 (17.9)	103 (38.3)	199 (24.7)
PARP inhibitor	36 (6.7)	65 (24.2)	101 (12.5)
Antiangiogenic	48 (8.9)	33 (12.3)	81 (10.0)
Checkpoint inhibitor	26 (4.8)	17 (6.3)	43 (5.3)
Antibody against folate receptor	11 (2.0)	7 (2.6)	18 (2.2)
Hormonal treatment	7 (1.3)	4 (1.5)	11 (1.4)
Check point kinase inhibitor	1 (0.2)	0	1 (0.1)
EGFR inhibitor	1 (0.2)	0	1 (0.1)
HER2 inhibitor	0	1 (0.4)	1 (0.1)
MEK inhibitor	1 (0.2)	0	1 (0.1)
No subsequent cancer therapy[b]	276 (51.4)	88 (32.7)	364 (45.2)

Source: AstraZeneca. Data on file [29].

Table 32. PARPi use in PAOLA

	Number (%) of patients		
	Olaparib/ bevacizumab (N=537)	**Placebo/ bevacizumab (N=269)**	**Total (N=806)**
Received PARP inhibitor[a]	36 (6.7)	65 (24.2)	101 (12.5)
First subsequent cancer therapy	28 (5.2)	55 (20.4)	83 (10.3)
Second subsequent cancer therapy	8 (1.5)	7 (2.6)	15 (1.9)
Third subsequent cancer therapy	2 (0.4)	3 (1.1)	5 (0.6)
Fourth subsequent cancer therapy	0	1 (0.4)	1 (0.1)
Patients who subsequently received olaparib	11 (2.0)	36 (13.4)	47 (5.8)

Source: AstraZeneca. Data on file [29].

9 References

1. DGCG, *Dansk Gynækologisk Cancer Gruppe. Retningslinier for visitation , diagnostik og kontrol af epitelial ovarie- , tuba- og primær peritonealcancer samt borderline tumorer*. 2016: Denmark. p. 1-10.
2. NORDCAN - Association of the Nordic Cancer. Kræftstatistik: Nøgetal og figurer. *Avaliable at: https://www-dep.iarc.fr/nordcan/dk/frame.asp*. 2017.
3. Ray-Coquard, I., et al., *Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer.* New England journal of medicine, 2019. **381**(25): p. 2416-2428.
4. Medicinrådet, *Baggrund for Medicinrådets behandlingsvejledning vedrørende lægemidler til BRCA-muteret kræft i æggestokkene, æggelederne eller primær kræft i bughinden*. 2020: https://medicinraadet.dk/media/zgpgy0to/baggrund-for-medicinr%C3%A5dets-behandlingsvejledning-vedr-l%C3%A6gemidler-til-brca-muteret-kr%C3%A6ft-i-%C3%A6ggestokkene-vers-1-1_adlegacy.pdf.
5. Poveda A, F.A., Ledermann J, et al. , *Final overall survival results from SOLO2/ENGOT-ov21: a phase III trial assessing survival after maintenance treatment with the PARP inhibitor olaparib in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA mutation.* Presented at: 2020 American Society of Clinical Oncology Virtual Scientific Program; May 29-31; online., 2020.
6. Banerjee S, e.a., *Presented at ESMO Virtual Congress 19-21 September.* 2020.
7. Moore, K., et al., *Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer.* New England journal of medicine, 2018. **379**(26): p. 2495-2505.
8. DiSilvestro, P., et al., *Efficacy of Maintenance Olaparib for Patients With Newly Diagnosed Advanced Ovarian Cancer With a BRCA Mutation: Subgroup Analysis Findings From the SOLO1 Trial.* J Clin Oncol, 2020. **38**(30): p. 3528-3537.
9. Burger, R.A., et al., *Incorporation of bevacizumab in the primary treatment of ovarian cancer.* New England journal of medicine, 2011. **365**(26): p. 2473-2483.
10. Norquist, B.M., et al., *Mutations in Homologous Recombination Genes and Outcomes in Ovarian Carcinoma Patients in GOG 218: An NRG Oncology/Gynecologic Oncology Group Study.* Clin Cancer Res, 2018. **24**(4): p. 777-783.
11. Monk, B.J., et al., *Patient reported outcomes of a randomized, placebo-controlled trial of bevacizumab in the front-line treatment of ovarian cancer: a Gynecologic Oncology Group Study.* Gynecol Oncol, 2013. **128**(3): p. 573-8.
12. Tewari, K.S., et al., *Final Overall Survival of a Randomized Trial of Bevacizumab for Primary Treatment of Ovarian Cancer.* Journal of clinical oncology, 2019. **37**(26): p. 2317-2328.
13. Perren, T.J., et al., *A phase 3 trial of bevacizumab in ovarian cancer.* N Engl J Med, 2011. **365**(26): p. 2484-96.
14. Oza, A.M., et al., *Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial.* The lancet. Oncology, 2015. **16**(8): p. 928-936.
15. Ray-Coquard IL, P.P., Pignata S, et al., *Phase III PAOLA-1/ENGOT-ov25 trial: Olaparib plus bevacizumab (bev) as maintenance therapy in patients (pts) with newly diagnosed, advanced ovarian treated with platinum-based chemotherapy (PCh) plus bev.*, in *ESMO Congress 2019*. Barcelona, Spain: 27 September–1 October. LBA2_PR.
16. Ray-Coquard I, P.P., Pignata S, et al. , *Phase III PAOLA-1/ENGOT-ov25 trial: Olaparib plus bevacizumab (bev) as maintenance therapy in patients (pts) with newly diagnosed, advanced ovarian cancer(OC) treated with platinum-based chemotherapy (PCh) plus bev.* Annals of Oncology 2019;30:v851-v934, 2019.
17. AstraZeneca, *Data on file. PAOLA-1 MAIC and ITCs*. 2020.

18. Clinicaltrials.gov, *Platine, Avastin and OLAparib in 1st Line (PAOLA-1). Available at: https://clinicaltrials.gov/ct2/show/NCT02477644 (Accessed 01 August 2019).*
19. AstraZeneca, *Data of file: PAOLA-1 Clinical study report: Randomized, Double-Blind, Phase III Trial of Olaparib vs. Placebo in Patients with Advanced FIGO Stage IIIB – IV High Grade Serous or Endometrioid Ovarian, Fallopian Tube, or Peritoneal Cancer treated with standard First Line Treatment, Combining Platinum-Taxane Chemotherapy and Bevacizumab Concurrent with Chemotherapy and in Maintenance (PAOLA-1).* 2019.
20. Aghajanian, C., et al., *Independent radiologic review: bevacizumab in combination with gemcitabine and carboplatin in recurrent ovarian cancer.* Gynecol Oncol, 2014. **133**(1): p. 105-10.
21. Burger, R.A., et al., *Independent radiologic review of the Gynecologic Oncology Group Study 0218, a phase III trial of bevacizumab in the primary treatment of advanced epithelial ovarian, primary peritoneal, or fallopian tube cancer.* Gynecol Oncol, 2013. **131**(1): p. 21-6.
22. Floquet A, V.I., Colombo N, et al., *Progression-free survival by local investigator versus independent central review: comparative analysis of the AGO-OVAR16 Trial.* Gynecol Oncol 2015;136:37-42., 2015.
23. Monberg, M.J., et al., *Real-world bevacizumab utilization and outcomes in first-line ovarian cancer.* Journal of Clinical Oncology, 2019. **37**(15_suppl): p. 5578-5578.
24. Banerjee S, M.K., Colombo N, et al, *Maintenance olaparib for patients with newly diagnosed, advanced ovarian cancer and a BRCA mutation: 5-year follow-up from SOLO-1*, in *ESMO Virtual Congress 2020. Abstract 811MO. Presented September 18, 2020.*
25. DGCG, *Dansk Gynækologisk Cancer Gruppe. Retningslinjer for visitation, diagnostik, behandling og opfølgning af epitelial ovarie-, tuba- og primær peritonealcancer samt borderline tumorer 6. udgave 2019*: http://www.dgcg.dk/index.php/guidelines/ovariecancer-guidelines.
26. Ledermann JA, R.F., Fotopoulou C, et al., *Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.* Ann Oncol 2013;24:vi24-vi32, 2013.
27. DGCG, *Dansk Gynækologisk Cancer Gruppe: DGCG Annual Report 2017-19* 2017-19: http://www.dgcg.dk/images/rsrapport_DGCD_2017-19.pdf.
28. AstraZeneca, *Data on file: A phase III, randomised, double blind, placebo controlled, multicentre study of olaparib maintenance monotherapy in patients with BRCA mutated advanced (FIGO Stage III-IV) ovarian cancer following first line platinum based chemotherapy.* 2018.
29. AstraZeneca, *Data on file: PAOLA-1 higher and lower risk group.* 2020.
30. EMEA, *Lynparza-H-C-3726-II-0035: EPAR - assesment report - variation*. 2020: https://www.ema.europa.eu/en/documents/variation-report/lynparza-h-c-3726-ii-0035-epar-assessment-report-variation_en.pdf.
31. I.B. Vergote, K.N.M., R. Hettle, K. Rhodes, M. Ouwens and I. Ray-Coquard, *Population adjusted indirect comparison of the SOLO1 and PAOLA-1/ENGOT-ov25 studies of olaparib with or without bevacizumab, bev alone and placebo in the maintenance treatment of women with newly diagnosed stage III/IV ovarian cancer with BRCA mutation*, in *Annual SGO conference* 2020: Toronto.
32. EMEA, *LYNPARZA: EPAR - product information*. 2020: https://www.ema.europa.eu/en/documents/product-information/lynparza-epar-product-information_en.pdf.
33. AstraZeneca data on file, *Clinical Study Report. A phase III, randomised, double blind, placebo controlled, multicentre study of olaparib maintenance monotherapy in patients with BRCA mutated advanced (FIGO stage III-IV) ovarian cancer following first line platinum based chemotherapy.* 2018.

10 Appendices

Literature search

See separate document for excluded studies/references

10.1 Main characteristics of included studies A2

Table A2 Study and baseline characteristics PAOLA

Trial name	PAOLA-1
NCT number	NCT02477644
Objective	Undersøge vedligeholdelsesbehandling af olaparib sammenlignet med placebo hos nydiagnosticerede ovarie cancer patienter som modtager kemoterapi + bevacizumab efterfulgt af bevacizumab, og uafhængigt af BRCA mutationsstatus.
Publications – title, author, journal, year	**Publicerede data:** 1. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer **Ray-Coquard I**, Pautier P, Pignata S, Pérol D, González-Martín A, Berger R, Fujiwara K, Vergote I, Colombo N, Mäenpää J, Selle F, Sehouli J, Lorusso D, Guerra Alía EM, Reinthaller A, Nagao S, Lefeuvre-Plesse C, Canzler U, Scambia G, Lortholary A, Marmé F, Combe P, de Gregorio N, Rodrigues M, Buderath P, Dubot C, Burges A, You B, Pujade-Lauraine E, Harter P. *N Engl J Med* 2019;381:2416–28 [3].
Study type and design	• Phase 3, randomised . Patients were randomisered 2:1 to olaparib + bevacizumab or placebo + bevacizumab • The study included patients between July 2015 and September 2017 • Stratification: BRCA status and 1st line treatment success • Tumor characteristics as assessed by the myChoice® HRD Plus assay (Myriad Genetic Laboratories, Inc • HRQoL tool EORTC QLQ-C30 • Kaplan–Meier was used to estimate PFS. • Hazard ratio(HR) and related 95% confidence intervals were calculated using stratified Cox proportional-hazards model. **Bevacizumab: 15 mg/kg, hver 3. uge ialt 15 måneder inklusiv perioden hvor det administreres sammen med kemoterapi.
Follow-up time	Median follow-up and median duration og treatement show below Follow-up og behandlingslængde

		Olaparib + bevacizumab	Placebo + bevacizumab
Randomized, n		537	269
Treated, n (%)		535 (99.6)	267 (99.3)
Discontinued study treatment, n (%)		331 (62)	194 (73)
	Disease progression per RECIST	182 (34)	155 (58)
	Disease progression non-RECIST	14 (3)	13 (5)
	TEAE	109 (20)	13 (5)
	Patient decision	17 (3)	10 (4)
	Death	1 (<1)	3 (1)
	Other*	8 (1)	0
Median duration of treatment, months (range)	Olaparib/placebo	17.3 (0.03–33.0)	15.6 (0.07–26.2)
	Bevacizumab	11.0 (0.69–21.4)	10.6 (0.69–17.1)
[redacted]		[redacted]	[redacted]

Population (inclusion and exclusion criteria)

Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
• Female patients ≥18 years with newly diagnosed advanced (FIGO stage IIIB, IIIC or IV) ovarian cancer, primary peritoneal cancer and/or fallopian tube cancer. • Postmenopausal or evidence of non-childbearing status for women of childbearing potential prior to first dose of study treatment. • Completed platinum-taxane chemotherapy prior to randomisation (minimum 6, maximum 9 cycles, unless discontinuation due to non-haematological toxicity after at least 4 cycles). • Randomised at least 3 weeks and no more than 9 weeks after their last dose of chemotherapy. • Received a minimum of 3 cycles of bevacizumab (15 mg/kg Q3W) in combination with the last 3 cycles of platinum-based chemotherapy. – In patients who have undergone IDS, a minimum of 2 cycles of bevacizumab (15 mg/kg Q3W) in combination with the last three cycles of platinum-based chemotherapy must have been received. • ECOG performance status 0 to 1.	• Patients whose tumours were of non-epithelial origin of the ovary, fallopian tube or peritoneum (germ cell tumours). • Patients with ovarian tumours of low malignant potential (e.g. borderline tumours) or mucinous carcinoma. • Patients with synchronous primary endometrial cancer, unless both of the following criteria were met: – stage <II AND – less than 60 years old at the time of diagnosis of endometrial cancer with stage IA or IB grade I or II, or stage IA grade III endometrial carcinoma OR – ≥60 years old at the time of diagnosis of endometrial cancer with stage IA grade I or II endometrioid adenocarcinoma. • Patients with serous or clear cell adenocarcinoma or carcinosarcoma of the endometrium. • Pregnant or lactating women. • Any previous treatment with PARPi, including olaparib.

Full list of inclusion and exclusion criteria:

https://www.nejm.org/doi/suppl/10.1056/NEJMoa1911361/suppl_file/nejmoa1911361_appendix.pdf).

Intervention

Intervention:

Patients were randomisered 2:1 to olaparib + bevacizumab or placebo + bevacizumab

Olaparib administrated as:

Olaparib 300mg BID + bevacizumab 15 mg/kg Q3W.

Olaparib or placebo maintenance treatment duration up to 24 months, bevacizumab maintenance treatment duration up to 15 months (including pre-randomisation period).

Comparator

<table>
<tr><td></td><td>Bevacizumab:
15 mg/kg every 3rd week(+ placebo DID) for up to 15 months including pre-randomisation period where the patient receiced platinum-based chemotherapy. Avastin from Roche is no longer patent protected in Denmark and two biosimilar product have been launched 13.07.2020</td></tr>
<tr><td>Cross-over</td><td>Cross-over to olaprib

<table>
<tr><th>Cross-over in PAOLA-1 study</th><th>Olaparib + bevacizumab (N=537)</th><th>Placebo + bevacizumab (N=269)</th></tr>
<tr><td>Received PARPi, n (%)</td><td>36 (6.7)</td><td>65 (24.2)</td></tr>
<tr><td>First subsequent cancer therapy</td><td>28 (5.2)</td><td>55 (20.4)</td></tr>
<tr><td>Second subsequent cancer therapy</td><td>8 (1.5)</td><td>7 (2.6)</td></tr>
<tr><td>Third subsequent cancer therapy</td><td>2 (0.4)</td><td>3 (1.1)</td></tr>
<tr><td>Fourth subsequent cancer therapy</td><td>0</td><td>1 (0.4)</td></tr>
<tr><td>Patients who subsequently received olaparib, n (%)</td><td>11 (2.0)</td><td>36 (13.4)</td></tr>
</table></td></tr>
<tr><td>Primære og sekundære endepunkter</td><td>Primary:

• PFS

Secondary:

• OS
• time to second disease progression or death
• time to start of first subsequent therapy or death (TFST)
• time to start of second subsequent therapy or death (TSST)
• QoL
• toxicity</td></tr>
<tr><td>Subgroups</td><td>BIOMARKER SUBGROUPS IN PAOLA-1

<table>
<tr><th></th><th>Olaparib + bevacizumab (N=537)</th><th>Placebo + bevacizumab (N=269)</th></tr>
<tr><td colspan="3">tBRCA status by laboratory testing as per randomisation, n (%)</td></tr>
<tr><td>tBRCAm</td><td>161 (30.0)</td><td>80 (29.7)</td></tr>
<tr><td>Absence of deleterious tBRCAm[a]</td><td>376 (70.0)</td><td>189 (70.3)</td></tr>
<tr><td colspan="3">tBRCA status by laboratory testing as per eCRF, n (%)</td></tr>
<tr><td>tBRCAm</td><td>157 (29.2)</td><td>80 (29.7)</td></tr>
<tr><td>Non- tBRCAm[b]</td><td>380 (70.8)</td><td>189 (70.3)</td></tr>
<tr><td colspan="3">tBRCA status by Myriad myChoice® HRD Plus test, n (%)</td></tr>
<tr><td>tBRCAm</td><td>158 (29.4)</td><td>77 (28.6)</td></tr>
<tr><td>Non- tBRCAm[b]</td><td>346 (64.4)</td><td>174 (64.7)</td></tr>
<tr><td>tBRCA test cancelled/failed</td><td>17 (3.2)</td><td>10 (3.7)</td></tr>
<tr><td>tBRCA missing</td><td>16 (3.0)</td><td>8 (3.0)</td></tr>
<tr><td colspan="3">HRD status by Myriad myChoice® HRD Plus test (tBRCAm or ≥42 cut-off), n (%)</td></tr>
<tr><td>HRD positive[c]</td><td>255 (47.5)</td><td>132 (49.1)</td></tr>
<tr><td>HRD positive (tBRCAm negative)[d]</td><td>97 (18.1)</td><td>55 (20.4)</td></tr>
<tr><td>HRD negative[e]</td><td>192 (35.8)</td><td>85 (31.6)</td></tr>
<tr><td>HRD unknown or missing[f]</td><td>90 (16.8)</td><td>52 (19.4)</td></tr>
</table></td></tr>
</table>

	[a]Includes inconclusive and unknown tBRCA status: 26 patients in the olaparib + bevacizumab arm and 7 patients in the placebo + bevacizumab arm. [b]Non-tBRCAm = tBRCAwt/VUS. [c]Tumour BRCA mutation or HRD score ≥42. [d]HRD score ≥42. [e]HRD score <42. [f]Includes Myriad HRD status test cancelled or failed, and Myriad HRD status missing. ***Source:** AstraZeneca Data on File (PAOLA-1 CSR) [19], Ray-Coquard et al. 2019 (Supplementary Appendices) [3].* All subgoups were predefined except for: • HRD negative • HRD unknown

PATIENT CHARACTERISTICS ITT POPULATION

Patient Characteristics	Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)
Age, median, years (range)	61 (32–87)	60 (26–85)
ECOG performance status, n (%)		
0	378 (70.4)	189 (70.3)
1	153 (28.5)	76 (28.3)
Missing data	6 (1.1)	4 (1.5)
Primary tumour location, n (%)		
Ovary	456 (84.9)	238 (88.5)
Fallopian tubes	39 (7.3)	11 (4.1)
Primary peritoneal	42 (7.8)	20 (7.4)
Histology, **n(%)**		
Serous[a]	519 (96.6)	253 (94.1)
Endometrioid	12 (2.2)	8 (3.0)
Other[b]	6 (1.2)	8 (3.0)
t*BRCA*m status[d], **n (%)**		
Deleterious t*BRCA*m	161 (30.0)	80 (29.7)
Absence of deleterious mutation[e]	376 (70.0)	189 (70.3)
FIGO stage, **n (%)**		
III[f]	378 (70.4)	186 (69.1)
IV	159 (29.6)	83 (30.9)
History of cytoreductive surgery, **n (%)**		
PDS	271 (50.5)	138 (51.3)
• Residual macroscopic disease	111/271 (41.0)	53/138 (38.4)
• No residual macroscopic disease	160/271 (59.0)	85/138 (61.6)

Patient Characteristics	Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)
IDS	228 (42.5)	110 (40.9)
• Residual macroscopic disease	65/228 (28.5)	35/110 (31.8)
• No residual macroscopic disease	163/228 (71.5)	75/110 (68.2)
No surgery	38 (7.1)	21 (7.8)
First line treatment outcome, **n (%)**		
NED with complete macroscopic resection at PDS	170 (31.7)	86 (32.0)
NED/CR with complete macroscopic resection at IDS	166 (30.9)	84 (31.2)
NED/CR with incomplete resection at PDS or IDS, or no debulking surgery	82 (15.3)	40 (14.9)
PR	119 (22.2)	59 (21.9)

Footnotes: *[a]Two patients had low-grade serous carcinoma with a BRCAm. [b]Other includes clear cell (2 patients assigned to olaparib + bevacizumab arm), undifferentiated (1 patient assigned to the olaparib + bevacizumab arm, 6 patients assigned to the placebo + bevacizumab arm) and other (3 patients assigned to the olaparib + bevacizumab arm, 2 patients assigned to the placebo + bevacizumab arm) histology. [d]Screening laboratory tBRCA status on tumour tissue, per randomisation schedule. [e]Includes inconclusive and unknown tBRCA status: 26 patients in the olaparib + bevacizumab arm and 7 patients in the placebo + bevacizumab arm.. [f]Includes FIGO stage IIIB and IIIC patients.*

Source: *Ray-Coquard et al. 2019, ESMO Congress Presentation [15], Ray-Coquard et al. 2019 [3], AstraZeneca Data on File (PAOLA-1 CSR) [19].*

Table A2 Study and baseline characteristics SOLO-1

Trial name	A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Patients with BRCA Mutated Advanced (FIGO Stage III-IV) Ovarian Cancer following First Line Platinum Based Chemotherapy.
NCT number	NCT01844986
Objective	To determine the efficacy of olaparib maintenance monotherapy compared to placebo in BRCA mutated high risk advanced ovarian cancer patients who are in clinical complete response or partial response following first line platinum based chemotherapy.
Publications – title, author, journal, year	Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. K. Moore, N. Colombo, G. Scambia, B.-G. Kim, A. Oaknin, M. Friedlander, A. Lisyanskaya, A. Floquet, A. Leary, G.S. Sonke, C. Gourley, S. Banerjee, A. Oza, A. González-Martín, C. Aghajanian, W. Bradley, C. Mathews, J. Liu, E.S. Lowe, R. Bloomfield, and P. DiSilvestro. N Engl J Med 2018; 379:2495-2505 [7].
Study type and design	A phase III, randomised, double-blind, placebo-controlled, multi-center study to assess the efficacy of olaparib maintenance monotherapy in high risk advanced ovarian cancer patients

	(including patients with primary peritoneal and / or fallopian tube cancer) with BRCA mutations [documented mutation in BRCA1 or BRCA2] that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) who have responded following first line platinum based chemotherapy. Patients will be randomised in a 2:1 ratio to the treatments as specified below: • olaparib tablets p.o. 300mg twice daily. • placebo tablets p.o. twice daily. Randomisation will be stratified by: • response to first line platinum chemotherapy (clinical complete response or partial response) Patients will be randomised within 8 weeks after their last dose of chemotherapy (last dose is the day of the last infusion). Patients in both treatment arms will have tumour assessments according to RECIST at baseline and every 12 weeks (±1 week) up to 120 weeks and then every 24 weeks (±1 week) relative to date of randomisation, until objective radiological disease progression according to RECIST. All CT/MRI scans will be sent to an AstraZeneca appointed Clinical Research Organisation (CRO) for blinded independent central review. After the primary Progression Free Survival (PFS) analysis, central review of scans will no longer be required.
Follow-up time	At the DCO of SOLO1, the median follow-up time was 41 months.
Population (inclusion and exclusion criteria)	Inclusion and exclusion criteria related to NCT number from www.clinicaltrials.gov: **Inclusion criteria:** • Female patients with newly diagnosed, histologically confirmed, high risk advanced (FIGO stage III - IV) BRCA mutated high grade serous or high grade endometrioid ovarian cancer, primary peritoneal cancer and / or fallopian - tube cancer who have completed first line platinum based chemotherapy (intravenous or intraperitoneal). • Stage III patients must have had one attempt at optimal debulking surgery (upfront or interval debulking). Stage IV patients must have had either a biopsy and/or upfront or interval debulking surgery. • Documented mutation in BRCA1 or BRCA2 that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function). • Patients who have completed first line platinum (e.g. carboplatin or cisplatin), containing therapy (intravenous or intraperitoneal) prior to randomisation: • Patients must have, in the opinion of the investigator, clinical complete response or partial response and have no clinical evidence of disease progression on the post treatment scan or rising CA-125 level, following completion of this chemotherapy course. Patients with stable disease on the post-treatment scan at completion of first line platinum-containing therapy are not eligible for the study. • Patients must be randomized within 8 weeks of their last dose of chemotherapy **Exclusion criteria:** • BRCA1 and/or BRCA2 mutations that are considered to be non detrimental (e.g. "Variants of uncertain clinical significance" or "Variant of unknown significance" or "Variant, favor polymorphism" or "benign polymorphism" etc). • Patients with early stage disease (FIGO Stage I, IIA, IIB or IIC) • Stable disease or progressive disease on the post-treatment scan or clinical evidence of progression at the end of the patient's first line chemotherapy treatment.

	• Patients where more than one debulking surgery has been performed before randomisation to the study. (Patients who, at the time of diagnosis, are deemed to be unresectable and undergo only a biopsy or oophorectomy but then go on to receive chemotherapy and interval debulking surgery are eligible). • Patients who have previously been diagnosed and treated for earlier stage ovarian, fallopian tube or primary peritoneal cancer. • Patients who have previously received chemotherapy for any abdominal or pelvic tumour, including treatment for prior diagnosis at an earlier stage for their ovarian, fallopian tube or primary peritoneal cancer. (Patients who have received prior adjuvant chemotherapy for localised breast cancer may be eligible, provided that it was completed more than three years prior to registration, and that the patient remains free of recurrent or metastatic disease). • Patients with synchronous primary endometrial cancer unless both of the following criteria are met: 1) stage <2 2) less than 60 years old at the time of diagnosis of endometrial cancer with stage IA or IB grade 1 or 2, or stage IA grade 3 endometrioid adenocarcinoma OR ≥ 60 years old at the time of diagnosis of endometrial cancer with Stage IA grade 1 or 2 endometrioid adenocarcinoma. Patients with serous or clear cell adenocarcinoma or carcinosarcoma of the endometrium are not eligible.
Intervention	391 patients were randomised using an Interactive Voice Response System / Interactive Web Response System (IVR/IWR system) in a 2:1 ratio to the treatments as specified below: • Olaparib tablets p.o. 300 mg twice daily • Placebo tablets p.o. twice daily Patients should continue to receive study treatment for up to two years or until objective radiological disease progression as per RECIST as assessed by the investigator, whichever is earlier, and as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria as outlined in section 5.8. Patients should continue with study treatment to RECIST progression as described above despite rises in CA125. Patients who continue to have evidence of stable disease at two years may continue to receive study treatment if, in the opinion of the investigator, it is in the patient's best interest. However, if at two years the patient has no evidence of disease, study treatment should be discontinued.

Baseline characteristics	<table><tr><th>Characteristic</th><th>Olaparib (N=260)</th><th>Placebo (N=131)</th></tr><tr><td colspan="3">Age, year</td></tr><tr><td>Median</td><td>53.0</td><td>53.0</td></tr><tr><td>Range</td><td>29–82</td><td>31–84</td></tr><tr><td>Median duration of follow-up for primary analysis (months)[a]</td><td>40.7 (34.9–42.9)</td><td>41.2 (32.2–41.6)</td></tr><tr><td colspan="3">ECOG performance status, n (%)</td></tr><tr><td>0 Normal activity</td><td>200 (76.9%)</td><td>105 (80.2%)</td></tr><tr><td>1 Restricted activity</td><td>60 (23.1%)</td><td>25 (19.1%)</td></tr><tr><td>Missing data</td><td>0</td><td>1 (0.8%)</td></tr><tr><td colspan="3">Myriad/BGI or locally reported BRCA gene name[b] n (%)</td></tr><tr><td>BRCA1</td><td>191 (73.5%)</td><td>91 (69.5%)</td></tr><tr><td>BRCA2</td><td>66 (25.4%)</td><td>40 (30.5%)</td></tr><tr><td>BRCA1 and BRCA2</td><td>3 (1.2%)</td><td>0</td></tr><tr><td colspan="3">Primary tumour location, n (%)</td></tr><tr><td>Ovary</td><td>220 (84.6%)</td><td>113 (86.3%)</td></tr><tr><td>Fallopian tubes</td><td>22 (8.5%)</td><td>11 (8.4%)</td></tr><tr><td>Primary peritoneal</td><td>15 (5.8%)</td><td>7 (5.3%)</td></tr><tr><td>Other[d]</td><td>3 (1.2%)</td><td>0</td></tr><tr><td colspan="3">Histology, n (%)</td></tr><tr><td>Serous</td><td>246 (94.6%)</td><td>130 (99.2%)</td></tr><tr><td>Endometrioid</td><td>9 (1.5%)</td><td>0</td></tr><tr><td>Mixed serous/endometrioid</td><td>5 (1.9%)</td><td>1 (0.8)</td></tr><tr><td colspan="3">FIGO stage, n (%)</td></tr><tr><td>Stage III</td><td>220 (84.6%)</td><td>105 (80.2%)</td></tr><tr><td>Stage IV</td><td>40 (15.4%)</td><td>26 (19.8%)</td></tr><tr><td colspan="3">Response to previous platinum chemotherapy, n (%)</td></tr><tr><td>Clinical CR</td><td>213 (81.9%)</td><td>107 (81.7%)</td></tr><tr><td>PR</td><td>47 (18.1%)</td><td>24 (18.3%)</td></tr></table> *[a]time from randomisation to date of censoring [b]gBRCAm patients reported using Myriad/BGI test were considered first before then considering locally reported BRCA gene name. The five randomised patients from China had a BGI test rather than a Myriad test. [c]Patients with unknown gBRCA status or patients with a local BRCA test that was not performed on a blood sample or whose sample type was indicated as unknown in the eCRF; [d]other includes fallopian tube, peritoneum and omentum cancer (n=1), ovary and peritoneum (n=1) and tubo-ovary (n=1).*
Primary and secondary endpoints	**Primary endpoint** was investigator assessed PFS as measured by RECIST 1.1 criteria. **Secondary endpoi**nts included PFS by Blinded independent central review (BICR), OS, PFS2, TFST, TSST, TDT, health-related quality of life (trial outcome index [TOI], functional assessment of cancer therapy for ovarian cancer [FACT-O] and safety and tolerability.
Method of analysis	The primary statistical analysis of the efficacy of olaparib will include all randomised patients and will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received. Patients who were randomised but did not subsequently go on to receive study treatment are included in the Full Analysis Set (FAS). Therefore, all efficacy and health-related quality of life (HRQoL) data will be summarised and analysed using the FAS on an intention-to-treat (ITT) basis. When assessing safety and tolerability, summaries will be produced based on the Safety Analysis Set. This will include all patients who receive at least one dose of randomised treatment (olaparib or placebo). The safety data will be summarised descriptively and will not be formally analysed. PFS will be analysed using a log rank test stratified by response to first line platinum chemotherapy (clinical complete response or partial response). The HR together with its 95% confidence interval and p-value will be presented (a HR less than 1 will favour olaparib). This analysis will be performed when approximately 206 progression events have occurred. The primary analysis will be based on investigator-recorded assessment of disease progression by RECIST; however, sensitivity analyses will be performed including using a blinded independent central review (BICR).
Subgroup analyses	Subgroup analyses will be conducted comparing PFS between treatments in the following subgroups of the full analysis set:

	• Response to previous platinum chemotherapy (clinical complete response or partial response) • ECOG performance status at baseline (0 or 1) • Baseline CA-125 value (≤ ULN vs > ULN) • Age at randomisation (<65 vs. >=65) • Stage of disease at initial diagnosis (III or IV)

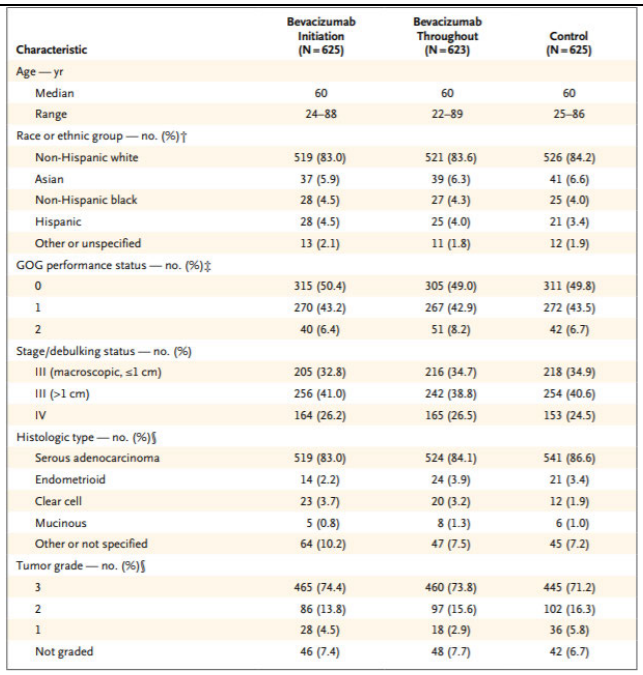
Table A2 Study and baseline characteristics GOG-218

Trial name	A Phase III Trial of Carboplatin and Paclitaxel Plus Placebo Versus Carboplatin and Paclitaxel Plus Concurrent Bevacizumab (NSC # 704865) Followed by Placebo, Versus Carboplatin and Paclitaxel Plus Concurrent and Extended Bevacizumab, in Women With Newly Diagnosed, Previously Untreated, Stage III or IV Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancer
NCT number	NCT00262847
Objective	To study carboplatin, paclitaxel, and bevacizumab to see how well they work compared to carboplatin, paclitaxel, and placebo in treating patients with stage III or stage IV ovarian epithelial, primary peritoneal, or fallopian tube cancer.
Publications – title, author, journal, year	Burger et al. Incorporation of Bevacizumab in the Primary Treatment of Ovarian Cancer. N Engl J Med 2011;365:2473-83 [9].
Study type and design	A phase III randomized study to evaluate new treatment programs for patients with advanced stage (International Federation of Gynecologic Oncology, FIGO, III-IV) epithelial ovarian or peritoneal primary cancer.
Follow-up time	102.9 months at final OS cut off.
Population (inclusion and exclusion criteria)	Inclusion and exclusion criteria related to NCT number from www.clinicaltrials.gov: **Inclusion criteria:** • Patients with a histologic diagnosis of epithelial ovarian cancer, peritoneal primary carcinoma or fallopian tube cancer; International Federation of Gynecology and Obstetrics (FIGO) stage III with any gross (macroscopic or palpable) residual disease or FIGO stage IV, defined surgically at the completion of initial abdominal surgery and with appropriate tissue available for histologic evaluation; the minimum surgery required was an abdominal surgery providing tissue for histologic evaluation and establishing and documenting the primary site and stage, as well as a maximal effort at tumor debulking; if additional surgery was performed, it should have been in accordance with appropriate surgery for ovarian or peritoneal carcinoma described in the Gynecologic Oncology Group (GOG) Surgical Procedures Manual; however, the surgeon is not required to have performed all of the items contained in this section of the GOG Surgical Procedures Manual; those patients with stage III cancer in which the largest maximal diameter of any residual tumor implant at the completion of this initial surgery is no greater than 1 cm will be defined as "optimal;" all others will be defined as "suboptimal;" measurable disease on post-operative imaging studies is not required for eligibility • Patients with the following histologic epithelial cell types are eligible: serous adenocarcinoma, endometrioid adenocarcinoma, mucinous adenocarcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, transitional cell carcinoma, malignant Brenner's Tumor, or adenocarcinoma not otherwise specified (N.O.S.); however, the histologic features of the tumor must be compatible with a primary Müllerian epithelial adenocarcinoma; if doubt exists, it is

	recommended that the investigator should have the slides reviewed by an independent pathologist or, if necessary, the Pathology Co-Chair, prior to entry; patients may have co-existing fallopian tube carcinoma in-situ so long as the primary origin of invasive tumor is ovarian, peritoneal or fallopian tube • Absolute neutrophil count (ANC) greater than or equal to 1,500/µl equivalent to Common Toxicity Criteria for Adverse Events version (v)3.0 (CTCAE) grade 1; this ANC cannot have been induced or supported by granulocyte colony stimulating factors • Platelets greater than or equal to 100,000/µl; (CTCAE grade 0-1) • Creatinine =< 1.5 x institutional upper limit normal (ULN), CTCAE grade 1 • Bilirubin less than or equal to 1.5 x ULN (CTCAE grade 1) • Serum glutamic oxaloacetic transaminase (SGOT) and alkaline phosphatase less than or equal to 2.5 x ULN (CTCAE grade 1) • Neuropathy (sensory and motor) less than or equal to CTCAE grade 1 • Prothrombin time (PT) such that international normalized ratio (INR) is =< 1.5 (or an in-range INR, usually between 2 and 3, if a patient is on a stable dose of therapeutic warfarin for management of venous thrombosis including pulmonary thrombo-embolus) and a partial thromboplastin time (PTT) < 1.2 times the upper limit of normal • Patients with a GOG Performance Status of 0, 1, or 2 • Patients must be entered between 1 and 12 weeks after initial surgery performed for the combined purpose of diagnosis, staging and cytoreduction • Patients with measurable and non-measurable disease are eligible; patients may or may not have cancer-related symptoms • Patients who have met the pre-entry requirements • An approved informed consent and authorization permitting release of personal health information must be signed by the patient or guardian • Patients in this trial may receive ovarian estrogen +/- progestin replacement therapy as indicated at the lowest effective dose(s) for control of menopausal symptoms at any time, but not progestins for management of anorexia while on protocol directed therapy or prior to disease progression **Exclusion criteria:** • Patients with a current diagnosis of borderline epithelial ovarian tumor (formerly "tumors of low malignant potential") or recurrent invasive epithelial ovarian, primary peritoneal or fallopian tube cancer treated with surgery only (such as patients with stage Ia or Ib low grade epithelial ovarian or fallopian tube cancers) are not eligible; patients with a prior diagnosis of a borderline tumor that was surgically resected and who subsequently develop an unrelated, new invasive epithelial ovarian, peritoneal primary or fallopian tube cancer are eligible, provided that they have not received prior chemotherapy for any ovarian tumor • Patients who have received prior radiotherapy to any portion of the abdominal cavity or pelvis are excluded; prior radiation for localized cancer of the breast, head and neck, or skin is permitted, provided that it was completed more than three years prior to registration, and the patient remains free of recurrent or metastatic disease • Patients who have received prior chemotherapy for any abdominal or pelvic tumor including neo-adjuvant chemotherapy for their ovarian, primary peritoneal or fallopian tube cancer are excluded; patients may have received prior adjuvant chemotherapy for localized breast cancer, provided that it was completed more than

	three years prior to registration, and that the patient remains free of recurrent or metastatic disease • Patients who have received any targeted therapy (including but not limited to vaccines, antibodies, tyrosine kinase inhibitors) or hormonal therapy for management of their epithelial ovarian or peritoneal primary cancer • Patients with synchronous primary endometrial cancer, or a past history of primary endometrial cancer, are excluded, unless all of the following conditions are met: stage not greater than I-B; no more than superficial myometrial invasion, without vascular or lymphatic invasion; no poorly differentiated subtypes, including papillary serous, clear cell or other FIGO grade 3 lesions • With the exception of non-melanoma skin cancer and other specific malignancies as noted above, patients with other invasive malignancies who had (or have) any evidence of the other cancer present within the last five years or whose previous cancer treatment contraindicates this protocol therapy are excluded • Patients with acute hepatitis or active infection that requires parenteral antibiotics • Patients with serious non-healing wound, ulcer, or bone fracture; this includes history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within 28 days; patients with granulating incisions healing by secondary intention with no evidence of fascial dehiscence or infection are eligible but require weekly wound examinations • Patients with active bleeding or pathologic conditions that carry high risk of bleeding, such as known bleeding disorder, coagulopathy, or tumor involving major vessels • Patients with history or evidence upon physical examination of central nervous system (CNS) disease, including primary brain tumor, seizures not controlled with standard medical therapy, any brain metastases, or history of cerebrovascular accident (CVA, stroke), transient ischemic attack (TIA) or subarachnoid hemorrhage within six months of the first date of treatment on this study • Patients with clinically significant cardiovascular disease; this includes: • Uncontrolled hypertension, defined as systolic > 150 mm Hg or diastolic > 90 mm Hg • Myocardial infarction or unstable angina < 6 months prior to registration • New York Heart Association (NYHA) grade II or greater congestive heart failure • Serious cardiac arrhythmia requiring medication; this does not include asymptomatic, atrial fibrillation with controlled ventricular rate • CTCAE grade 2 or greater peripheral vascular disease (at least brief (< 24 hrs) episodes of ischemia managed non-surgically and without permanent deficit) • History of CVA within six months • Patients with known hypersensitivity to Chinese hamster ovary cell products or other recombinant human or humanized antibodies • Patients with clinically significant proteinuria; urine protein should be screened by urine protein-creatinine ratio (UPCR); the UPCR has been found to correlate directly with the amount of protein excreted in a 24 hour urine collection; specifically, a UPCR of 1.0 is equivalent to 1.0 gram of protein in a 24 hour urine collection; obtain at least 4 ml of a random urine sample in a sterile container (does not have to be a 24 hour urine); send sample to lab with request for urine protein and creatinine levels [separate requests]; the lab will measure protein concentration (mg/dL) and creatinine concentration (mg/dL); the UPCR is derived as follows: protein concentration (mg/dL)/creatinine (mg/dL); patients must have a UPCR < 1.0 to allow participation in the study

	• Patients with or with anticipation of invasive procedures as defined below: • Major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to the first date of bevacizumab/placebo therapy (cycle 2) • Major surgical procedure anticipated during the course of the study; this includes, but is not limited to abdominal surgery (laparotomy or laparoscopy) prior to disease progression, such as colostomy or enterostomy reversal, interval or secondary cytoreductive surgery, or second look surgery; please consult with the study chair prior to patient entry for any questions related to the classification of surgical procedures • Core biopsy, within 7 days prior to the first date of bevacizumab/placebo therapy (cycle 2) • Patients with GOG Performance Grade of 3 or 4 • Patients who are pregnant or nursing; bevacizumab should not be administered to nursing women; patients of childbearing potential must agree to use contraceptive measures during study therapy and for at least six months after completion of bevacizumab therapy • Patients who have received prior therapy with any anti-vascular endothelial growth factor (VEGF) drug, including bevacizumab • Patients with clinical symptoms or signs of gastrointestinal obstruction and who require parenteral hydration and/or nutrition • Patients with medical history or conditions not otherwise previously specified which in the opinion of the investigator should exclude participation in this study; the investigator should feel free to consult the study chair or study co-chairs for uncertainty in this regard
Intervention	A total of 1873 patients were randomised in equal proportions to the following three arms: • CPP arm: Five cycles of placebo (started cycle 2) in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles followed by placebo alone, for a total of up to 15 months of therapy • CPB15 arm: Five cycles of Avastin (15 mg/kg q3w started cycle 2) in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m2) for 6 cycles followed by placebo alone, for a total of up to 15 months of therapy • CPB15+ arm: Five cycles of Avastin (15 mg/kg q3w started cycle 2) in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m2) for 6 cycles followed by continued use of Avastin (15 mg/kg q3w) as single agent for a total of up to 15 months of therapy

Baseline characteristics	 *Burger et all. 2011[3]*
Primary and secondary endpoints	The primary endpoint was PFS based on investigator's assessment of disease progression based on radiological scans or CA 125 levels, or symptomatic deterioration per protocol. In addition, a prespecified analysis of the data censoring for CA-125 progression events was conducted, as well as an independent review of PFS as determined by radiological scans. Secondary Outcome Measures Overall Survival [Time Frame: From study entry to death or last contact, up to 6 years] Median overall survival (OS) Frequency and Severity (Grade 3 or Above) of Adverse Events Assessed by Common Terminology Criteria for Adverse Events Version 3.0 [Time Frame: Up to 5 years] Eligible and Evaluable patients Impact on Quality of Life Measured by the Functional Assessment of Cancer Therapy-Ovary Trial Outcome Index (FACT-O TOI) [Time Frame: At baseline, 9, 18, 36, 60, and 84 weeks] Estimated least squares means from a mixed module of Quality of Life (QOL) scores at each assessment point, adjusted for baseline score and patient's age. Note: The range of possible scores of the FACT-O TOI is 0 - 104 for all treatment groups and at all visits. A higher score indicates better QOL. Baseline mean scores are raw means.
Method of analysis	The primary analyses of overall survival will include all patients enrolled onto the study regardless of eligibility or compliance to their assigned study regimen. Patients will be grouped by their randomized treatment for intention-to-treat analyses (ITT). Safety endpoints will be summarized with descriptive statistics for the patients in the safety analysis dataset. The safety analysis dataset will include all patients enrolled to the study who receive any of their assigned study treatment and the patients will be grouped by their assigned treatment. Patients who do not receive any of their assigned study treatment will not be included in these analyses.
Subgroup analyses	Patients determined by presence of clinically measurable of disease (clinically measurable vs non-measurable), site of primary disease (ovarian vs extra-ovarian), stage of disease (III vs IV), histologic cell type (papillary serous vs mucinous vs clear cell vs other cell types), Grade (1 and 2 vs 3) and age (<= 60 vs > 60 years). The exploratory analysis will include an estimate of the treatment hazard ratios among only those patients deemed eligible for the study.

Characteristic	Bevacizumab Initiation (N = 625)	Bevacizumab Throughout (N = 623)	Control (N = 625)
Age — yr			
Median	60	60	60
Range	24–88	22–89	25–86
Race or ethnic group — no. (%)†			
Non-Hispanic white	519 (83.0)	521 (83.6)	526 (84.2)
Asian	37 (5.9)	39 (6.3)	41 (6.6)
Non-Hispanic black	28 (4.5)	27 (4.3)	25 (4.0)
Hispanic	28 (4.5)	25 (4.0)	21 (3.4)
Other or unspecified	13 (2.1)	11 (1.8)	12 (1.9)
GOG performance status — no. (%)‡			
0	315 (50.4)	305 (49.0)	311 (49.8)
1	270 (43.2)	267 (42.9)	272 (43.5)
2	40 (6.4)	51 (8.2)	42 (6.7)
Stage/debulking status — no. (%)			
III (macroscopic, ≤1 cm)	205 (32.8)	216 (34.7)	218 (34.9)
III (>1 cm)	256 (41.0)	242 (38.8)	254 (40.6)
IV	164 (26.2)	165 (26.5)	153 (24.5)
Histologic type — no. (%)§			
Serous adenocarcinoma	519 (83.0)	524 (84.1)	541 (86.6)
Endometrioid	14 (2.2)	24 (3.9)	21 (3.4)
Clear cell	23 (3.7)	20 (3.2)	12 (1.9)
Mucinous	5 (0.8)	8 (1.3)	6 (1.0)
Other or not specified	64 (10.2)	47 (7.5)	45 (7.2)
Tumor grade — no. (%)§			
3	465 (74.4)	460 (73.8)	445 (71.2)
2	86 (13.8)	97 (15.6)	102 (16.3)
1	28 (4.5)	18 (2.9)	36 (5.8)
Not graded	46 (7.4)	48 (7.7)	42 (6.7)

Table A2 Study and baseline characteristics ICON7

Trial name	ICON7 - A randomised, two-arm, multi-centre Gynaecologic Cancer InterGroup trial of adding bevacizumab to standard chemotherapy (carboplatin and paclitaxel) in patients with epithelial ovarian cancer
NCT number	NCT00483782
Objective	To determine whether the addition of bevacizumab to standard chemotherapy improves Progression Free Survival (PFS) and Overall Survival (OS) when compared to standard chemotherapy alone.
Publications – title, author, journal, year	Perren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med 2011;365:2484-96 [13].
Study type and design	A randomised controlled phase III trial in patients with high risk early stage (FIGO stage I or IIA clear cell or Grade 3 carcinoma) or advanced stage (FIGO stage IIB or greater, all grades and all histological subtypes) epithelial ovarian carcinoma, primary peritoneal carcinoma or fallopian tube carcinoma, to evaluate the addition of bevacizumab to standard chemotherapy with carboplatin and paclitaxel.
Follow-up time	48.9 months at the time of the OS cut off.
Population (inclusion and exclusion criteria)	Inclusion and exclusion criteria related to NCT number from www.clinicaltrials.gov: **DISEASE CHARACTERISTICS**: Histologically confirmed ovarian epithelial, fallopian tube, or primary peritoneal cavity cancer Newly diagnosed disease Meets 1 of the following staging criteria: High-risk stage I or IIA disease (grade 3 disease or clear cell carcinoma only) Stage IIB-IV disease (all grades and all histological types) Must have undergone initial surgery (e.g., debulking cytoreductive surgery or a biopsy if the patient has stage IV disease) within the past 6 weeks Patients with stage IV disease for which initial surgical debulking was not appropriate are eligible provided the following criteria are met: Stage IV disease diagnosed by histology No planned surgery prior to disease progression, including interval debulking surgery Patients with prior early-stage ovarian epithelial or fallopian tube carcinoma treated with surgery alone are eligible at the time of diagnosis of abdominopelvic recurrence provided no further interval cytoreductive therapy is planned prior to disease progression Synchronous primary endometrial carcinoma or a past history of primary endometrial carcinoma allowed provided the following criteria are met: Disease ≤ stage IB No more than superficial myometrial invasion

	No lymphovascular invasion Not poorly differentiated (i.e., no grade 3, papillary serous, or clear cell disease) Measurable or nonmeasurable disease No ovarian nonepithelial cancer, including malignant mixed Müllerian tumors No borderline tumors (e.g., tumors of low malignant potential) No history or clinical suspicion of brain metastases or spinal cord compression CT scan or MRI of the brain is mandatory (within 4 weeks prior to randomization) in case of suspected brain metastases Spinal MRI is mandatory (within 4 weeks prior to randomization) in case of suspected spinal cord compression **PATIENT CHARACTERISTICS**: ECOG performance status 0-2 Life expectancy > 12 weeks ANC ≥ 1,500/mm^3 Platelet count ≥ 100,000/mm^3 Hemoglobin ≥ 9 g/dL (can be post-transfusion) INR ≤ 1.5 APTT ≤ 1.5 times upper limit of normal (ULN) Bilirubin ≤ 1.5 times ULN ALT and AST ≤ 2.5 times ULN Creatinine ≤ 2.0 mg/dL Proteinuria ≤ 1+ by urine dipstick OR ≤ 1 g by 24-hour urine collection Not pregnant or nursing Negative pregnancy test Fertile patients must use effective contraception during and for ≥ 6 weeks after completion of study therapy No significant traumatic injury within the past 4 weeks No cerebrovascular accident, transient ischemic attack, or subarachnoid hemorrhage within the past 6 months No other malignancies within the past 5 years except for adequately treated carcinoma in situ of the cervix, and/or basal cell skin cancer, and/or early endometrial carcinoma No pre-existing sensory or motor neuropathy ≥ grade 2 No history or evidence of CNS disease (e.g., uncontrolled seizures) by neurological examination unless adequately treated with standard medical therapy No history or evidence of thrombotic or hemorrhagic disorders No uncontrolled hypertension (i.e., blood pressure > 150/100 mm Hg despite antihypertensive therapy) No known hypersensitivity to bevacizumab and its excipients, chemotherapy, or Cremophor EL No nonhealing wound, ulcer, or bone fracture

	Patients with granulating incisions healing by secondary intention with no evidence of facial dehiscence or infection are eligible but require three weekly wound examinations No clinically significant cardiovascular disease, including any of the following: Myocardial infarction or unstable angina within the past 6 months New York Heart Association class II-IV congestive heart failure Poorly controlled cardiac arrhythmia despite medication Rate-controlled atrial fibrillation allowed Peripheral vascular disease ≥ grade 3 (i.e., symptomatic and interfering with activities of daily living requiring repair or revision) No evidence of other disease or condition, metabolic dysfunction, physical examination findings, or laboratory findings that would contraindicate the use of an investigational drug or put the patient at high-risk for treatment-related complications PRIOR CONCURRENT THERAPY: See Disease Characteristics More than 4 weeks since other prior surgery or open biopsy No prior systemic therapy for ovarian cancer (e.g., chemotherapy, monoclonal antibody therapy, tyrosine kinase inhibitor therapy, or hormonal therapy) Prior adjuvant chemotherapy allowed for other malignancies (e.g., breast or colorectal carcinoma) if malignancy was diagnosed over 5 years ago with no evidence of subsequent recurrence No prior mouse CA 125 antibody No prior radiotherapy to the abdomen or pelvis More than 10 days since prior and no concurrent chronic use of acetylsalicylic acid (> 325 mg/day) Low-dose (< 325 mg/day) acetylsalicylic acid allowed More than 10 days since prior and no concurrent full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic purposes Use of therapy for line patency allowed provided INR < 1.5 More than 30 days since prior and no other concurrent investigational agent or participation in another clinical trial No other concurrent systemic antitumor agents No concurrent surgery No concurrent maintenance chemotherapy or intraperitoneal chemotherapy (including cytotoxic chemotherapy)
Intervention	A total of 1528 patients were randomised in equal proportions to the following two arms: • CP arm: Carboplatin (AUC 6) and paclitaxel (175 mg/m2) for 6 cycles of 3 weeks duration • CPB7.5+ arm: Carboplatin (AUC 6) and paclitaxel (175 mg/m2) for 6 cycles of 3 weeks plus Avastin (7.5 mg/kg q3w) for up to 12 months (Avastin was started at cycle 2 of chemotherapy if treatment was initiated within 4 weeks of surgery or at cycle 1 if treatment was initiated more than 4 weeks after surgery).
Baseline characteristics	The majority of patients included in the study were White (96%), the median age was 57 years in both treatment arms, 25% of patients in each treatment arm were 65 years of age or over, and approximately 50% of patients had an ECOG PS of 1; 7% of patients in each treatment arm had an ECOG PS of 2. The majority of patients had EOC (87.7%) followed by PPC (6.9%) and FTC (3.7%) or a mixture of the three origins (1.7%). Most patients were FIGO Stage III (both 68%)

	followed by FIGO Stage IV (13% and 14%), FIGO Stage II (10% and 11%) and FIGO Stage I (9% and 7%). The majority of the patients in each treatment arm (74% and 71%) had poorly differentiated (Grade 3) primary tumours at baseline. The incidence of each histologic sub-type of EOC was similar between the treatment arms; 69% of patients in each treatment arm had serous adenocarcinoma histologic type.
Primary and secondary endpoints	Primary Outcome Measures : • The primary endpoint was PFS as assessed by the investigator using RECIST. Secondary Outcome Measures: • Duration of overall survival • Objective response rate • Duration of response • Biological progression-free interval as measured by increasing CA 125 levels • Safety as measured by NCI CTAE version 3.0 • Quality of life • Health economics
Method of analysis	The following populations will be defined for efficacy and safety analyses • Intent-to-treat Population (ITT) The ITT population is defined as all patients randomised in the study, regardless of whether they actually received treatment. The treatment group will be analysed as randomised. • Safety Population The safety population comprises all patients randomised and having received at least one dose of study treatment. The treatment group will be analysed as treated. Patients who received at least one dose of bevacizumab will be counted in the bevacizumab group. **Efficacy Analyses** The primary analysis of this trial will be a non-stratified log-rank test for the difference in the distribution of progression-free survival (PFS) between the bevacizumab group and the control group (two-sided at an α-level of 5%). Kaplan-Meier estimates for median PFS with the corresponding 95% confidence intervals will be presented and a stratified log-rank test (twosided at an α-level of 5%, stratifying for the factors used for randomisation) will also be ICON7 performed to assess the robustness of the result. In addition, stratified and non-stratified Cox regression analyses will be performed to analyse the influence of baseline covariates. For overall survival and duration of response, the same analyses as for PFS will be performed. For response rates in the two treatment arms 95% Pearson-Clopper69confidence intervals will be provided. Response rates will be compared using a χ2–test (with Schouten correction70, a 95% confidence interval for the difference in response rates will be presented (using the HauckAnderson correction71. These analyses will be performed for all the types of response defined above. Efficacy analyses will be performed according to ITT. The analysis of PFS will include at least 684 events. The result of the analysis will be reported a minimum of 12 months after the last patient has been randomised to the trial. This is to ensure that all patients have completed treatment on trial, before the results are made public. The analysis of OS will include at least 715 deaths. **Censoring** Patients with no follow up information following randomisation will be censored at the time of randomisation. For PFS, patients who have neither progressed nor died at the time of the analysis or who are lost to follow-up will be censored at the date that they were last known not to have progressed. In the analysis of overall survival, patients without an event at the time of the analysis will be censored at the last time known to be alive. Patients with no baseline tumour measurements (both radiological and CA 125) will be censored at time of randomisation for evaluation of response, progression and biological

	progression. Patients with missing CA 125 values will be censored for assessment of biological progression at the last recorded CA 125. **Safety Analyses** The safety analyses will be based on the safety population. All safety parameters will be summarized and also listed by patient. Summary tables will be presented for incidence rates (number of patients with at least one incidence) of AEs, SAEs, AEs that led to premature withdrawal of trial treatment and interruptions/dose modifications, as well as summaries of severity (CTCAE v3.0 grades) and causal relationship. Tables of change from baseline will be presented for clinical laboratory assessments, vital signs and ECOG performance score. Laboratory abnormalities will also be summarized in tables showing shifts in grade.
Subgroup analyses	FIGO stage (category 1: stage I-III with residual disease ≤ 1 cm, category 2: Stage I-III with residual disease > 1 cm, category 3: FIGO stage IV and inoperable FIGO stage III), intent to start chemotherapy ≤ 4 weeks following surgery versus intent to start chemotherapy > 4 weeks after surgery and GCIG group.

10.1.1 Main result per study A3

Trial name:	SOLO-1									
NCT number:	NCT01844986									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	
PFS (Inv) 5 year update in brackets	Olaparib	260	NA (56,0 months)	NA (32,2 m)	NA	NA	HR = 0.30 (HR= 0.33)	(0.23, 0.41) (0.25–0.43)	*P*<0.0001	Kaplan-Meier estimates of progression-free survival (PFS) based on investigator assessment, censoring for non–protocol-specified therapy (randomly assigned patients)
	Placebo	131	13,8 months (13.8 months)							
PFS (BIRC)	Olaparib	260	Not reached	NA	NA	NA	HR = 0.28	(0.20, 0.39)	*P*<0.0001	Kaplan-Meier estimates of progression-free survival (PFS) assessed by independent review committee, censoring for non–protocol-specified cancer therapy (randomly assigned patients).
	Placebo	131	14,1 months							
PFS (residual disease)	Olaparib	55	29,4 months	18.1	NA	NA	HR = 0.44	(0.25, 0.77)	NA	Kaplan-Meier estimates of progression-free survival (PFS) assessed by independent review committee, censoring for non–protocol-specified cancer therapy (randomly assigned patients).
	Placebo	29	11,3 months							
2-year PFS rate	Olaparib	260	73.6%	39.0 %	NA	NA	HR=0.30	(0.23 –0.41)	NA	KM estimates of PFS based on investigator assessment, censoring for non–protocol-specified therapy (randomly assigned patients). Norquist et al.
	Placebo	131	34.6%							

3-year OS rate	Olaparib	260	84%	4 %	NA	NA	HR=0.95	(0.60 – 1.53)	NA	At the time of the DCO (17 May 2018), data were immature (82/391 events, 21.0% maturity) Final OS analysis will be conducted at approximately 60% maturity and is expected 2023. Norquist et al
	Placebo	131	80%							

Median OS	Olaparib	260	Not reached. 70.4 % alive	0.9 %	NA	NA	HR=0.95	(0.60, 1.53)	*P*=0.8903	At the time of the DCO (17 May 2018), data were immature (82/391 events, 21.0% maturity) Final OS analysis will be conducted at approximately 60% maturity and is expected 2023.
	Placebo	131	Not reached. 69.5 % alive							
Discontinuations	Olaparib	260	11,5 %	9,2 %	(4.0 – 14.5)	NA	RR = 5.0	(1.56, 16,08)	NA	RR calculated by AstraZeneca
	Placebo	131	2,3 %							
HQoL 24 months	Olaparib	237	0.3 (-0.72, 1.32)	- 3.00	(-4.8 - -1.2)	*P*=0.001	NA	NA	NA	TOI scorer. Baseline 73.6 (SD 12.8) and 75 (SD 13.1)
	Placebo	125	3.3 (1.84, 4.76)							
AE of CTCAE grade 3 or higher	Olaparib	260	39.2 %	20,7 %	(11.4 – 30.4)	NA	RR = 2,13	(1.44, 3.14).	NA	Calculated by AstraZeneca
	Placebo	131	18.5 %							

A3. Results per study PAOLA

Trial name:	PAOLA-1									
NCT number:	NCT02477644									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	
PFS HRD+ incl. BRCAm	Olaparib + bex	255	37.2 (36.0, NR)	19.5 months			HR=0.33	0.25; 0.45	0.0001	Stratified by Myriad myChoice® HRD Plus status (≥42 cut-off). [a]Estimated using Kaplan-Meier techniques. [b]Estimated from a Cox proportional hazards model including treatment, subgroup of interest and subgroup of interest by treatment interaction terms.
	Placebo + bev	135	17.7 (15.8, 19.9)							
PFS HRD+ nonBRCAm	Olaparib + bev	97	28.1	11.5 months	NA	NA	HR=0.43	0.28; 0.66	NA	
	Placebo + bev	55	16.6							
PFS ITT	Olaparib + bev		22.1 months	5.5 months	NA	NA	HR=0.59	0.49; 0.72	p<0.0001	As above
	Placebo + bev		16.6 months							
Discontinuations HRD+	Olaparib + bev	255	48 (18.8 %)	12,7 %	5.5; 19.5	NA	RR=2.99	1,46; 6,12	NA	Calculated by AstraZeneca
	Placebo + bev	127	8 (6.1%)							
AE of CTCAE grade 3 or Higher. HRD+	Olaparib + bev	255	144 (56.5%)	5,4 %	-5.9¸16.5	NA	RR=1.1	0,90; 1,35	NA	Calculated by AstraZeneca
	Placebo + bev	127	65 (51.1 %)							

OS HRD+ BRCAm	Olaparib + bev	255	NR(NR, NR)	NA	NA	NA	HR= 0.55	0.33, 0.92	0.0189	
	Placebo + bev	135	NR(NR, NR)							
HQoL (QLQ-C30)	Olaparib + bev	537	0.13 (1.02, 1.27)	0.59	-1.40, 2.57	P = 0.5626	NA	NA	NA	The analysis was performed using an MMRM analysis of the change from baseline QLQ-C30 QoL score for all post-baseline visits (up to study treatment discontinuation) with treatment, visit and treatment by visit interaction included as explanator variables and the baseline QLQ-C30 QoL score included as a covariate along with the baseline QLQ-C30 QoL score by visit interaction.
	Placebo + bev	269	-0.46 (-2.08, 1.16)							
AE of CTCAE grade 3 Higher Risk	Olaparib + bev	398	6.5%	(-2.4 ; 15.5)	NA	RR=1.1	0.96; 1.33	NA	NA	Calculated by AstraZenca. DCO March 2019
	Placebo + bev	194								
Discontinuations HRD+ non- BRCAm Higher Risk	Olaparib + bev	398	13.1 %	(7.7 ; 18.6)	NA	R=3.3	1.81; 6,11	NA	NA	Calculated by AstraZenca. DCO March 2019
	Placebo + bev	194								
AE of CTCAE grade 3 Lower Risk	Olaparib + bev	137	19,3%	(1.8 ; 21.0)	NA	RR=4,53	1,67, 12,3	NA	NA	Calculated by AstraZenca. DCO March 2019
	Placebo	73								
Discontinuations non- BRCAm Lower Risk	Olaparib + bev	137	3,4%	(-22.7 ; 6.5)	NA	RR=1.07	0.82;1.39	NA	NA	Calculated by AstraZenca. DCO March 2019
	Placebo	73								

A3. Results per study GOG218

Trial name:	GOG218									
NCT number:	NCT00262847									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	
PFS	Standard + bevacizumab	625	11.2 m	0.9 m	NA	NA	HR= 0.91	(0.80 – 1.04)	P=0.16	DCO: Feb 2010. Burger et al.
	Carboplatin/paclitaxel	625	10.3 m							
	Standard + bev → bev	623	14.1 m	2.9 m	NA	NA	HR= 0.72	(0.63 – 0.82)	P<0.001	
PFS (BRCAm)	Standard + bev → bev	120	19.6 m	4.2 m	NA	NA	HR= 0.95	(0.71 – 1.26)		Tewari et al. DCO: Jan 2018. Follow-up 102,9 m
	Carboplatin/paclitaxel	108	15.4 m							
OS	Standard + bevacizumab	625	40.8 m	0.3 m	NA	NA	HR= 1.06	(0.94-1.20)	P=0.34	Tewari et al. DCO: Jan 2018. Follow-up 102,9 m
	Carboplatin/paclitaxel	625	41.1 m							
	Standard + bev → bev	623	43.4 m	2.3 m	NA	NA	HR= 0.96	(0.85 – 1.09)	P=0.53	
OS (BRCAm)	Standard + bev → bev	120	62.6 m	0.1 m	NA	NA	HR=0.62	(0.52 - 0.73)	NA	Updated OS data 2019. Tewari et al
	Carboplatin/paclitaxel	108	62.5 M							
Grade 3 or more AE	Standard + bevacizumab	625								

	Carboplatin/paclitaxel	625								AE of grade 3 or more is not possible to extract from Burger et al.
	Standard + bev → bev	623								
Discontinuations	Standard + bevacizumab	625	15 %	3 %	NA		RR=1,27	0.96; 1.67	NA	Only absolut values are available. Burger et al. supplementary. RR calculated by AstraZeneca
	Carboplatin/paclitaxel	625	12 %							
	Standard + bev → bev	623	17 %	5 %	NA		RR=1.44	1.09; 1.89		
HQoL	Standard + bevacizumab	625		-2.7 points	CI 98,3 (0.88 – 4.57)	P=0.001	NA	NA	NA	Burger et al. FACT-O TIO. Monk et al.
	Carboplatin/paclitaxel	625								
	Standard + bev → bev	623		- 3.0 points	CI 98,3 (1.13-4.78)	P=0.001				

A3. Results per study ICON7

Trial name:	ICON7									
NCT number:	NCT00262847									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	
PFS Primary analysis Perren et al	Standard + bevacizumab	764	19.0 m	1.7 m	NA	NA	HR=0.81	(0.70–0.94)	p=0.004	Unstratified log-lank test. Cox regression analyses Median follow-up 19.4 months
	Carboplatin/paclitaxel	764	17.3 m							
PFS High risk Perren	Standard + bevacizumab	764	15.9 m	5.4 m	NA	NA	HR=0.68	(0.55 – 0.85)	p=0.001	Unstratified log-lank test. Cox regression analyses. Median follow-up 19.4 months
	Carboplatin/paclitaxel	764	10.5 m							
PFS High risk Update by Oza 2015	Standard + bevacizumab	248	16.0 m (14.2 – 17.8)	5.5 m	NA	NA	HR=0.73	(0.61-0.88)	p=0.001	Unstratified log-lank test. Cox regression analyses. Median follow-up 10.1 m and 15.6 m
	Carboplatin/paclitaxel	254	10.5 m (9.3-12.0)							
AE of CTCAE grade 3 or Higher Perren et al	Standard + bevacizumab	764	66%	10 %	(4.95 – 14.95)	NA	RR=1.18	(1.08, 1.78)	NA	Unstratified log-lank test. Cox regression analyses. Median follow-up 19.4 m. RR calculated by AstraZeneca
	Carboplatin/paclitaxel	764	56%							
Median OS Update by Oza 2015	Standard + bevacizumab	764	58.6 m (53.5 – 67.5)	0.6 m	NA	NA	HR= 0.85	(0.85 - 1.14)	p=0.02	DCO March 2013. Median follow-up 48.9 m.

	Carboplatin/paclitaxel	764	58.0 m (52.4 – 66.9)							Unstratified log-lank test. Cox regression analyses
Median OS High Risk Update by Oza 2015	Standard + bevacizumab	248	30.2 m (27.0 – 34.3)	9.5 m	NA	NA	HR= 0.78	(0.63 – 0.97)	p=0.01	DCO March 2013. Median follow-up 29 m and 38.9 m
	Carboplatin/paclitaxel	254	39.7 m (36.0 – 44.2)							
Median OS (restricted mean survival time). ITT Update by Oza 2015	Standard + bevacizumab	764	45.5 m (44·2–46·7)	0.9 m	(-0.8 – 2.6)	P=0.85	HR= 0.99	(0.85 - 1.14)	p=0.02	DCO March 2013. Median follow-up 48.9 m
	Carboplatin/paclitaxel	764	44.6 m (43.2, 45.9)							
Median OS (retricted mean survival time) High risk Update by Oza 2015	Standard + bevacizumab	248	34.5 m (32.0, 37.0)	4.8 m	(1.5 -8.1)	NA	HR=0.78	(0.63-0.97)	p=0.01	DCO March 2013. Median follow-up 29 m and 38.9 m
	Carboplatin/paclitaxel	254	39.3 m (37.0, 41.7)							
HQoL EORTC QLQ-C30 High Risk Update by Oza 2015	Standard + bevacizumab	44	72.4 points	4.3 p	(-4.9 – 13.4)	p= 0.36	NA	NA	NA	76 weeks. The difference is considered of non-significance
	Carboplatin/paclitaxel	26	76.7 points							

10.1.2 Table A4 Results per PICO

This section contains data that are to be considered confidential. It is marked with [redacted]

Table A4 Results referring to Clinical Question 1								
Results per outcome:	.							
	Absolute difference in effect				**Relative difference in effect**			**Methods used for quantitative synthesis**
	Studies included in the analysis	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**	
Median PFS PAOLA BRCAm	PAOLA	15.2 m	NA	NA	HR=0.34	0.20, 0.47		Stratified by tBRCA status as per randomisation. [a]Estimated using Kaplan-Meier techniques. [b]Estimated from a Cox proportional hazards model including treatment, subgroup of interest and subgroup of interest by treatment interaction terms. DCO March 2019. Median follow up is 22.7 m in olaparib + b arm and 24 m in placebo + b arm
PFS at 24m BRCAm	PAOLA	35,2 %	NA	NA	NA	NA	NA	*Progression-free survival is defined as time from randomisation until date of RECIST (using modified RECIST version 1.1)progression or death. Median PFS calculated using Kaplan-Meier techniques. DCO March 2020. AstraZeneca Data on file. Median follow-up is 26.4 m and 28.7 m*

Table A4 Results referring to Clinical Question 1								
Median PFS PAOLA vs SOLO1	PAOLA-1 vs SOLO1	NA	NA	NA	HR = 0.71	0.45,1.09	NA	*Results based on weighted outcomes after matching tumour location status, ECOG status, FIGO stage, type of surgery (interval versus initial), residual disease status after surgery (yes or no), response to first-line treatment and age to SOLO1*
PFS rate at 24 months PAOLA vs SOLO1	PAOLA-1 Vs. SOLO1	9%	NA	NA	NA	NA	NA	*Results based on weighted outcomes after matching tumour location status, ECOG status, FIGO stage, type of surgery (interval versus initial), residual disease status after surgery (yes or no), response to first-line treatment and age to SOLO1. DCO March 2019*
Median OS HRD+	PAOLA-1	NR	NA	NA	HR=0.55	0.33, 0.92	0.0189	
Median OS BRCAm	PAOLA-1 vs. SOLO1	NR/NA	NA	NA	NA	NA	NA	*Data from both SOLO1 and PAOLA-1 are immature and cannot be compared in an indirect comparison*
[redacted]								
OS at 48 months. BRCAm	PAOLA-1 vs. SOLO1	NR/NA	NA	NA	NA	NA	NA	*Data from both SOLO1 and PAOLA-1 are immature and cannot be compared in an indirect comparison*

Table A4 Results referring to Clinical Question 1								
Discontinuations HRD+	PAOLA-1	12,7 %	11.4; 30.4	NA	NA	RR=3.0	NA	*When compared with other Phase III studies in the olaparib clinical development programme, the olaparib discontinuation rate in PAOLA-1 due to AEs,* ***patient decision and other causes unrelated to disease progression (combined)*** *was similar to the rates reported in other studies*
Discontinuations BRCAm	PAOLA-1 vs SOLO1	7.3%	4.0; 14.5	NA	NA	NA	NA	*The PAIC/NMA do not cover an indirect comparison for* ***discontinuationa.*** *A narrative comparison with SOLO1(BRCAm) show that discontinuations in PAOLA(HRD+) was numerical higher than in SOLO1(BRCAm) 18.8 % vs. 11.5 %. When compared with other Phase III studies in the olaparib clinical development programme, the olaparib discontinuation rate in PAOLA-1 due to AEs,* ***patient decision and other causes unrelated to disease progression (combined)*** *was similar to the rates reported in other studies*
Grade 3 or more AE	PAOLA	5,9%	NA	NA	RR = 1.1	NA	NA	*RR Calculated by AstraZeneca*
Grade 3 or more AE BRCAm	PAOLA-1 vs. SOLO1	17,5%	NA	NA	NA	NA	NA	*The PAIC/NMA do not compare AEs ≥ 3 vs. olaparib alone and also no specific data for BRCAm in PAOLA. A narrative comparison with SOLO1(BRCAm) is not relevant as some of the SAEs ≥ 3 in the combination arm in PAOLA are related to bevacizumab. Numerically SAEs ≥ 3 in PAOLA(HRD+) were higher than in SOLO1(BRCAm) 56,5 % vs 39 %. However in the bevacizumab alone arm in PAOLA 49,6% experienced AEs ≥ 3*
HQoL ITT	PAOLA-1	0,59	-1.40, 2.57	P = 0.5626	NA	NA	NA	*The analysis was performed using an MMRM analysis of the change from baseline QLQ-C30 QoL score for all post-baseline visits (up to study treatment discontinuation) with treatment, visit and treatment by visit interaction included as explanator variables and the baseline QLQ-C30 QoL score included as a covariate along with the baseline QLQ-C30 QoL score by visit interaction.*

Table A4 Results referring to Clinical Question 1								
HQoL BRCAm	PAOLA-1 vs. SOLO1	NR	NA	NA	NA	NA	NA	*We have not be able to compare results from PAOLA ITT with olaparib mono from SOLO1*

Table A4 Results referring to Clinical Question 2								
Results per outcome:								
	Absolute difference in effect				**Relative difference in effect**			**Methods used for quantitative synthesis**
	Studies included in the analysis	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**	
PFS 24 months HRD+ non BRCAm Higher Risk	PAOLA-1	20.8 %.	NA	NA	NA	NA	NA	DCO March 2019. Median follow-up 22.7 m and 24.0 m
Median PFS HRD+ Non BRCAm Higher Risk	PAOLA-1	4.9 months.	NA	NA	HR = 0.51	0,31 – 0.83	NA	DCO March 2019
Median OS HRD+ non-BRCAm	PAOLA-1	NR	NA	NA	NA	NA	NA	

Table A4 Results referring to Clinical Question 2								
OS at 48 months. HRD+ non-BRCAm	PAOLA-1	NR	NA	NA	NA	NA	NA	
[redacted]								
HQoL Non BRCAm Higher Risk	PAOLA-1	NA	NA	NA	NA	NA	NA	*Results not available for the Lower Risk group. Results are not expected to be different from HRD+/ITT population. See results from HRD+/ITT population. DCO March 2019*

Table A4 Results referring to Clinical Question 3								
Results per outcome:								
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**	
PFS 24 months HRD+ non BRCAm	PAOLA-1	35,9%	NA	NA	NA	NA	NA	DCO March 2019. Median follow-up 22.7 m and 24.0 m
[redacted]								
Median OS HRD+ non-BRCAm	PAOLA-1	NR	NA	NA	NA	NA	NA	
OS at 48 months. HRD+ non-BRCAm	PAOLA-1	NR	NA	NA	NA	NA	NA	
[redacted]								

Table A4 Results referring to Clinical Question 3

[redacted]

HQoL Non BRCAm Lower Risk	PAOLA-1	NA	NA	NA	NA	NA	NA	*Results not available for the Lower Risk group. Results are not expected to be different from HRD+/ITT population. See results from HRD+/ITT population. DCO March 2019*

AstraZeneca

Lynparza (olaparib) for maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a BRCA1/2 mutation and/or genomic instability

Kontaktinformation

Navn	Mattias Ekman
Titel	Sundhedsøkonom
Ansvarsområde	Sundhedsøkonomi
Telefon	+46 767 988 667
E-mail	mattias ekman@astrazeneca com
Navn	Søren Clausen
Titel	Market Access Direktør
Ansvarsområde	Market Access og medicintilskud
Telefon	+45 2361 5584
E-mail	soren clausen@astrazeneca com

Executive summary

Background

Olaparib (Lynparza™) as combination therapy with bevacizumab was recently approved by the European Commission as maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a BRCA1/2 mutation and/or genomic instability The approved maintenance monotherapy dose for olaparib tablets is 300 mg twice daily, which equates to taking 4 tablets per day (twice, 2 x 150 mg tablets taken 12 hours apart) (EMA 2020) It is estimated that around 130 new patients per year will be eligible for treatment with olaparib + bevacizumab in the first-line ovarian cancer indication from 2021 to 2025 in Denmark It should be noted that BRCAm positive patients are already treated with olaparib monotherapy in the first line setting

Analysis

In the cost analysis olaparib + bevacizumab is compared to olaparib, bevacizumab or watch and wait depending on HRD subgroup In addition to acquisition costs for these treatments, the analyses also include a possibility for subsequent chemotherapy and bevacizumab use in later lines Subsequent therapy plays less of a role here compared with the SOLO-1 appraisal for first-line olaparib monotherapy in BRCAm positive ovarian cancer, as olaparib and bevacizumab are included as comparators and PARP inhibitors are not yet recommended for non-BRCAm positive patients in the relapsed ovarian cancer setting in Denmark

The model includes the average cost per patient over the time horizon, and a calculation on budget impact for each subgroup The model was populated with epidemiology, healthcare resource use, and cost data that are relevant in a Danish setting The analyses include costs for treatment acquisition, monitoring, patient time and treatment-related AEs List prices from medicinpriser dk were used for pharmaceuticals Based on the data on time to treatment discontinuation and subsequent therapy, the time horizon is 10 years in the analysis of average cost per patient The budget impact analysis has a 5-year horizon, following Medicinrådet guidelines

Results

Cost per patient estimations:

In the BRCA positive population, the results on average cost per patient showed that for patients treated with olaparib + bevacizumab, the costs over 10 years are DKK 1 554 322, compared with DKK 1 251 789 olaparib monotherapy, i e a difference of DKK 302 533 The drug acquisition constitutes the major part of the costs, and therefore results were most sensitive to changes in drug acquisition costs for olaparib and bevacizumab, and relatively insensitive to other variables

In the HRD+ non-BRCAm subpopulation who are bevacizumab candidates, the results on average cost per patient showed that for patients treated with olaparib + bevacizumab, the costs over 10 years are DKK 1 349 220, compared with DKK 684 652 for bevacizumab monotherapy, i e a difference of DKK 664 567 The drug acquisition constitutes the major part of the costs, and therefore results were most sensitive to changes in drug acquisition costs for olaparib, and relatively insensitive to other variables

In the HRD+ non-BRCAm subpopulation who are not bevacizumab candidates, the results on average cost per patient showed that for patients treated with olaparib + bevacizumab, the costs over 10 years are DKK 1 656 962, compared with DKK 460 335 for watch and wait, i e a difference of DKK 1 196 626 The drug

acquisition constitutes the major part of the costs, and therefore results were most sensitive to changes in drug acquisition costs for olaparib and bevacizumab, and relatively insensitive to other variables

Budget impact estimations:

In the BRCA positive population, the budget impact of treatment with olaparib + bevacizumab per year compared with olaparib monotherapy increases from 3 4 million DKK in 2021 to a maximum of 11 5 million DKK in 2023 Thereafter the yearly incremental budget impact decreases slightly to 10 5 million DKK in 2025 The budget impact of the new scenario increases from 14% in 2021 to a maximum of 20% in 2023 and then decreases to 15% in 2025

In the HRD+ non-BRCAm subpopulation who are bevacizumab candidates, the budget impact for treatment with olaparib + bevacizumab per year compared with bevacizumab increases from 3 5 million DKK in 2021 to a maximum of 22 7 million DKK in 2025 The budget impact of the new scenario increases from 28% in 2021 to a maximum of 88% in 2025

In the HRD+ non-BRCAm subpopulation who are not bevacizumab candidates, the budget impact for treatment with olaparib + bevacizumab per year compared with watch and wait increases from 3 6 million DKK in 2021 to a maximum of 14 9 million DKK in 2025 The budget impact of the new scenario increases from 60% in 2021 to 74% in 2022 but decreases to 67% in 2025

Conclusion

The cost per patient and budget impact for bevacizumab + olaparib varied in a predictable way depending on subpopulation and comparator It should be noted that list prices for pharmaceuticals were used for the calculations of the acquisition costs Real tender prices will in general be lower than the list prices For example, three biosimilars are now available for bevacizumab, which has historically resulted in substantial reductions in the net prices This also has an impact on the real budget impact for Danish health care, which will be lower in practice than what is reported here based on list prices

Abbreviations

AE	Adverse Events
AIP	Apotekernes Indkøbspris
Bev	Bevacizumab
BIM	Budget Impact Model
BRCAm	Breast Cancer Antigene-mutated
BRCAwt	BRCA wild type, i e not BRCA mutated
CTCAE	Common Terminology Criteria for AEs
EMA	European Medicines Agency
FDA	Food and Drug Administration
HR	Hazard Ratio
HRD	Homologous recombination deficiency
IV	Intravenous
KM	Kaplan-Meier
OC	Ovarian cancer
OS	Overall Survival
PARP	Poly (ADP-Ribose) Polymerase
PFS	Progression Free Survival
SPC	Summary of Product Characteristics
TTD	Time to treatment discontinuation
WW	Watch and wait

Contents

1 Background

Olaparib (Lynparza™) was recently (5th November 2020) approved in the EU as a maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a BRCA1/2 mutation and/or genomic instability Olaparib in combination with bevacizumab is a further targeted treatment option in patients with HRD mutated advanced (Stage III–IV) ovarian cancer following first-line platinum-based chemotherapy

In the phase III PAOLA-1 trial, the use of maintenance therapy with olaparib and bevacizumab provided a substantial benefit with regard to progression-free survival among women with newly diagnosed HRD psoitive advanced ovarian cancer, with a 67% lower risk of disease progression or death with olaparib + bevacizumab compared with bevacizumab (HR=0 33; 95% CI: 0 25 – 0 45 (Ray-Coquard et al , 2019) In the HRD+ population, the median duration of investigator-assessed PFS in the olaparib + bevacizumab arm was over three years (37 2 months), and over twice as long vs patients in the placebo + bevacizumab arm (17 7 months) At the time of the primary PFS analysis, after a median follow-up of 24 4 months in both arms, nearly two-thirds (65 9%) of patients in the olaparib + bevacizumab arm were progression-free, vs just 29 4% of patients in the placebo + bevacizumab arm

Despite complete surgical resection and first-line platinum-based chemotherapy, most patients with newly diagnosed advanced ovarian cancer eventually relapse PAOLA-1 investigated adding olaparib to active treatment with bevacizumab, with the intention of achieving maximum therapeutic benefit by producing a clinical response and continuing long-term remission for as long as possible

PAOLA-1 investigated olaparib maintenance vs placebo when added to bevacizumab, in a broad patient population irrespective of surgical status and biomarker status (Ray-Coquard et al , 2019) Bevacizumab is the guideline-recommended active maintenance treatment, and a standard of care treatment in advanced ovarian cancer

On the 26th of October 2020, Medicinrådet published a protocol for evaluation of the clinical added value of olaparib in the indication for patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status (Medicinrådet, 2020)

Olaparib for 2nd line treatment in BRCAm ovarian cancer was recommended by KRIS in 2015 and olaparib for 1st line treatment by Medicinrådet in 2019

1.1 Aim

This document provides a high-level summary of the medical background to olaparib + bevacizumab in the first-line ovarian cancer setting and presents a cost analysis, both average costs per patient and budget consequences, for olaparib + bevacizumab compared with current standard therapy for patients within the new indication

1.2 Patient population

In the first-line setting, olaparib as monotherapy is also indicated for the for the maintenance treatment of adult patients with newly diagnosed BRCA1/2-mutated (germline and somatic) advanced (FIGO stage III and IV) ovarian cancer (OC), who are in response (complete or partial) after first-line platinum-based chemotherapy The new indication included treatment in combination with bevacizumab in a population with HRD positive status, i e a broader range of genomic instabilities than just BRCA

The present cost analysis will focus on the first line-setting but is also taking the impact on subsequent treatment lines into account The use of PARP inhibitors (olaparib, niraparib) in the BRCAm population in the relapsed setting is recommended and reimbursed in Denmark, while the use of PARP inhibitors in the non-BRCA population in second line and later is not recommended

1.3 Treatment with Lynparza and bevacizumab

Olaparib (Lynparza) is an oral poly(ADP-ribose) polymerase (PARP) inhibitor that has shown significant clinical activity in ovarian cancer Olaparib traps PARP at sites of DNA damage, blocking base-excision repair and resulting in the collapse of DNA replication forks and the accumulation of DNA double-strand breaks Induced synthetic lethality is seen with olaparib in tumours that are deficient in homologous recombination repair pathways (Ledermann et al , 2014)

The approved maintenance monotherapy dose for olaparib tablets is 300 mg twice daily, which equates to taking 4 tablets per day (twice, 2 x 150 mg tablets taken 12 hours apart) (EMA 2020) A 100 mg tablet strength is also available for dose reduction but is priced equal to the 150 mg tablet

In PAOLA-1, bevacizumab was initiated in combination with chemotherapy and was continued after randomization as maintenance therapy at a dose of 15 mg per kilogram of body weight every 3 weeks for a total duration of up to 15 months

In Danish clinical practice, bevacizumab treatment with either 7 5 or 15 mg/kg body weight is given every 3 weeks until disease progression, while the PAOLA-1 study only used 15 mg/kg in line with the indication in the SPC

1.4 Comparators

Medicinrådet identified three different subpopulations for the new indication in the protocol for evaluation of the clinical added value of olaparib + bevacizumab (Medicinrådet, 2020):

1 Olaparib + bevacizumab vs olaparib in the BRCAm subpoulation

2 Olaparib + bevacizumab vs bevacizumab in the HRD+ non-BRCAm subpopulation (bevacizumab candidates)

3 Olaparib + bevacizumab vs placebo in the HRD+ non-BRCAm subpopulation (not bevacizumab candidates)

Hence, olaparib monontherapy, bevacizumab (infusion, given in combination with chemotherapy every second week, and as monotherapy every third week) and watch and wait treatment regimen should be the comparators to olaparib + bevacizumab, depending on HRD subpopulation and whether patients are

candidates for bevacizumab or not Bevacizumab is used in the control arm in the PAOLA-1 (Ray-Coquard et al , 2019)

1.5 Time horizon

Medicinrådet does not state a time horizon in their protocol for evaluation of the clinical added value of olaparib (Medicinrådet, 2020) AstraZeneca proposes a time horizon of 10 years for the base-case analysis of average costs per patient and year The time horizon for the cost per patient is long enough to capture the cost per patient for both olaparib and the comparators, as well as subsequent therapies A 5-year time horizon and a 25-year time horizon for the cost per patient are tested in scenario analysis A 5-year time horizon is used for the total budget impact, based on Medicinrådet guidelines This might not be long enough to capture all subsequent therapies fully, but an even longer time perspective is also associated with more uncertainty regarding for example future market shares In addition, the presented analysis is based on current list prices, while both list and net prices may change in the future, especially as bevacizumab biosimilars are already available on the market

2 Model description

The model includes one calculation on the average cost per patient over the time horizon, and a calculation on budget impact The model structure follows the standard format for calculating the budget impact of new treatments and is closely aligned with other budget impact models (BIMs) in oncology that have been presented and accepted by health technology appraisal (HTA) authorities The cost per patient analysis follows Medicinrådet guidelines The model was populated with epidemiology, inclusion/exclusion of treatments, healthcare resource use, and cost data that are relevant in a Danish setting

Market share data for relevant treatment comparators in the current scenario (without olaparib) are based on AstraZeneca's internal information, sales statistics from DLI and DGCG guidelines Data on eligible patients, market shares and duration of treatments were combined to estimate the number of patients on each treatment per year The cost analyses include costs for drug acquisition, monitoring, administration, patient time and transport, and treatment-related adverse event (AE) costs

First line treatment for ovarian cancer starts with chemotherapy, or a chemotherapy in combination with bevacizumab Olaparib can then be used as maintenance therapy after chemotherapy, either as monotherapy or in combination with bevacizumab The cost for chemotherapy at start of first line is assumed to be same in all arms and is therefore not included in the estimated costs

The treatment initiation of olaparib occurs after one treatment period of chemotherapy (6 cycles) and defines the starting point of the model Treatment with bevacizumab includes two phases, first the concomitant phase in which bevacizumab is given in combination with chemotherapy, which implies more frequent administrations and monitoring, and thereafter the maintenance phase in which patients receive treatment with only bevacizumab Thus, the treatment with bevacizumab starts earlier than treatment with olaparib Since the total cost for bevacizumab must be considered, the costs for bevacizumab occurring prior to the bevacizumab maintenance phase is included as if the treatments had the same starting point

3 Model inputs

3.1 Eligible population

The model uses the total female population as a starting point and the specific target population is estimated based on the disease characteristics of patients in the indication, such as stage, proportion with high-grade serous disease, epithelial ovarian cancer, HRD and BRCA positive status, receiving and responding to platinum-based first-line chemotherapy

Given the epidemiology and an assumption of the proportion of patients who receive and respond to 1st line chemotherapy, it is estimated that around 130 patients per year would be eligible for treatment with olaparib + bevacizumab in the ovarian HRD positive setting (Table 1, Figure 1)

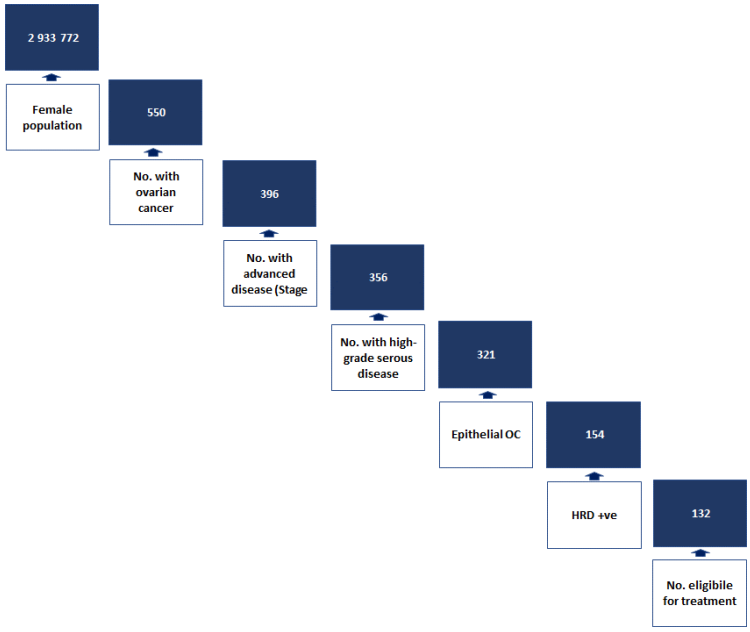
The eligible population (Table 1) refers to adult patients HRD positive advanced (FIGO stage III and IV) ovarian cancer (OC), who are in response (complete or partial) after first-line platinum-based chemotherapy (Lynparza SPC, EMA 2020)

In the protocol from Medicinrådet (page 5), it is estimated that approximately 160 of the total 300 newly diagnosed patients with advanced ovarian cancer patients per year in Denmark are HRD mutated (60 with BRCA mutation and 100 with other HRD mutations) Our own patient funnel estimates that around 130 patients would be eligible for treatment with olaparib + bevacizumab In our base case, we are thus assuming around 130 new patients per year eligible for the treatment (132 to be precise)

Table 1. Model inputs used to estimate the number of patients eligible for treatment with olaparib

Parameter	Figure	Source
Total female population in Denmark	2 933 772	Statistics Denmark, retrieved December 2020
Incidence of OC (per 100 000)	18 75	The Nordcan project
Proportion with advanced OC: Stage IIb to IV	72%	DGCD 2017 National Årsrapport 2016/2017
Proportion of with high-grade serous OC	90%	Romero et al (2012)
Proportion with epithelial OC	90%	DGCG Årsrapport 2010-12
Proportion with positive HRD status	48%	PAOLA-1 (Ray-Coquard 2019)
Patients who receive and respond (CR/PR) to 1st line chemotherapy	85 5%	Receive 1L 95% (AstraZeneca's internal assumption); complete or partial response 90%

Figure 1. Estimation of population eligible for treatment with olaparib + bevacizumab in first-line ovarian cancer.



3.2 Treatments and comparators

The overarching goal of treating ovarian cancer is cure, or at least prolonging survival and improving quality of life According to the Danish ovarian cancer guidelines, the primary treatment is surgical, with the goal of removing all visible tumour tissue (macroscopic radical surgery) and perform adequate staging (GGCG 2019) Surgery is usually extensive to remove as much of the tumour tissue as possible ('debulking surgery')

After macroscopic surgery, nearly all patients are subsequently offered 6 cycles of platinum-based combination chemotherapy with carboplatin and a taxane (usually paclitaxel, but docetaxel or doxorubicin can also be used) Patients with residual macroscopic tumor tissue, i e non-radically operated patients (and all stage IV and inoperable patients) are offered 1st line therapy with platinum-based chemotherapy either as monotherapy or in combination with bevacizumab followed by maintenance therapy with bevacizumab Bevacizumab is offered to high-risk patients, i e patients in FIGO stage III with residual disease (macroscopic tumour tissue > 1 cm) after surgery or FIGO stage IV patients

Olaparib is mentioned in the guidelines (GGCG 2019) as a maintenance treatment option for patients with advanced high-grade serous/endometrioid cancer and a BRCA1/2 germline/somatic mutation and who achieve partial or complete response to platinum-based chemotherapy It is also mentioned in the latest Danish guidelines that olaparib should be offered for at most 2 years or until progression, toxicity or the patient's wish to stop treatment

In 2019, olaparib treatment in the first line setting was also recommended by Medicinrådet as maintenance treatment for patients with advanced high-grade serous/endometrioid cancer and a BRCA1/2 germline/somatic mutation and who achieve partial or complete response to platinum-based chemotherapy Hence, it is a relevant comparator to olaparib + bevacizumab for patients with BRCA mutations

For non-BRCA patients with FIGO stage III or IV, the Danish guidelines mention that that standard treatment of patients with residual disease after surgery may consist of carboplatin, taxane and bevacizumab Bevacizumab should be continued for a total of 15 months or until progression if this occurs before 15 months The dose is 7 5 mg/kg or 15 mg/kg every 3 weeks (GGCG 2019) For patients with no residual disease after surgery, bevacizaumab is not recommended and standard treatment is 6 cycles of chemotherapy with carboplatin and a taxane After that, non-BRCA patients with no residual disease would receive no active therapy until they have a recurrence

3.3 Market shares

Market shares have been estimated separately for each subpopulation identified by Medicinrådet

The current bevacizumab market share is difficult to estimate as the drug has multiple indications and we do not have access to sales per indication The assumed market shares are based on sales statistics and is in line with other countries where sales per indication is available The assumption is based on the national level, thus including use from all regions, which differ in dosing (15 mg in region Hovedstaden and 7 5 mg in other regions) In the base case, we assume 50% with 15 mg and 50% with 7 5 mg in Denmark

Another PARP inhibitor, niraparib, might also get reimbursed in the 1st line advanced ovarian cancer setting This treatment will then probably also receive some market shares, but this has not been included in the market share estimates as niraparib is not yet recommended in this setting

3.3.1 Olaparib + bevacizumab vs. olaparib in the BRCAm subpoulation

In the BRCAm population, it is not assumed that all patients would get the combination therapy Even with a recommendation, it is primarily high-risk patients with residual disease after surgery who would get the combination At peak-years sales, around 50% would are estimated to get the combination therapy, while most other BRCAm positive patients would receive olaparib monotherapy The combination therapy could be expected to take market shares from olaparib monotherapy and in a few cases bevacizumab monotherapy and is hence adding a treatment (either bevacizumab or olaparib) to these patients rather than replacing any current treatment

Table 2. Scenario without olaparib + bevacizumab

Year	Olaparib+bev	Routine surveillance	Bevacizumab	Olaparib mono
2021	0%	5%	5%	90%
2022	0%	5%	5%	90%
2023	0%	5%	5%	90%
2024	0%	5%	5%	90%
2025	0%	5%	5%	90%

Table 3. Scenario with olaparib + bevacizumab

Year	Olaparib+bev	Routine surveillance	Bevacizumab	Olaparib mono
2021	20%	5%	0%	75%
2022	35%	5%	0%	60%
2023	50%	5%	0%	45%
2024	50%	5%	0%	45%
2025	50%	5%	0%	45%

3.3.2 Olaparib + bevacizumab vs. bevacizumab in the HRD+ non-BRCAm subpopulation (bevacizumab candidates)

In the HRD positive non-BRCAm population with bevacizumab candidates, it is assumed that a majority of all patients will get the combination therapy at peak-years sales Around 75% would are estimated to get the combination therapy, while most other patients would receive watch and wait The combination therapy could be expected to take market shares from bevacizumab monotherapy and is hence adding olaparib to these patients rather than replacing any current treatment

Table 4. Scenario without olaparib + bevacizumab

Year	Olaparib+bev	Routine surveillance	Bevacizumab	Olaparib mono
2021	0%	20%	80%	0%
2022	0%	20%	80%	0%
2023	0%	20%	80%	0%
2024	0%	20%	80%	0%
2025	0%	20%	80%	0%

Table 5. Scenario with olaparib + bevacizumab

Year	Olaparib+bev	Routine surveillance	Bevacizumab	Olaparib mono
2021	20%	20%	60%	0%
2022	35%	20%	45%	0%
2023	50%	20%	30%	0%
2024	65%	20%	15%	0%
2025	75%	20%	5%	0%

3.3.3 Olaparib + bevacizumab vs. placebo in the HRD+ non-BRCAm subpopulation (not bevacizumab candidates).

In the HRD positive non-BRCAm population who are not bevacizumab candidates, it is assumed that a majority of all patients will get the combination therapy at peak-years sales Around 60% would are estimated to get the combination therapy, while other patients would receive watch and wait Here the combination therapy is adding active treatment to a patient population not previously treated with either PARP inhibitors or bevacizumab as maintenance treatment after chemotherapy This makes the market share estimates more uncertain for this patient population

Table 6. Scenario without olaparib + bevacizumab

Year	Olaparib+bev	Routine surveillance	Bevacizumab	Olaparib mono
2021	0%	100%	0%	0%
2022	0%	100%	0%	0%
2023	0%	100%	0%	0%
2024	0%	100%	0%	0%
2025	0%	100%	0%	0%

Table 7. Scenario with olaparib + bevacizumab

Year	Olaparib+bev	Routine surveillance	Bevacizumab	Olaparib mono
2021	20%	80%	0%	0%
2022	30%	70%	0%	0%
2023	40%	60%	0%	0%
2024	50%	50%	0%	0%
2025	60%	40%	0%	0%

3.4 Treatment duration

3.4.1 Olaparib + bevacizumab

The treatment duration was based on the time to treatment discontinuation for olaparib + bevacizumab and in PAOLA-1 As there is a 2-year treatment cap on olaparib and 15-month treatment cap on bevacizumab, the time to treatment discontinuation curves are used directly as a basis for the treatment duration

Figure 2 shows the time to treatment discontinuation (TTD) for the three subpopulations identified by Medicinrådet As can be seen, the difference in TTD is quite large for HRD positive non-BRCA positive patients depending on whether they are candidates for bevacizumab or not The bevacizumab candidates tend to be at higher risk of disease recurrence, as reflected by shorter PFS (and treatment duration) compared

with those who are not candidates for bevacizumab (see PFS sections in the main application document) This also affects the TTD

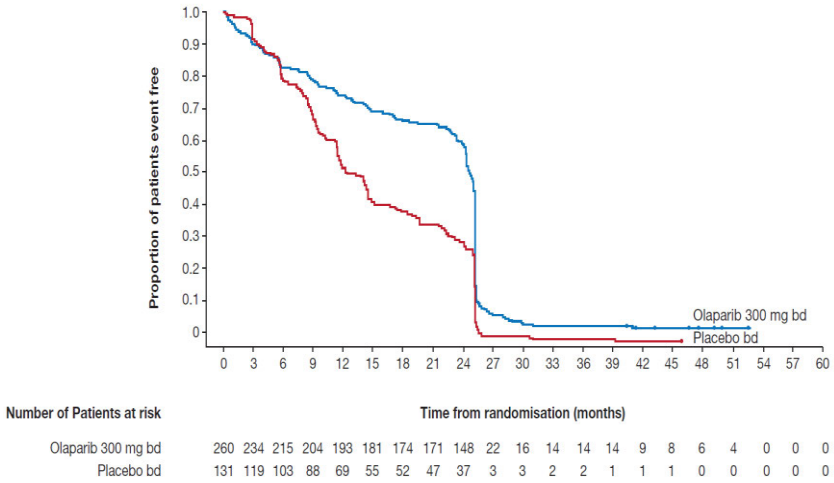
Source: AZ data-on-file

3.4.2 Olaparib monotherapy and watch and wait

The treatment duration for olaparib monotherapy and for watch and wait was based on SOLO-1 Although the patient populations in PAOLA-1 and SOLO-1 are slightly different, the SOLO-1 trial is the best source for TTD in a BRCA positive population, as olaparib monotherapy or watch and wait were not included in PAOLA-1

As there was a 2-year treatment cap on olaparib also in SOLO-1, the time to treatment discontinuation curve is used directly as a basis for the treatment duration A Kaplan-Meier plot of TTD is shown in Figure 3 Placebo represents watch and wait in Figure 3

Figure 3. Kaplan-Meier plot of TTD or death



3.4.3 Bevacizumab monotherapy

The treatment duration for bevacizumab monotherapy was based on the time to treatment discontinuation for bevacizumab in PAOLA-1 As there is a 15-month treatment cap on bevacizumab, the time to treatment discontinuation curves are used directly as a basis for the treatment duration The TTD curves are overlapping for the first three months, but after that the TTD is shorter for the bevacizumab candidates as this is a population with higher risk of disease progression (Figure 4)

[redacted]

The treatment duration curves are truncated at 15 months, as the indication for bevacizumab in first line epithelial ovarian, fallopian tube and primary peritoneal cancer is the following: "Avastin is administered in addition to carboplatin and paclitaxel for up to 6 cycles of treatment followed by continued use of Avastin as single agent until disease progression or for a maximum of 15 months or until unacceptable toxicity, whichever occurs earlier"

The PAOLA-1 trial used 15 mg/kg dosing, but the model can use both 7 5 mg/kg and 15 mg/kg based on the ICON7 and the GOG-0218 trials, respectively Both of these studies are referred to in the Danish ovarian cancer guidelines (DGCG 2018):

> "På baggrund af de to ovennævnte undersøgelser har Sundhedsstyrelsen efter ansøgning fra DGCG d 25 juni 2012 godkendt bevacizumab 15 mg/kg hver 3 uge givet fra 2 serie og sammenlagt 15 måneders behandling som 1 linje behandling til ovariecancer patienter med restsygdom På grundlag af GOG218 og ICON7 studierne som anført ovenfor, og i lyset af, at ICON7 studiet med dosering på 7½ mg har vist en overlevelsesgevinst på 7,8 måneder hos patienter med resttumor efter primær kirurgi (post hoc analyse), er det ovariecancergruppens opfattelse, at 7½ mg/kg og 15 mg/kg er ligeværdige doseringer, og at basisbehandling af patienter med restsygdom kan bestå i carboplatin, taxan og bevacizumab »

3.4.4 Subsequent treatments

Summary of subsequent treatments in the model

Table 8. Assumptions regarding subsequent treatments in the model

Patient population	Subsequent therapy by treatment group
BRCAm patients	• Olaparib + bevacizumab group: Chemotherapy only • Olaparib group: Chemotherapy and in addition bevacizumab for a proportion of the patients (8 8%) ➢ Treatment duration chemotherapy: 6 three-week cycles corresponding to 3 5 months ➢ Treatment duration bevacizumab: 11 7 months on average based on the time to treatment discontinuation in the OCEANS study (Roche 2012)
HRD+ non-BRCAm pat ents who are candidates for bevacizumab	• Olaparib + bevacizumab group: Chemotherapy only • Bevacizumab group: Chemotherapy only ➢ Treatment duration chemotherapy: 6 three-week cycles corresponding to 3 5 months
HRD+ non-BRCAm pat ents who are not candidates for bevacizumab	• Olaparib + bevacizumab group: Chemotherapy only • Watch and wait group: Chemotherapy and in addition bevacizumab for a proportion of the patients (12 5%), as it is assumed that some relapsed patients could become eligible for bevazizumab ➢ Treatment duration chemotherapy: 6 three-week cycles corresponding to 3 5 months ➢ Treatment duration bevacizumab: 11 7 months on average based on the time to treatment discontinuation in the OCEANS study (Roche 2012)

The time to subsequent therapy depends on the type of subsequent therapy The time to first subsequent PARP inhibitor was based on PAOLA-1 data, but due to the nature of the populations and the Danish guidelines, this is not used as an option in the base case cost analysis The PAOLA-1 KM data on time to first subsequent PARP inhibitor are used directly in the model and are not extrapolated , but once patients are on treatment the extrapolated time to treatment discontinuation from SOLO-2 is used

For time to first subsequent chemotherapy, data was based on the SOLO-1 trial, as these data were more mature and included more information on subsequent chemotherapies In addition, the comparator arm in PAOLA-1 is bevacizumab rather than olaparib or watch and wait, but SOLO-1 are providing those arms For consistency, the same approach is used in the HRD+ non-BRCA patients who are candidates for bevacizumab However, the time to first subsequent therapy is longer in SOLO-1 than in PAOLA-1, as there are differences in the patients populations with , on average, slightly more severe disease in PAOLA-1 than in SOLO-1 In practice, the time to first subsequent chemotherapy is transformed to a proportion on treatment in each monthly cycle in the model Those proportions are renormalized so that all subsequent therapy is assumed to occur within 10 years, as will be described in more detail below This is completely reasonable, as late relapses beyond 5 years are increasingly unlikely In that respect, extrapolations with "thick tails", such as lognormal and loglogistic, are not realistic for the long run Due to the renormalization, it does not matter that much if data from SOLO-1 or PAOLA-1 are used for subsequent chemotherapy The cost results will be similar

A summary of median and mean time to subsequent therapy in PAOLA-1 and SOLO-1 is shown in Table 9

Table 9. Summary of median and mean time to first subsequent therapy.

Endpoint	Median (months)	Mean (months) (RMST)	Extrapolated mean (months)
Time to first subsequent PARPi PAOLA-1			
• Olaparib + bevacizumab	34	31	Not extrapolated; KM data directly used
• Bevacizumab	22	22	
Time to first subsequent therapy SOLO-1			
• Olaparib	52	38	104[1]
• Placebo	15	23	32[1]
Time to second subsequent therapy SOLO-1			
• Olaparib	NR	42	117[2]
• Placebo	41	36	55[2]
Time to first subsequent therapy PAOLA-1			
• Olaparib + bevacizumab	25	26	44[1]
• Bevacizumab	18	20	26[1]
Time to second subsequent therapy PAOLA-1			
• Olaparib + bevacizumab	34	31	38[3]
• Bevacizumab	30	28	32[3]

RMST Restricted mean survival time (to the end of follow up)
[1] Loglogistic; [2] Lognormal; [3] Weibull (extrapolation)

Subsequent PARP inhibitors

Subsequent PARP inhibitors are not included in the base case, as reuse is not recommended and PARP inhibitors are not recommended for non-BRCA patients The option is still implemented in the model and could potentially be relevant for scenario analyses

Crossover to olaparib was not permitted within the PAOLA-1 study design However, on progression, patients could have received a PARP inhibitor outside of the study and subsequent PARP inhibitor use was documented In total, 29 5% in the bevacizumab monotherapy arm and 3 9% in the olaparib + bevacizumab arm received a PARP inhibitor following the study (DCO2) Greater use of PARP inhibitor therapies amongst patients in the bevacizumab monotherapy arm confounds and underestimates the true PFS2, TSST, and OS benefit achieved from the addition of olaparib to bevacizumab maintenance treatment The option to estimate costs for subsequent PARP inhibitor use were included in the economic model based on PAOLA-1 data

The costs of subsequent PARP inhibitor treatment were estimated via the following steps and is in line with the approach used in the SOLO-1 appraisal:

1 An estimate of the proportion of patients who receive a subsequent PARP inhibitor was taken from the PAOLA-1 study (29 5% for the bevacizumab monotherapy arm and 3 9% for olaparib and bevacizumab) and from SOLO-1 for watch and wait (51%) However, as retreatment with olaparib is not recommended, 0% use of olaparib in later lines is assumed for patients treated with olaparib + bevacizumab or olaparib monotherapy as first line treatment

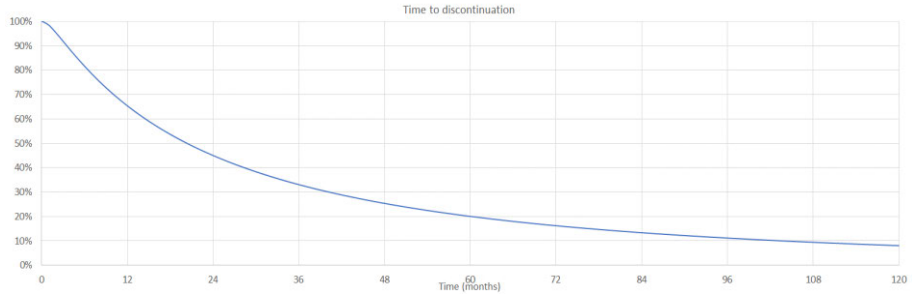
2 Data on the time to first subsequent PARP inhibitor therapy in PAOLA-1 were used to estimate the proportion of patients starting therapy in each model cycle

3 Data on the time from randomization to discontinuation of olaparib sourced from SOLO2 (Pujade-Lauraine, Ledermann et al 2017) were used to estimate the proportion of patients on therapy in each cycle after starting subsequent PARP inhibitor therapy Parametric models were fitted to Kaplan-Meier data and the best fitting model, the generalized gamma model, was used The lognormal distribution has the second best fit

Combining steps 2 and 3 allowed us to estimate the average number of patients receiving subsequent PARP inhibitor treatment by cycle in the model and to accurately apply future discounting of costs A schematic of the calculation of the proportion of patients on subsequent PARP inhibitor treatment for each model cycle, with associated calculation notes, is presented in Appendix A The Appendix A is based on the SOLO-1 appraisal, but the same principle was used here

Since there are two PARP inhibitors, olaparib and niraparib currently reimbursed for ovarian cancer patients in Denmark, the use of olaparib and niraparib was split by 50% and 50%, respectively No administration costs were assumed as both medications are administered orally Licensed doses for both olaparib tablets (600 mg) and niraparib capsules (300 mg) were applied

Figure 5. Parametric generalized gamma distributions for time to treatment discontinuation in SOLO2.



Subsequent chemotherapy

The cost of subsequent chemotherapies are calculated based on the total cost of each therapy (medication acquisition and administration), the share of patients receiving each therapy (informed by the SOLO-1 appraisal for olaparib), and an average number of treatment lines

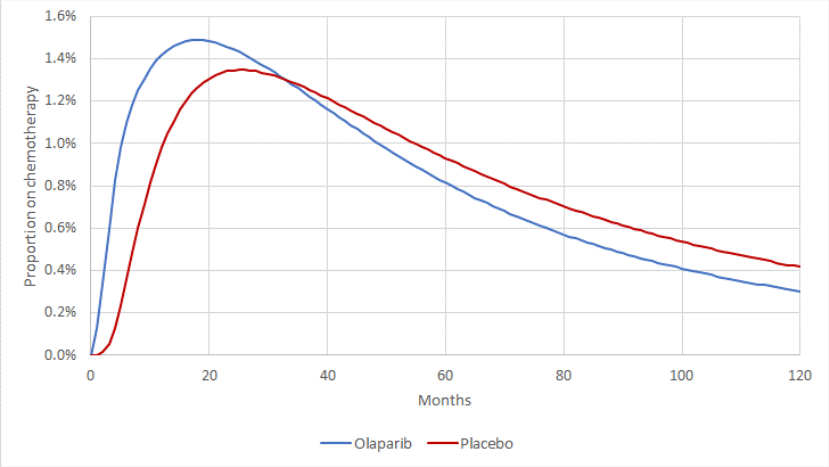
The start time for subsequent chemotherapy treatments was based on time to first subsequent therapy and second subsequent therapy However, the time to subsequent therapy curves are not used directly in the budget impact model, as the curves need to be transformed into the proportion of patients on subsequent therapy during each time period This can be calculated based on the proportion of patients new on chemotherapy each month, in combination with the treatment duration, which is assumed to be 6 three-week cycles corresponding to 3 5 months (15 weeks) of treatment For example, if 1% of the population is initiated on chemotherapy each month, then 3 5 * 1% = 3 5% of patients will be on treatment with chemotherapy each month in the steady state In reality, the proportion initiated on chemotherapy varies over time The percentage on subsequent treatment in a patient cohort will increase over time to a peak as more and more patients get further lines of therapy and then decline over time (Figure 6)

It is assumed that all chemotherapy is dispensed within 10 years, which we refer to as renormalization According to the SOLO-1 TFST curve, 77 4 % in the olaparib group and 96 5% in the control group have had subsequent therapy within 10 years In PAOLA-1, the corresponding probabilities are for olaparib + bevacizumab 94% and 98% for bevacizumab alone Renormalization means that the probability in each month for being on treatment in the unadjusted data are divided by the cumulative probability of getting treatment within 10 years Hence, the probability of getting subsequent therapy within 10 years adds up to 100%, which is clinically more plausible than subsequent therapy beyond 10 years Note that for the control arm in SOLO-1 and for both arms in PAOLA-1, the renormalized data will differ little from the original data, as the probability of getting subsequent therapy is at least 94% for all of these groups

As the time to progression is long for both olaparib + bevacizumab in PAOLA-1 and for olaparib monotherapy in SOLO-1, it is plausible to assume that a proportion of the patients will never have any relapse at all In the first line, the treatment has curative intent, and a majority of the patients in PAOLA-1 and SOLO-1 had no residual disease after surgery (Moore 2018, Ray-Coquard 2019) Therefore, it is assumed that patients undergo on average 3 lines of subsequent chemotherapy after olaparib+bev / olaparib and 4 after bevacizumab or watch and wait within this time frame In Study 19, a trial investigating olaparib as 2nd line treatment and beyond, on average 4 subsequent lines of chemotherapy were used within a time frame of 6 5 years of median follow up (Friedlander 2018)

Overall, at the time of the data cut-off for the PFS analysis in SOLO-1, the proportion of patients in the placebo arm that had started a first subsequent therapy was 72% compared with 35% the olaparib arm, i e twice as much for watch and wait A large part of this difference is driven by PARP inhibitors as first subsequent therapy in the placebo arm, but chemotherapy was also used as subsequent therapy at some point by 58% in the placebo arm vs 36% in the olaparib arm (AZ data on file 2018) On the other hand, over the whole follow-up time in Study 19, the average number of chemotherapy lines was very similar in both arms, 4 1 in the olaparib arm vs 4 2 in the placebo arm (Friedlander 2018) This means that olaparib is adding a treatment line rather than replacing chemotherapy in the second-line setting and beyond In the first-line setting, however, there is a possibility a proportion of the patients with no residual disease after surgery will not relapse in a long time, which could diminish the use of subsequent chemotherapy, in particular in the olaparib + bev arm in PAOLA-1 and the olaparib arm of SOLO-1, compared with Study 19 (2nd line treatment and beyond) Therefore, three subsequent lines of chemotherapy seems like a reasonable assumption in this setting for olaparib + bev and olaparib, while 4 would be a plausible assumption for bevacizumab or watch and wait The number of subsequent lines of chemotherapy is varied in a sensitivity scenario

Figure 6. Proportion of patients on chemotherapy as subsequent therapy over time (estimated so that 100% of the chemotherapy is dispensed over 10 years).



Subsequent bevacizumab

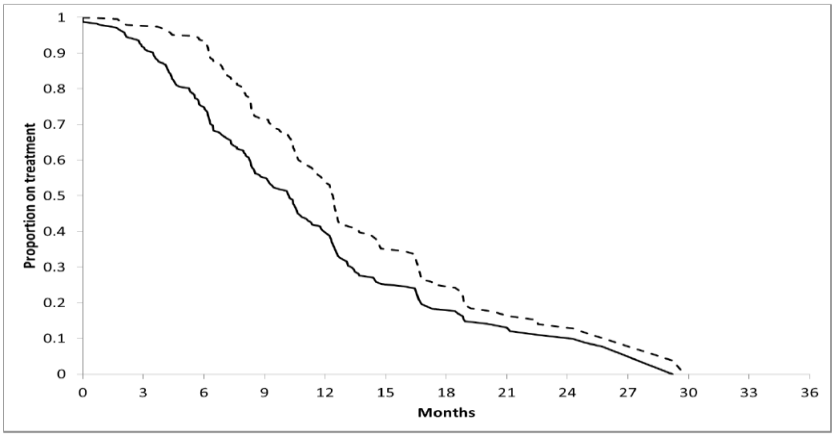
Subsequent bevacizumab is limited as it is used in the treatment arm and also for one of the comparisons in the cost analysis Subsequent bevacizumab was used for the olaparib arm in the olaparib monotherapy comparison (BRCA+ population) and as a possibility for the watch and wait arm in the non-BRCA HRD positive population who are not candidates for first-line bevacizumab As for subsequent chemotherapy, SOLO-1 is used as data source for these subsequent bevacizumab, as PAOLA-1 did not include an olaparib monotherapy arm or a watch and wait arm It is assumed that a proportion of these patients would quality for bevacizumab use in later lines As for subsequent chemotherapy, the start time for subsequent bevacizumab treatments was based on time to first subsequent therapy and second subsequent therapy

However, the time to subsequent therapy curves are not used directly in the budget impact model, as the curves need to be transformed into the proportion of patients on subsequent therapy during each time period This can be calculated based on the proportion of patients new on chemotherapy each month, in combination with the treatment duration, which for bevacizumab is assumed to be 11 7 months on average based on the time to treatment discontinuation in the OCEANS study (Roche 2012) (Figure 7) OCEANS was a randomized, double-blind, phase III trial, comparing the efficacy and safety of chemotherapy (gemcitabine and carboplatin) plus bevacizumab (bevacizumab arm) and gemcitabine and carboplatin plus placebo (placebo arm) in patients with platinum-sensitive relapsed ovarian cancer (Aghajanian 2012)

Apart from the longer mean treatment duration, the calculation is performed in the same way as for chemotherapy For example, if 1% of the population is initiated on chemotherapy each month, then 11 7 * 1% = 11 7% of patients will be on treatment with bevacizumab each month in the steady state In reality, the proportion initiated on chemotherapy and bevacizumab varies over time The percentage on subsequent treatment in a patient cohort will increase over time to a peak as more and more patients get further lines of therapy and then decline over time

It is assumed that all chemotherapy and bevacizumab is dispensed within 10 years after diagnosis

Figure 7. Proportion of patients in OCEANS remaining on bevacizumab (solid line) compared to progression (dotted line).



Source Roche (2012)

In SOLO-1, 9 patients in the olaparib arm (8 8% of patients who progressed in olaparib arm [9/102]) and 12 patients in watch and wait arm (12 5% of patients receiving who progressed in watch and wait arm [12/96]) received bevacizumab in addition to chemotherapy in the relapsed disease setting (second and further lines) These are also the proportions of subsequent bevacizumab used in the base case The proportion of patients receiving bevacizumab in the relapsed disease setting in current Danish clinical practice is probably higher than that Hence, the proportion of patients receiving subsequent bevacizumab therapy sourced from SOLO1 may be a conservative assumption We used SOLO1 as the base case for the proportion of patients receiving subsequent therapy with bevacizumab but tested higher proportions of second line bevacizumab in sensitivity scenarios It is notable that even though PAOLA-1 included bevacizumab as first line treatment in both arms, 48 patients in the olaparib + bevacizumab arm (8 9%) and 33 patients in watch and wait arm (12 3%) received antiangiogenic therapy, presumably mostly with bevacizumab, in addition to chemotherapy in the relapsed disease setting (second and further lines)

3.5 Drug acquisition costs

Drug acquisition costs were calculated based on available formulations; pack sizes, unit costs and price per mg for each (combination of) treatment included in the model The dosing information was sourced from the European Medicines Agency (EMA) label for each treatment and the drug acquisition costs were sourced from medicinpriser dk (AIP)

Table 10 summarizes the treatment dosing, administration frequency and drug acquisition costs for the treatments included in the base case Niraparib is only used as subsequent therapy, not as a comparator as previously mentioned Bevacizumab has a weight-based dosing regimen The average weight from PAOLA-1, 63 3 kg,[1] is applied in the model and gives 712 mg bevacizumab per dose based on the assumption of 50%

[1] No information on average body weight is given in the ICON7 (Perren 2011) and GOG-0218 (Burger 2011) clinical trial publications

on 7 5 mg/kg and 50% on 15 mg per kg (7 5 mg/kg in ICON7 and 15 mg/kg in GOG-0218) For subsequent bevacizumab, 15 mg/kg is used based on the OCEANS trial (Aghajanian 2012)

Table 10. Treatment dosing, administration and drug acquisition costs for olaparib, niraparib and bevacizumab

Maintenance therapy	Available formulations	Pack size	Mg/ Daily dose	Doses/ month	Cost/ Pack (DKK)	Cost/ Dose (DKK)	Cost/ month
Olaparib	150 mg	56	600	30 44	18 219 87	1 301 42	39 612
Niraparib	100 mg	84	300	30 44	62 010 00	2 214 64	67 414
Bevacizumab	25 mg/ml	4 ml	712	1 44	2 092 80	15 416	22 352
	25 mg/ml	16 ml	712	1 44	7 707 76		

For bevacizumab the cheapest combination of the 4 ml and the 16 ml packs is used in the analysis This generates a cost per 3-week cycle of DKK 15 416, which equals a cost per month of DKK 22 352 It should be noted that the list price for bevacizumab is used here Tender prices for the bevacizumab biosimilars that are now available could be expected to be lower

Treatment dosing, administration frequency and drug acquisition costs for subsequent chemotherapy are summarized in Table 11

Table 11. Treatment dosing, administration and drug acquisition costs for chemotherapy

Maintenance therapy	Formulation (mg/ml)	Vial size (ml)	Cost/ pack (DKK)	Average cost / mg (DKK)	Dose (mg)	Cost/ cycle (DKK)	Doses / month***	Cost/ month
Doxorubicin	2	25	120	2 40	30/m^2	120*	1 09	174
Carboplatin	10	45	203	0 45	AUC 4 (472)	406**	1 45	589
Paclitaxel	6	50	201 50	0 67	175/m^2	403*	1 45	584
Docetaxel	20	4	150	1 88	75/m^2	300*	1 45	435
Cisplatin	1	100	200	2 00	75/m^2	400*	1 45	580

Based on a body surface are of 1 75m^2; **Based on area under the curve concentration AUC 4 mg/mL·min, Calvert formula: Dose (mg) = target AUC x (GFR + 25);*Average number of days per months divided by cycle length of 3 or 4 weeks (30 44/21 = 1 45; 30 44/28 = 1 09)*

3.6 Drug administration costs

The administration frequency was based on the EMA licensed posology information for each treatment For olaparib, which is an oral treatment, no cost of administration was applied For bevacizumab and chemotherapy, it is assumed that the tariff forDRG 13MA98, i e MDC13 1-dagsgruppe, pat mindst 7 år, represents the cost of chemotherapy administration MDC 13 applies to Diseases and Disorders of the Female Reproductive System in ICD-10 and dagsgruppe represent ambulant care, as chemotherapy is administered in the outpatient setting The administration costs are outlined in Table 12

Table 12. Drug administration unit costs

	Unit costs (DKK)	Code /description	Source
Chemotherapy administration	DKK 1636	DRG 13MA98 MDC13 1-dagsgruppe, pat	DRG takster 2021*

* DRG Takster 2021 (https //sundhedsdatastyrelsen dk/da/afregning-og-finansiering/takster-drg/takster-2021)

The total administration cost per month for bevacizumab and chemotherapy is summarized in Table 13

Table 13. Monthly drug administration costs per treatment

	Unit costs (DKK)	Administrations/ month	Administration cost/ month (DKK)
Bevacizumab	1 636	1 45	2 372 20
Chemotherapy	1 636	1	1 636

3.7 Drug monitoring costs

The monitoring unit costs are found in Table 14 The cost of blood tests is not included, as one blood test is assumed to be included in doctor visits

Table 14. Unit costs

Cost item	Cost* (DKK)	Code	Code description	Source
Doctor or nurse visit	1 636	13MA98	MDC13 1-dagsgruppe, pat mindst 7 år	DRG takster 2021*
CT scan	2 007	30PR06	CT-scanning, kompliceret	DRG takster 2021*
Vaginal ultrasound	1 820	30PR10	UL-scanning, kompliceret	DRG takster 2021*

*DRG Takster 2021 (https //sundhedsdatastyrelsen dk/da/afregning-og-finansiering/takster-drg/takster-2021)

Since there is an absence of drug monitoring information and frequency data in the respective EMA summary of product characteristics for the included treatments, the estimates are based on AstraZeneca's assumptions from the medical department which in turned are based on discussion with clinicians Table 15 shows the resource use in terms of the average number of visits and diagnostic procedures per month for olaparib, bevacizumab and watch and wait For example, a health care contact occurring once every third month corresponds to a quantity of 1/3 = 0 33 per month

Table 15. Monitoring frequency and total monthly costs for olaparib, bevacizumab, watch and wait, chemotherapy

Cost unit	Olaparib+ Bevacizumab	Olaparib	Bevacizumab	Watch and wait	Chemotherapy
Doctor visit	1	1	0 33	0 33	1
Nurse visit	1 45	1	1 45	0 33	1
CT scan	0 33	0 33	0 33	0 33	0 33
Vaginal ultrasound	0 2	0 2	0 2	0 2	0 2
Total monthly cost per patient	DKK 5 244	DKK 4 305	DKK 3 954	DKK 2 129	DKK 4 305

3.8 Adverse event costs

AE costs were included to account for the potential cost of experiencing AEs whilst on treatment AE costs are applied to patients receiving treatment each year These costs are calculated by multiplying the rate AEs by the unit cost of treating the AE Since AEs usually are more frequent in the beginning of a treatment the AE costs are applied at treatment initiation

The costs for AEs are likely to differ depending on grade The model uses the probability of AEs of grade 3 or higher with a frequency of at least 2% in one of the arms in PAOLA-1 For olaparib monotherapy and watch and wait the AEs reported in the SOLO1 publication Moore (2018), Table 2, was used

The resource utilization related to AEs are presented in Table 16 The cost items were sourced from the Danish DRG/DAGS codes recommended in Medicinrådet guidelines Overall, the assumption is that the medicines associated with AE treatment are not costly and therefore excluded

Table 16. Cost items related to AE

AE associated to cost item	Cost item	Cost* (DKK)	Code	Code description	Source
Several AEs	Doctor or nurse visit	1 636	13MA98	1 MDC13 1-dagsgruppe, pat mindst 7 år	DRG takster 2021*
Nausea / vomiting / diarrhoea	Hospitalization	22 789	DRG06MA14	Andre sygdomme i fordøjelsesorganerne, pat mindst 18 år	DRG takster 2021*
Anemia	Blood transfusion	4 628	16PR02	Transfusion af blod, øvrig	DRG takster 2021*
Hypertension	Hospitalization	14 155	DRG05MA11	Hypertension	DRG takster 2021*

*DRG Takster 2021 (https //sundhedsdatastyrelsen dk/da/afregning-og-finansiering/takster-drg/takster-2021)

The cost items in Table 16 are combined for each AE, the resulting unit cost with the associated justification are presented in Table 17

Table 17. Unit costs for AEs for olaparib, bevacizumab, and watch and wait

Treatment	Unit cost (DKK)	Justification
Diarrhea	1 600 98	70% of patients have one additional doctor visit, 2% of patients are hospitalized
Anemia	4 029 60	80% of these patients get blood transfusions The 20% without need for transfusion have 1 extra nurse visit in the outpatient clinic
Hypertension	7 077 50	50% of patients get hospitalized
Neutropenia	1 636	One additional doctor visit
Fatigue or Asthenia	1 636	One additional doctor visit
Lymphopenia	1 636	One additional doctor visit

AEs were incorporated into the economic model through applying the proportion of patients expected to experience an AE per year for each treatment as reported in PAOLA-1 The model includes grade 3 or above adverse events considered to have a large impact on patient HRQoL and/or are associated with significant costs Grade ≥3 AEs taken into consideration are listed in Table 18 The AE incidence rates for olaparib monotherapy and watch and wait in Table 18 were sourced from SOLO1 (Moore et al , 2018) The incidence rates were derived from treatment-related AEs of grade ≥3 according to the Common Terminology Criteria for Adverse Events (CTCAE)

Table 18. Incidence rates and costs for grade 3 or 4 adverse events for olaparib, bevacizumab, and watch and wait.

Treatment	Olaparib + bevacizumab (N = 535)	Olaparib (n = 260)	Bevacizumab mono (n = 267)	Watch and wait (n = 130)
Anemia	17 4%	21 5%	0 4%	1 5%
Diarrhea	2 2%	3 1%	1 9%	0%
Hypertension	18 7%	0%	30 3%	0%
Neutropenia	6 4%	8 5%	3%	3 1%
Fatigue or Asthenia	5 2%	3 8%	1 5%	1 5%
Lymphopenia	5 9%	0%	1 1%	0%
Total cost / patient	DKK 2 361	DKK 1 118.53	DKK 2 283.73	DKK 137.50

3.9 Patient time and patient transport

Patient costs were estimated based on Medicinrådet guidelines The patient costs are calculated based on drug monitoring visits, thus AE related visits are excluded The average time for each health care visit includes the effective time in the health care unit (Table 19), and the associated waiting time and transport time is included as patient transport time The estimated time for CT scan is the same as the values accepted by Amgros in the evaluation of alectinib

Table 19. Patient time associated with drug monitoring visits

Cost unit	Patient time (minutes)
Consultation (office visit)	20
CT scan	30
Vaginal ultrasound	30

Table 20 shows the costs for patient time and transport This includes the average number of visits to the health care clinic per month for olaparib, bevacizumab, watch and wait, and associated patient time and patient costs The estimate for total time cost per month, off treatment, is the same as for watch and wait The doctor visit and vaginal ultrasound is assumed to occur in the same visit, when applicable CT-scans are always assumed to require separate visits as these diagnostic investigations are performed in separate facilities

The patient time for visits is multiplied with the monetary value for patient time according to Medicinrådet guidelines, DKK 179 per hour The transport cost to and from visits to the health care clinic is set to DKK 100, also based on Medicinrådet guidelines The total patient costs are the sum of the patient time costs and the transport costs

Table 20. Estimated patient costs for time and transport for olaparib, bevacizumab and watch and wait

Cost unit	Olaparib+ Bevacizumab	Olaparib	Bevacizumab	Watch and Wait/ Off treatment	Chemoterapy
Number of visits per month	2 78	2 33	1 98	1 00	2 33
Patient time, visits (hours)	0 93	0 93	0 86	0 49	0 93
Patient time cost (DKK)	201	167	154	88	167
Transport time (hours)	4 67	4 67	4 22	2 01	4 67
Transport cost (DKK)	557	467	422	201	467
Total patient cost per month, patient time + transport (DKK)	751	634	576	289	634

3.10 Overall survival

Overall survival is used in the model for estimation of monitoring costs and patient time costs over time The probability of being alive at each time point is multiplied with the monthly monitoring or patient time cost The treatment costs are not affected by this as these cost were based on time to treatment discontinuation data

The overall survival extrapolations are described in Appendix D Separate overall survival data estimations were used for the BRCAm positive group (section 9 1 and 9 2) and for the HRD positive non-BRCAm group (section 9 3) For the BRCAm group, a matched and adjusted indirect comparison was performed using individual patient data from the SOLO-1 trial with individual patient data from the subset of patients with confirmed tBRCA mutations (per eCRF) in the PAOLA-1 trial For the HRD positive non-BRCAm group, data was used directly from a subgroup analysis based the clinical trial data

3.11 BRCA and HRD test

BRCA and HRD tests could for most patients be expected to be performed prior to treatment with olaparib and are therefore not included in the current cost analyses HRD testing is not yet fully implemented, but is expected to have a cost similar to BRCA testing The cost for a BRCA or HRD test is included in sensitivity analysis and is estimated to be between 6000 – 8000 DKK per test in Denmark In the sensitivity analysis, 7000 DKK is used

3.12 Discount rate for the cost analysis

In the cost analysis, a discount rate of 3 5% was used according to the latest recommendations from the Ministry of Finance (https://fm dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021 pdf)

3.13 Basic assumptions for the base case analysis

Table 21. Basic assumptions for the base case analysis

Variable	Assumption	Comment
Time horizon	10 years	Time horizon long enough to capture the major costs Longer time horizon would go far beyond patent expiry for olaparib and would not be very meaningful 5-year and 25-year time horizons are tested in scenar o analysis
Discount rate	3 5%	Based on latest recommendations from the Danish Finance ministry 2 5% and 4 5% tested in sensitivity analysis
Included costs	• Pharmaceutical costs • Administration costs • Monitoring costs • Adverse event costs • Patient and transport costs • Subsequent therapies	Standard cost elements
Dose	• Lynparza (olparib): 600 mg (2 x 300 mg) per day as in SmPC • Bevacizumab: Mix of 15 mg/kg and 7 5 mg/kg bevacizumab based on Danish clinical practice (15 mg/kg in SmPC but 7 5 mg/kg common based on ICON7 • Base case 50% 15 mg/kg and 50% 7 5 mg/kg	The dosing in the SmPCs is bevacizumab 15 mg/kg for both olaparib + bevacizumab and bevacizumab alone However, the 7 5 mg/kg dosing is preferred by many clinicians based on the results of the ICON7 study It is not expected that the combination therapy would lead to changed dosing of bevacizumab in the 1st line setting
Treatment line	1st line	As per indication and protocol
Subsequent therapies included	Yes	As the choice of in tial 1st line therapy affects subsequent therapies
Time on treatment for Lynparza and comparators	Based on KM data for time to treatment discontinuation as treatment durat on is limited to 2 years for most patients	No need to extrapolate as KM data covers the relevant time horizon
Overall survival	Based on parametric extrapolations based on statistical fit and clin cal plausibil ty	Only used for estimat on of monitoring costs and patient time costs over time Treatment and administration costs covered by time to treatment discontinuation data
Subsequent PARP inhibitors	Not included	Not reused after olaparib in the first line and not recommended for non-BRCAm patients
Subsequent chemotherapy	Included	Based on time to first subsequent therapy (TFST) In the base case TFST from SOLO-1
Subsequent bevacizumab	Included	Included for the comparison with olaparib monotherapy (BRCAm population) and with watch and wait (HRD+ non-BRCA patients who are not cand dates for bevacizumab in the first line

Inclusion of wastage	Yes, for bevacizumab and chemotherapy	Vial sharing is possible as an option for bevacizumab and chemotherapy
Cost for HRD testing included	No	Genetic testing is not only driven by treatment, but is of wider interest for physicians and patients Hence, thorough genetic testing should be performed at diagnosis and the cost for this should not be allocated to a specific treatment

4 Results

4.1 Average cost per patient: Olaparib + bevacizumab vs. olaparib in the BRCAm subpoulation

4.1.1 Base case for olaparib + bevacizumab vs. olaparib in the BRCAm subpoulation

The results of the cost analysis for patients with BRCAm positive platinum-sensitive ovarian cancer show the average costs per patient over 10 years, including subsequent therapy (Table 22, Figure 8) The drug acquisition costs constitute the major part of the total costs for all treatments Costs for drug administration and patient monitoring and follow-up are the second or third largest costs, while patient time and travel costs and in particular costs for adverse events are smaller For adverse events, however, only costs for first-line treatments have been included

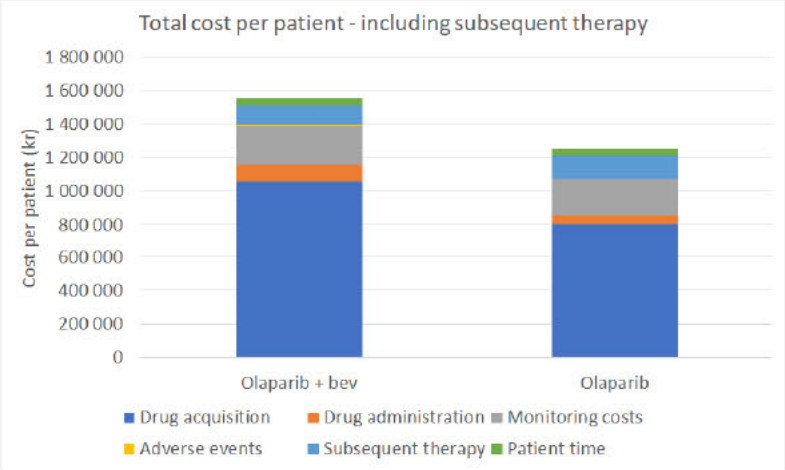
The total costs per patient over ten years show that treatment with olaparib + bevacizumab is DKK 302 533 more expensive than olaparib monotherapy This is primarily due to a higher acquisition cost for the combination therapy, as bevacizumab is added

Table 22. Average costs per patient for olaparib + bevacizumab vs olaparib monotherapy, year 1, year 2, years 3-10, and total over 10 years, base case (DKK)

Treatment	Cost item	Year 1 (2021)	Year 2 (2022)*	Year 3 to 10 * (2023 - 2030)	Total - Year 1 to 10* (2021 - 2030)
Olaparib + bevacizumab	Drug acquisition	649 451	376 478	33 234	1 059 162
	Drug administration	33 418	37 962	30 374	101 754
	Monitoring costs	58 474	48 874	123 287	230 634
	Adverse events	2 361	0	0	2 361
	Subsequent therapy	13 808	22 499	81 361	117 668
	Patient time	8 353	10 630	23 759	42 742
	Total	**765 865**	**496 443**	**292 014**	**1 554 322**
Olaparib	Drug acquisition	408 155	313 098	80 833	802 086
	Drug administration	8 945	15 245	33 778	57 968
	Monitoring costs	48 154	41 483	124 393	214 031
	Adverse events	1 119	0	0	1 119
	Subsequent therapy	14 960	26 356	98 192	139 508
	Patient time	7 055	6 132	23 891	37 078
	Total	**488 389**	**402 314**	**361 086**	**1 251 789**
Difference		*277 476*	*94 129*	*-69 072*	*302 533*

*Discounted costs in line with Medicinrådet guidelines (2020) Discount rate of 3 5% used based on latest recommendation from the Danish Ministry of Finance (https //fm dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021 pdf)

Figure 8. Average costs per patient for olaparib + bevacizumab vs olaparib monotherapy over 10 years, base case



4.1.2 One-way sensitivity analysis

A one-way sensitivity analysis was also performed for key variables in the model The variables included in the one-way sensitivity analysis were the discount rate, drug acquisition costs, administration costs, monitoring costs, patient time and transport costs, and AE costs (Table 23) Except for the discount rate, all variables were varied with ±20% The results were most sensitive to drug acquisition costs for olaparib and bevacizumab and the administration cost, but relatively insensitive to other variables The bevacizumab cost has the largest impact by far, because other costs are fairly similar in the two treatment arms

Table 23. Sensitivity analysis: Difference in average costs per patient over 10 years (DKK)

Parameter	Variation	Total cost year 1 to 10		Olaparib + bev vs olaparib monotherapy	
		Olaparib + bevacizumab	Olaparib monotherapy	Difference	% Change
Base case	-	1 554 322	1 251 789	302 533	-
Discount rate	2 5%	1 571 258	1 269 958	301 300	-0 4%
	4 5%	1 538 194	1 234 507	303 688	0 4%
Drug acquisition cost: Olaparib	-20%	1 402 194	1 091 372	310 822	2 7%
	+20%	1 706 450	1 412 206	294 244	-2 7%
Drug acquisition cost: Bevacizumab	-20%	1 494 618	1 251 789	242 829	-19 7%
	+20%	1 614 026	1 251 789	362 237	19 7%
Monitoring cost	-20%	1 508 195	1 208 983	299 212	-1 1%
	+20%	1 600 449	1 294 595	305 854	1 1%
Administration cost	-20%	1 544 545	1 251 789	292 756	-3 2%
	+20%	1 564 099	1 251 789	312 310	3 2%
Patient time and transport cost	-20%	1 549 806	1 248 496	301 310	-0 4%
	+20%	1 558 838	1 255 082	303 756	0 4%

Parameter	Variation	Total cost year 1 to 10		Olaparib + bev vs olaparib monotherapy	
		Olaparib + bevacizumab	Olaparib monotherapy	Difference	% Change
AE cost	-20%	1 553 850	1 251 565	302 285	-0 1%
	+20%	1 554 794	1 252 013	302 782	0 1%

4.1.3 Scenario analysis: Excluding subsequent therapy

In this scenario treatments with olaparib + bevacizumab and olaparib monotherapy are included, and all costs related to subsequent therapy are excluded Since subsequent PARP inhibitors are not recommended for patients who used these in the first line and chemotherapy will be used in clinical practice in both the arms, this scenario does not differ hugely from the base case The difference for olaparib + bevacizumab vs olaparib monotherapy is DKK 319 749 over 10 years (Table 24), compared with a difference of DKK 302 533 in the base case

Table 24. Average costs per patient for olaparib + bevacizumab vs olaparib monotherapy, year 1, year 2, years 3-10, and total over 10 years, base case

Treatment	Cost item	Year 1 (2021)	Year 2 (2022)	Year 3 to 10 (2023 - 2030)	Total - Year 1 to 10 (2021 - 2030)
Olaparib + bevacizumab	Drug acquisition	649 451	376 478	33 234	1 059 162
	Drug administration	33 418	37 962	30 374	101 754
	Monitoring costs	58 200	49 241	172 300	279 741
	Adverse events	2 361	0	0	2 361
	Patient time	8 305	6 987	23 371	38 663
	Total	**751 735**	**470 668**	**259 279**	**1 481 682**
Olaparib	Drug acquisition	408 155	313 098	80 833	802 086
	Drug administration	8 945	15 245	33 778	57 968
	Monitoring costs	47 969	41 884	174 127	263 980
	Adverse events	1 119	0	0	1 119
	Patient time	7 019	6 073	23 688	36 780
	Total	**473 207**	**376 300**	**312 425**	**1 161 932**
Difference		*278 528*	*94 368*	*-53 146*	*319 749*

4.1.4 Scenario analysis: 5-year time frame

This scenario uses a 5-year time frame instead of 10 years as in the base case In this scenario, the difference for olaparib + bevacizumab vs olaparib monotherapy is DKK 309 235 over 5 years (Table 25), compared with a difference of DKK 302 533 in the 10-year base case Hence, the longer time perspective has only a small impact on the total cost difference

If the time horizon is extended to 25 years, the total per patient cost is DKK 1 666 200 for olaparib + bevacizumab and DKK 1 346 738 for olaparib, giving a cost difference of DKK 319 462

Table 25. Average costs per patient for olaparib + bevacizumab vs olaparib monotherapy, year 1, year 2, years 3-10, and total over 5 years (DKK)

Treatment	Cost item	Year 1 (2021)	Year 2 (2022)*	Year 3 to 5* (2023 - 2025)	Total - Year 1 to 5 *(2021 - 2025)
Olaparib + bevacizumab	Drug acquisition	649 451	376 478	33 234	1 059 162
	Drug administration	33 418	37 962	30 374	101 754
	Monitoring costs	58 474	48 874	63 325	170 673
	Adverse events	2 361	0	0	2 361
	Subsequent therapy	13 808	22 499	49 023	85 329
	Patient time	8 353	10 630	10 143	29 126
	Total	**765 865**	**496 443**	**186 098**	**1 448 406**
Olaparib	Drug acquisition	408 155	313 098	80 833	802 086
	Drug administration	8 945	15 245	33 778	57 968
	Monitoring costs	48 154	41 483	64 573	154 211
	Adverse events	1 119	0	0	1 119
	Subsequent therapy	14 960	26 356	59 084	100 400
	Patient time	7 055	6 132	10 200	23 387
	Total	**488 389**	**402 314**	**248 468**	**1 139 171**
Difference		*277 476*	*94 129*	*-62 370*	*309 235*

*Discounted costs in line with Medicinrådet guidelines (2020) Discount rate of 3 5% used based on latest recommendation from the Danish Ministry of Finance (https //fm dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021 pdf)

4.1.5 Scenario analysis: Proportion of patients receiving subsequent bevacizumab therapy in the olaparib monotheray arms

The proportion of patients receiving subsequent bevacizumab therapy in the olaparib monotherapy arm was sourced from SOLO-1, but this may be a conservative assumption Once SOLO-1 data become more mature, the bevacizumab use in 2nd and further lines of therapy could be expected to increase In this scenario analysis, 60% 2nd line bevacizumab use is tested for the olaparib monotherapy arm It is assumed that there would be no retreatment with bevacizumab for patients treated with olaparib + bevacizumab in the first line

In the scenario with 60% subsequent bevacizumab use for olaparib monotherapy, the results show that the difference for olaparib + bevacizumab vs olaparib monotherapy is DKK 146 288 over 10 years (Table 26), compared with a difference of DKK 302 533 in the base case Hence, a higher and presumably more realistic percentage of subsequent bevacizumab use in the olaparib arm leads to a lower difference in costs

Table 26 .Average costs per patient for olaparib + bevacizumab vs olaparib monotherapy year 1, year 2, years 3-10, and total over 10 years, 60% subsequent PARP inhibitor use in the olaparib arm (DKK).

Treatment	Cost item	Year 1 (2021)	Year 2 (2022)	Year 3 to 10 (2023 - 2030)	Total - Year 1 to 10 (2021 - 2030)
Olaparib + bevacizumab	Drug acquisition	649 451	376 478	33 234	1 059 162
	Drug administration	33 418	37 962	30 374	101 754
	Monitoring costs	58 474	48 874	123 287	230 634
	Adverse events	2 361	0	0	2 361
	Subsequent therapy	13 808	22 499	81 361	117 668
	Patient time	8 353	10 630	23 759	42 742
	Total	**765 865**	**496 443**	**292 014**	**1 554 322**
Olaparib	Drug acquisition	408 155	313 098	80 833	802 086
	Drug administration	11 207	22 813	53 521	87 541
	Monitoring costs	48 154	41 483	124 393	214 031
	Adverse events	1 119	0	0	1 119
	Subsequent therapy	21 645	48 726	195 810	266 181
	Patient time	7 055	6 132	23 891	37 078
	Total	**497 335**	**432 253**	**478 447**	**1 408 034**
Difference		*268 531*	*64 190*	*-186 433*	*146 288*

*Discounted costs in line with Medicinrådet guidelines (2020) Discount rate of 3 5% used based on latest recommendation from the Danish Ministry of Finance (https //fm dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021 pdf)

4.1.6 Scenario analysis: Time to subsequent therapy from PAOLA-1 rather than SOLO-1

PAOLA-1 did not include an olaparib monotherapy arm or a wait and wait arm, but could be seen as more relevant for time to subsequent therapy in the olaparib + bevacizumab and bevacizumab arms For consistency, SOLO-1 data was used in the base case for all comparisons, but the PAOLA-1 data are also tested for all comparisons in the sensitivity scenarios In the scenario with PAOLA-1 data for subsequent chemotherapy, the results show that the difference for olaparib + bevacizumab vs olaparib monotherapy is DKK 300 411 over 10 years (Table 27), compared with a difference of DKK 302 533 in the base case Hence, the use of PAOLA-1 for time to subsequent therapy had a minor impact on the cost difference

Table 27 Average costs per patient for olaparib + bevacizumab vs olaparib monotherapy year 1, year 2, years 3-10, and total over 10 years, with PAOLA-1 data used for time to subsequent chemotherapy (DKK).

Treatment	Cost item	Year 1 (2021)	Year 2 (2022)	Year 3 to 10 (2023 - 2030)	Total - Year 1 to 10 (2021 - 2030)
Olaparib + bevacizumab	Drug acquisition	649 451	376 478	33 234	1 059 162
	Drug administration	37 071	46 868	31 315	115 254
	Monitoring costs	58 613	49 207	123 090	230 909
	Adverse events	2 361	0	0	2 361
	Subsequent therapy	19 703	36 872	65 606	122 180
	Patient time	8 374	10 630	23 759	42 762
	Total	**775 572**	**520 054**	**277 003**	**1 572 629**
Olaparib	Drug acquisition	408 155	313 098	80 833	802 086
	Drug administration	12 718	24 918	35 244	72 881
	Monitoring costs	48 251	41 716	124 255	214 223
	Adverse events	1 119	0	0	1 119
	Subsequent therapy	21 212	42 999	80 602	144 814
	Patient time	7 071	6 170	23 857	37 097
	Total	**498 526**	**428 901**	**344 791**	**1 272 218**
Difference		*277 046*	*91 153*	*-67 787*	*300 411*

*Discounted costs in line with Medicinrådet guidelines (2020) Discount rate of 3 5% used based on latest recommendation from the Danish Ministry of Finance (https //fm dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021 pdf)

4.1.7 Scenario analysis: Vial sharing

The base case does not assume vial sharing, but vial sharing could occur at some clinics for chemotherapy and also for bevacizumab In the scenario with vial sharing, the results that the difference for olaparib + bevacizumab vs olaparib monotherapy is DKK 272 682 over 10 years (Table 28), compared with a difference of DKK 302 533 in the base case Not surprisingly, the effect of vial sharing is somewhat larger in the olaparib + bevacizumab arm, while the costs for subsequent chemotherapy is reduced in similar proportions in all arms as a consequence of vial sharing

Table 28. Average costs per patient for olaparib + bevacizumab vs olaparib monotherapy year 1, year 2, years 3-10, and total over 10 years, with vial sharing for chemotherapy and bevacizumab (DKK).

Treatment	Cost item	Year 1 (2021)	Year 2 (2022)	Year 3 to 10 (2023 - 2030)	Total - Year 1 to 10 (2021 - 2030)
Olaparib + bevacizumab	Drug acquisition	623 717	369 421	33 234	1 026 372
	Drug administration	33 418	37 962	30 374	101 754
	Monitoring costs	58 474	48 874	123 287	230 634
	Adverse events	2 361	0	0	2 361
	Subsequent therapy	12 105	19 724	71 327	103 156
	Patient time	8 353	10 630	23 759	42 742
	Total	**738 429**	**486 611**	**281 980**	**1 507 020**
Olaparib	Drug acquisition	408 155	313 098	80 833	802 086
	Drug administration	8 939	15 225	33 726	57 890
	Monitoring costs	48 154	41 483	124 393	214 031
	Adverse events	1 119	0	0	1 119
	Subsequent therapy	13 107	23 076	85 953	122 135
	Patient time	7 055	6 132	23 891	37 078
	Total	**486 529**	**399 014**	**348 795**	**1 234 338**
Difference		*251 899*	*87 597*	*-66 815*	*272 682*

*Discounted costs in line with Medicinrådet guidelines (2020) Discount rate of 3 5% used based on latest recommendation from the Danish Ministry of Finance (https //fm dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021 pdf)

4.2 Average cost per patient: Olaparib + bevacizumab vs. bevacizumab in the HRD+ non-BRCAm subpopulation (bevacizumab candidates)

4.2.1 Base case for olaparib + bevacizumab vs. bevacizumab in the HRD+ non-BRCAm subpopulation (bevacizumab candidates)

The results of the cost analysis for patients in the HRD+ non-BRCAm subpopulation (bevacizumab candidates) show the average costs per patient over 10 years, including subsequent therapy (Table 29, Figure 9) The drug acquisition costs constitute the major proportion of the total costs for all treatments Costs for drug administration and patient monitoring and follow-up are the second or third largest costs, while patient time and travel costs and in particular costs for adverse events are smaller For adverse events, however, only costs for first-line treatments have been included

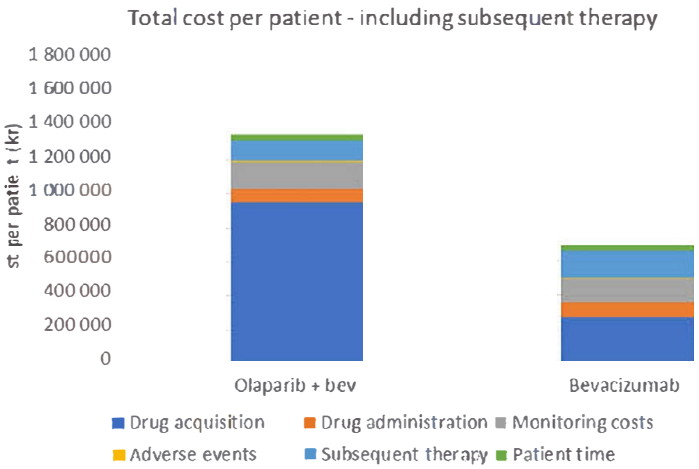
The total costs per patient over ten years show that treatment with olaparib + bevacizumab is DKK 664 567 more expensive than bevacizumab over 10 years This is primarily due to a higher acquisition cost for the combination therapy, as olaparib is added to bevacizumab In addition, there are no large cost offsets for subsequent therapy, as bevacizumab has already been used in the first line in both arms, olaparib used in one arm and no PARP inhibitor is recommended in 2nd line use for non-BRCA patients

Table 29. Average costs per patient for olaparib + bevacizumab vs bevacizumab alone, year 1, year 2, years 3-10, and total over 10 years, base case (DKK).

Treatment	Cost item	Year 1 (2021)	Year 2 (2022)	Year 3 to 10 (2023 - 2030)	Total - Year 1 to 10 (2021 - 2030)
Olaparib + bevacizumab	Drug acquisition	616 599	281 045	53573	951 217
	Drug administration	32 161	13 940	30374	76 474
	Monitoring costs	56 653	36 585	68 835	162073
	Adverse events	2 361	0	0	2 361
	Subsequent therapy	13 808	22 499	81 361	117 668
	Patient time	8 108	7 536	23 782	39 427
	Total	**729 690**	**361 605**	**257 924**	**1 349 220**
Bevacizumab	Drug acquisition	223 170	46 183	0	269 353
	Drug administration	33 737	16 380	35 691	85 808
	Monitoring costs	43 826	26 862	67 872	138 561
	Adverse events	2 284	0	0	2 284
	Subsequent therapy	18 206	29 665	107 276	155 147
	Patient time	6 359	3 986	23 154	33499
	Total	**327 582**	**123 077**	**233 994**	**684 652**
Difference		*402 108*	*238 529*	*23 931*	*664 567*

*Discounted costs in line with Medicinrådet guidelines (2020) Discount rate of 3 5% used based on latest recommendation from the Danish Ministry of Finance (https //fm dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021 pdf)

Figure 9. Average costs per patient olaparib + bevacizumab vs bevacizumab alone over 10 years, base case



4.2.2 One-way sensitivity analysis

A one-way sensitivity analysis was also performed for key variables in the model The variables included in the one-way sensitivity analysis were the discount rate, drug acquisition costs, administration costs, monitoring costs, patient time and transport costs, and AE costs (Table 30) Except for the discount rate, all variables were varied with ±20% The results were most sensitive to drug acquisition costs for olaparib, and relatively insensitive to other variables The olaparib cost has the largest impact by far, because other costs are fairly similar in the two treatment arms

Table 30. Sensitivity analysis: Difference in average costs per patient over 10 years (DKK).

Parameter	Variation	Total cost year 1 to 10		Olaparib + bev vs bevacizumab	
		Olaparib + bevacizumab	Bevacizumab monotherapy		% Change
Base case	-	1 349 220	684 652	664 567	-
Discount rate	2 5%	1 362 258	695 474	666 785	0 3%
	4 5%	1 336 766	674 409	662 357	-0 3%
Drug acquisition cost: Olaparib	-20%	1 227 603	684 652	542 951	-18 3%
	+20%	1 470 837	684 652	786 184	18 3%
Drug acquisition cost: Bevacizumab	-20%	1 280593	630 782	649 811	-2 2%
	+20%	1 417 847	738523	679324	2 2%
Monitoring cost	-20%	1 316805	656 940	659865	-0 7%
	+20%	1 381 635	712365	669 270	0 7%
Administration cost	20%	1 344 499	679916	664 583	0 0%
	+20%	1 353 941	689 389	664 552	0 0%
	-20%	1 345 430	682 039	663391	-0 2%

Parameter	Variation	Total cost year 1 to 10		Olaparib + bev vs bevacizumab	
		Olaparib + bevacizumab	Bevacizumab monotherapy		% Change
Patient time and transport cost	+20%	1 353 009	687 266	665 744	0 2%
AE cost	-20%	1 348 748	684196	664 552	0 0%
	+20%	1 349 692	685 109	664583	0 0%

4.2.3 Scenario analysis: Excluding subsequent therapy

In this scenario treatments with olaparib + bevacizumab and bevacizumab monotherapy are included, and all costs related to subsequent therapy are excluded Since subsequent PARP inhibitors in the bevacizumab arm are excluded, this scenario is quite different from the base case The difference for olaparib + bevacizumab vs olaparib monotherapy is DKK 705 540 over 10 years (Table 31), compared with a difference of DKK 664 567 in the base case The relatively similar costs are primarily driven by the absence of subsequent PARP inhibitor costs and bevacizumab costs when subsequent therapies are included in the base case The difference is hence driven by differences in subsequent chemotherapy

Table 31. Average costs per patient for olaparib + bevacizumab vs bevacizumab alone, year 1, year 2, years 3-10, and total over 10 years, excluding subsequent therapy (DKK).

Treatment	Cost item	Year 1 (2021)	Year 2 (2022)	Year 3 to 10 (2023 - 2030)	Total - Year 1 to 10 (2021 - 2030)
Olaparib + bevacizumab	Drug acquisition	616599	281045	53 573	951 217
	Drug administration	32 161	13940	30 374	76 474
	Monitoring costs	56 549	38 815	172 380	267743
	Adverse events	2 361	0	0	2 361
	Patient time	8 060	5 440	23 383	36 882
	Total	**715 729**	**339 240**	**279 709**	**1 334 678**
Bevacizumab	Drug acquisition	223 170	46 183	0	269353
	Drug administration	33 737	16 380	35 691	85 808
	Monitoring costs	43765	28 455	169 687	241 906
	Adverse events	2 284	0	0	2 284
	Patient time	3 461	3 343	22983	29787
	Total	**306 416**	**94 362**	**228 361**	**629 139**
Difference		*409 313*	*244 878*	*51 348*	*705 540*

*Discounted costs in line with Medicinrådet guidelines (2020) Discount rate of 3 5% used based on latest recommendation from the Danish Ministry of Finance (https //fm dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021 pdf)

4.2.4 Scenario analysis: 5-year time frame

This scenario uses a 5-year time frame instead of 10 years as in the base case In this scenario, the difference for olaparib + bevacizumab vs bevacizumab monotherapy is DKK 675 659 over 5 years (Table 32),

compared with a difference of DKK 664 567 in the 10-year base case Hence, the longer time perspective has only a moderate impact on the total cost difference in this case

If the time horizon is extended to 25 years, the total per patient cost is DKK 1 385 443 for olaparib + bevacizumab and DKK 693 700 for olaparib, giving a cost difference of DKK 691 743

Table 32. Average costs per patient for olaparib + bevacizumab vs bevacizumab monotherapy, year 1, year 2, years 3-5, and total over 5 years (DKK).

Treatment	Cost item	Year 1 (2021)	Year 2 (2022)	Year 3 to 5 (2023 - 2025)	Total - Year 1 to 5 (2021 - 2025)
Olaparib + bevacizumab	Drug acquisition	616 599	281045	53 573	951217
	Drug administration	32 161	13 940	30374	76 474
	Monitoring costs	56 653	36 585	45 448	138 686
	Adverse events	2 361	0	0	2 361
	Subsequent therapy	13808	22499	49 023	85 329
	Patient time	8 108	7 536	10166	25811
	Total	**729 690**	**361 605**	**188 583**	**1 279 879**
Bevacizumab	Drug acquisition	223170	46 183	0	269 353
	Drug administration	33 737	16 380	35 691	85 808
	Monitoring costs	43 826	26 862	43758	114447
	Adverse events	2 284	0	0	2 284
	Subsequent therapy	18 206	29 665	64 637	112 508
	Patienttime	6 359	3 986	9 474	19818
	Total	**327 582**	**123 077**	**153 561**	**604 219**
Difference		*402 108*	*238 529*	*35 022*	*675 659*

*Discounted costs in line with Medicinrådet guidelines (2020) Discount rate of 3 5% used based on latest recommendation from the Danish Ministry of Finance (https //fm dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021 pdf)

4.2.5 Scenario analysis: Number of subsequent chemotherapy lines

In the base case, it was assumed that first-line olaparib would be followed by 3 lines of chemotherapy and bevacizumab and watch and wait by 4 lines of chemotherapy This scenario explores 3 or 4 lines of chemotherapy for olaparib +bevacizumab and bevacizumab (Table 33)

Table 33. Mean and median treatment duration for olaparib and bevacizumab

Treatment	Number of lines of subsequent chemotherapy		
	Base case	Scenarios	
Olaparib + bevacizumab	3	3	4
Bevacizumab	4	3	4

In the scenario with 3 subsequent lines of chemotherapy for all treatments, the difference for olaparib + bevacizumab vs bevacizumab is DKK 718 885 over 10 years, vs DKK 664 567 in the base case (Table 34)

Table 34. Average costs per patient for olaparib + bevacizumab vs bevacizumab monotherapy, year 1, year 2, years 3-10, and total over 10 years, three lines of subsequent chemotherapy for all treatments (DKK).

Treatment	Cost item	Year 1 (2021)	Year 2 (2022)	Year 3 to 10 (2023 - 2030)	Total - Year 1 to 10 (2021 - 2030)
Olaparib + bevacizumab	Drug acquisition	616 599	281 045	53 573	951 217
	Drug administration	32 161	13 940	30 374	76 474
	Monitoring costs	56 653	36 585	68 835	162 073
	Adverse events	2 361	0	0	2 361
	Subsequent therapy	13 808	22 499	81 361	117 668
	Patient time	8 108	7 536	23 782	39 427
	Total	**729 690**	**361 605**	**257 924**	**1 349 220**
Bevacizumab	Drug acquisition	223 170	46 183	0	269 353
	Drug administration	31 224	12 285	26 768	70 277
	Monitoring costs	43 826	26 862	67 872	138 561
	Adverse events	2 284	0	0	2 284
	Subsequent therapy	13 655	22 249	80 457	116 360
	Patient time	6 359	3 986	23 154	33 499
	Total	**320 517**	**111 565**	**198 252**	**630 335**
Difference		*409 173*	*250 040*	*59 672*	*718 885*

*Discounted costs in line with Medicinrådet guidelines (2020) Discount rate of 3 5% used based on latest recommendation from the Danish Ministry of Finance (https //fm dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021 pdf)

In the scenario with 4 subsequent lines of chemotherapy for all treatments, the difference for olaparib + bevacizumab vs bevacizumab is DKK 721 413 over 10 years, vs DKK 664 567 in the base case (Table 35)

Table 35. Average costs per patient for olaparib + bevacizumab vs bevacizumab monotherapy, year 1, year 2, years 3-10, and total over 10 years, four lines of subsequent chemotherapy for all treatments (DKK).

Treatment	Cost item	Year 1 (2021)	Year 2 (2022)	Year 3 to 10 (2023 - 2030)	Total - Year 1 to 10 (2021 - 2030)
Olaparib + bevacizumab	Drug acquisition	616 599	281 045	53 573	951 217
	Drug administration	35 012	18 587	40 498	94 097
	Monitoring costs	56 653	36 585	68 835	162 073
	Adverse events	2 361	0	0	2 361
	Subsequent therapy	18 411	29 998	108 482	156 891
	Patient time	8 108	7 536	23 782	39 427
	Total	**737 144**	**373 752**	**295 169**	**1 406 066**
Bevacizumab	Drug acquisition	223 170	46 183	0	269 353
	Drug administration	33 737	16 380	35 691	85 808
	Monitoring costs	43 826	26 862	67 872	138 561
	Adverse events	2 284	0	0	2 284
	Subsequent therapy	18 206	29 665	107 276	155 147
	Patient time	6 359	3 986	23 154	33 499
	Total	**327 582**	**123 077**	**233 994**	**684 652**
Difference		*409 563*	*250 675*	*61 176*	*721 413*

*Discounted costs in line with Medicinrådet guidelines (2020) Discount rate of 3 5% used based on latest recommendation from the Danish Ministry of Finance (https //fm dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021 pdf)

4.2.6 Scenario analysis: Time to subsequent therapy from PAOLA-1 rather than SOLO-1

PAOLA-1 did not include an olaparib monotherapy arm or a wait and wait arm, but could be seen as more relevant for time to subsequent therapy in the olaparib + bevacizumab and bevacizumab arms For consistency, SOLO-1 data was used in the base case for all comparisons, but the PAOLA-1 data are also tested for all comparisons in the sensitivity scenarios In the scenario with PAOLA-1 data for subsequent chemotherapy, the results show that the difference for olaparib + bevacizumab vs olaparib monotherapy is DKK 661 324 over 10 years (Table 36), compared with a difference of DKK 664 567 in the base case

Table 36. Average costs per patient for olaparib + bevacizumab vs bevacizumab year 1, year 2, years 3-10, and total over 10 years, with PAOLA-1 data used for time to subsequent chemotherapy (DKK).

Treatment	Cost item	Year 1 (2021)	Year 2 (2022)	Year 3 to 10 (2023 - 2030)	Total - Year 1 to 10 (2021 - 2030)
Olaparib + bevacizumab	Drug acquisition	616 599	281 045	53 573	951 217
	Drug administration	35 813	22 845	31 315	89 974
	Monitoring costs	56 791	36 900	68 797	162 488
	Adverse events	2 361	0	0	2 361
	Subsequent therapy	19 703	36 872	65 606	122 180
	Patient time	8 129	7 536	23 782	39 447
	Total	**739 396**	**385 198**	**243 073**	**1 367 667**
Bevacizumab	Drug acquisition	223 170	46 183	0	269 353
	Drug administration	38 029	26 845	36 797	101 671
	Monitoring costs	43 924	27 116	67 385	138 425
	Adverse events	2 284	0	0	2 284
	Subsequent therapy	25 979	48 616	86 502	161 097
	Patient time	6 371	4 017	23 125	33 513
	Total	**339 757**	**152 777**	**213 809**	**706 343**
Difference		*399 639*	*232 422*	*29 264*	*661 324*

*Discounted costs in line with Medicinrådet guidelines (2020) Discount rate of 3 5% used based on latest recommendation from the Danish Ministry of Finance (https //fm dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021 pdf)

4.2.7 Scenario analysis: Vial sharing

The base case does not assume vial sharing, but vial sharing could occur at some clinics for chemotherapy and also for bevacizumab In the scenario with vial sharing, the results that the difference for olaparib + bevacizumab vs bevacizumab monotherapy is DKK 660 869 over 10 years (Table 37), compared with a difference of DKK 664 567 in the base case The effect of vial sharing is very small as expected, as both costs for bevacizumab and the costs for subsequent chemotherapy are reduced in similar proportions in all arms as a consequence of vial sharing

Table 37. Average costs per patient for olaparib + bevacizumab vs bevacizumab monotherapy year 1, year 2, years 3-10, and total over 10 years, with vial sharing for chemotherapy and bevacizumab (DKK).

Treatment	Cost item	Year 1 (2021)	Year 2 (2022)	Year 3 to 10 (2023 - 2030)	Total - Year 1 to 10 (2021 - 2030)
Olaparib + bevacizumab	Drug acquisition	592 167	269 909	51 450	913 526
	Drug administration	32 161	13 940	30 374	76 474
	Monitoring costs	56 653	36 585	68 835	162 073
	Adverse events	2 361	0	0	2 361
	Subsequent therapy	12 105	19 724	71 327	103 156
	Patient time	8 108	7 536	23 782	39 427
	Total	**703 555**	**347 695**	**245 767**	**1 297 017**
Bevacizumab	Drug acquisition	198 656	41 110	0	239 766
	Drug administration	33 737	16 380	35 691	85 808
	Monitoring costs	43 826	26 862	67 872	138 561
	Adverse events	2 284	0	0	2 284
	Subsequent therapy	15 986	26 048	94 196	136 230
	Patient time	6 359	3 986	23 154	33 499
	Total	**300 848**	**114 387**	**220 913**	**636 148**
Difference		*402 707*	*233 308*	*24 854*	*660 869*

*Discounted costs in line with Medicinrådet guidelines (2020) Discount rate of 3 5% used based on latest recommendation from the Danish Ministry of Finance (https //fm dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021 pdf)

4.2.8 Scenario analysis: Including the cost of HRD testing

The cost of HRD testing was excluded from the base case, as most patients would be expected to be tested at the time of diagnosis In addition, patients in the first line treated with bevacizumab or watch and wait would be tested at the later stage if not tested at diagnosis The testing cost is thus not driven by the introduction of first-line olaparib and bevacizumab In addition, HRD tests are only required for those without a positive BRCA test

In a scenario where the HRD testing cost is only applied to first-line olaparib + bevacizumab, difference for olaparib + bevacizumab vs bevacizumab is DKK 681 624 over 10 years, vs DKK 664 567 in the base case

In a scenario where the HRD testing cost is applied also to bevacizumab, the cost differences are the same in the base case, as the testing cost is applied in equal measure to all treatment arms

4.3 Average cost per patient: Olaparib + bevacizumab vs. watch and wait in the HRD+ non-BRCAm subpopulation (not candidates for bevacizumab)

4.3.1 Base case for olaparib + bevacizumab vs. watch and wait in the HRD+ non-BRCAm subpopulation (not candidates for bevacizumab)

The results of the cost analysis for patients in the HRD+ non-BRCAm subpopulation, who are not bevacizumab candidates, show the average costs per patient over 10 years, including subsequent therapy (Table 38, Figure 10) The drug acquisition costs constitute the major proportion of the total costs for all treatments Costs for drug administration and patient monitoring and follow-up are the second or third largest costs, while patient time and travel costs and in particular costs for adverse events are smaller For adverse events, however, only costs for first-line treatments have been included

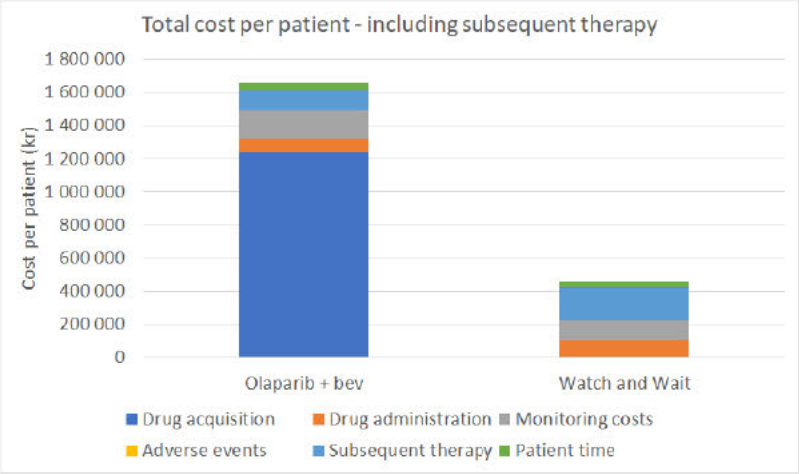
The total costs per patient over ten years show that treatment with olaparib + bevacizumab is DKK 1 196 626 more expensive than watch and wait over 10 years This is primarily due to a higher acquisition cost for the combination therapy

Table 38. Average costs per patient for olaparib + bevacizumab vs watch and wait, year 1, year 2, years 3-10, and total over 10 years, base case (DKK).

Treatment	Cost item	Year 1 (2021)	Year 2 (2022)	Year 3 to 10 (2023 - 2030)	Total - Year 1 to 10 (2021 - 2030)
Olaparib + bevacizumab	Drug acquisition	647 282	554 290	38 461	1 240 033
	Drug administration	33 335	13 940	30 374	77 649
	Monitoring costs	58 183	49 132	68 429	175 744
	Adverse events	2 361	0	0	2 361
	Subsequent therapy	13 808	22 499	81 361	117 668
	Patient time	8 337	11 613	23 557	43 507
	Total	**763 306**	**651 473**	**242 182**	**1 656 962**
Watch and wait	Drug acquisition	0	0	0	0
	Drug administration	30 368	39 446	36 031	105 845
	Monitoring costs	26 588	24 216	68 917	119 722
	Adverse events	138	0	0	138
	Subsequent therapy	50 831	69 158	79 217	199 205
	Patient time	6 656	5 404	23 366	35 426
	Total	**114 581**	**138 224**	**207 530**	**460 335**
Difference		*648 726*	*513 249*	*34 652*	*1 196 626*

*Discounted costs in line with Medicinrådet guidelines (2020) Discount rate of 3 5% used based on latest recommendation from the Danish Ministry of Finance (https //fm dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021 pdf)

Figure 10. Average costs per patient olaparib + bevacizumab vs watch and wait over 10 years, base case



4.3.2 One-way sensitivity analysis

A one-way sensitivity analysis was also performed for key variables in the model The variables included in the one-way sensitivity analysis were the discount rate, drug acquisition costs, administration costs, monitoring costs, patient time and transport costs, and AE costs (Table 39) Except for the discount rate, all variables were varied with ±20% The results were most sensitive to drug acquisition costs for olaparib and bevacizumab, and relatively insensitive to other variables The olaparib cost has the largest impact, because other costs are fairly similar in the two treatment arms

Table 39. Sensitivity analysis: Difference in average costs per patient over 10 years (DKK).

Parameter	Variation	Total cost year 1 to 10		Olaparib + bev vs watch and wait	
		Olaparib + bevacizumab	Watch and wait	Difference	% Change
Base case	-	1 656 962	460 335	1 196 626	-
Discount rate	2 5%	1 672 404	469 183	1 203 221	0 6%
	4 5%	1 642 143	451 913	1 190 230	-0 5%
Drug acquisition cost: Olaparib	-20%	1 498 419	460 335	1 038 083	-13 2%
	+20%	1 815 505	460 335	1 355 169	13 2%
Drug acquisition cost: Bevacizumab	-20%	1 567 498	460 335	1 107 163	-7 5%
	+20%	1 746 425	460 335	1 286 090	7 5%
Monitoring cost	-20%	1 621 813	436 391	1 185 422	-0 9%
	+20%	1 692 110	484 280	1 207 831	0 9%
Administration cost	-20%	1 652 006	460 335	1 191 670	-0 4%
	+20%	1 661 918	460 335	1 201 582	0 4%
Patient time and transport cost	-20%	1 652 295	457 262	1 195 032	-0 1%
	+20%	1 661 629	463 409	1 198 220	0 1%

Parameter	Variation	Total cost year 1 to 10		Olaparib + bev vs watch and wait	
		Olaparib + bevacizumab	Watch and wait	Difference	% Change
AE cost	-20%	1 656 489	460 308	1 196 182	0 0%
	+20%	1 657 434	460 363	1 197 071	0 0%

4.3.3 Scenario analysis: Excluding subsequent therapy

In this scenario treatments with olaparib + bevacizumab and watch and wait are included, and all costs related to subsequent therapy are excluded Since subsequent chemotherapy and bevacizumab in the watch and wait arm are excluded, this scenario is quite different from the base case The difference for olaparib + bevacizumab vs watch and wait is DKK 1 384 016 over 10 years (Table 40), compared with a difference of DKK 1 196 626 in the base case

Table 40 Average costs per patient for olaparib + bevacizumab vs watch and wait, year 1, year 2, years 3-10, and total over 10 years, base case (DKK).

Treatment	Cost item	Year 1 (2021)	Year 2 (2022)	Year 3 to 10 (2023 - 2030)	Total - Year 1 to 10 (2021 - 2030)
Olaparib + bevacizumab	Drug acquisition	647 282	554 290	38 461	1 240 033
	Drug administration	33 335	13 940	30 374	77 649
	Monitoring costs	58 091	52 552	171 620	282 264
	Adverse events	2 361	0	0	2 361
	Patient time	8 289	7 478	23 270	39 037
	Total	**749 359**	**628 260**	**263 725**	**1 641 344**
Watch and wait	Drug acquisition	0	0	0	0
	Drug administration	30 368	39 446	36 031	105 845
	Monitoring costs	25 549	24 685	67 388	117 623
	Adverse events	138	0	0	138
	Patient time	3 748	3 899	26 076	33 722
	Total	**59 803**	**68 030**	**129 494**	**257 328**
Difference		*689 556*	*560 229*	*134 231*	*1 384 016*

*Discounted costs in line with Medicinrådet guidelines (2020) Discount rate of 3 5% used based on latest recommendation from the Danish Ministry of Finance (https //fm dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021 pdf)

4.3.4 Scenario analysis: 5-year time frame

This scenario uses a 5-year time frame instead of 10 years as in the base case In this scenario, the difference for olaparib + bevacizumab vs watch and wait is DKK 1 179 510 over 10 years (Table 41), compared with a difference of DKK 1 196 626 in the base case

If the time horizon is extended to 25 years, the total per patient cost is DKK 1 693 185 for olaparib + bevacizumab and DKK 469 662 for olaparib, giving a cost difference of DKK 1 223 523

Table 41. Average costs per patient for olaparib + bevacizumab vs watch and wait, year 1, year 2, years 3-10, and total over 5 years

Treatment	Cost item	Year 1 (2021)	Year 2 (2022)	Year 3 to 5 (2023 - 2025)	Total - Year 1 to 5 (2021 - 2025)
Olaparib + bevacizumab	Drug acquisition	647 282	554 290	38 461	1 240 033
	Drug administration	33 335	13 940	30 374	77 649
	Monitoring costs	58 183	49 132	45 042	152 357
	Adverse events	2 361	0	0	2 361
	Subsequent therapy	13 808	22 499	49 023	85 329
	Patient time	8 337	11 613	9 941	29 891
	Total	**763 306**	**651 473**	**172 841**	**1 587 620**
Watch and wait	Drug acquisition	0	0	0	0
	Drug administration	30 368	39 446	36 031	105 845
	Monitoring costs	26 588	24 216	45 141	95 945
	Adverse events	138	0	0	138
	Subsequent therapy	50 831	69 158	64 403	184 391
	Patient time	6 656	5 404	9 731	21 791
	Total	**114 581**	**138 224**	**155 306**	**408 111**
Difference		*648 726*	*513 249*	*17 535*	*1 179 510*

*Discounted costs in line with Medicinrådet guidelines (2020) Discount rate of 3 5% used based on latest recommendation from the Danish Ministry of Finance (https //fm dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021 pdf)

4.3.5 Scenario analysis: Vial sharing

The base case does not assume vial sharing, but vial sharing could occur at some clinics for chemotherapy and also for bevacizumab In the scenario with vial sharing, the results that the difference for olaparib + bevacizumab vs watch and wait is DKK 1 157 953 over 10 years (Table 42), compared with a difference of DKK 1 196 626 in the base case Not surprisingly, the effect of vial sharing is somewhat larger in the olaparib + bevacizumab arm, while the costs for subsequent chemotherapy is reduced in similar proportions in all arms as a consequence of vial sharing

Table 42. Average costs per patient for olaparib + bevacizumab vs watch and wait year 1, year 2, years 3-10, and total over 10 years, with vial sharing for chemotherapy and bevacizumab (DKK)..

Treatment	Cost item	Year 1 (2021)	Year 2 (2022)	Year 3 to 10 (2023 - 2030)	Total - Year 1 to 10 (2021 - 2030)
Olaparib + bevacizumab	Drug acquisition	621 634	532 327	36 937	1 190 898
	Drug administration	33 335	13 940	30 374	77 649
	Monitoring costs	58 183	49 132	68 429	175 744
	Adverse events	2 361	0	0	2 361
	Subsequent therapy	12 105	19 724	71 327	103 156
	Patient time	8 337	11 613	23 557	43 507
	Total	**735 956**	**626 735**	**230 624**	**1 593 315**
Watch and wait	Drug acquisition	0	0	0	0
	Drug administration	30 347	39 384	35 960	105 691
	Monitoring costs	26 588	24 216	68 917	119 722
	Adverse events	138	0	0	138
	Subsequent therapy	44 531	60 536	69 319	174 386
	Patient time	6 656	5 404	23 366	35 426
	Total	**108 260**	**129 540**	**197 562**	**435 362**
Difference		*627 695*	*497 195*	*33 062*	*1 157 953*

*Discounted costs in line with Medicinrådet guidelines (2020) Discount rate of 3 5% used based on latest recommendation from the Danish Ministry of Finance (https //fm dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021 pdf)

4.3.6 Scenario analysis: Including the cost of HRD testing

The cost of HRD testing was excluded from the base case, as most patients would be expected to be tested at the time of diagnosis In addition, patients in the first line treated with bevacizumab or watch and wait would be tested at the later stage if not tested at diagnosis The testing cost is thus not driven by the introduction of first-line olaparib and bevacizumab

In a scenario where the HRD testing cost is only applied to first-line olaparib + bevacizumab, difference for olaparib + bevacizumab vs watch and wait is DKK 1 213 683 over 10 years, vs DKK 1 196 626 in the base case

In a scenario where the HRD testing cost is applied also to watch and wait, the cost differences are the same in the base case, as the testing cost is applied in equal measure to all treatment arms

4.4 Budget impact analysis

The model compares two scenarios to assess the budget impact of introducing olaparib + bevacizumab in Denmark:

- Scenario without olaparib + bevacizumab: based on the current and forecasted market shares when olaparib is not reimbursed
- Scenario with olaparib + bevacizumab: based on the current and forecasted market shares when olaparib is introduced by taking market share from other treatments

Olaparib + bevacizumab is assumed to take market shares mainly from olaparib, watch and wait, and bevacizumab in different proportions depending on the population In the different subpopulations, the total number of eligible patients for treatment with olaparib + bevacizumab will also differ, but the total HRD positive population is estimated to be around 130 new patients per year from 2021 to 2025 (please see section 3 1 for further details)

The budget impact calculations include cost implications for the included comparators, olaparib, bevacizumab, and watch and wait, and for subsequent PARP inhibitors, bevacizumab and chemotherapy Subsequent PARP inhibitor use is however limited, as reuse is not recommended and PARP inhibitors are not recommended for non-BRCA patients Subsequent bevacizumab is also limited as it is used in the treatment arm and also for one of the comparisons in the cost analysis Hence, subsequent therapies play a smaller role here than for olaparib monotherapy vs watch and wait or bevacizumab for BRCA positive patients The costs included costs for drug acquisition and administration, monitoring (including patient time and transport costs), and AE costs

Based on the epidemiology, the patient numbers are expected to be 55 in the BRCA+ subpopulation, 45 in the HRD+ non-BRCAm subpopulation who are bevacizumab candidates and 32 for those who are not bevacizumab candidates

Table 43. Number of patients per year in the model for the subpopulations

Year	BRCAm	BRCAwt HRD+ bev	BRCAwt HRD+ ww	All HRD+
2021	55	45	32	132
2022	55	45	33	132
2023	55	45	33	133
2024	55	45	33	133
2025	56	45	33	134

Table 44-46 presents a summary of the results for the different subpopulations

4.4.1 Olaparib + bevacizumab vs. olaparib in the BRCAm subpoulation

The incremental total cost for the 55 patients eligible for treatment with olaparib + bevacizumab per year increases from 3 4 million DKK in 2021 to a maximum of 10 5 million DKK in 2023 Thereafter the yearly incremental budget impact decreases slightly to 9 0 million DKK in 2025 The budget impact of the new scenario increases from 14% in 2021 to a maximum of 20% in 2023 and then decreases to 15% in 2025

Table 44. Summary of the incremental results: Base case for olaparib + bevacizumab vs. olaparib in the BRCAm subpoulation

Budget year	Scenario with olaparib+bev (DKK)	Scenario without olaparib+bev (DKK)	Incremental total cost (DKK)	Budget impact of new scenario vs. current scenario (%)
2021	28 323 492	24 910 648	3 412 844	14%
2022	54 162 729	46 002 078	8 160 651	18%
2023	63 350 306	52 827 462	10 522 844	20%
2024	67 163 219	57 654 944	9 508 275	16%
2025	70 106 118	61 130 893	8 975 225	15%

4.4.2 Olaparib + bevacizumab vs. bevacizumab in the HRD+ non-BRCAm subpopulation (bevacizumab candidates)

The incremental total cost for the 45 patients eligible for treatment with olaparib + bevacizumab per year increases from 3 5 million DKK in 2021 to a maximum of 22 7 million DKK in 2025 The budget impact of the new scenario increases from 28% in 2021 to a maximum of 88% in 2025

Table 45. Summary of the incremental results: Base case for olaparib + bevacizumab vs. bevacizumab in the HRD+ non-BRCAm subpopulation (bevacizumab candidates)

Budget year	Scenario with olaparib+bev (DKK)	Scenario without olaparib+bev (DKK)	Incremental total cost (DKK)	Budget impact of new scenario vs. current scenario (%)
2021	15 981 398	12 469 294	3 512 104	28%
2022	28 140 805	18 219 909	9 920 896	54%
2023	36 436 268	21 379 193	15 057 075	70%
2024	43 614 974	23 824 149	19 790 825	83%
2025	48 430 600	25 731 440	22 699 160	88%

4.4.3 Olaparib + bevacizumab vs. watch and wait in the HRD+ non-BRCAm subpopulation (not candidates for bevacizumab)

The incremental total cost for the 45 patients eligible for treatment with olaparib + bevacizumab per year increases from 3 6 million DKK in 2021 to a maximum of 14 9 million DKK in 2025 The budget impact of the new scenario increases from 60% in 2021 to 74% in 2022 and then decreases to 67% in 2025

Table 46. Summary of the incremental results: Base case for olaparib + bevacizumab vs. watch and wait in the HRD+ non-BRCAm subpopulation (not candidates for bevacizumab)

Budget year	Scenario with olaparib (DKK)	Scenario without olaparib (DKK)	Incremental total cost (DKK)	Budget impact of new scenario vs. current scenario (%)
2021	9 453 651	5 903 069	3 550 582	60%
2022	21 903 902	12 587 523	9 316 379	74%
2023	28 461 167	17 074 988	11 386 178	67%
2024	33 042 615	20 146 184	12 896 431	64%
2025	37 251 223	22 360 315	14 890 908	67%

4.4.4 Scenario analysis: Increased/decreased market shares for olaparib + bevacizumab

The sensitivity analyses and scenarios would have a similar impact on budgets as on the cost per patient, but market shares are also important for the total budget impact Hence, the sensitivity analysis for the budget impact focuses on market shares Since the market shares for olaparib + bevacizumab in the new scenarios may differ from the base case estimates, scenario analyses were created with higher and lower market shares for olaparib Table 47 and 48 show budget impact results where market shares for olaparib + bevacizumab have been either increased or decreased by 10 percentage points compared with the base case market shares in section 3 3 In all scenarios, market shares were adjusted accordingly for other comparators (increase or decrease with 5 or 10 percentage points depending on the scenario)

The results are as expected, but it is notable that in particular the BRCA+ subpopulation is sensitive to decreased market shares compared with the base case assumptions With a decrease of 10 percentage points, the combination therapy becomes nearly cost neutral in terms of budget impact and even cost saving in the first year

Table 47. Summary of the incremental results: Scenario analyses with increased market shares (+10 percentage points)

Budget year	1. Olaparib + bevacizumab vs. olaparib in the BRCAm subpoulation			
	Scenario with olaparib (DKK)	Scenario without olaparib (DKK)	Incremental total cost (DKK)	Budget impact of new scenario vs. current scenario (%)
2021	30 855 052	24 910 648	5 944 404	24%
2022	57 954 822	46 002 078	11 952 744	26%
2023	67 122 733	52 827 462	14 295 271	27%
2024	70 865 520	57 654 944	13 210 576	23%
2025	73 810 518	61 130 893	12 679 625	21%
Budget year	2. Olaparib + bevacizumab vs. bevacizumab in the HRD+ non-BRCAm subpopulation (bevacizumab candidates)			
	Scenario with olaparib (DKK)	Scenario without olaparib (DKK)	Incremental total cost (DKK)	Budget impact of new scenario vs. current scenario (%)
2021	18 240 712	12 469 294	5 771 418	46%
2022	31 460 796	18 219 909	13 240 887	73%
2023	39 900 465	21 379 193	18 521 273	87%
2024	47 126 250	23 824 149	23 302 101	98%
2025	51 954 061	25 731 440	26 222 621	102%

Budget year	3. Olaparib + bevacizumab vs. placebo in the HRD+ non-BRCAm subpopulation (not bevacizumab candidates).			
	Scenario with olaparib (DKK)	Scenario without olaparib (DKK)	Incremental total cost (DKK)	Budget impact of new scenario vs. current scenario (%)
2021	11 403 792	5 903 069	5 500 723	93%
2022	25 429 526	12 587 523	12 842 004	102%
2023	31 946 129	17 074 988	14 871 141	87%
2024	36 444 942	20 146 184	16 298 758	81%
2025	40 615 513	22 360 315	18 255 198	82%

Table 48. Summary of the incremental results: Scenario analyses with decreased market shares (-10 percentage points)

Budget year	1. Olaparib + bevacizumab vs. olaparib in the BRCAm subpoulation			
	Scenario with olaparib (DKK)	Scenario without olaparib (DKK)	Incremental total cost (DKK)	Budget impact of new scenario vs. current scenario (%)
2021	23 749 615	24 910 648	-1 161 033	-5%
2022	46 833 415	46 002 078	831 337	2%
2023	55 810 928	52 827 462	2 983 466	6%
2024	59 516 061	57 654 944	1 861 117	3%
2025	62 332 550	61 130 893	1 201 658	2%
Budget year	2. Olaparib + bevacizumab vs. bevacizumab in the HRD+ non-BRCAm subpopulation (bevacizumab candidates)			
	Scenario with olaparib (DKK)	Scenario without olaparib (DKK)	Incremental total cost (DKK)	Budget impact of new scenario vs. current scenario (%)
2021	12 771 588	12 469 294	302 294	2%
2022	23 930 030	18 219 909	5 710 121	31%
2023	32 153 868	21 379 193	10 774 676	50%
2024	39 258 043	23 824 149	15 433 894	65%
2025	44 003 369	25 731 440	18 271 929	71%
Budget year	3. Olaparib + bevacizumab vs. placebo in the HRD+ non-BRCAm subpopulation (not bevacizumab candidates).			
	Scenario with olaparib (DKK)	Scenario without olaparib (DKK)	Incremental total cost (DKK)	Budget impact of new scenario vs. current scenario (%)
2021	7 209 839	5 903 069	1 306 770	22%
2022	17 818 128	12 587 523	5 230 606	42%
2023	24 197 784	17 074 988	7 122 796	42%
2024	28 682 510	20 146 184	8 536 326	42%
2025	32 785 339	22 360 315	10 425 025	47%

5 Concluding discussion

The cost analyses present the incremental costs of introducing olaparib + bevacizumab as a first line treatment for platinum-sensitive ovarian cancer patients with HRD mutations in Denmark

The cost analyses included treatment acquisition, monitoring costs, patient-related costs and treatment-related AE costs The treatment acquisition cost is by far the largest for all treatments in the base case analysis

Three distinct subpopulations of the HRD positive population, each with a different comparator, was included:

1 Olaparib + bevacizumab vs olaparib in the BRCAm subpoulation

2 Olaparib + bevacizumab vs bevacizumab in the HRD+ non-BRCAm subpopulation (bevacizumab candidates)

3 Olaparib + bevacizumab vs placebo in the HRD+ non-BRCAm subpopulation (not bevacizumab candidates)

In the BRCA positive population, the results on average cost per patient showed that for patients treated with olaparib + bevacizumab, the costs over 10 years are DKK 1 554 322, compared with DKK 1 251 789 olaparib monotherapy, i e a difference of DKK 302 533 The drug acquisition constitutes the major part of the costs, and therefore results were most sensitive to changes in drug acquisition costs for olaparib and bevacizumab, and relatively insensitive to other variables

In the HRD+ non-BRCAm subpopulation who are bevacizumab candidates, the results on average cost per patient showed that for patients treated with olaparib + bevacizumab, the costs over 10 years are DKK 1 349 220, compared with DKK 684 652 for bevacizumab monotherapy, i e a difference of DKK 664 567 The drug acquisition constitutes the major part of the costs, and therefore results were most sensitive to changes in drug acquisition costs for olaparib, and relatively insensitive to other variables

In the HRD+ non-BRCAm subpopulation who are <u>not</u> bevacizumab candidates, the results on average cost per patient showed that for patients treated with olaparib + bevacizumab, the costs over 10 years are DKK 1 656 962, compared with DKK 460 335 for watch and wait, i e a difference of DKK 1 196 626 The drug acquisition constitutes the major part of the costs, and therefore results were most sensitive to changes in drug acquisition costs for olaparib and bevacizumab, and relatively insensitive to other variables

As mentioned in the introduction, bevacizumab has a concomitant phase with chemotherapy, while olaparib treatment is initiated after platinum-based chemotherapy However, the earlier start of bevacizumab treatment is not a problem in practice for the cost analysis Bevacizumab is discounted more with the same starting point as olaparib compared with a slightly earlier start, but this discounting effect is very small and can be neglected for practical purposes

The budget impact calculations include cost implications for introducing olaparib + bevacizumab in Danish clinical practice In the BRCA positive population, the base case results showed that such an introduction would on average cause a budget increase of 14% in year 2021, 18% in year 2022, 20% in 2023 and then decreasing to 15% in year 2025 In the HRD+ non-BRCAm subpopulation who are bevacizumab candidates, there was budget increase from 28% in year 2021 to 88% in year 2025 In the HRD+ non-BRCAm subpopulation who are <u>not</u> bevacizumab candidates, there was budget increase of 60% in year 2021, and 74% in year 2022, but then decreasing to 67% in year 2025

The cost per patient and budget impact for bevacizumab + olaparib varied in a predictable way depending on subpopulation and comparator It should be noted that list prices for pharmaceuticals were used for the

calculations of the acquisition costs Real tender prices will in general be lower than the list prices For example, three biosimilars are now available for bevacizumab, which has historically resulted in substantial reductions in the prices This also has an impact on the real budget impact for Danish health care, which will be lower in practice than what is reported here based on list prices

6 Appendix A: Subsequent PARP inhibitor treatment

Data are here based on SOLO1, but the principles are exactly the same for PAOLA-1

Figure 11. Schematic of calculation of the proportion of patients on subsequent PARP inhibitor treatment in each model cycle

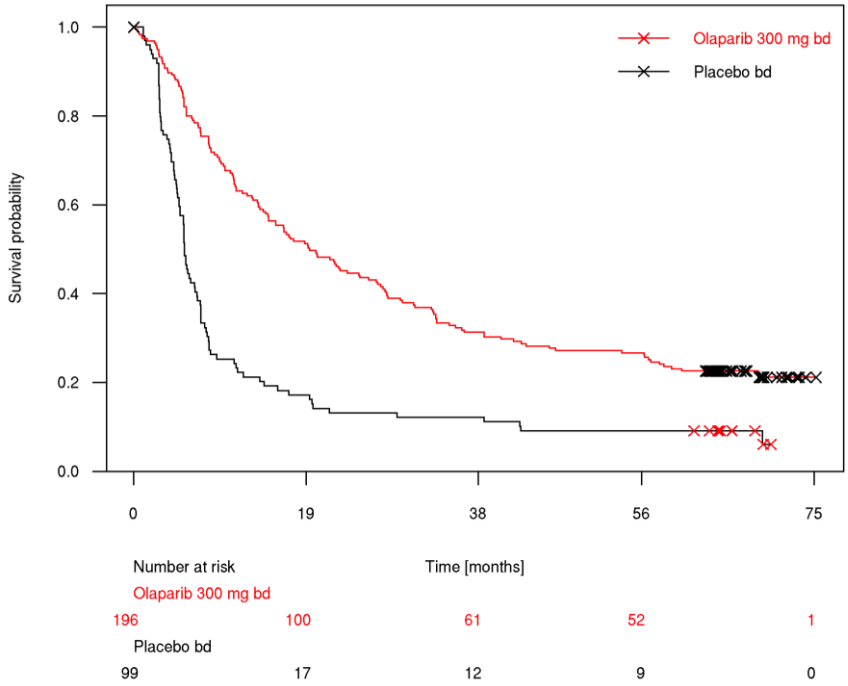
#	Colour	Calculation note
1		The proportion of patients who have been recorded as having started subsequent PARP inhibitor therapy in an arm of SOLO1
2		The proportion of patients who are subsequent-PARP inhibitor-treatment-free (calculated as multiplication of the proportion starting subsequent PARP inhibitor treatment by cumulative probabilities of time to subsequent PARP inhibitor treatment data in SOLO1
3		The proportion of patients starting subsequent PARP inhibitor treatment in a given cycle (calculated as the difference in cumulative survival probabilities of being subsequent-PARP inhibitor-treatment-free between a given cycle and the preceding cycle)
4		The distribution of patients starting treatment in a given cycle over time (calculated via multiplication of the proportion starting subsequent PARP inhibitor treatment in a given cycle with the cumulative probabilities of time to subsequent PARP inhibitor treatment discontinuation data)
5		Time to subsequent PARP inhibitor treatment discontinuation (defined as time from randomisation to treatment discontinuation in SOLO2)
6		The proportion of patients on subsequent PARP inhibitor treatment in a given model cycle (month) (calculated as the sum of the columns indicated by the red box)

Time (since randomisation)		0	1	2	3	4	5	6	7	8	9	10		
		51.6%	51.6%	51.6%	51.6%	51.6%	51.6%	51.6%	49.4%	49.4%	49.4%	48.4%		
Time since starting treatment	TDT of sub. PARPi		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.2%	0.0%	0.0%	1.0%	Total	Month
0	100.0%		0.0%										0.0%	0
1	99.1%		0.0%	0.0%									0.0%	1
2	95.9%		0.0%	0.0%	0.0%								0.0%	2
3	91.0%		0.0%	0.0%	0.0%	0.0%							0.0%	3
4	85.2%		0.0%	0.0%	0.0%	0.0%	0.0%						0.0%	4
5	79.1%		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%					0.0%	5
6	73.2%		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.2%				2.2%	6
7	67.7%		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.1%	0.0%			2.1%	7
8	62.6%		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.1%	0.0%	0.0%		2.1%	8
9	58.0%		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.0%	0.0%	0.0%	1.0%	3.0%	9
10	53.9%		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.8%	0.0%	0.0%	1.0%	2.9%	10
11	50.3%		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.7%	0.0%	0.0%	1.0%	2.7%	11
12	47.1%		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.6%	0.0%	0.0%	0.9%	2.5%	12
13	44.2%		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.5%	0.0%	0.0%	0.9%	2.3%	13
14	41.6%		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.4%	0.0%	0.0%	0.8%	2.2%	14
15	39.2%		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.3%	0.0%	0.0%	0.8%	2.0%	15
16	37.1%		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.2%	0.0%	0.0%	0.7%	1.9%	16
17	35.2%		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.1%	0.0%	0.0%	0.6%	1.7%	17
18	33.5%		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.0%	0.0%	0.0%	0.6%	1.6%	18
19	32.0%		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.0%	0.0%	0.0%	0.6%	1.5%	19
20	30.5%		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.9%	0.0%	0.0%	0.5%	1.4%	20

7 Appendix B: Subsequent PARP inhibitor: Time to treatment discontinuation in SOLO2

The time to treatment discontinuation (TTD) KM curve from SOLO2 is shown in Figure 12 SOLO2 is n international, multicentre, double-blind, randomised, placebo-controlled, phase 3 trial evaluating olaparib tablet maintenance treatment in platinum-sensitive, relapsed ovarian cancer patients with a BRCA1/2 mutation who had received at least two lines of previous chemotherapy (Pujade-Lauraine 2017)

Figure 12: TTD for olaparib and placebo based on the final data cut-off for SOLO-2



TTD is extrapolated beyond the follow-up of SOLO-2 using parametric survival models Independent parametric survival models were fitted to the olaparib only arm, given that TTD was not required for the placebo arm

A series of parametric survival models were fitted to patient-level data on the time from randomization to discontinuation of olaparib in SOLO2 Statistical goodness of fit was assessed via the AIC and BIC values shown in Table 49

Table 49. Summary of goodness of fit data for the parametric survival analysis of TTD data in SOLO2

Distribution	Olaparib arm	
	AIC	BIC
Exponential	989 05	992 33
Weibull	990 95	996 37
Log normal	985 36	991 81
Log-logistic	986 56	992 95
Generalized Gamma	984 91	991 03
Gompertz	989 87	996 42

AIC Akaike Information Criterion, BIC Bayesian Information Criterion, TTD Progression-Free Survival

According to AIC and BIC, the best fitting model was the generalized gamma followed by the log normal The AIC and BIC values for these models are similar suggesting that either option may be suitable The generalized gamma was selected for the base case analysis

The TTD curve was validated by comparing modelled landmark probabilities to the corresponding Kaplan-Meier data from SOLO2 (Table 50)

Table 50: Comparison of model predictions versus Kaplan-Meier data for TTD in the olaparib arm of SOLO2

Time point (month)	TTD SOLO2		
	Model predictions	Study results	Absolute difference
6	81 5%	80 0%	+1 53%
12	65 3%	62 6%	+2 71%
18	53 7%	51 8%	+1 86%
24	45 0%	44 8%	+0 20%
Median	20	19 4	+0 6

The model provides a plausible prediction of the landmark probabilities for TTD in the olaparib treated population There were small absolute differences in predicted survival versus the Kaplan-Meier, with increments ranging from 0 2% to 2 7% at landmarks between 6 and 24 months Median TTD in the model was approximately 20 months, versus 19 4 months in the study Median TTD can only be estimated to the nearest month due to the monthly cycle periods in the model Hence, the model estimates are subject to an error of between -1 and +1 month The predicted median TTD is within one cycle length of the trial estimate, and hence is judged to provide a plausible prediction of median TTD

A summary of the fitted coefficients for the generalized gamma model for the olaparib group of SOLO2 is presented in Table 51

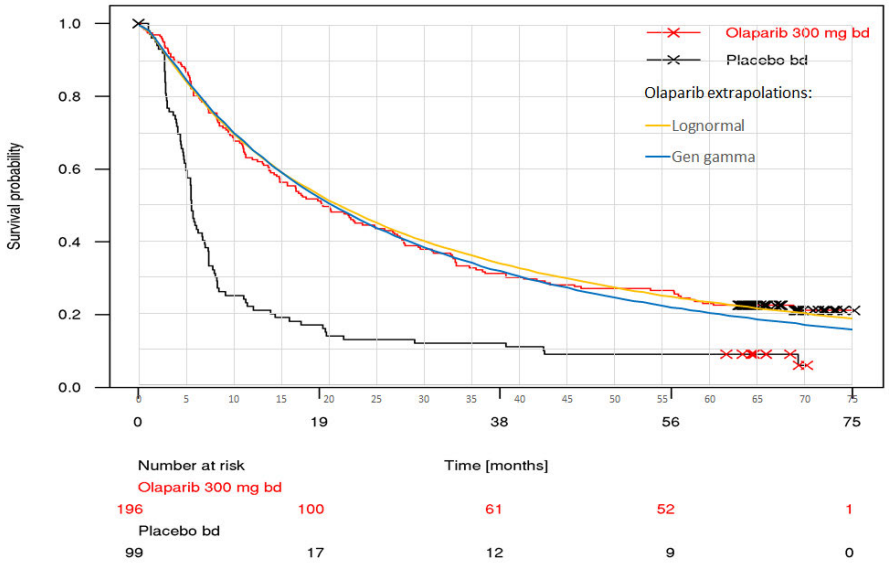
Table 51 Parameter estimates for the generalized gamma model fitted to TTD

Parameter	Estimate
Mu	3 09
Sigma	1 32
Q	0 18

TTD Progression-Free Survival

In Figure 13, the generalized gamma distribution is compared with the TTD KM data and also with the next best fitting distribution, which was the log normal The generalized gamma and log normal distributions have very similar visual fit until 20 months Between 20 and 48 months, generalized gamma has the best visual fit, while log normal has the best fit beyond that However, it should be noted that the TTD KM has a lot of censoring after 60 months, which makes the KM data unreliable after this point in time

Figure 13. The generalized gamma and log normal distributions compared with the TTD KM data in SOLO2.



8 Appendix C: Parametric estimates of time to first and second subsequent therapy

The statistical analysis of time to subsequent therapy was conducted using the approach outlined in the Technical Support Document for survival analysis published by NICE Decision Support Unit (Latimer 2011) Following the selection of model type, the most plausible parametric models are selected based upon statistical and visual fit to the observed data and the clinical plausibility of the extrapolation two types of models were considered:

- Independent survival models (e g a separate model fitted to a dataset containing only one treatment group from SOLO1)
- Treatment covariate models (e g a model fitted to a dataset containing both treatment groups from SOLO1, and including a covariate for treatment that acts on the scale or related parameter)

The choice of model type was based on visual inspection of the cumulative event plots (e g log cumulative hazard plots) to assess the possibility of a proportional treatment effect If the cumulative event curves plotted for each arm of the study were parallel, then a proportional effects model may be applied If the curves are not parallel, then independent models may be more suitable

Following Latimer et al, the best fitting models were chosen based on an assessment of the internal goodness of fit of the models using the Bayesian Information Criterion (BIC), Akaike Information Criterion (AIC), and visual inspection of the fit of the model to the Kaplan-Meier curves (Latimer 2011)

8.1 Time to first subsequent therapy

8.2 Semi-parametric analysis

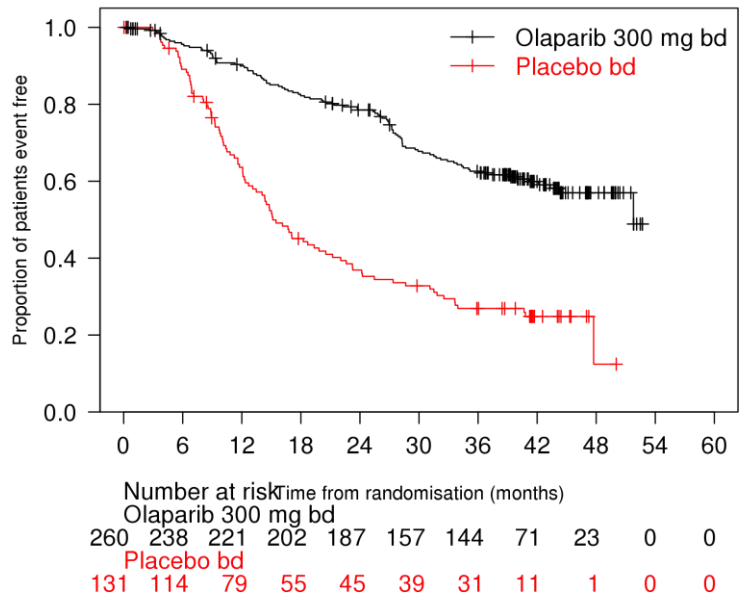
The median time to first subsequent therapy is included in Table 52 and Figure 14

Table 52. Total number of events and median time-to-event (if defined, otherwise NA).

	Placebo bd (total=131)	Olaparib 300 mg bd (total=260)
Total number of events	94	99
Median time to event (months)	15 15	51 78
95% lower CI	12 68	44 25
95% upper CI	20 53	NA

8.2.1 Kaplan Meier plot

Figure 14. Kaplan Meier survival curve per arm in SOLO1



8.2.2 Restricted means

Restricted means are calculated until the last time point where each arm has observations, using the area under KM curve with confidence interval at the 95% level

Table 53. Restricted means for time to first subsequent therapy.

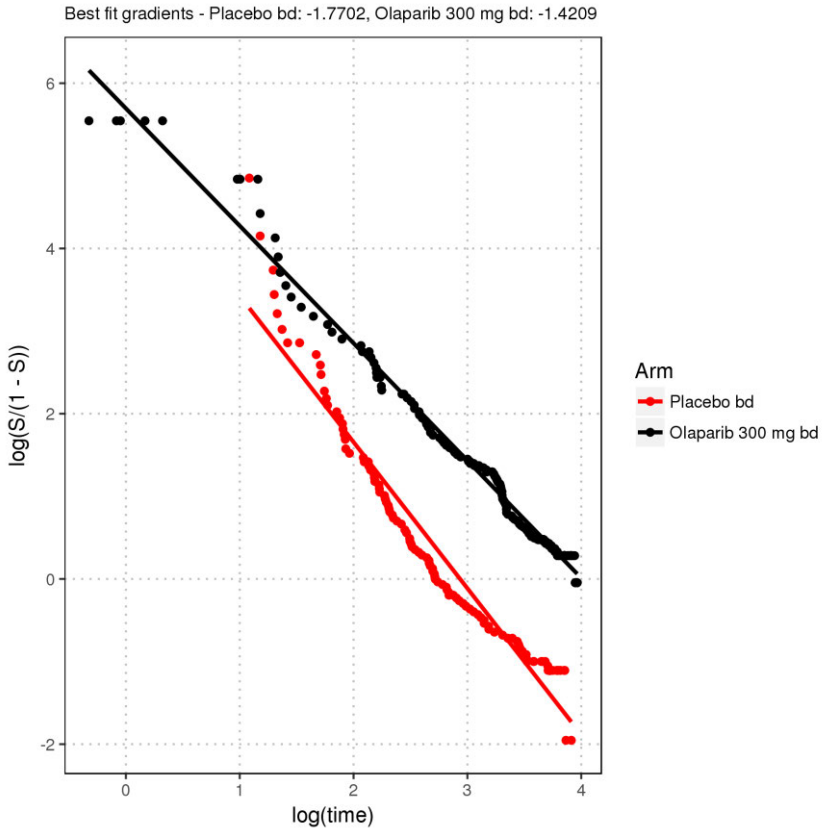
Arm	RMST	SE	Lower CI	Upper CI	p-value
Placebo bd	23 143	1 517	20 169	26 116	
Olaparib 300 mg bd	38 081	1 015	36 091	40 071	
Difference	14 938	1 825	11 361	18 516	< 0 001

8.2.3 Cumulative Hazards plots

The following are diagnostic plots to check assumptions Linear trends indicate that there are no clear violations to the model assumptions for the corresponding distribution In the Loglogistic diagnostic plot, parallel lines indicate proportional odds As lines are not parallel, this would suggest that hazards are not proportional and separate distributions fitted per arm are more suitable

Figure 15. Cumulative hazard plot for time to first subsequent therapy

Loglogistic distribution with log(ODDs(S)) vs log(time):



8.3 Separate distributions fitted per arm

8.3.1 AIC/BIC

Akaike and Bayesian information criteria by treatment arm are shown in Table 54 The models with lower values fit data better For olaparib, the loglogistic distribution has the lowest AIC and BIC values For placebo, generalized gamma has the lowest AIC and BIC values However, for chemotherapy as subsequent therapy, time to second subsequent therapy is used instead, as a majority of the patients in the placebo group use PARP inhibitor as first subsequent therapy

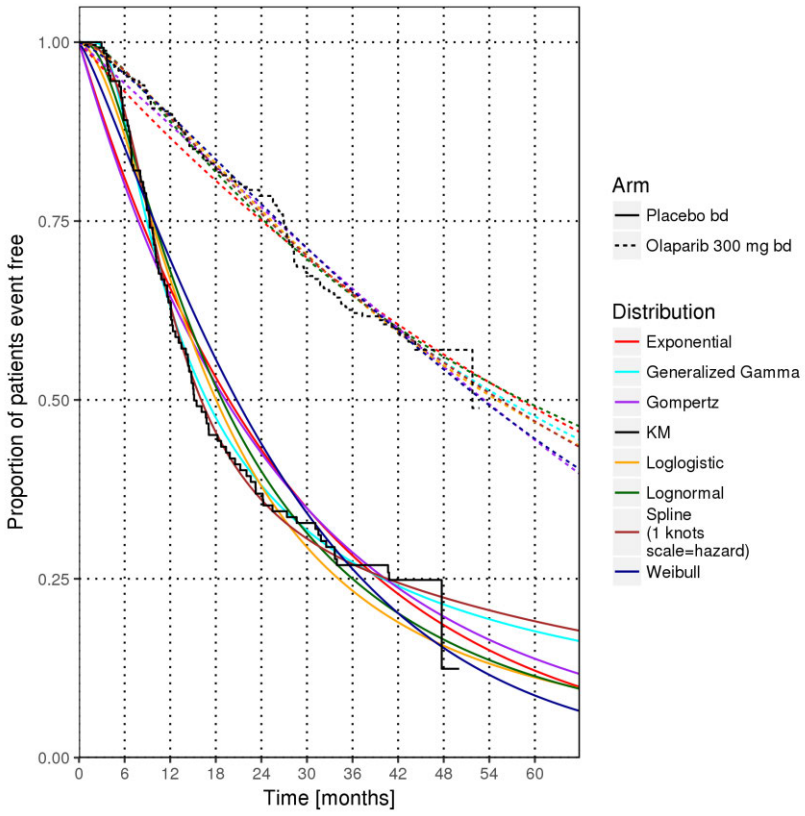
Table 54. Parametric fit according to Akaike and Bayesian information criteria.

	Olaparib 300 mg bd		Placebo bd	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Loglogistic	1071 38	1078 51	800 52	806 27
Lognormal	1071 50	1078 62	796 17	801 92
Generalized Gamma	1072 93	1083 61	786 02	794 64
Weibull	1073 15	1080 28	817 87	823 62
Spline (1 knots scale=hazard)	1073 30	1083 98	786 76	795 39
Exponential	1076 60	1080 16	819 63	822 51
Gompertz	1076 65	1083 77	821 39	827 14

8.3.2 Parametric survival curves

The models are plotted with the KM data to illustrate how well they capture the trends

Figure 16. Parametric distributions for time to first subsequent therapy vs KM data.



The best model is Loglogistic which had the lowest AIC and BIC values for the olaparib arm, as well as relatively good visual fit to the KM data

8.3.3 Model parameter estimates

Table 55. Model parameter estimates for time to first subsequent therapy.

Placebo bd

Loglogistic	est	L95%	U95%
shape	1 7222	1 4585	2 0335
scale	18 043	15 068	21 606

Olaparib 300 mg bd

Loglogistic	est	L95%	U95%
shape	1 4232	1 1946	1 6956
scale	54 989	45 229	66 856

8.3.4 Time to first subsequent therapy in PAOLA-1

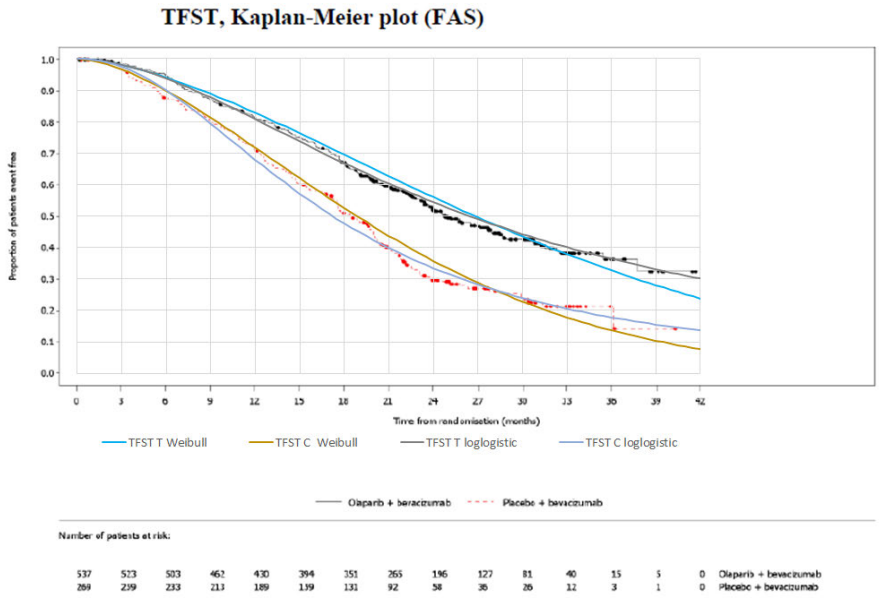
Data on subsequent therapy from PAOLA-1 was used for sensitivity analysis. For time to first subsequent therapy in PAOLA-1, the loglogistic distribution also had the best fit as in SOLO-1, but the Weibull distribution is also included in Figure 17.

The median time to first subsequent therapy is included in Table 56

Table 56. Total number of events and median time-to-event (if defined, otherwise NA).

	Olaparib/bevacizumab (N=537)	Placebo/bevacizumab (N=269)
Total number of events	275	190
Median time to event (months)	24 8	18 5
95% lower CI	23 4	17 2
95% upper CI	27 9	20 1

Figure 17. Time to first subsequent therapy in PAOLA-1. KM data and loglogistic and Weibull distributions fitted to the KM data.



TFST: Time to first subsequent therapy; T: Treatment arm, i e olaparib + bevacizumab; C: Control arm, i e bevacizumab

8.4 Time to second subsequent therapy

8.5 Semi-parametric analysis

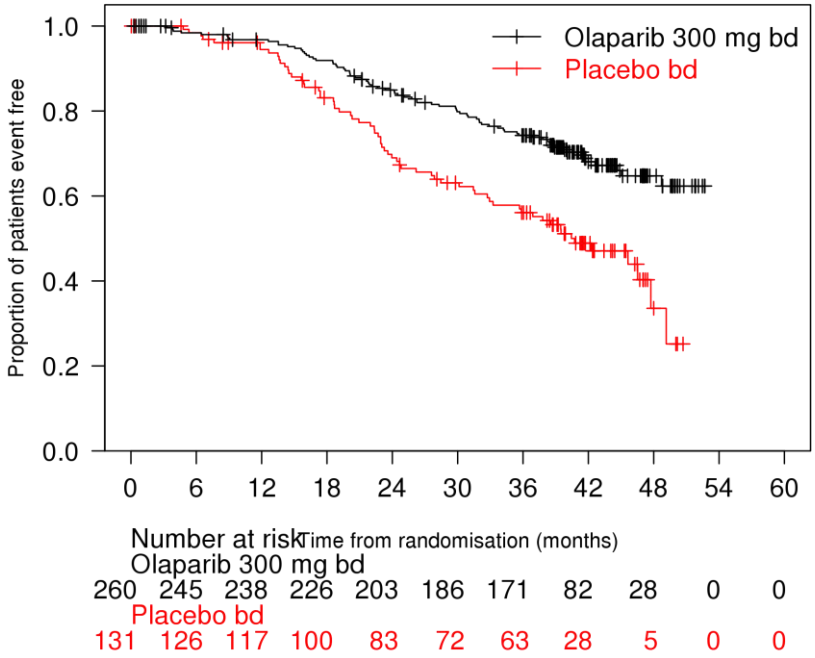
The median time to second subsequent therapy is included in Table 57 and Figure 18 Due to immaturity of the data (and a slow event rate), the median time to second subsequent therapy has not been reached for olaparib

Table 57. Total number of events and median time-to-event (if defined, otherwise NA).

	Placebo bd (total=131)	Olaparib 300 mg bd (total=260)
Total number of events	65	77
Median time to event (months)	40 74	NA
95% lower CI	32 92	NA
95% upper CI	47 74	NA

8.5.1 Kaplan Meier plot

Figure 18. Kaplan Meier survival curve per arm for second subsequent therapy in SOLO1



8.5.2 Restricted means

Restricted means are calculated until the last time point where each arm has observations, using the area under KM curve with confidence interval at the 95% level

Table 58. Restricted means for time to second subsequent therapy.

Arm	RMST	SE	Lower CI	Upper CI	p-value
Placebo bd	35 847	1 364	33 175	38 520	
Olaparib 300 mg bd	42 274	0 858	40 592	43 955	
Difference	6 426	1 611	3 269	9 584	< 0 001

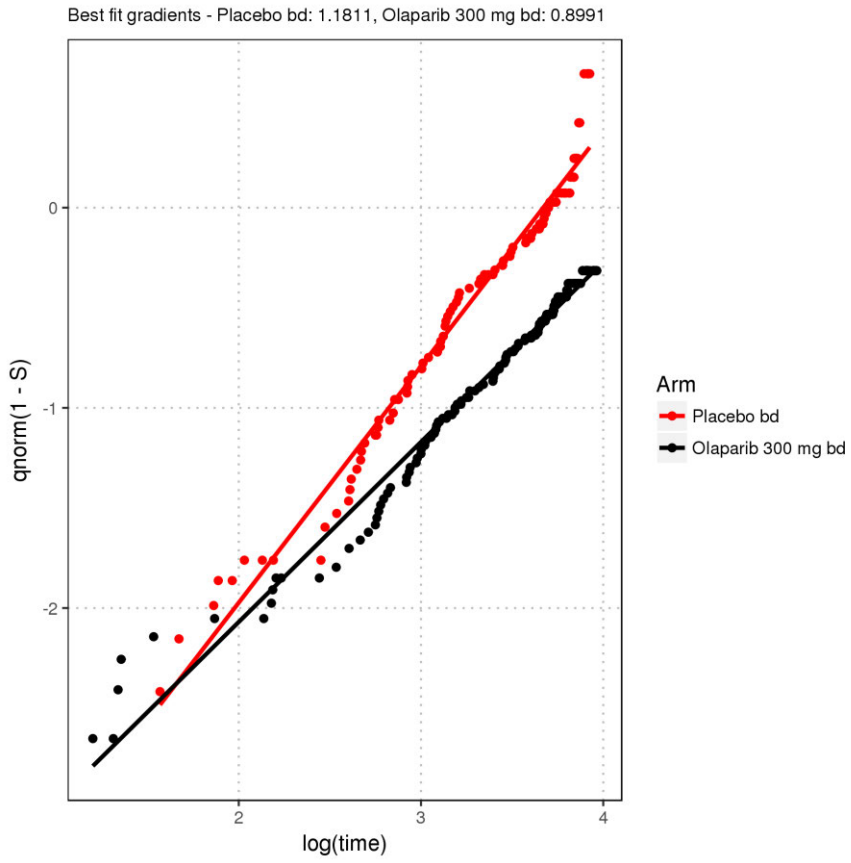
8.5.3 Cumulative Hazards plots

The following are diagnostic plots to check assumptions Linear trends indicate that there are no clear violations to the model assumptions for the corresponding distribution In the Lognormal diagnostic plot,

parallel lines indicate constant acceleration As lines are clearly not parallel, this would suggest that hazards are not proportional and separate distributions fitted per arm are more suitable

Figure 19. Cumulative hazard plot for time to first subsequent therapy

Lognormal distribution with Inv(norm(S)) vs time:



8.6 Separate distributions fitted per arm

8.6.1 AIC/BIC

Akaike and Bayesian information criteria are output The models with lower values fit data better

Table 59. Parametric fit according to Akaike and Bayesian information criteria (AIC and BIC presented split by treatment arm).

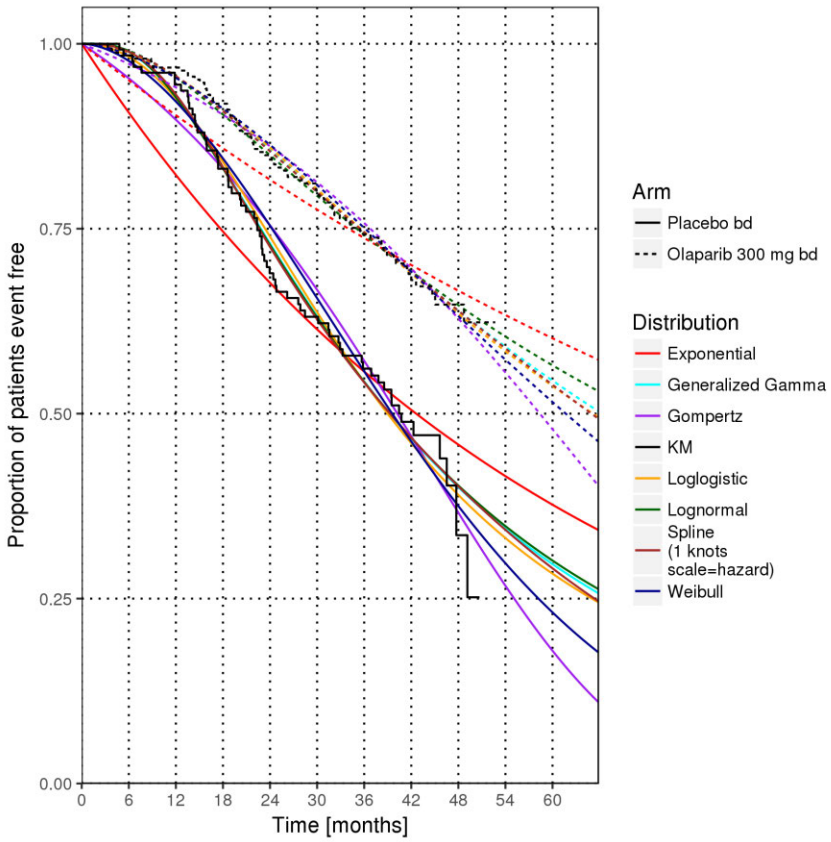
	Olaparib 300 mg bd		Placebo bd	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Lognormal	874 08	881 20	643 60	649 35
Loglogistic	873 52	880 64	644 86	650 61

	Olaparib 300 mg bd		Placebo bd	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Spline (1 knots scale=hazard)	875 43	886 12	644 96	653 59
Generalized Gamma	875 38	886 07	645 58	654 21
Weibull	874 53	881 65	646 54	652 29
Gompertz	880 46	887 58	653 58	659 33
Exponential	890 94	894 50	667 45	670 33

8.6.2 Parametric survival curves

The models are plotted with the KM data to illustrate how well they capture the trends Exponential and Gompertz distribution have poor visual fit, while other distributions have relatively good visual fit

Figure 20. Parametric distributions for time to second subsequent therapy vs KM data.



The best model is Lognormal which had the lowest AIC and BIC values for the placebo arm, as well as good visual fit to the KM data

Figure 21. Averaged survival curve for best-fitting model.

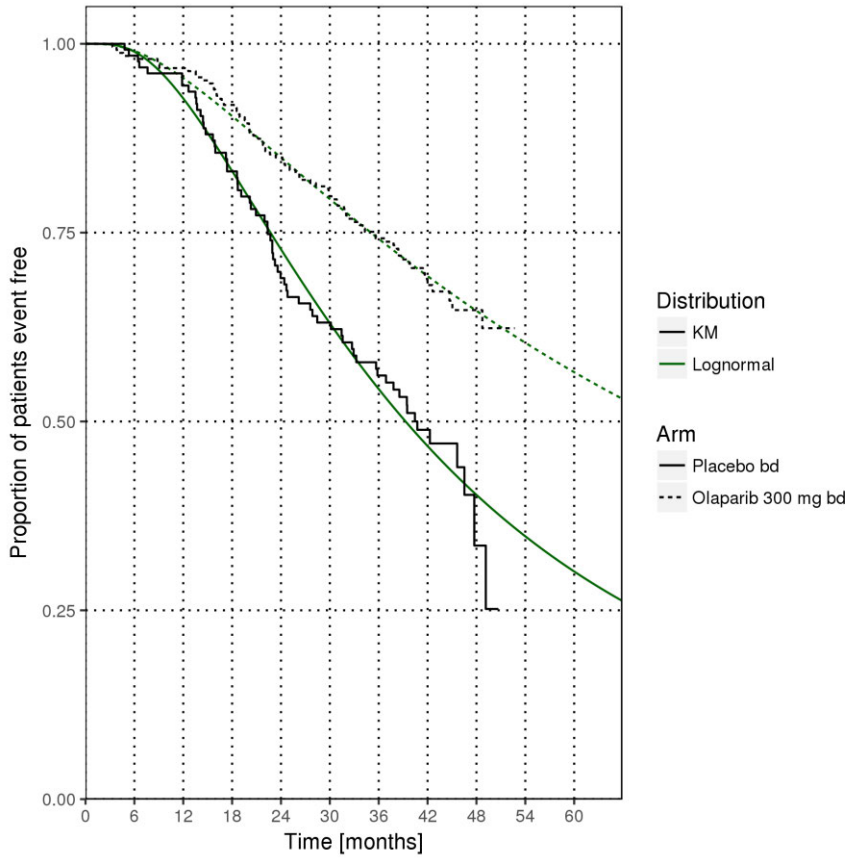


Table 60. Lognormal restricted means

time	Inf
Placebo bd	54 699
Olaparib 300 mg bd	124 367
difference	69 668

8.6.3 Model parameter estimates:

Table 61. Model parameter estimates for time to second subsequent therapy.

Placebo bd

Lognormal	est	L95%	U95%
meanlog	3 6712	3 4989	3 8435
sdlog	0 8132	0 67456	0 98033

Olaparib 300 mg bd

Lognormal	est	L95%	U95%
meanlog	4 2676	4 0471	4 4882
sdlog	1 0541	0 88069	1 2618

8.6.4 Time to second subsequent therapy in PAOLA-1

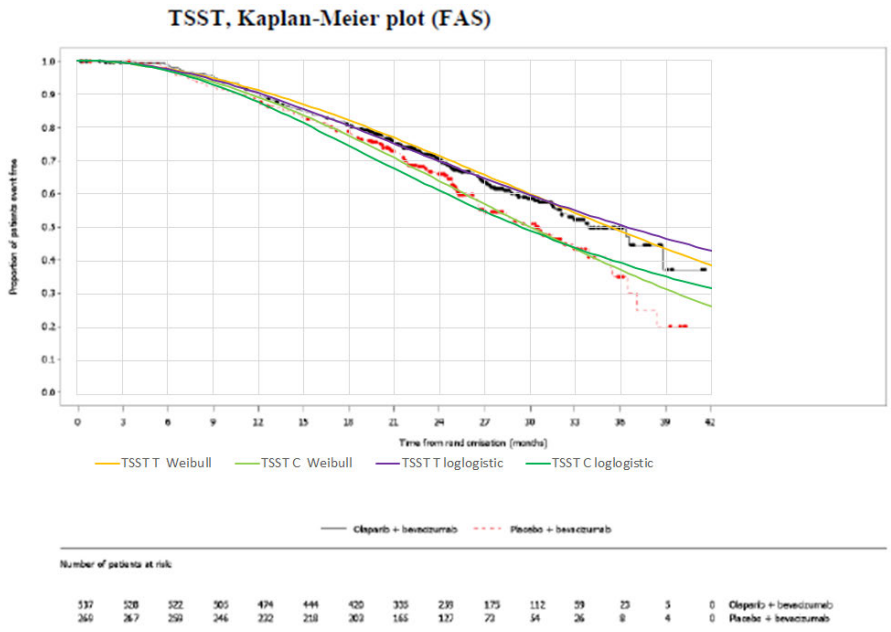
Data on subsequent therapy from PAOLA-1 was used for sensitivity analysis. For time to second subsequent therapy in PAOLA-1, the Weibull distribution had the best fit, but the loglogistic distribution is also included in Figure 22.

The median time to second subsequent therapy is included in Table 62

Table 62. Total number of events and median time-to-event (if defined, otherwise NA).

	Olaparib/bevacizumab (N=537)	Placebo/bevacizumab (N=269)
Total number of events	194	119
Median time to event (months)	33 8	30 4
95% lower CI	31 6	26 5
95% upper CI	NA	33 9

Figure 22. Time to second subsequent therapy in PAOLA-1. KM data and loglogistic and Weibull distributions fitted to the KM data.



TSST: Time to second subsequent therapy; T: Treatment arm, i e olapar b + bevacizumab; C: Control arm, i e bevacizumab

9 Appendix D: Parametric estimates of overall survival

9.1 Clinical efficacy in the BRCAm population

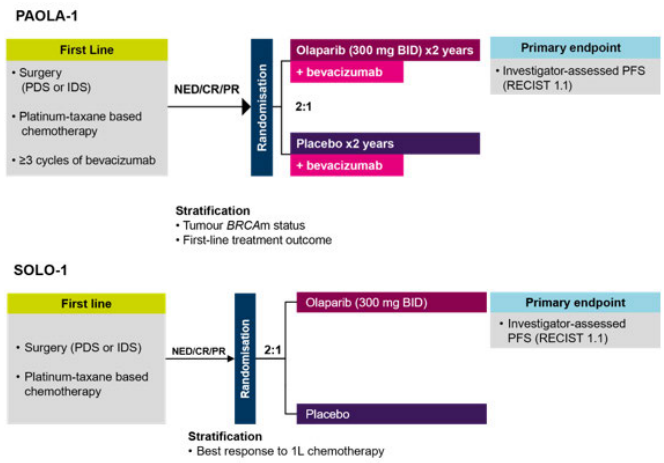
For the comparison of olaparib plus bevacizumab versus olaparib monotherapy in BRCA mutated newly diagnosed ovarian cancer, OS were modelled using data from the population-adjusted indirect comparison (PAIC) of SOLO-1 (DCO1) and the tBRCA subset of PAOLA-1 (DCO2) (Vergote, Moore et al 2020) The originally performed PAIC (Vergote, Moore et al 2020) was performed on the PAOLA-1 data collected at the first data cut-off (DCO1) For the purpose of this analysis and to align with the efficacy data used in the economic evaluation for the HRD+ population, the PAIC was updated with PAOLA-1 data collected at DCO2 (March 2020)

9.2 Population-adjusted indirect comparison – PAOLA-1 BRCAm vs. SOLO-1

9.2.1 SOLO-1 vs. PAOLA-1

As described in the clinical sections of the dossier to Medicinrådet, the clinical trials in the 1L ovarian cancer setting differ in their design (Figure 23)

Figure 23. Design of the SOLO-1 and PAOLA-1 trials



Abbreviations: 1L first-line; BID: twice daily; BRCA: breast cancer susceptibility gene; CR: complete response; HRD: homologous recombination deficiency; IDS: interval debulking surgery; NACT: neo-adjuvant chemotherapy; NED: no evidence of disease; PDS: primary debulking surgery; PR: partial response; QD: once daily

Source: AstraZeneca Data on File (SOLO-1 CSR) ,(AstraZeneca Data on File 2018) AstraZeneca Data on File (PAOLA-1 CSR),(AstraZeneca Data on File 2019)

The PAOLA-1 and SOLO-1 trials showed several differences in their patient populations that are presented in Table 63 It is notable that the proportion of patients with stage IV disease and the proportion with complete response lower in PAOLA-1, i e a population with, on average, more severe disease than in SOLO-1 Hence, there is a need for a population-adjusted comparison

Table 63. Unadjusted comparison of patients included in the SOLO-1 and PAOLA-1 trials

	SOLO-1	**PAOLA-1**
Study size	N=391	N=806
Arms	Olaparib vs placebo as maintenance therapy	Olaparib + bevacizumab vs placebo + bevacizumab as maintenance therapy
Patients included	*BRCA*m	All-comers HRD testing (Myriad myChoice® HRD plus, ≥42 and ≥33 cut-offs) *BRCA* testing
Includes patients with NED following primary surgery?	Yes	Yes
Patient characteristics		
Disease stage	Stage III: 85% Stage IV: 15%	Stage III: 70% Stage IV: 30%
Surgery	PDS: 62% IDS: 36% None: 2%	PDS: 51% IDS: 42% None: 7%
1L treatment outcome	CR: 82% PR: 18%	CR: 73% PR: 27%

Abbreviations: BRCA: breast cancer susceptibility gene; BRCAm: BRCA mutation; CR: complete response; CT: chemotherapy; HRD: homologous recombination deficiency; IDS: interval debulking surgery; NACT: neo-adjuvant chemotherapy; NED: no evidence of disease; PDS: primary debulking surgery; PR: partial response

Source: AstraZeneca Data on File (SOLO-1 CSR),(AstraZeneca Data on File 2018) AstraZeneca Data on File (PAOLA-1 CSR),(AstraZeneca Data on File 2019)

9.2.2 Methodology

The unanchored matching adjusted indirect comparison was performed using individual patient data from the SOLO-1 trial with individual patient data from the subset of patients with confirmed tBRCA mutations (per eCRF) in the PAOLA-1 trial (AstraZeneca Data on File 2020)

A propensity score weighting technique was used to adjust for imbalances in matching variables, whereby BRCAm patients in each arm of PAOLA-1 was weighted such that the cohort had similar overall baseline matching variables to the olaparib arm of SOLO-1 The olaparib arm of SOLO-1 was selected as the target population for the matching analysis since it represents the current standard-of-care in this setting, and because of the larger sample size in this arm versus the corresponding placebo cohort due to the 2:1 randomization in SOLO-1 The propensity weighting method does not impose parametric assumptions on the outcome variable and can be used to estimate the average treatment effect of olaparib + bevacizumab in the SOLO1 population The propensity weighting method was also preferred to matching methods, which

would not have made use of available data on all individuals and hence resulted in loss of generalizability and precision (AstraZeneca Data on File 2020)

The variables considered in the weighting analysis were pre-specified by subject matter experts (external statisticians) and included patient age and ECOG performance status, disease stage, tumour location, and histology, type of surgery (primary debulking versus interval), residual disease status after surgery (yes or no), and response to 1L treatment The subject matter experts also pre-specified an interaction between residual disease and type of surgery as important variables to adjust for Age was included as a continuous variable and ≥65 years as an indicator of age, to account for the impact of age-related general mortality on PFS (AstraZeneca Data on File 2020)

For each patient, the propensity score was estimated using a logistic regression model in which arm membership (SOLO-1 olaparib arm versus PAOLA-1 arm) was regressed on the matching variables and the interactions listed above The estimated propensity scores were then used to weight the individuals in PAOLA-1 by their odds of being in the olaparib arm of SOLO-1 This approach assigns greater weights to those PAOLA-1 patients who best match those in SOLO-1 and lower weights to those PAOLA-1 patients who are dissimilar to SOLO-1 patients in their measured values of matching variables To aid the interpretation of results, the weights assigned to PAOLA-1 patients were scaled so that they sum to the original sample size of PAOLA-1; this has no impact on the distributions of the baseline covariates in the weighted PAOLA-1 sample or the analysis estimates (e g HR) Patients in the SOLO-1 placebo arm were not weighted because baseline characteristics were already close to the target olaparib arm, due to the randomization in SOLO-1 (AstraZeneca Data on File 2020)

The appropriateness of the derived weights to control for population imbalances was assessed In addition, the effective sample size (ESS) was estimated and differences in means (after dividing by the standard deviation of the variable in SOLO-1) and proportions of matching variables were assessed across trials A difference in matching variables exceeding 0 1 was pre-specified to indicate imbalance between trials (AstraZeneca Data on File 2020)

Weighted Cox regression and Kaplan-Meier analyses were performed to estimate the efficacy of different treatment strategies in the SOLO-1 population The 95% CI for the estimated HRs were estimated using non-parametric bootstrapping methods that allowed for uncertainty in the estimation of the weights An unadjusted indirect comparison was also undertaken to assess the implications of the matching adjustment As sensitivity analysis, weighted Cox models were fitted with adjustment for response status after 1L chemotherapy (complete response versus partial response), since this was a common stratification variable in both studies All analyses were performed in patients with complete data on matching variables; the implications of removing those with missing data were assessed

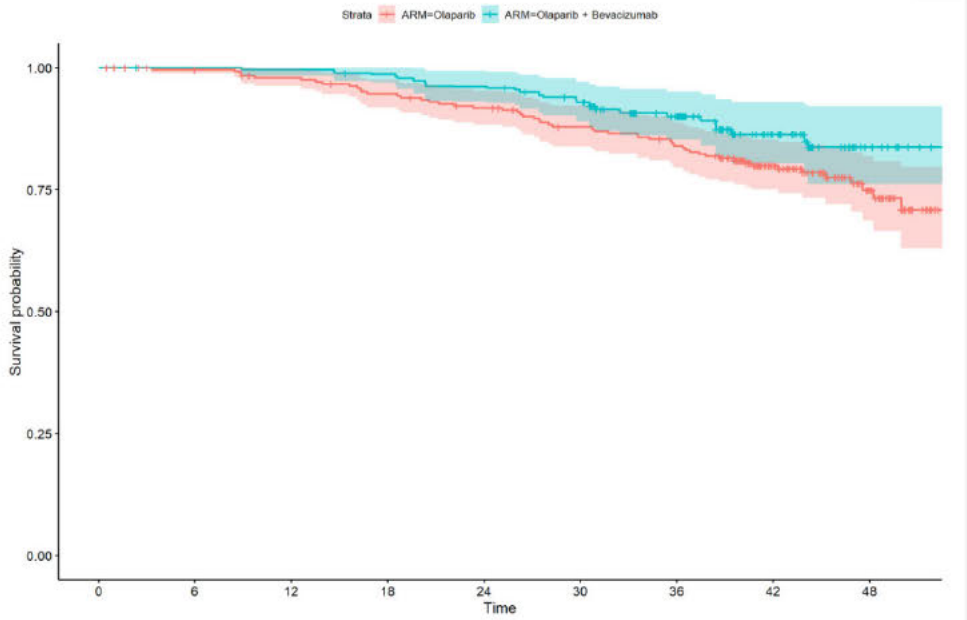
9.2.3 Results: Overall survival

Table 64. Modelling approach for overall survival.

OS	Modelling approach	Parametric distribution
Base case	Standard parametric model	Lognormal
OS data were modelled by fitting standard parametric models up to the point where the cumulative survival probabilities were predicted to be equal to or less than the cumulative survival of PFS, at which point the curves followed the trajectory of PFS		

Parametric curves were fitted to PAOLA-1 OS data for the olaparib maintenance eligible population
Parametric models were independently fitted to each treatment arm (KMs depicted in Figure 24)

Figure 24. OS Kaplan-Meier curve for the BRCA population (full data set, SOLO1, PAOLA-1 DCO2)



The lognormal distribution was chosen in the base case as it had a superior statistical fit (lowest AIC across arms), Table 65 The loglogistic distribution had the second best statistical fit

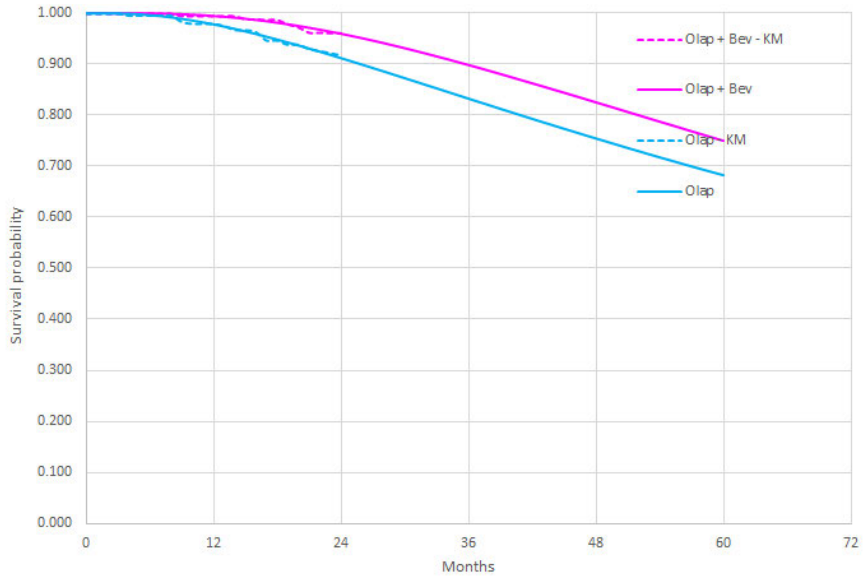
Table 65. Fit statistics of OS parametric extrapolation (independently fitted)

Treatment	Olaparib + bevacizumab		Olaparib monotherapy	
Extrapolation	AIC	BIC	AIC	BIC
Lognormal	238 369	244 403	656 732	663 806
Loglogistic	239 071	245 106	656 404	663 479
Weibull	239 282	245 317	656 51	663 585
Generalized Gamma	240 256	249 308	658 209	668 821
Gompertz	241 934	247 968	659 924	666 999
Exponential	248 594	251 611	671 869	675 406

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival

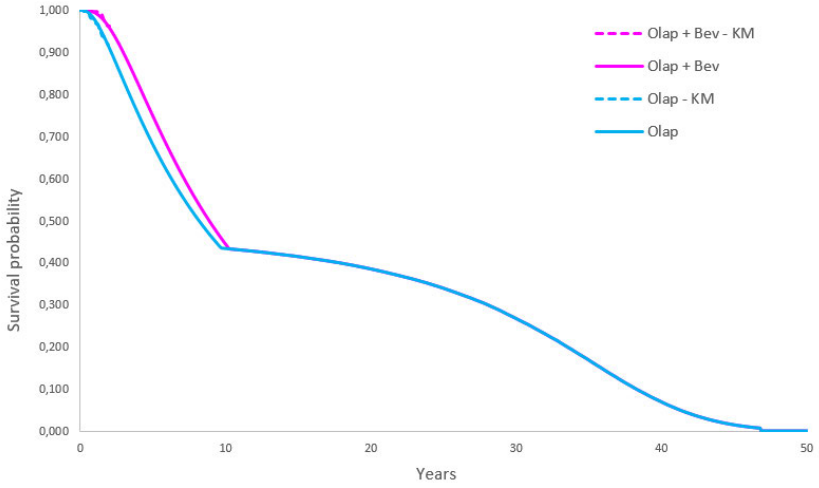
Figure 25 presents the modelled overall survival in the BRCAm ovarian cancer population used in the cost-effectiveness analysis

Figure 25. Modelled overall survival (Standard parametric model lognormal)



In long run extrapolations, it is assumed that patients who live longer than 10 years are cured and have a mortality close to that of the normal population (Figure 26) This is supported by data showing low excess mortality beyond 10 years after diagnosis

Figure 26. Modelled overall survival in the long run (Standard parametric model lognormal + parametric mixture cure model beyond 10 years).



9.3.2 Kaplan Meier plot

9.3.3 Logrank test(s)

9.3.4 Restricted means

Restricted means are calculated until the last time point where each arm has observations, using the area under KM curve with confidence interval at the 95% level

9.3.5 Cumulative Hazards plots

The following are diagnostic plots to check assumptions Linear trends indicate that there are no clear violations to the model assumptions for the corresponding distribution In the exponential diagnostic plot, the gradient corresponds to the hazards and parallel lines indicate proportional hazards In the Weibull, parallel lines indicate proportional hazards and a gradient of 1 indicates exponential survival In the Loglogistic diagnostic plot, parallel lines indicate proportional odds and in the Lognormal diagnostic plot, parallel lines indicate constant acceleration

Figure 28. Exponential distribution with log(S) vs time

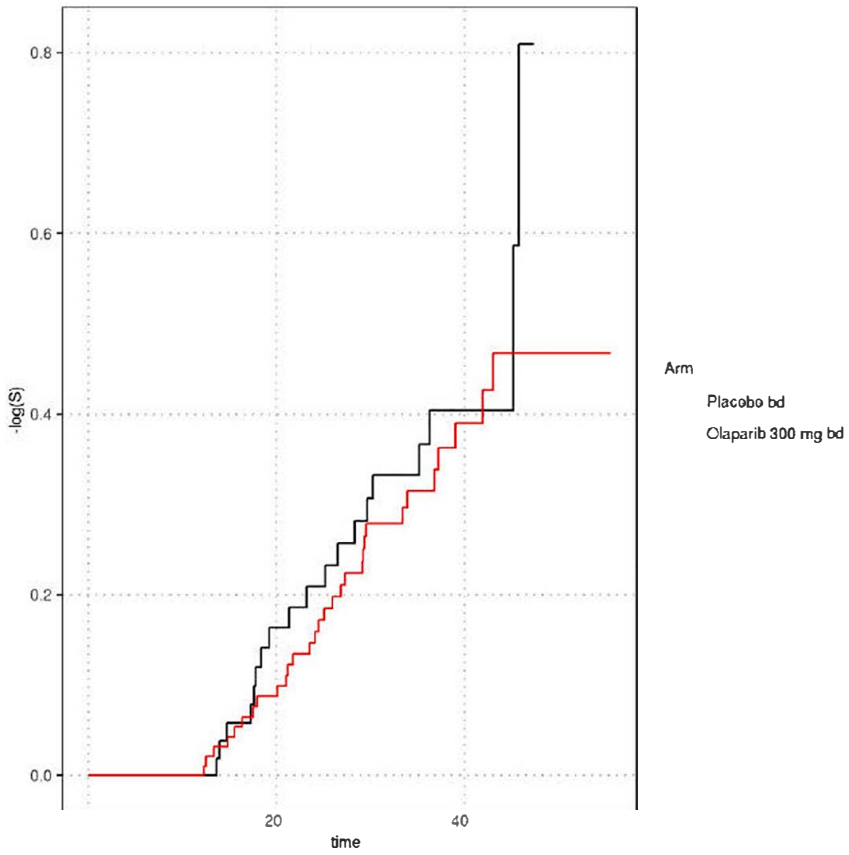


Figure 29. Weibull distribution with log(-log(S)) vs log(time)

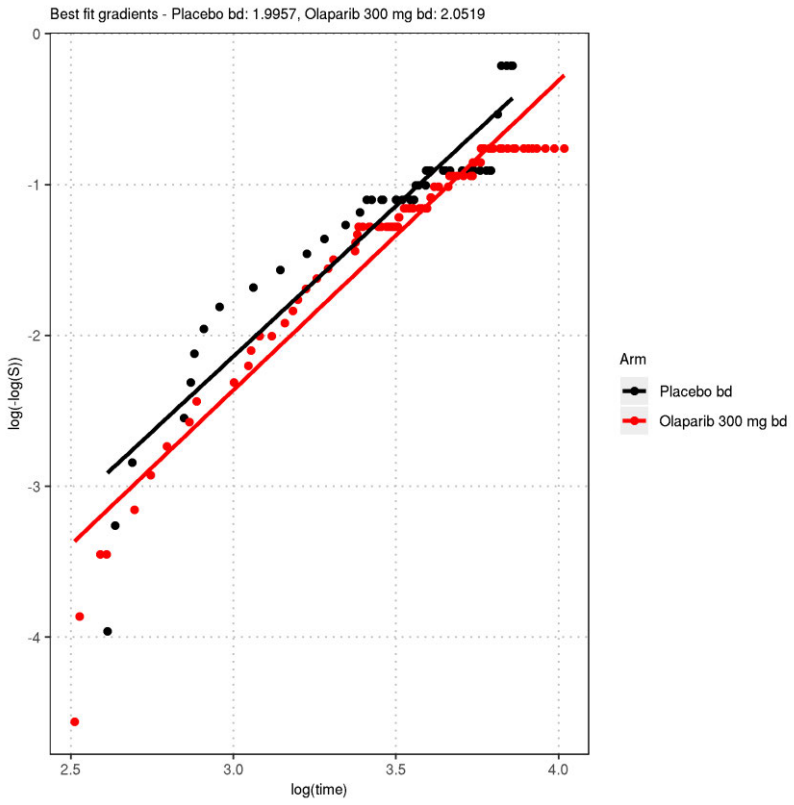


Figure 30. Loglogistic distribution with log(ODDs(S)) vs log(time)

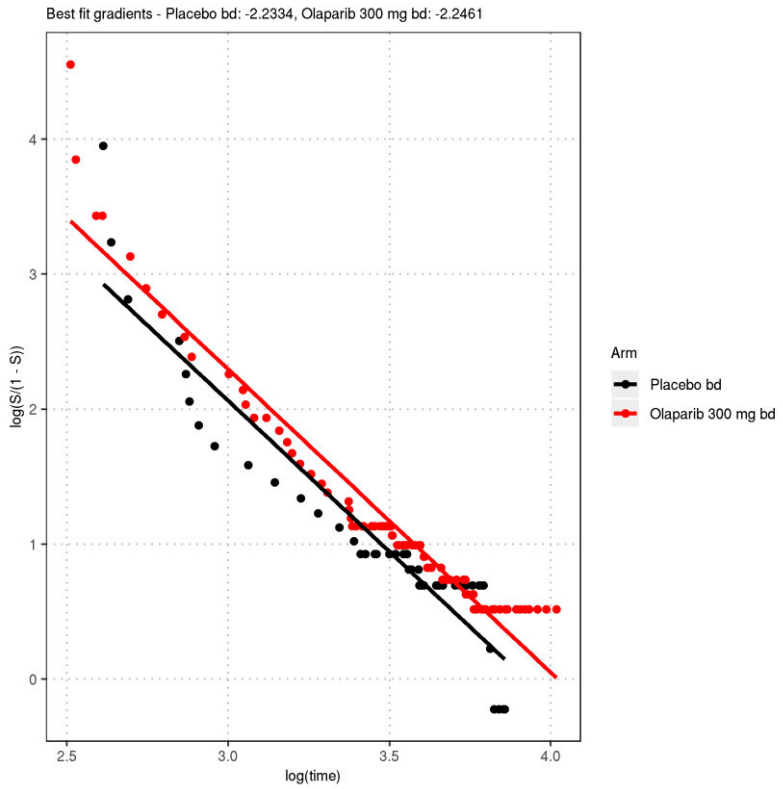
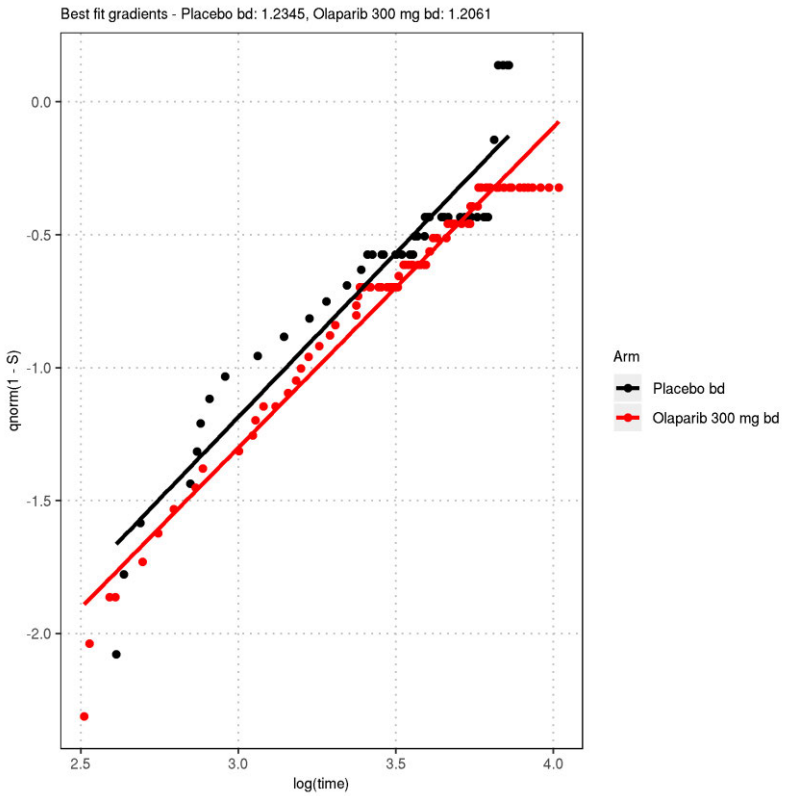


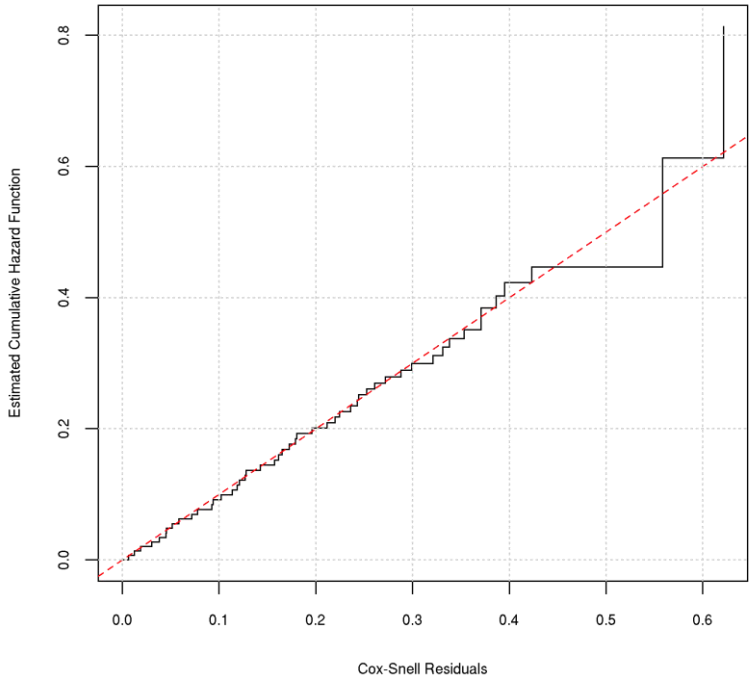
Figure 31. Lognormal distribution with Inv(norm(S)) vs log(time)



9.3.6 Cox Snell residuals

A straight line with slope=1 in the Cox Snell residuals plot indicates that a Cox model fits the data well

Figure 32. Cox Snell residuals



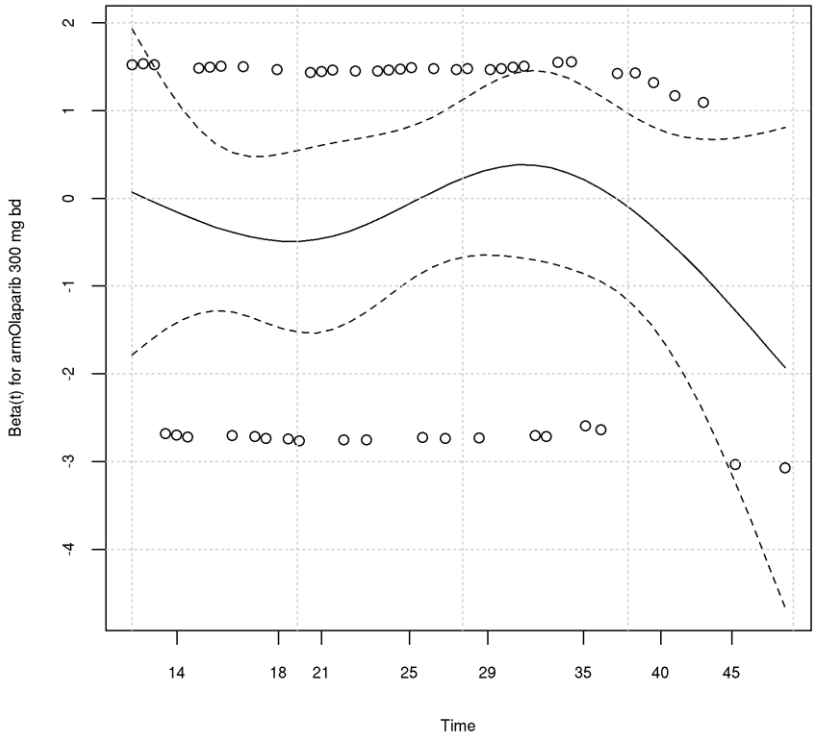
9.3.7 Schoenfeld residuals

Table 69. Schoenfeld residuals calculated using the km transform.

	rho	chisq	p
Olaparib 300 mg bd	-0 018	0 016	0 899

The Schoenfeld residuals can be used to test the proportional hazard assumption If PH, the plot of the residuals against time should show a linear trend with slope=0 The visual inspection of this plot is more important than the test, however, a p-value is also output as the result of a test of non-negative slope (Therneau and Grambsch)

Figure 33. Schoenfeld residuals



9.3.8 Separate distributions fitted per arm

Akaike and Bayesian information criteria are output The models with lower values fit data better

Table 70. AIC and BIC values

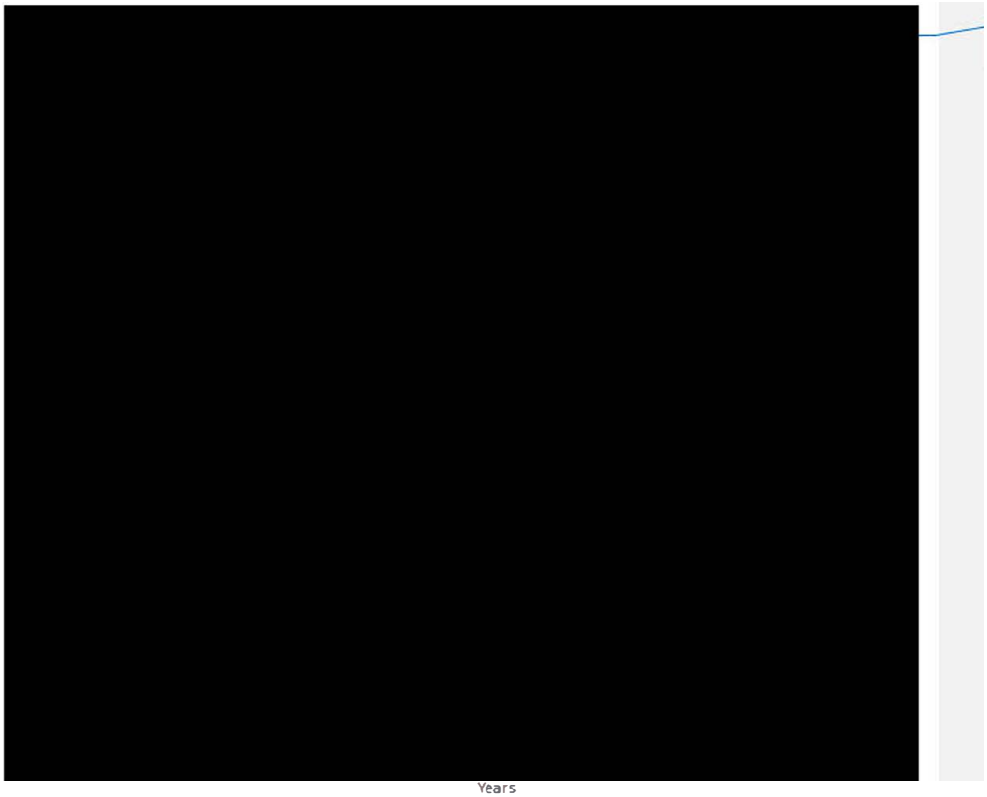
	Olaparib 300 mg bd		Placebo bd	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Generalized Gamma	326 87	334 59	197 77	203 79
Lognormal	328 98	334 13	203 03	207 04
Loglogist c	331 58	336 73	204 72	208 74
Weibull	333 23	338 38	205 37	209 39
Gompertz	339 15	344 30	208 47	212 49
Exponential	345 23	347 81	213 23	215 24

9.3.9 Parametric survival curves

The models are plotted with the KM data to illustrate how well they capture the trends

The best fitting model is generalized gamma which had the lowest AIC, but it is not clinically plausible, as it has the most extreme spread and does not provide realistic long-term extrapolations in the control group Hence, the next best fitting curve, the lognormal, is chosen as base case

Long-run extrapolation with the lognormal distribution is shown in Figure 35 Cure beyond 10 years could be assumed also here, but would have less impact than in the BRCA mutation positive population


Years

10 References

Aghajanian, C , Blank, S V , Goff, B A , Judson, P L , Teneriello, M G , et al (2012) OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer J Clin Oncol 30(17): 2039-2045

AstraZeneca data on file (2018) A phase III, randomised, double blind, placebo controlled, multicentre study of olaparib maintenance monotherapy in patients with BRCA mutated advanced (FIGO stage III-IV) ovarian cancer following first line platinum based chemotherapy

Burger RA, Brady MF, Bookman MA, et al Incorporation of bevacizumab in the primary treatment of ovarian cancer N Engl J Med 2011;365(26):2473-83

DGCD 2012 Årsrapport 2012 Dansk Gynækologisk Cancer Database, Copenhagen Available at: https://www sundhed dk/content/cms/63/1863_dgcd-%C3%A5rsrapport-2012-v2 pdf

DGCD 2017 National Årsrapport 2016/2017 Dansk Gynækologisk Cancer Database, Copenhagen Available at: http://www dgcg dk/images/Grupper/Databasegruppen/rsrapport_DGCD_2016-17_endelig_anonymiseret pdf

DGCG 2018 Ovariecancer retningslinier Retningslinjer for visitation, diagnostik, behandling og opfølgning af epitelial ovarie-, tuba- og primær peritonealcancer samt borderline tumorer 6 udgave 2018 Kapitel 5 - Version 07 12 2018 Dansk Gynækologisk Cancer Gruppe (DGCG), Copenhagen Available at : http://www dgcg dk/images/Grupper/Ovariecancergruppen/Retningslinier2016/nye_filer/Nye/Kap_5_rev_dec_18_uden_koder pdf

DGCG 2019 Ovariecancer retningslinier Retningslinier for visitation, diagnostik, behandling og opfølgning af epitelial ovarie-, tuba- og primær peritonealcancer samt borderline tumorer 6 udgave 2019 Kapitel 5 - Version 24 04 2019 Dansk Gynækologisk Cancer Gruppe (DGCG), Copenhagen Available at : http://www dgcg dk/images/Grupper/Ovariecancergruppen/Retningslinier_2019/Kapitel_5_OPDATERET_version_24_04_19_nye_koder pdf

EMA (2020) Lynparza: EPAR – Product Information Last updated: 06/11/2020 Available at: https://www ema europa eu/en/documents/product-information/lynparza-epar-product-information_en pdf

Friedlander M, Matulonis U, Gourley C, et al Long-term efficacy, tolerability and overall survival in patients with platinum-sensitive, recurrent high-grade serous ovarian cancer treated with maintenance olaparib capsules following response to chemotherapy Br J Cancer 2018 Oct;119(9):1075-1085

Ledermann J, Harter P, Gourley C, et al Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial The Lancet Oncology 2014;15(8):852-861

Lynparza EPAR (2018) Committee for Medicinal Products for Human Use (CHMP) CHMP assessment report on extension of marketing authorisation grouped with a variation EMA/64964/2018

Lynparza EPAR (PAOLA-1) (2020) EMA, Committee for Medicinal Products for Human Use (CHMP) CHMP assessment report on extension of marketing authorisation grouped with a variation EMA/523504/2020 Available at: https://www ema europa eu/en/documents/variation-report/lynparza-h-c-3726-ii-0035-epar-assessment-report-variation_en pdf

Medicinrådet (2019) Medicinrådets protokol for vurdering af olaparib til behandling af nydiagnosticeret avanceret BRCA-muteret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden Available at: https://medicinraadet dk/media/11833/medicinraadets-protokol-for-vurdering-af-olaparib-til-behandling-af-kraeft-i-aeggestokkene pdf

Medicinrådet (2020) Værdisætning af enhedsomkostninger Version 1 3 Available at: https://medicinraadet dk/media/weslftgk/vaerdisaetning-af-enhedsomkostninger-vers-13_adlegacy pdf

Medicinrådet (2020) Medicinrådets protokol for vurdering af olaparib i kombination med bevacizumab til 1 linje vedligeholdelsesbehandling af avanceret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden med homolog recombinationsdefekt Available at: https://medicinraadet dk/media/r2il03z1/medicinr%C3%A5dets-protokol-for-vurdering-af-olaparib-bevacizumab-til-nydiagnosticeret-kr%C3%A6ft-i-%C3%A6ggestokkene-vers-1-0_adlegacy pdf

Moore K, Colombo N, Scambia G, et al Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer N Engl J Med 2018;379(26):2495-2505

Nordcan project, retrieved 2020-12-08 from: http://www-dep iarc fr/NORDCAN/DK/frame asp

Perren TJ, Swart AM, Pfisterer J, et al A phase 3 trial of bevacizumab in ovarian cancer N Engl J Med 2011;365(26):2484-96

Pujade-Lauraine E, Ledermann JA, Selle F, et al Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial Lancet Oncol 2017;18(9):1274-1284

Ray-Coquard I, Pautier P, Pignata S, et al Olaparib plus bevacizumab as first-line maintenance in ovarian cancer N Engl J Med 2019 Dec 19;381(25):2416-2428

Roche (2012) NICE submission STA 285 Bevacizumab for the treatment of recurrent advanced ovarian cancer https://www nice org uk/guidance/ta285/documents/ovarian-fallopian-tube-and-primary-peritoneal-cancer-recurrent-advanced-platinumsensitive-partially-platinumsensitive-bevacizumab-roche2

Romero, I , & Bast, R C (2012) Minireview: human ovarian cancer: biology, current management, and paths to personalizing therapy Endocrinology, 153, 1593-1602

Vergote, I , K Moore, R Hettle, K Rhodes, M Ouwens and I Ray-Coquard (2020) "Population adjusted indirect comparison of the SOLO1 and PAOLA-1/ENGOT-ov25 studies of olaparib with or without bevacizumab, bevacizumab alone and placebo in the maintenance treatment of women with newly diagnosed stage III/IV ovarian cancer with BRCA mutation Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer "

Medicinrådet

Medicinrådets protokol for vurdering af olaparib i kombination med bevacizumab til 1. linje vedligeholdelsesbehandling af avanceret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden med homolog recombinationsdefekt

Versionsnr.: 1.0

Medicinrådet

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 deres endelige ansøgning. Til hvert spørgsmål knytter sig en definition af patientgruppen, det lægemiddel vi undersøger, den behandling vi 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, 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 ansøgende virksomhed få besked.

Godkendt af Medicinrådet 26. oktober 2020
Dokumentnummer 99072
Versionsnummer 1.0

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

Indhold

1 Begreber og forkortelser

CI	Konfidensinterval
BRCA	*Breast Cancer* (tumorsuppressorgen)
EMA	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EPAR	*European Public Assessment Report*
FDA	*U.S. Food and Drug Administration*
FIGO	*International Federation of Gynecology and Obstetrics* (system til at inddele kræftsygdomme I stadier fra I-IV)
GRADE	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HR	*Hazard ratio*
HRD	Homolog rekombinationsreparations defekt (*homologous recombination repair deficiency*)
ITT	*Intention-to-treat*
OR	*Odds ratio*
OS	Samlet overlevelse (*Overall survival*)
PARP	Poly-ADP-Ribose-Polymerase
PARPi	Poly-ADP-Ribose-Polymerasehæmmer (*inhibitor*)
PFS	Progressionsfri overlevelse (*progression free survival*)
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*
VEGF	*Vascular endothelial growth factor*

2 Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra AstraZeneca, som ønsker, at Medicinrådet vurderer olaparib (Lynparza®) i kombination med bevacizumab (Avastin®) til vedligeholdelsesbehandling af nydiagnosticeret high-grade kræft i æggestokkene, æggelederne eller primær bughulekræft med homolog rekombinationsdefekt (HRD). Vi modtog den foreløbige ansøgning den 29. september 2020.

2.1 Kræft i æggestokkene, æggelederne eller primær bughulekræft

Kræft i æggestokkene, æggelederne og primær bughulekræft benævnes herefter samlet som kræft i æggestokkene.

Kræft i æggestokkene er den fjerde hyppigste kræftdødsårsag hos kvinder i Danmark. Der diagnosticeres omkring 450-550 nye tilfælde om året, og ved udgangen af 2016 levede 4697 kvinder med diagnosen [1,2]. Kræft i æggestokkene udgør i alt 2,8 % af alle kræfttilfælde hos kvinder, og livstidsrisikoen for at udvikle sygdommen er ca. 2 %. Median alder for diagnosen er 63 år, og overlevelsen er afhængig af alder ved diagnosen samt sygdomsstadiet (FIGO stadium, herfra blot benævnt stadium). 5-års overlevelsesrater for stadium I, II, III og IV er henholdsvis 93, 76, 41 og 23 % med faldende respektive værdier ved stigende alder på diagnosetidspunktet [3,4]. Tidlige stadier af sygdommen er ofte asymptomatiske på grund af æggestokkenes frie beliggenhed i det lille bækken. Således har ca. 70-80 % af patienter med kræft i æggestokkene på diagnosetidspunktet lokal spredning eller avanceret sygdom (stadium II-IV) [1], hvilket er kraftigt medvirkende til en samlet 5-års overlevelse på ca. 40-50 % [4,5].

Kræft i æggestokkene er overordnet set en heterogen gruppe. Dog er omkring 90 % af tilfældene af epitelial type (karcinomer), og størstedelen af disse er af typen high grade serøst karcinom (HGSC) (268-307 patienter per år fra 2016-2019 svarende til ca. 55 % af alle tilfælde) [4].

Mutationer i *Breast Cancer* (BRCA) 1 eller 2-genet er en væsentlig arvelig risikofaktor for udviklingen af kræft i æggestokkene. Forekomsten er ca. 15-20 % med en højere forekomst hos patienter med HGSC [6–8]. BRCA-mutationer kan være både arvelige eller somatiske. I dansk klinisk praksis behandles disse på samme måde, hvorved BRCA-mutationer i denne protokol bruges som fællesbetegnelse for begge typer. Patienter med BRCA-mutation har generelt en bedre prognose, da mutationerne medfører et signifikant bedre respons på både platin-baseret kemoterapi og hæmmere af Poly-ADP-Ribose-Polymerase (PARPi) [9–11].

BRCA er involveret i homolog rekombination, som er en vital celleproces til reparation af DNA-skader [10,12]. Tumorer med BRCA-mutation vil oftest også have homolog rekombinationsdefekt (HRD), men HRD kan også forekomme i ikke-BRCA-muterede tumorer. Flere studier har dokumenteret HRD i op mod 40 % af platin-sensitive tumorer i æggestokkene uden BRCA-mutation, hvorved gruppen med HRD er op mod dobbelt så stor som gruppen med BRCA-mutation [7,11,13–15]. I studierne var HRD defineret som enten BRCA-mutation eller en genomisk ustabilitetsscore over 42 målt vha. MYRIAD myChoice CDx. Dette er en kompleks molekylærbiologisk analyse, der kombinerer genomic scar assays, hhv. ”Telomeric Allelic Imbalance”, ”Loss Of Heterozygosity” og ”Large Scale Transition” med en samlet tærskelværdi på 42 til bestemmelse af HRD positivitet.

Det anbefales i dag, at alle patienter udredes i forhold til BRCA-mutationsstatus [16], men der findes ingen nationale guidelines i forbindelse med udredning af HRD-status. Derfor vil det forventes, at en væsentlig gruppe af danske patienter uden påvist BRCA-mutation har tumorer, der udviser HRD. *U.S. Food and Drug Administration* (FDA) har i 2020 godkendt et companion diagnostics til at identificere HRD i high-grade kræft i æggestokkene [17]. Denne diagnostiske metode er anvendt i flere kliniske forsøg med PARPi i

Danmark, heriblandt på Herlev Hospital, Odense Universitetshospital, Rigshospitalet og Aarhus Universitetshospital, hvor mere end 100 patienter er blevet testet [11,14,18].

Tilstedeværelsen af en patientgruppe uden BRCA-mutation men med HRD, gør det relevant at opdele den samlede patientgruppe. Ud fra de tidligere data på forekomsten af BRCA-mutation og HRD forventes det, at omkring 300 patienter i alt vil have avanceret high-grade kræft i æggestokkene, og omkring 60 af disse vil have en BRCA-mutation. Derudover forventes det, at omkring 100 vil have HRD-positive tumorer uden BRCA-mutation, ud fra forekomsten rapporteret i de kliniske studier med MYRIAD myChoice CDx. De resterende 140 vil hverken have tumorer uden BRCA-mutation eller HRD.

2.2 Olaparib og bevacizumab

Olaparib og bevacizumab er godkendt af Europakommisionen som kombinationsbehandling til vedligeholdelsesbehandling af nydiagnosticerede patienter med avanceret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden, som responderer på platinbaseret kemoterapi (komplet eller partielt respons), og hvor der er konstateret homolog rekombinationsdefekt (HRD) i en tumorprøve.

Olaparib er i forvejen indikeret som monoterapi til vedligeholdelsesbehandling af patienter med recidiverende platinsensitiv high-grade kræft i æggestokkene af stadium III eller IV eller af nydiagnosticerede patienter med platinsensitiv high-grade kræft i æggestokkene af stadium III eller IV i patienter med mutation i BRCA1/2 [19]. Olaparib som monoterapi er anbefalet til både 1. og 2. linje vedligeholdelsesbehandling i Medicinrådets behandlingsvejledning vedrørende lægemidler til BRCA-muteret, platinsensitiv high-grade kræft i æggestokkene med en standarddosering på 600 mg dagligt i 2 år eller indtil progression eller uacceptabel toksicitet [20].

Olaparib tilhører gruppen af selektive PARPi, der hæmmer aktivering af enzymerne, PARP-1, -2 og -3 [19]. PARP indgår i cellens DNA-reparationsrespons, hvor de faciliterer reparation af enkeltstrengsbrud på DNA'et. Hæmning af denne proces resulterer i yderligere brud på DNA'et kaldet DNA dobbeltstrengsbrud. Disse brud repareres normalt via homolog rekombination, men i celler med HRD (som er tilfældet i BRCA-mutationer) vil dobbeltstrengsbrud akkumulere og medføre celledød i tumoren [21].

Bevacizumab er et monoklonalt antistof, der hæmmer angiogenesen via binding til *vascular endothelial growth factor* (VEGF). Dette hæmmer dannelsen af nye blodkar i tumoren og normaliserer de eksisterende blodkar, hvorved tumorvæksten hæmmes [22]. Bevacizumab er indikeret til kombinationsbehandling med carboplatin og paclitaxel i første eller anden linje af kræft i æggestokkene af stadium III eller IV. Derudover er det indikeret i kombination med paclitaxel, topotecan eller pegyleret liposomal doxorubicin til platinresistent – recidiverende kræft i æggestokkene, hvor der ikke tidligere er anvendt VEGF hæmmere, og hvor patienter ikke har gennemgået mere end to tidligere kemoterapibehandlinger.

I dansk klinisk praksis stilles yderligere krav til patientens sygdom for at anvende bevacizumab (se afsnit 2.3), og det anbefales ikke som rutinemæssig behandling i Medicinrådets behandlingsvejledning på området [20]. Ved behandling gives enten 7,5 eller 15 mg/kg hver 3. uge indtil sygdomsprogression.

Der kan være en potentiel synergistisk effekt ved at kombinere olaparib og bevacizumab eller anden VEGF-hæmmer. Dette er observeret i et fase II klinisk studie, hvor patienterne modtog enten olaparib monoterapi eller olaparib i kombination med cediranib (en VEGF-receptorinhibitor) [23]. Her sås en signifikant øget progressionsfri overlevelse (PFS) og generel overlevelse (OS) ved kombinationsbehandlingen overfor olaparib alene i subpopulationen uden BRCA-mutationer, hvorimod der ikke sås nogen signifikante forskelle i populationen med BRCA-mutation.

2.3 Nuværende behandling

Det overordnede mål for behandlingen af kræft i æggestokkene er helbredelse, alternativt at forlænge overlevelsen og/eller at øge livskvaliteten. Den primære behandling er kirurgisk, hvor målet er at fjerne alt synligt kræftvæv (radikal operation) samt korrekt stadieinddeling [1,24]. Dette opnås for ca. 70 % af patienter med stadium III eller IV enten primært eller efter indledende kemoterapi [4]. Efterfølgende behandling afhænger af patientens sygdomsstadie, operationsresultat og sundhedsmæssige status. I klinisk praksis skelnes der mellem patienter, hvor der er efterladt mindre end eller mere end eller lig med 1 cm tumorvæv efter operation.

Patienter i stadium IIB-IV uden makroskopisk tumorvæv efter operation (< 1 cm) behandles som standard med adjuverende platinbaseret kombinationskemoterapi bestående af carboplatin og paclitaxel. Behandlingen gives i 6 serier, med mindre der opstår progression eller uacceptabel toksicitet [25]. Patienter med BRCA-mutation, som responderer på kemoterapibehandlingen, tilbydes vedligeholdelsesbehandling med olaparib, som beskrevet i afsnit 2.2. Patienter uden BRCA-mutation tilbydes ikke yderligere vedligeholdelsesbehandling.

Patienter i stadium III med efterladt makroskopisk tumorvæv efter operation (≥ 1 cm) samt patienter i stadium IV og inoperable patienter behandles som standard også med carboplatin og paclitaxel. Patienter med BRCA-mutation tilbydes vedligeholdelsesbehandling med olaparib som beskrevet ovenfor, hvorimod patienter uden BRCA-mutation kan tilbydes behandling med bevacizumab i kombination med og/eller efter kemoterapibehandlingen [20].

Størstedelen af patienterne (60-80 %) responderer på 1. linjebehandlingen, men omkring 80 % af disse vil opleve tilbagefald inden for 2-3 år efter afsluttet kemoterapi [1]. Disse patienter har generelt dårligere prognose end nydiagnosticerede patienter og vil typisk opleve kortere progressionsfri overlevelse (PFS) efter gentagne kemoterapibehandlingslinjer [26]. Det nuværende behandlingsforløb, samt hvorledes olaparib i kombination med bevacizumab vil indtræde ved en eventuel anbefaling, er illustreret i figur 1.

Figur 1: Olaparib i kombination med bevacizumabs indplacering som vedligeholdelsesbehandling efter den nuværende 1. linjebehandling med platinbaseret kemoterapi af kræft i æggestokkene. EMA-indikationen for olaparib i kombination med bevacizumab dækker alle patienter med nydiagnosticeret kræft i æggestokkene, der responderer på platin og har diagnosticeret HRD, men den samlede patientpopulation opdeles i denne protokol for at belyse effekterne i de

forskellige subgrupper, BRCA-mutation, BRCA-vildtype med HRD og bevacizumab/ikke-bevacizumabkandidater.

Denne protokol vedrører kun 1. linjebehandling, hvorfor der ikke gives nærmere beskrivelse af efterfølgende behandling af platinsensitiv recidiverende kræft i æggestokkene.

3 Kliniske spørgsmål

Medicinrådet bruger kliniske spørgsmål til vores vurderinger af lægemidlers værdi for patienterne. Til hvert spørgsmål knytter sig en definition af patientgruppen (population), af det lægemiddel vi undersøger (interventionen), af den behandling vi sammenligner med (komparator(er)) og af effektmålene.

Det overordnede kliniske spørgsmål opdeles, da den nuværende standardbehandling varierer, afhængig af om patienten har en påvist BRCA-mutation, og om de kandiderer til bevacizumab. Derfor er det relevant at tage stilling til olaparib i kombination med bevacizumabs kliniske værdi overfor tre forskellige standardbehandlinger. Patienter med BRCA-mutation vil med nuværende praksis modtage olaparib monoterapi, uagtet om de kandiderer til bevacizumab eller ej. Denne population vil derfor indeholde både patienter med stadium III og stadium IV BRCA-muteret high-grade kræft i æggestokkene uagtet operationsstatus. Nuværende praksis for vedligeholdelsesbehandling af patienter uden BRCA-mutation afhænger af om de kandiderer til bevacizumab eller ej. Derfor opdeles denne population efter stadium samt operationsresultat, som beskrevet nedenfor.

3.1 Klinisk spørgsmål 1

Hvilken værdi har olaparib i kombination med bevacizumab sammenlignet med olaparib monoterapi som vedligeholdelsesbehandling for nydiagnosticerede patienter med avanceret BRCA-muteret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden, som responderer på platinbaseret kemoterapi (komplet eller partiel respons).

Population
Nydiagnosticerede patienter med avanceret (stadium III-IV) BRCA-muteret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden, som responderer på platinbaseret kemoterapi (komplet eller partiel respons).

Intervention
Olaparib og bevacizumab som beskrevet i 2.2.

Komparator
Olaparib monoterapi, som beskrevet i 2.2

Effektmål
De valgte effektmål står i tabel 1.

Klinisk spørgsmål 2

Hvilken værdi har olaparib i kombination med bevacizumab sammenlignet med bevacizumab monoterapi for nydiagnosticerede patienter med avanceret ikke-BRCA-muteret, HRD-positiv high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden, som responderer på platinbaseret kemoterapi (komplet eller partiel respons) og kandiderer til bevacizumab?

Population
Nydiagnosticerede patienter med avanceret (stadium III-IV) ikke-BRCA-muteret, HRD-positiv high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden, som responderer på platinbaseret kemoterapi (komplet eller partiel respons), og som vurderes at være kandidater til bevacizumab (patienter med mere end eller lig med 1 cm efterladt tumorvæv, patienter med efterladt tumorvæv udenfor bughulen (stadium IV), og patienter, som er primært og/eller sekundært (interval kirurgi) inoperable.

Intervention
Olaparib og bevacizumab som beskrevet i 2.2.

Komparator
Bevacizumab monoterapi som beskrevet i 2.2.

Effektmål
De valgte effektmål står i tabel 1.

Klinisk spørgsmål 3

Hvilken værdi har olaparib i kombination med bevacizumab sammenlignet med placebo som vedligeholdelsesbehandling for nydiagnosticerede patienter med avanceret ikke-BRCA-muteret, HRD-positiv high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden, som responderer på platinbaseret kemoterapi (komplet eller partiel respons) og ikke kandiderer til bevacizumab?

Population
Nydiagnosticerede patienter med stadium III, ikke-BRCA-muteret, HRD-positiv high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden, som responderer på platinbaseret kemoterapi (komplet eller partiel respons), og som har mindre end 1 cm tumorvæv efterladt efter operation.

Intervention
Olaparib og bevacizumab som beskrevet i 2.2.

Komparator
Ingen vedligeholdelsesbehandling

Effektmål
De valgte effektmål står i tabel 1.

3.2 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, vi har nævnt i tabel 1. For hvert effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel (MKRF). I det følgende afsnit argumenterer vi for valget af effektmål og de mindste klinisk relevante forskelle.

Tabel 1. Effektmål.

Effektmål	Vigtighed	Effektmålsgruppe	Måleenhed	Mindste klinisk relevante forskel
Samlet overlevelse (OS)	Kritisk	Dødelighed	Median OS i antal måneder	En forskel på 4 måneder
			OS rate ved 5 år	En forskel på 5 procentpoint
Progressions-fri overlevelse (PFS)	Kritisk	Livskvalitet samt alvorlige symptomer og bivirkninger	Median PFS i antal måneder	En forskel på 6 måneder
			PFS rate ved 2 år	En forskel på 10 procentpoint
Bivirkninger	Kritisk	Livskvalitet samt alvorlige symptomer og bivirkninger	Andel af patienter, som ophører behandling pga. bivirkninger	En forskel på 5 procentpoint
			Andel af patienter, som oplever en eller flere grad 3-4 bivirkninger	En forskel på 10 procentpoint
			Kvalitativ gennemgang af bivirkningstyperne med henblik på at vurdere alvorlighed, håndterbarhed og tyngde af bivirkningerne	Kvalitativ vurdering
Livskvalitet	Vigtig	Livskvalitet samt alvorlige symptomer og bivirkninger	Andel af patienter, der ikke viser statistisk signifikant forværring i livskvalitet	En forskel på 10 procentpoint

For alle effektmål ønsker vi data med længst mulig opfølgningstid, med mindre andet er angivet.

3.2.1 Kritiske effektmål

Samlet overlevelse (OS)

Forbedret samlet overlevelse (OS) med mindst mulig toksicitet er det optimale mål for kræftbehandling. OS defineres som tiden fra randomisering eller behandlingsstart til død uanset årsag. For OS anvendes to mål til at vurdere den absolutte effekt: median OS og OS-rate. De to mål supplerer hinanden.

Kræft i æggestokkene er en livstruende sygdom, og fagudvalget betragter derfor OS som et kritisk effektmål. For patienter med kræft i æggestokkene stadie III-IV er 5-årsoverlevelsen ca. 30 % med median OS på ca. 3 år [4]. Fagudvalget vurderer derfor, at en absolut forskel i OS-rate ved 5 år på 5 procentpoint og en absolut forskel for median OS på 4 måneder mellem intervention og komparator er klinisk relevant.

Progressionsfri overlevelse (PFS)

Progressionsfri overlevelse (PFS) defineres som tiden fra randomisering eller behandlingsstart til første dokumentation af progression i henhold til Response Evaluation Criteria i Solid Tumors (RECIST)-kriterierne [27] eller til død.

PFS anvendes som surrogatmål for OS og livskvalitet inden for området. Hvis der ikke findes modne data på OS, vil fagudvalget anvende data på PFS som surrogatmål for OS. PFS påvirkes ikke af akkumulerede effekter af efterfølgende behandlinger på samme måde som OS, og data må forventes at have nået en større modenhed for PFS, hvilket medfører sikrere estimater. Fagudvalget er dog opmærksomme på, at validiteten af PFS som surrogat er uklar, fordi sammenhængen mellem OS og PFS ikke er dokumenteret for behandling af kræft i æggestokkene. Tværtimod viste to nylige metaanalyser af behandling af kræft i æggestokkene mangel på sammenhæng mellem PFS og OS ud fra hazard ratios [28,29]. Dog viste den ene analyse en bedre korrelation ved at sammenligne forskelle i medianer mellem kontrol og aktive behandlinger for PFS og OS [29]. Fagudvalget sætter derfor højere krav til effekten på PFS end på OS, hvilket er afspejlet i effektmålenes indplacering i effektmålsgruppe (se tabel 1).

PFS ved vedligeholdelsesbehandling afspejler desuden tiden til næste linje med platinbaseret kemoterapi. Længden af det platinfrie interval er bestemmende for valg af efterfølgende behandling, og fagudvalget anser dette som en vigtig patientrelateret parameter.

Fagudvalget vurderer på denne baggrund, at PFS er et kritisk effektmål. For patienter med BRCA-mutation er PFS-raten ved 2 år ca. 40 %, og median PFS er ca. 14 måneder [30]. Fagudvalget vurderer derfor, at en absolut forskel i PFS-rate ved 2 år på 10 %-point og en absolut forskel på median PFS på 6 måneder mellem intervention og komparator er klinisk relevant. Fagudvalget vurderer, at patienter med HRD har en sammenlignelig prognose med BRCA-muterede patienter.

Bivirkninger

Bivirkninger (toksicitet) belyser de negative konsekvenser, patienterne kan opleve ved behandling med lægemidlet. Forbedret OS med mindst mulig toksicitet er det optimale mål for kræftbehandling. Fagudvalget anser derfor bivirkninger som et kritisk effektmål. Effektmålet vurderes samlet ud fra behandlingsophør på grund af bivirkninger, bivirkninger grad 3-4 samt en kvalitativ gennemgang af bivirkningerne. Behandlingsophør på grund af bivirkninger og bivirkninger grad 3-4 er to kvantitative opgørelser, som belyser henholdsvis tolerabilitet og hyppigheden af alvorlige og livstruende bivirkninger.

<u>Behandlingsophør på grund af bivirkninger</u>

Fagudvalget ønsker en opgørelse over forskellen i andel af patienter, som ophører behandling grundet bivirkninger ved længst mulig opfølgningstid. Fagudvalget vurderer, at en mindste klinisk relevant forskel er 5 procentpoint.

<u>Bivirkninger grad 3-4</u>

Forekomst af bivirkninger grad 3-4, defineret i henhold til National Cancer Institute CTCAE version 4.0 [31], er et udtryk for alvorlig, men ikke fatal toksicitet af lægemidlet.

Fagudvalget ønsker en opgørelse over andelen af patienter, som oplever en eller flere bivirkninger af grad 3 og/eller 4 ved længst mulig opfølgningstid. Fagudvalget vurderer, at en mindste klinisk relevant forskel er 10 procentpoint.

Kvalitativ gennemgang af bivirkningerne

Fagudvalget ønsker en kvalitativ gennemgang af de konkrete bivirkninger forbundet med olaparib i kombination med bevacizumab samt komparatorer med henblik på at vurdere bivirkningernes alvorlighed, hyppighed og håndterbarhed. Ansøger bedes bidrage med bivirkningsdata fra både kliniske studier samt lægemidlernes produktresumé.

Fagudvalget er meget opmærksomme på, at op til 80 % af bivirkningerne forbundet med behandling med PARP-hæmmere er håndterbare og dosistitrerbare. Fagudvalget vil tage højde for dette i den samlede kategorisering.

Vigtige effektmål

Livskvalitet

Ændring i livskvalitet er et patientrelevant effektmål, som kan give indblik i, hvordan lægemidlernes fordele og ulemper samlet set påvirker patienten. Baseline FACT-O TOI-score er uafhængigt prognostisk for PFS og OS, hvor forbedring sammenlignet med forværring i livskvalitet er forbundet med forlænget PFS og OS hos kvinder med kræft i æggestokkene [32]. På baggrund af dette betragter fagudvalget livskvalitet som et vigtigt effektmål for alle prognosegrupper.

Livskvalitet kan for patienter med kræft i æggestokkene måles med forskellige spørgeskemaer. Fagudvalget ønsker livskvalitet opgjort som andel patienter, der ikke viser en signifikant forværring i livskvalitet vha. spørgeskemaet EORTC-QLQ-OV28:

- EORTC-QLQ-OV28 eller C-30. European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30 (EORTC QLQ-C30) er et hyppigt anvendt generisk måleredskab, som består af fem funktionsskalaer, tre symptomskalaer og en 'global' livskvalitetsskala. Der anvendes en scoringsskala fra 0-100 [33]. EORTC Quality of Life Group and the Quality of Life Unit har udviklet og valideret et supplement til dette, som er specifikt for kræft i æggestokkene, -OV28 [34]. Det foretrækkes, at ansøger leverer data fra det specifikke spørgeskema, -OV28.

Hvis der foreligger data fra EORTC-QLQ-OV28 vil vurderingen baseres på dette. Hvis dette ikke er tilgængeligt, men ansøger har data for et andet måleinstrument, ønsker fagudvalget at se en opgørelse for dette. Denne opgørelse skal inkludere en beskrivelse af værktøjet samt argumentation og dokumentation for mindste klinisk relevant forskel. Alternative måleinstrumenter kunne være:

- Functional Assessment of Cancer Therapy-Ovarian (FACT-O). FACT-O er et sygdomsspecifikt spørgeskema, som anvendes til vurdering af helbredsrelateret livskvalitet hos patienter med kræft i æggestokkene. Spørgeskemaet består af fem domæner (fysisk velvære, socialt velvære, følelsesmæssigt velvære, funktionelt velvære og øvrige bekymringer), som scores på en 5-point Likertskala fra 0 (ingen) til 4 (rigtig meget). En høj samlet score repræsenterer høj livskvalitet [35].

- FACT Ovarian Symptom Index (FOSI). FOSI er et valideret 8-spørgsmåls måleinstrument omhandlende sygdomsrelaterede symptomer. Spørgsmålene er taget fra FACT-O-spørgeskemaet. Scoreskalaen går fra 0 (alvorlige symptomer) til 32 (ingen symptomer) [36].

- EQ-5D: EQ-5D er et velvalideret generisk spørgeskema, som anvendes til vurdering af helbredsrelateret livskvalitet (EuroQol Group). Spørgeskemaet består af fem dimensioner (bevægelighed, personlig pleje, sædvanlige aktiviteter, smerte/ubehag og angst/depression).

Spørgeskemaet indeholder desuden en visuel analog skala (VAS), der går fra 0 (værst tænkeligt helbred) til 100 (bedst tænkeligt helbred) [37].

Fagudvalget vurderer, at en forskel på 10 procentpoint i andel patienter, der ikke viser forværring i livskvalitet mellem lægemidlerne, er klinisk relevant.

4 Litteratursøgning

Medicinrådet har på baggrund af den foreløbige ansøgning undersøgt, om der findes en eller flere fuldtekstartikler publiceret i videnskabelige, fagfællebedømte tidsskrifter, hvor olaparib i kombination med bevacizumab er sammenlignet direkte med henholdsvis olaparib, bevacizumab eller placebo.

Klinisk spørgsmål 1:

Medicinrådet har ikke fundet fuldtekstartikler, der indeholder en direkte sammenligning mellem olaparib i kombination med bevacizumab og olaparib monoterapi. Derfor skal ansøger søge efter artikler til en indirekte sammenligning. Søgestrengen fremgår nedenfor. Derudover skal ansøger konsultere Det Europæiske Lægemiddelagenturs (EMA) European public assessment reports (EPAR) for både det aktuelle lægemiddel og dets komparator(er).

Søgestreng til PubMed:

Sæt	**Søgetermer**	**Kommentarer**
1	Ovarian Neoplasms[mh]	Termer for population
2	(ovary[ti] OR ovari*[ti]) AND (cancer[ti] OR carcinoma*[ti] OR neoplasm*[ti] OR tumor*[ti] OR tumour*[ti])	
3	Fallopian Tube Neoplasms[mh]	
4	(fallopian tube*[ti] OR tubal[ti] OR oviduct[ti] OR tuba[ti]) AND (cancer[ti] OR carcinoma*[ti] OR neoplasm*[ti] OR tumor*[ti] OR tumour*[ti])	
5	Peritoneal Neoplasms[mh]	
6	(peritoneal[ti] OR peritoneum[ti] OR serous surface papillary[ti] OR extra-ovarian serous[ti] OR primary serous papillary[ti]) AND (cancer[ti] OR carcinoma*[ti] OR neoplasm*[ti] OR tumor*[ti] OR tumour*[ti])	
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	
8	newly diagnosed[tiab]	
9	1L[tiab] OR firstline[tiab] OR first-line[tiab] OR frontline[tiab] OR front-line[tiab] OR primary treatment[tiab] OR primary therapy[tiab]	
10	#7 AND (#8 OR #9)	
11	olaparib[nm] OR olaparib[tiab] OR Lynparza*[tiab] OR Bevacizumab[mh] OR bevacizumab[tiab] OR Avastin*[tiab] OR Mvasi*[tiab] OR HRD[tiab] OR homologous recombination[tiab]	Termer for lægemidler og HRD defekt
12	#10 AND #11	Kombination population og lægemidler
13	Randomized Controlled Trial[pt] OR Controlled Clinical Trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR Clinical Trials as Topic[mh:noexp] OR randomly[tiab] OR trial[ti]	Filter til identifikation af randomiserede forsøg
14	#12 AND #13	
15	Animals[mh] NOT Humans[mh]	Eksklusion af dyr og irrelevante pub.typer
16	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR case report[ti]	
17	Review[pt] OR Systematic Review[pt] OR Meta-Analysis[pt] OR review[ti] OR meta-analys*[ti]	
18	#15 OR #16 OR #17	
19	**#14 NOT #18**	**Resultater til screening - alle kliniske spørgsmål**

Søgestreng til CENTRAL:

Sæt	Søgetermer	Kommentarer
1	[mh "Ovarian Neoplasms"]	Termer for populationen
2	((ovary OR ovari*) AND (cancer OR carcinoma* OR neoplasm* OR tumor* OR tumour*)):ti,kw	
3	[mh "Fallopian Tube Neoplasms"]	
4	((fallopian next tube* OR uterine next tube* OR tubal OR oviduct OR tuba) AND (cancer OR carcinoma* OR neoplasm* OR tumor* OR tumour*)):ti,kw	
5	[mh "Peritoneal Neoplasms"]	
6	((peritoneal OR peritoneum OR serous surface papillary OR extra-ovarian serous OR primary serous papillary) AND (cancer OR carcinoma* OR neoplasm* OR tumor* OR tumour*)):ti,kw	
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	
8	("newly diagnosed"):ti,ab	
9	(1L OR firstline OR first-line OR frontline OR front-line OR "primary treatment" OR "primary therapy"):ti,ab	
10	#7 AND (#8 OR #9)	
11	(olaparib OR Lynparza* OR bevacizumab OR Avastin* OR Mvasi* OR HRD OR "homologous recombination"):ti,ab,kw	Termer for lægemidler og HRD defekt
12	#10 AND #11	Kombination population og lægemidler
13	("conference abstract" OR review):pt OR (abstract OR meeting OR review):ti OR (abstract OR meeting):so	Eksklusion irrelevante pub.typer
14	(clinicaltrials.gov OR trialsearch):so	
15	NCT*:au	
16	#13 OR #14 OR #15	
17	#12 NOT #16	**Resultater til screening - alle kliniske spørgsmål**

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 har fundet følgende fuldtekstartikel/fuldtekstartikler, som indeholder en direkte sammenligning mellem olaparib i kombination med bevacizumab og bevacizumab monoterapi:

- Ray-Coquard I, Pautier P, Pignata S, Pérol D, González-Martín A, Berger R, et al. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. N Engl J Med. 2019;381(25):2416–28.

Det er ikke tilstrækkeligt datagrundlag til en komplet besvarelse af det kliniske spørgsmål, da studiepopulationen ikke svarer til populationen i det kliniske spørgsmål. Patientpopulationen i ovenstående studie indeholder 40 %, der ikke er kandidater til bevacizumab ifølge dansk klinisk praksis, hvorved populationerne for klinisk spørgsmål 2 og 3 i nærværende protokol er blandet i studiet.

Ansøger skal derfor undersøge, om der findes andre fuldtekstartikler, som indeholder de angivne mangler. Søgestrengen fremgår nedenfor.

Ansøger skal på baggrund af artiklerne lave en indirekte sammenligning til at besvare den del af det kliniske spørgsmål, som den direkte sammenligning ikke kan besvare.

Ansøger skal derudover konsultere Det Europæiske Lægemiddelagenturs (EMA) European public assessment reports (EPAR) for både det aktuelle lægemiddel og dets komparator(er).

Søgestreng til PubMed:

Se søgestreng under klinisk spørgsmål 1

Søgestreng til CENTRAL:

Se søgestreng under klinisk spørgsmål 1

Virksomheden 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 3

Medicinrådet har ikke fundet fuldtekstartikler, der indeholder en direkte sammenligning mellem olaparib i kombination med bevacizumab og placebo. Derfor skal ansøger søge efter artikler til en indirekte sammenligning. Søgestrengen fremgår nedenfor. Derudover skal ansøger konsultere Det Europæiske Lægemiddelagenturs (EMA) European public assessment reports (EPAR) for både det aktuelle lægemiddel og dets komparator(er).

Søgestreng til PubMed:

Se søgestreng under klinisk spørgsmål 1

Søgestreng til CENTRAL:

Se søgestreng under klinisk spørgsmål 1

Ansøger skal ekskludere artikler med andre populationer end de, der er specificeret i protokollen, og artikler der ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

Kriterier for litteratursøgning

Ansøger skal søge relevant litteratur i databaserne PubMed og CENTRAL (via Cochrane Library). Ansøger skal dokumentere søgningen for hver af de to databaser, 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 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 ekskludere først 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 (http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx).

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 Databehandling og -analyse

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 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 (jævnfør 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 (jævnfør 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'- 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.

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 vi kan have tiltro til den evidens, vi baserer vurderingen af lægemidlets værdi på.

7 Andre overvejelser

Det ønskes, at ansøger redegør for en mulig strategi til at diagnosticere HRD i dansk klinisk praksis, da diagnosen af HRD er afgørende for at identificere patienter, der potentielt kan modtage olaparib i kombination med bevacizumab til indikationen.

Fagudvalget ønsker en opgørelse af tid til progression på den efterfølgende behandling (PFS2) for at supplere data for PFS og for at opnå et indblik i patienternes forløb efter 1. progression ved behandling med olaparib i kombination med bevacizumab.

Fagudvalget ønsker 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.

8 Relation til behandlingsvejledning

Fagudvalget vil i forbindelse med vurderingen af olaparib i kombination med bevacizumab tage stilling til, hvor det foreløbig kan placeres i Medicinrådets behandlingsvejledning for lægemidler til BRCA-muteret kræft i æggestokkene, æggelederne eller primær kræft i bughinden.

9 Referencer

1. Mosgaard BJ, Pedersen LK, Bjørn SF, Christiansen T, Markauskas A, Lund B, et al. Retningslinier for visitation, diagnostik, behandling og opfølgning af epitelial ovarie-, tuba- og primær peritonealcancer samt borderline tumorer. Kapitel 1: Introduktion. 2016;(5):1–9.
2. NORDCAN - Association of the Nordic Cancer Registries. Kræftstatistik: Nøgetal og figurer. 2017.
3. NORDCAN - Association of the Nordic Cancer Registries. Æggestok, æggeleder mv. 5-års aldersspecifik relativ overlevelse, diagnoseår 2012-2016. 2017.
4. Dansk Gynækologisk Cancer Database. Landsdækkende klinisk database for gynækologisk kræft. National Årsrapport 2017/2018 og 2018/2019. 2019.
5. NORDCAN - Association of the Nordic Cancer Registries. Æggestok, æggeleder mv. Alders-standardiseret relativ overlevelse (2012-2016), alder 0-89. 2017.
6. Bolton KL, Chenevix-Trench G, Goh C, Sadetzki S, Ramus SJ, Karlan BY, et al. Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer. JAMA. 2012;307(4):382–90.
7. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature. 2011;474(7353):609–15.
8. Zhang S, Royer R, Li S, McLaughlin JR, Rosen B, Risch HA, et al. Frequencies of BRCA1 and BRCA2 mutations among 1,342 unselected patients with invasive ovarian cancer. Gynecol Oncol. 2011;121(2):353–7.
9. Huang Y. Association of BRCA1/2 mutations with ovarian cancer prognosis: An updated meta-analysis. Medicine (Baltimore). 2018;97(2):e9380.
10. Hoppe MM, Sundar R, Tan DSP, Jeyasekharan AD. Biomarkers for homologous recombination deficiency in cancer. J Natl Cancer Inst. 2018;110(7):704–13.
11. Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med. 2016;375(22):2154–64.
12. Pellegrino B, Mateo J, Serra V, Balmaña J. Controversies in oncology: are genomic tests quantifying homologous recombination repair deficiency (HRD) useful for treatment decision making? ESMO open. 2019;4(2):e000480.
13. Mirza MR, Coleman RL, González-Martín A, Moore KN, Colombo N, Ray-Coquard I, et al. The forefront of ovarian cancer therapy: update on PARP inhibitors. Ann Oncol. 2020;31(9):1148–59.
14. Mirza MR, Åvall Lundqvist E, Birrer MJ, dePont Christensen R, Nyvang GB, Malander S, et al. Niraparib plus bevacizumab versus niraparib alone for platinum-sensitive recurrent ovarian cancer (NSGO-AVANOVA2/ENGOT-ov24): a randomised, phase 2, superiority trial. Lancet Oncol. 2019;20(10):1409–19.
15. Takaya H, Nakai H, Takamatsu S, Mandai M, Matsumura N. Homologous recombination deficiency status-based classification of high-grade serous ovarian carcinoma. Sci Rep. 2020;10(1):1–8.
16. Charlotte Lautrup, Uffe Birk Jensen, Anders Bojesen, Mads Thomassen, Thomas van Overeem Hansen, Anne-Marie Gerdes, Jan Blaakær, Henrik Roed, Ulla Peen, Karina Dahl Steffensen, Bente Lund, Lotte Nedergaard Thomsen EH. Forslag til national guideline for genetisk udredning af patienter med ovariecancer . 2018. 1-4 sider.
17. MYRIAD ONCOLOGY. MYRIAD myChoice CDx [internet]. [citeret 20. august 2020]. Tilgængelig

fra: https://myriad-oncology.com/mychoice-cdx/

18. Coleman RL, Fleming GF, Brady MF, Swisher EM, Steffensen KD, Friedlander M, et al. Veliparib with first-line chemotherapy and as maintenance therapy in ovarian cancer. N Engl J Med. 2019;381(25):2403–15.

19. European Medicines Agency EMA. EPAR - Assessment report - Lynparza. 2019.

20. Medicinrådet. Medicinrådets behandlingsvejledning vedrørende lægemidler til BRCA-muteret kræft i æggestokkene, ægge-lederne eller primær kræft i bughinden. 2020.

21. O'Connor MJ. Targeting the DNA Damage Response in Cancer. Mol Cell. 2015;60(4):547–60.

22. European Medicines Agency EMA. EPAR - Assessment report - Avastin. 2017.

23. Liu JF, Barry WT, Birrer M, Lee JM, Buckanovich RJ, Fleming GF, et al. Overall survival and updated progression-free survival outcomes in a randomized phase II study of combination cediranib and olaparib versus olaparib in relapsed platinum-sensitive ovarian cancer. Ann Oncol. 2019;30(4):551–7.

24. Mosgaard BJ, Pedersen LK, Bjørn SF, Christiansen T, Markauskas A, Lund B, et al. Retningslinier for visitation, diagnostik, behandling og opfølgning af epitelial ovarie-, tuba- og primær peritonealcancer samt borderline tumorer. Kapitel 3: Kirurgisk behandling af epitheliale ovarietumorer. 2019;(6):1–19.

25. Mosgaard BJ, Pedersen LK, Bjørn SF, Christiansen T, Markauskas A, Lund B, et al. Retningslinier for visitation, diagnostik, behandling og opfølgning af epitelial ovarie-, tuba- og primær peritonealcancer samt borderline tumorer. Kapitel 5: Ikke-kirurgisk behandling af epiteliale tumorer. 2019;(6):1–36.

26. Hanker LC, Loibl S, Burchardi N, Pfisterer J, Meier W, Pujade-Lauraine E, et al. The impact of second to sixth line therapy on survival of relapsed ovarian cancer after primary taxane/platinum-based therapy. Ann Oncol. 2012;23(10):2605–12.

27. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228–47.

28. Paoletti X, Lewsley LA, Daniele G, Cook A, Yanaihara N, Tinker A, et al. Assessment of Progression-Free Survival as a Surrogate End Point of Overall Survival in First-Line Treatment of Ovarian Cancer: A Systematic Review and Meta-analysis. JAMA Netw open. 2020;3(1):e1918939.

29. Sjoquist KM, Lord SJ, Friedlander ML, John Simes R, Marschner IC, Lee CK. Progression-free survival as a surrogate endpoint for overall survival in modern ovarian cancer trials: a meta-analysis. Ther Adv Med Oncol. 2018;10(6):1758835918788500.

30. Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2018;379(26):2495–505.

31. National Institute of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. 2009.

32. Phippen NT, Secord AA, Wolf S, Samsa G, Davidson B, Abernethy AP, et al. Quality of life is significantly associated with survival in women with advanced epithelial ovarian cancer: An ancillary data analysis of the NRG Oncology/Gynecologic Oncology Group (GOG-0218) study. Gynecol Oncol. 2017;147(1):98–103.

33. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European

Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365–76.

34. Greimel E, Bottomley A, Cull A, Waldenstrom A-C, Arraras J, Chauvenet L, et al. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-OV28) in assessing the quality of life of patients with ovarian cancer. Eur J Cancer. 2003;39(10):1402–8.

35. Basen-Engquist K, Bodurka-Bevers D, Fitzgerald MA, Webster K, Cella D, Hu S, et al. Reliability and validity of the functional assessment of cancer therapy-ovarian. J Clin Oncol. 2001;19(6):1809–17.

36. Beaumont J, Yount S, Lalla D, Lubeck D, Derynck M, Karlan B, et al. Validation of the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) Symptom Index (FOSI) in a phase II clinical trial of pertuzumab in patients with advanced ovarian cancer. J Clin Oncol. 2007;25(18_suppl):16021.

37. EuroQol Group. EuroQol - a new facility for the measurement of health-related quality of life. Health Policy. 1990;Dec(16(3)):199–208.

10 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende kræft i æggestokkene

Formand	**Indstillet af**
Trine Jakobi Nøttrup Overlæge, ph.d.	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Jacob Christian Lindegaard Overlæge, dr.med.	Region Midtjylland
Trine Lembrecht Jørgensen Afdelingslæge	Region Syddanmark
Bente Lund Overlæge	Region Nordjylland
Kan ikke udpege en kandidat der opfylder Medicinrådets habilitetskrav	Region Sjælland og Region Hovedstaden
Trine Zeeberg Iversen Afdelingslæge, ph.d.	Dansk Selskab for Klinisk Onkologi
Troels K. Bergmann Overlæge, klinisk lektor, ph.d.	Dansk Selskab for Klinisk Farmakologi
Maria Kaaberbøl Thorberg Farmaceut	Dansk Selskab for Sygehusapoteksledelse
Birthe Lemley Patient/patientrepræsentant	Danske Patienter
Dorte Blou Patient/patientrepræsentant	Danske Patienter

Medicinrådets sekretariat

Medicinrådet
Dampfærgevej 27-29, 3. th.
2100 København Ø
+ 45 70 10 36 00
medicinraadet@medicinraadet.dk

11 Versionslog

Version	**Dato**	**Ændring**
1.0	26.11.2020	Godkendt af Medicinrådet.