Medicinrådet

Baggrund for Medicinrådets anbefaling vedrørende olaparib som mulig standardbehandling til kræft i æggestokkene, æggelederne eller primær kræft i bughinden

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

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

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

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

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

Om anbefalingen

Anbefalingen er Medicinrådets vurdering af, om omkostningerne ved behandling lægemidlet er rimelige i forhold til lægemidlets kliniske værdi.

Lægemidlet vurderes efter Metodehåndbog for Medicinrådets arbejde med at udarbejde fælles regionale vurderinger af nye lægemidlers og nye indikationers kliniske merværdi – version 1. Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	10. april 2019
Ikrafttrædelsesdato	10. april 2019
Dokumentnummer	46509
Versionsnummer	1.0

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 10. april 2019

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Lynparza®
Generisk navn	Olaparib
Firma	AstraZeneca
ATC-kode	L01XX46
Virkningsmekanisme	Olaparib er en selektiv hæmmer af enzymerne poly (adenosine disphosphate [ADP]-ribose) polymerase (PARP) 1/2/3, der deltager i DNA-reparation. Blokering af PARP 1/2/3 i tumorceller, som i forvejen har mange genomiske skader, inducerer celledød.
Administration/dosis	2 tabletter á 150 mg, to gange dagligt.
EMA-indikation	"Lynparza is indicated as 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 or partial) to platinum-based chemotherapy."

2 Medicinrådets anbefaling

Medicinrådet **anbefaler ikke** olaparib som mulig standardbehandling til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende high-grade epitelialt karcinom i æggestokkene, æggelederne eller primær kræft i bughinden og respons på platinbaseret kemoterapi.

Medicinrådet vurderer, at der ikke er et rimeligt forhold mellem lægemidlets kliniske merværdi og omkostningerne ved behandling med olaparib sammenlignet med ingen behandling. Datagrundlaget for den kliniske merværdi ved behandling med olaparib sammenlignet med bevacizumab er utilstrækkeligt.

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

Hvilken klinisk merværdi tilbyder vedligeholdelsesbehandling med olaparib sammenlignet med placebo hos patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende high-grade epitelialt karcinom og respons på platinbaseret kemoterapi?

Hvilken klinisk merværdi tilbyder vedligeholdelsesbehandling med olaparib sammenlignet med bevacizumab hos patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende high-grade epitelialt karcinom og respons på platinbaseret kemoterapi?

3 Formål

Formålet med Baggrund for Medicinrådets anbefaling vedrørende olaparib som mulig standardbehandling til kræft i æggestokkene, æggelederne eller primær kræft i bughinden er at skabe gennemsigtighed om det materiale, der ligger til grund for Medicinrådets anbefaling.

4 Baggrund

Kræft i æggestokkene, herunder kræft i æggelederne og primær kræft i bughinden, er den fjerde hyppigste kræftdødsårsag hos kvinder i Danmark. Der diagnosticeres omkring 550 nye tilfælde pr. år, og omkring 4.600 kvinder lever med diagnosen.

Kræft i æggestokkene er en heterogen gruppe med forskellige histologiske undertyper. Serøst adenokarcinom, herunder undertypen high-grade serøst adenokarcinom (HGSC), er en af de hyppigste undertyper.

Den primære behandling er kirurgisk. Næsten alle patienter, der opereres makroskopisk radikalt, tilbydes efterfølgende adjuverende platinbaseret kombinationskemoterapi. Omkring 60-80 % af patienterne vil opnå komplet eller partielt respons efter 1. linjebehandling med platinbaseret kombinationskemoterapi i form af carboplatin og paclitaxel (6 serier), eventuelt i kombination med bevacizumab, men ca. 80 % af disse patienter vil få tilbagefald inden for 2-3 år efter afsluttet kemoterapi. Patienter med tilbagefald har generelt en dårlig prognose, og formålet med videre behandling er symptomlindring og levetidsforlængelse.

Patienter med recidiv ≥ 6 måneder fra endt kemoterapi, som har haft primær effekt, betragtes som platinsensitive. For disse patienter anbefales der i 2. linjebehandling en platinbaseret kombinationskemoterapi i form af enten carboplatin og paclitaxel eller carboplatin og pegyleret liposomal doxorubicin. Behandlingen afhænger endvidere af patienternes BRCA1/2-mutationsstatus. Patienter uden BRCA1/2-mutation, der ikke har fået bevacizumab i 1. linje, tilbydes bevacizumab i kombination med platinbaseret kombinationskemoterapi i 2. linje, efterfulgt af bevacizumab vedligeholdelsesbehandling, der fortsættes i 15 måneder eller til progression. Bevacizumab gives kun én gang i patientens behandlingsforløb.

Olaparib er godkendt til behandling af patienter med platinsensitiv, recidiverende high-grade epitelialt karcinom i æggestokkene, æggelederne eller primær kræft i bughinden og respons på platinbaseret kemoterapi uafhængig af påvist BRCA1/2-mutation. Denne anbefaling vedrører patienter uden BRCA1/2-mutation. Det vurderes, at der i Danmark er omkring 175 patienter uden BRCA1/2-mutation per år, der vil være kandidater til behandling med olaparib.

4.1 Sagsbehandlingstid og proces for Medicinrådets vurdering

Medicinrådet modtog den foreløbige ansøgning vedrørende olaparib den 19. marts 2018 og den endelige ansøgning (bilag 5) den 25. januar 2019.

Fagudvalgets vurdering af klinisk merværdi blev godkendt af Medicinrådet den 13. marts 2019. Medicinrådet har gennemført vurderingen af olaparib på 10 uger og 5 dage (75 dage).

5 Medicinrådets vurdering af samlet klinisk merværdi

Medicinrådet vurderer, at olaparib til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende high-grade epitelialt karcinom i æggestokkene, æggelederne eller primær kræft i bughinden og respons på platinbaseret kemoterapi giver en **ingen klinisk merværdi** sammenlignet med placebo. Evidensens kvalitet er meget lav.

Medicinrådet vurderer, at olaparib til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende high-grade epitelialt karcinom i æggestokkene, æggelederne eller primær kræft i bughinden og respons på platinbaseret kemoterapi giver en **ikkedokumenterbar klinisk merværdi** sammenlignet med bevacizumab. Evidensens kvalitet er ikke vurderet.

6 Høring

Ansøger har den 20. marts 2019 indsendt et høringssvar, som ikke gav anledning til en ændring af Medicinrådets vurdering af klinisk merværdi. Høringssvaret er vedlagt som bilag 3.

7 Resumé af økonomisk beslutningsgrundlag

Meromkostningerne ved behandling med olaparib sammenlignet med ingen behandling (placebo) til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende high-grade epitelialt karcinom i æggestokkene, æggelederne eller primær kræft i bughinden og respons på platinbaseret kemoterapi er ikke rimelige i forhold til den kliniske merværdi, lægemidlet tilbyder.

Amgros har ikke vurderet forholdet mellem meromkostningerne og den kliniske merværdi for olaparib sammenlignet med bevacizumab, da fagudvalget vedrørende kræft i æggestokkene ikke har fundet det muligt at udføre en meningsfuld sammenligning grundet forskelle mellem de anvendte kliniske studier.

Meromkostningerne i sammenligningen med ingen behandling (placebo) er primært drevet af prisen på olaparib. Amgros har tidligere indgået en aftale med AstraZeneca om indkøb af olaparib til en aftalepris, som er lavere end AIP. Konklusionen er baseret på denne aftalepris.

Amgros' beslutningsgrundlag og Amgros' sundhedsøkonomiske analyse er vedlagt som bilag 1 og 2.

8 Overvejelser omkring alvorlighed/forsigtighed

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

9 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende kræft i æggestokkene

Formand	***Indstillet af***
Jørn Herrstedt *Forskningsleder, professor, overlæge, dr.med.*	Lægevidenskabelige Selskaber
Medlemmer	***Udpeget af***
Kan ikke udpege	Region Nordjylland, Region Syddanmark, Region Sjælland og Region Hovedstaden
Mette Hæe *Afdelingslæge*	Region Midtjylland
Gabor Liposits *Overlæge*	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
Ekspert	
Bente Lund *Overlæge*	

Medicinrådets sekretariat

Medicinrådet Dampfærgevej 27-29, 3. 2100 København Ø + 45 70 10 36 00 medicinraadet@medicinraadet.dk
Sekretariatets arbejdsgruppe Ditte Marie Irwin-Clugston (projekt- og metodeansvarlig) Anne Sofie Gram (projektdeltager) Tina Klitmøller Sørensen Agander (projektdeltager) Agla Fridriksdottir (projektdeltager) Ilse Linde (fagudvalgskoordinator) Kirsten Holdt Henningsen (teamleder)

10 Versionslog

Version	Dato	Ændring
1.0	10.04.2019	Godkendt af Medicinrådet.

11 Bilag

Bilagsliste:

- Amgros' beslutningsgrundlag
- Amgros' sundhedsøkonomiske analyse
- Høringssvar fra ansøger
- Vurdering af den kliniske merværdi af olaparib til behandling af kræft i æggestokkene, æggelederne eller primær kræft i bughinden - vers. 1.0
- Ansøgers endelige ansøgning
- Protokol for vurdering af den kliniske merværdi af olaparib til behandling af kræft i æggestokkene, æggelederne eller primær kræft i bughinden - vers. 1.0

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Beslutningsgrundlag til Medicinrådet

Dette dokument er Amgros' vurdering af olaparib (Lynparza) til vedligeholdelsesbehandling af voksne patienter med platinsensitiv, recidiverende high-grade serøst adenokarcinom (HGSC) i æggestokkene, herunder kræft i æggelederne og primær kræft i bughinden. Vurderingen er baseret på lægemidlets gennemsnitlige inkrementelle omkostninger, baseret på SAIP (sygehusapotekets indkøbspris) sammenholdt med Medicinrådets vurdering af den kliniske merværdi.

Dato for Medicinrådsbeslutning	10-04-2019
Firma	AstraZeneca (ansøger)
Lægemiddel	Olaparib (Lynparza)
Indikation	Monoterapi til vedligeholdelsesbehandling af voksne patienter med platinsensitiv, recidiverende high-grade serøst adenokarcinom (HGSC) i æggestokkene, herunder kræft i æggelederne og primær kræft i bughinden.

Amgros' vurdering

- Fagudvalget vedrørende kræft i æggestokkene har ikke fundet det muligt at udføre en meningsfuld sammenligning grundet forskelle mellem de anvendte kliniske studier. Derfor har Amgros **ikke** vurderet forholdet mellem meromkostningerne og den kliniske merværdi for olaparib (Lynparza) sammenlignet med bevacizumab (P1)
- Amgros vurderer, at der **ikke** er et rimeligt forholdet mellem meromkostningerne og den kliniske merværdi for olaparib (Lynparza) som mulig standardbehandling ved sammenligning med placebo (P2)

Overordnet konklusion

Medicinrådet har vurderet, at olaparib (Lynparza) sammenlignet med placebo giver **ingen klinisk merværdi.**

Behandling med olaparib (lynparza) er forbundet med meget høje meromkostninger sammenlignet med placebo. Amgros vurderer, at der **ikke** er rimeligt forhold mellem den kliniske merværdi olaparib (Lynparza), sammenlignet med behandling med komparator. Meromkostninger drives af prisen på olaparib (lynparza).

Konklusion for populationen

Tabel 1 Merværdi, meromkostninger og Amgros' vurdering (baseret på SAIP)

Population	Komparator	Merværdi	Usikkerhed for klinisk merværdi	Amgros' konklusion om forholdet mellem meromkostninger og merværdi
Patienter med platinsensitiv, recidiverende high-grade serøst adenokarcinom (HGSC) i æggestokkene, herunder kræft i æggelederne og primær kræft i bughinden	Placebo	Ingen klinisk merværdi	Meget lav evidenskvalitet	Ikke rimeligt

Supplerende informationer (resumé af resultaterne fra afrapporteringen)

Konklusion på omkostnings- og budgetkonsekvensanalyserne

Resultatet fra Amgros' afrapportering på omkostningsanalyserne er gengivet i det følgende. For uddybende gennemgang af analyse og resultater henvises til afrapporteringen på http://www.amgros.dk.

Amgros' afrapportering - Inkrementelle omkostninger per patient

Behandling med olaparib (Lynparza) er forbundet med meget høje meromkostninger sammenlignet med placebo.

I tabel 2 ses de inkrementelle omkostninger for olaparib (Lynparza) og placebo.

Amgros' hovedanalyse resulterer i gennemsnitlige meromkostninger per patient for olaparib (Lynparza) sammenlignet med placebo på ca. [redacted].

Hvis analysen udføres på baggrund af AIP, bliver lægemiddelomkostningerne for olaparib (Lynparza) ca. 889.000, mens de total inkrementelle omkostninger bliver ca. 968.000 DKK per patient.

Tabel 2: Resultatet af Amgros' hovedanalyse for olaparib (Lynparza) sammenlignet med placebo, DKK.

	Olaparib (Lynparza)	Placebo	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	74.339	6.632	67.707
Patientomkostninger	14.627	4.026	10.600
Totale omkostninger	[redacted]	[redacted]	[redacted]

Amgros' afrapportering – Budgetkonsekvenser

Amgros vurderer at anbefaling af olaparib (Lynparza) som mulig standardbehandling, vil resultere i budgetkonsekvenser på ca. [redacted] per år efter første års anbefaling.

Hvis analysen udføres med AIP bliver budgetkonsekvenserne ca. 73 mio. per år efterfølgende første år.

OLAPARIB (LYNPARZA)

KRÆFT I ÆGGESTOKKENE, ÆGGELEDERNE ELLER PRIMÆR KRÆFT I BUGHINDEN

AMGROS

AMGROS 26. marts 2019

OPSUMMERING

Baggrund

Olaparib (Lynparza) er som monoterapi indiceret til vedligeholdelsesbehandling af voksne patienter med platin-sensitiv, recidiverende high-grade serøst adenokarcinom (HGSC) i æggestokkene, herunder kræft i æggeledere og primær kræft i bughinden. Omkring 175 nye patienter per år kandiderer årligt til behandling af den ansøgte indikation i Danmark. Amgros' vurdering tager udgangspunkt i dokumentation indsendt af AstraZeneca.

Analyse

I analysen estimeres de inkrementelle omkostninger forbundet med behandling med Olaparib (Lynparza) sammenlignet med bevacizumab (P1) og placebo (P2) som vedligeholdelsesbehandling af patienter uden BRCA1/2-mutation.

Inkrementelle omkostninger og budgetkonsekvenser

Amgros har vurderet de gennemsnitlige meromkostninger per patient ved brug af Olaparib (Lynparza) sammenlignet med placebo. De inkrementelle omkostninger er angivet i SAIP.

I scenariet Amgros mener er mest sandsynligt, er de gennemsnitlige meromkostninger for Olaparib (Lynparza) ca. [redacted] sammenlignet med placebo. Hvis analysen udføres med AIP bliver de inkrementelle omkostninger til sammenligning 968.000 DKK per patient.

Amgros vurderer, at budgetkonsekvenserne for regionerne per år ved anbefaling af Olaparib (Lynparza) som standardbehandling vil være ca. [redacted]. Hvis analysen udføres med AIP, er budgetkonsekvenser ca. 73 mio. DKK om året.

Konklusion

Behandling med Olaparib (Lynparza) er forbundet med betydelige meromkostninger sammenlignet med behandling med placebo. De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne for Olaparib (Lynparza).

Hvis efterfølgende kemoterapi inkluderes i analysen, reduceres de inkrementelle omkostninger, men resulterer dog fortsat i betydelige meromkostninger.

Liste over forkortelser

AIP	Apotekernes indkøbspris
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
HGSC	High-Grade serøst adenokarcinom
BRCA	Breast cancer
gBRCAmut	Patienter med BRCA-mutation
non-gBRCAmut	Patienter uden BRCA-mutation
SAIP	Sygehusapotekernes indkøbspriser

INDHOLD

LOG

Ansøgning	
Lægemiddelfirma:	AstraZeneca
Handelsnavn:	Lynparza
Generisk navn:	Olaparib
Indikation:	Monoterapi til vedligeholdelsesbehandling af voksne patienter med platinsensitiv, recidiverende high-grade serøst adenokarcinom (HGSC) i æggestokkene, herunder kræft i æggelederne og primær kræft i bughinden.
ATC-kode:	L01XX46

Proces	
Ansøgning modtaget hos Amgros:	31-01-2019
Endelig rapport færdig:	06-03-2019
Sagsbehandlingstid fra endelig ansøgning:	34 dage
Arbejdsgruppe:	**Pernille Winther Johansen** Line Brøns Jensen Lianna Geertsen Louise Greve Dal Mark Friborg

Priser
Denne rapport bygger på analyser udført på baggrund sygehusapotekernes indkøbspriser (SAIP). Enkelte steder er analysens resultat yderligere angivet på baggrund af listepriser (AIP).

1 BAGGRUND

Olaparib (Lynparza) er indiceret som vedligeholdelsesbehandling til voksne patienter med platinsensitiv, recidiverende high-grade serøst adenokarcinom (HGSC) i æggestokkene, herunder kræft i æggelederne og primær kræft i bughinden. AstraZenica (herefter omtalt som ansøger) er markedsføringstilladelsesindehaver af olaparib (Lynparza) og har den 31.01.2019 indsendt en ansøgning til Medicinrådet om anbefaling af olaparib (Lynparza) som standardbehandling på danske hospitaler af den nævnte indikation. Som et led i denne ansøgning vurderer Amgros, på vegne af Medicinrådet de økonomiske analyser, ansøger har sendt som en del af den samlede ansøgning til Medicinrådet. Denne rapport er Amgros' vurdering af de fremsendte økonomiske analyser (herefter omtalt som analysen).

1.1 Problemstilling

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger per patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af olaparib (Lynparza) som standardbehandling på danske hospitaler af den nævnte indikation. I analyserne sammenlignes behandling med olaparib (Lynparza) med behandling med bevacizumab og placebo.

1.2 Patientpopulation

Kræft i æggestokkene, herunder kræft i æggelederne og primær kræft i bughinden, opstår i epitelceller. Fremadrettet bliver de samlet kaldt for kræft i æggestokkene. Kræft i æggestokkene er en heterogen gruppe med forskellige histologiske undertyper. Dette gør subklassificering og dermed behandlingsvalg til en kompleks proces, der kræver tæt samarbejde mellem gynækologer, patologer, billeddiagnostikere og kliniske onkologer (1,2). Kræft i æggestokkene er den 4. hyppigste kræftdødsårsag hos kvinder i Danmark. Medianalder for sygdomsdebut er 63 år og 80 % af patienterne er postmenopausale (2). Der diagnosticeres omkring 550 nye tilfælde pr. år, og omkring 4600 kvinder lever med diagnosen i Danmark (3). Kræft i æggestokkene har den højeste dødelighed blandt de gynækologiske kræftsygdomme, dels fordi kræften oftest bliver opdaget i stadium III-IV på grund af uspecifikke symptomer, hvor spredning udover æggestokkene allerede har fundet sted, men også på grund af høj frekvens af recidivudvikling (ca. 80 % af patienterne) (2). Overlevelsen er bl.a. afhængig af sygdomsstadiet på diagnosepunktet. Ifølge Dansk Gynækologisk Cancer Database (DGCD) ligger 5-års overlevelsen for patienter med kræft i æggestokkene i stadie I, II, III eller IV på henholdsvis 87 %, 70 %, 30 % og 15 % (tal fra 2005-2016) (2).

Årsagen til kræft i æggestokkene er ikke kendt, men en række risikofaktorer har været beskrevet. Antal fødsler og brug af p-piller spiller en væsentlig rolle i livstidsrisikoen for at udvikle kræft i æggestokkene (1). Desuden menes ca. 30 % af HGSC-tilfældene at være genetisk betinget, med breast cancer (BRCA) 1 eller 2 genmutationer (arvelige eller somatiske) som de mest kendte (2).

1.3 Nuværende behandling

Det overordnede mål med behandling af kræft i æggestokkene er at forlænge overlevelsen og øge livskvaliteten. Den primære behandling er kirurgisk, hvor målet er at få fjernet alt synligt kræftvæv (makroskopisk radikal operation) samt korrekt stadieinddeling (2). Næsten alle patienter, der opereres makroskopisk radikalt, tilbydes efterfølgende adjuverende platinbaseret kombinationskemoterapi i form af carboplatin og paclitaxel (6 serier). Patienter med efterladt makroskopisk tumorvæv (og alle stadium IV-patienter) tilbydes samme slags kemoterapi i kombination med bevacizumab efter operation (se nedenfor) (4). Omkring 60-80 % af patienterne vil opnå komplet eller partielt respons efter 1. linjebehandling, men ca. 80 % af disse patienter vil få tilbagefald inden for 2-3 år efter afsluttet kemoterapi (2). Patienter med tilbagefald har generelt en dårlig prognose, og formålet med videre behandling er symptomlindring og levetidsforlængelse. Her er en af de vigtigste prognostiske faktorer det platinfrie interval, det vil sige tidsrummet fra afslutning af platinbaseret kombinationskemoterapi til recidiv. Dette tidsinterval er afgørende for valg af efterfølgende behandling (4). Patienter, der primært blev makroskopisk radikalt opereret, vil også blive vurderet med henblik på mulighed for ny operation.

Patienter med recidiv ≥ 6 måneder fra endt kemoterapi, som har haft primær effekt, betragtes som platinsensitive. For disse patienter anbefales der i 2. linjebehandling en platinbaseret kombinationskemoterapi i form af enten carboplatin og paclitaxel eller carboplatin og pegyleret liposomal doxorubicin. Behandlingen afhænger endvidere af patienternes BRCA1/2 mutationsstatus:

Patienter med BRCA 1/2-mutaion (arvelige eller somatiske)

Til patienter med mutation i BRCA1/2 og platinsensitivt recidiv tilbydes vedligeholdelsesbehandling med polymerase (PARP)-hæmmeren olaparib, såfremt de har respons på 2. linje platinbaseret kombinationskemoterapi (4).

Patienter uden BRCA 1/2-mutation

Størstedelen af patienterne, der ikke får bevacizumab i 1. linjebehandling, tilbydes bevacizumab i kombination med ovenstående platinbaserede kombinationskemoterapi i 2.linjebehandling, efterfulgt af bevacizumab vedligeholdelsesbehandling der fortsættes i alt 15 måneder eller til progression. Bevacizumab gives kun en gang i patientens behandlingsforløb (4).
Hvis patienten oplever platinsensitivt tilbagefald efter 2. linjebehandling, introduceres en ny linje platinbaseret kemoterapi. Hvis patienten ikke har fået bevacizumab tidligere, kan det tilbydes som beskrevet ovenfor. Nuværende behandlingsalgoritme efter 1. linjebehandling for patienter med platinsensitiv, recidiverende kræft i æggestokkene er opsummeret i tabel 1 nedenfor.

Tabel 1: Behandlingsalgoritme for patienter med platinsensitiv, recidiverende HGSC i æggestokkene efter 1.linjebehandling.

	Patienter med BRCA1/2-mutation	Patienter uden BRCA1/2 mutation	
2. linjebehandling*	Platinbaseret kombinationskemoterapi efterfulgt af olaparib vedligeholdelsesbehandling	Platinbaseret kombinationskemoterapi i kombination med bevacizumab efterfulgt af bevacizumab vedligeholdelsesbehandling	Platinbaseret kombinationsterapi
Efterfølgende behandlingslinjer**	Ny linje platinbaseret kemoterapi		

*1. linjebehandling er typisk carboplatin og paclitaxel (6 serier), eventuelt i kombination med bevacizumab (patienter med efterladt makroskopisk tumorvæv og/eller stadium IV sygdom).
**Patienter kan få bevacizumab i forbindelse med deres platinbaseret kombinationskemoterapi, hvis de ikke har modtaget den før. Beslutningen er baseret på en individuel vurdering i samarbejde med patienten. Bevacizumab kan kun gives en gang.

1.3 Behandling med olaparib (Lynparza®)

Indikation

Olaparib (Lynparza) er indiceret som monoterapi til vedligeholdelsesbehandling af voksne patienter med platinsensitiv, recidiverende high-grade serøst adenokarcinom (HGSC) i æggestokkene, herunder kræft i æggelederne og primær kræft i bughinden.

Olaparib blev godkendt af det Europæiske Lægemiddelagentur (*E*MA) i 2014 som vedligeholdelsesbehandling til patienter med BRCA1/2-mutation og recidiverende HGSC i æggestokkene som responderer på platinbaseret kemoterapi. Koordineringsrådet for ibrugtagning af sygehusmedicin (KRIS) godkendte den 11. juni 2015 olaparib som standardbehandling til patienter dækket af den oprindelige EMA-indikation.

Platinsensitivitet vurderes at være forbundet med PARP-hæmmersensitivitet pga. høj prævalens af forandringer/mutationer i DNA-reparationsmekanismer i platinfølsom kræft i æggestokkene. På baggrund af dette har ansøger søgt EMA om udvidelse af indikationen til at dække platinsensitive patienter med high-grade epitelial kræft i æggestokkene, herunder æggelederne og primær kræft i bughinden, *uafhængigt af BRCA-mutationsstatus og histologisk undertype*. Dermed tager Medicinrådets protokol kun udgangspunkt i den udvidede patientpopulation, dvs. patienter uden BRCA1/2-mutation.

Virkningsmekanisme

Olaparib (Lynparza) er en selektiv hæmmer af PARP 1/2/3. PARP 1/2/3 er cellekerneproteiner, der detekterer DNA-skader og fremmer deres reparation. Tumorceller har tit defekter i deres DNA-reparationsmekanismer, såsom BRCA-mutationer eller defekt homolog rekombination (*homologous recombination deficiency* (HRD)), hvilket resulterer i genomisk ustabilitet og akkumulering af mutationer. Rationalet er, at den celledræbende effekt af PARP-inhibition er særlig udtalt hos patienter med BRCA1/2 mutation eller positiv HRD. Celledøden sker primært i tumorcellerne, da normale celler ikke har samme mængder af genomiske skader som tumorceller (5).

Dosering
Indikationsudvidelsen medfører også en ændring i administrationsformen. Olaparib (Lynparza) er tidligere blevet givet i kapselform (50 mg, 8 kapsler ad gangen, 2 gange dagligt). Med indikationsudvidelsen ændres dette til tabletform (150 mg, 2 tabletter ad gangen, 2 gange dagligt) indtil progression.

1.3.1 Komparator

Medicinrådet har defineret bevacizumab og placebo som komparatorer for hhv. P1 og P2, se tabel 2.

Tabel 2: Definerede populationer og komparatorer.

Population	Komparator
P1: Patienter uden BRCA1/2-mutation og med recidiverende HGSC i æggestokkene, herunder æggeleder eller primær kræft i bughinden, som vurderes at være kandidater til bevacizumab. Patienterne skal være platinsensitive, dvs. responderet (komplet eller partiel respons) på platinbaseret kemoterapi.	Bevacizumab
P2: Patienter uden BRCA1/2-mutation og med recidiverende HGSC i æggestokkene, herunder æggeleder eller primær kræft i bughinden, som vurderes at være kandidater til bevacizumab. Patienterne skal være platinsensitive, dvs. responderet (komplet eller partiel respons) på platinbaseret kemoterapi.	Placebo

1.4 Medicinrådets kliniske spørgsmål

Medicinrådet har vurderet den kliniske merværdi af olaparib (Lynparza) som vedligeholdelsesbehandling for følgende populationer:

- **P1:** Hvilken klinisk merværdi tilbyder vedligeholdelsesbehandling med olaparib (Lynparza) sammenlignet med bevacizumab hos patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende high-grade epitelialt karcinom og respons på platinbaseret kemoterapi?
- **P2:** Hvilken klinisk merværdi tilbyder vedligeholdelsesbehandling med olaparib (Lynparza) sammenlignet med placebo hos patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende high-grade epitelialt karcinom og respons på platinbaseret kemoterapi?

2 VURDERING AF INDSENDT ØKONOMISK ANALYSE

I analysen af inkrementelle omkostninger per patient sammenlignes behandling med olaparib (Lynparza) med behandling med bevacizumab og placebo. Analysen inkluderer omkostninger til lægemidler, monitorering, administration, patienttid, transport og behandlingsrelaterede bivirkninger.

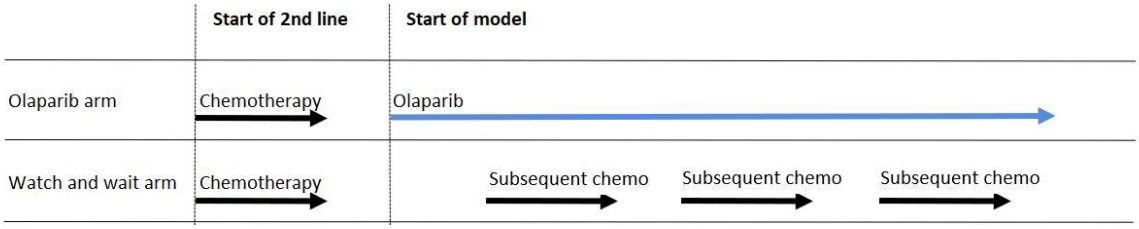
Ansøger har indsendt en analyse der sammenligner olaparib (Lynparza) med både placebo og bevacizumab. Sammenligningen med bevacizumab er lavet på baggrund af data fra to kliniske studier. Studierne bygger på forskellige grundlag, der ikke findes sammenlignelige af Medicinrådet fagudvalg vedrørende kræft i æggestokkene. Et af argumenterne til at sammenligningen ikke findes meningsfuld er forskel i opgørelsen af patienter. I studiet for bevacizumab (OCEANS) er der ikke lavet en opgørelse af patienternes BRCA1/2-mutation, hvilket er tilfældet i studiet for olaparib (Lynparza) (Studie 19) der inddeler patienterne i to kohorter. På baggrund af dette finder Amgros ikke, at sammenligningen mellem olaparib (Lynparza) og bevacizumab kan anvendes til at estimere de inkrementelle omkostninger ved de to behandlinger og sammenligningen vil derfor ikke blive præsentereret.

2.1 Model, metode og forudsætninger

2.1.1 Modelbeskrivelse

Ansøgers analyse har til formål at estimere de inkremenetelle omkostninger ved 2. linjebehandling af ovariecancer. Behandling med olaparib (Lynparza) initieres efter en behandlingsperiode med kemoterapi (seks cyklusser) og definerer modellens startpunkt.

Efterfølgende behandling med kemoterapi antages at være forskellig mellem behandlingsarmene, da der ikke gives kemoterapi i olaparib (Lynparza) armen, hvilket er tilfældet for placeboarmen. Figur 1 viser modellens struktur.



Figur 1: Beskrivelse af modelstrukturen i omkostningsanalysen.

Ansøger har baseret behandlingslængden for olaparib (Lynparza) på gennemsnitlig tid til behandlingsophør. Det argumenteres at progressionsfri overlevelse (PFS) også ville være mulig til at estimere behandlingslængden, men da den gennemsnitlige tid til behandlingsophør er længere, benyttes denne. Tiden patienten befinder sig i PFS for olaparib (Lynparza) er 13,3 måneder, mens gennemsnitlig tid til behandlingsophør er estimeret til at være 22,3 måneder.
For placebo er gennemsnitlig PFS 6,2 måneder mens gennemsnitlig tid til behandlingsophør er 5,7 måneder. Da placebo ikke er forbundet med nogle behandlingsomkostninger, er det af mindre vigtighed hvor lang den gennemsnitlige behandlingstid estimeres at være. I ansøgers hovedanalyse estimeres gennemsnitlig behandlingslængde at være identisk med gennemsnitlig tid til behandlingsophør.

Amgros' vurdering

Ansøger har valgt at inkludere efterfølgende kemoterapi i deres analyse. Dette findes ikke relevant, da komparator i Medicinrådets protokol for olaparib (Lynparza) er defineret som placebo. Ved at inkludere kemoterapi inkluderes en ekstra linje behandling til analysen for placeboarmen.

Amgros vælger at ekskludere efterfølgende kemoterapi fra ansøgers analyse og præsentere dette som Amgros' hovedanalyse. Modellens andre valg accepteres.

2.1.2 Analyseperspektiv

Ansøger har indsendt en omkostningsanalyse med et begrænset samfundsperspektiv. Analysen har en tidshorisont på 2 år. Dette er valgt, da ansøger argumenterer, at den gennemsnitlige behandlingslængde med olaparib (Lynparza) og komparatorer ligger inden for denne tidshorisont. Omkostninger der ligger efter det første år, er diskonteret med en rate på 4 %.

Amgros' vurdering

Analysens begrænsede samfundsperspektiv og diskonteringsrate er i tråd med Amgros' retningslinjer og accepteres.

2.1.3 Omkostninger

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

Lægemiddelomkostninger

Ansøger har inkluderet omkostninger til lægemidler. Anvendte doser er hentet i de respektive produkters SPC'er og priserne er fra Amgros, se tabel 3.

Tabel 3: Anvendte lægemiddelpriser, SAIP.

Lægemiddel	Styrke	Mg/dosis	Pakningsstørrelse	Pris [DKK]	Kilde
Olaparib (Lynparza)	150 mg	600	56 stk.	[redacted]	Amgros

Ansøgers analyse inkluderer udover omkostninger til intervention og komparator også omkostninger til kemoterapi, se tabel 4. Doxorubicin er doseret efter kropsoverfladeareal (BSA) og ansøger har antaget, at den gennemsnitligt er på 1,75 m^2 i analysen.

Tabel 4: Lægemiddelpriser for kemoterapi, SAIP.

	Styrke [mg/ml]	Pakningsstørrelse [ml]	Dosis [mg]	Pris [DKK]	Kilde
Doxorubicin	2	10	30/m^2	[redacted]	Amgros
Carboplastin	10	15	700	[redacted]	Amgros
	10	45	700	[redacted]	Amgros

Amgros' vurdering

Amgros ekskluderer omkostninger til efterfølgende kemoterapi i Amgros' hovedanalyse. Ansøgers tilgang accepteres ellers.

Hospitalsomkostninger

Da olaparib (Lynparza) administreres oralt, har ansøger ikke inkluderet nogle administrationsomkostninger. For kemoterapi har ansøger inkluderet omkostninger til administration af lægemidlerne. Det er gjort i form af DRG-takster, se tabel 5. Ansøger antager at taksten for lægebesøg og cancer add-on dækker 90 minutter og derudover er en takst for 50 % af en sygeplejerske omkostning blevet tilføjet for de resterende 60 minutter.

Tabel 5: Omkostninger til lægemiddeladministration.

	Enhedsomkostning [DKK]	Kode	Kilde
Lægebesøg	672	BG50A	Ambulante DRG-takser 2017
Cancer add-on	1.219	DG30L	Ambulante DRG-takser 2017
Tillæg per time	262	Timeomkostning (sygeplejerske)	Amgros værdisætning af enheds-omkostninger

Omkostningen per administration afhænger af en række antagelser, som ansøger har lavet for hver behandling.

Behandling med kemoterapi inkluderer 60 minutter for doxorubicin og 60 minutter for carboplatin, hvorved den totale tid for kemoterapi antages at være 120 minutter af ansøger. Ansøgers antagelser kan ses i tabel 6.

Tabel 6: Ansøgers antagelser vedrørende kemoterapi.

	Administrationstid	Enhedspris	Administration/ måned	Administrationsom-kostning/ måned
Kemoterapi	120	2.153	1	3.264

Ansøger har inkluderet omkostninger til monitorering af lægemidlerne hvor der er inkluderet omkostninger til lægebesøg, Sygeplejerske og forskellige scanninger.

Amgros' vurdering

Ansøgers tilgang accepteres, men omkostninger til efterfølgende kemoterapi ekskluderes fra Amgros' hovedanalyse.

Omkostninger til bivirkninger

Omkostninger til behandlingsrelaterede bivirkninger er inkluderet i ansøgers analyse. Ansøger har inkluderet omkostningen for bivirkninger ved behandlingsstart, da det argumenteres, at bivirkninger forekommer oftere ved behandlingsstart, se tabel 7.
Ansøgers model benytter sandsynligheder for bivirkning af grad 3 eller mere. For olaparib (Lynparza) og placebo har ansøger benyttet de rapporterede bivirkningsrater for hele patientpopulationen (både BRCA muterede og ikke-muterede patienter) fra et fase to studie (7). Ansøger argumenterer, at dette er repræsentativt da forskellen mellem BRCA-muterede patienter og den overordnede patientpopulation kun varierede i mindre grad.
Ressourcerne brugt i forbindelse med de forskellige bivirkninger har ansøger baseret på DRG/DAGS-takster. Ansøger har i forbindelse med ressourceforbruget ved bivirkninger antaget, at de lægemidler, der benyttes i forbindelse med bivirkninger, ikke udgør nogen stor omkostning og har derfor valgt at ekskludere dem.

Tabel 7: Rapporterede bivirkningsfrekvenser ved behandling med olaparib (Lynparza) og placebo.

	Olaparib [%]	Placebo [%]
Træthed	7	3
Anæmi	5	<1
Neutropeni	4	<1

Amgros' vurdering

Amgros finder ansøgers tilgang acceptabel.

Patientomkostninger

Ansøger har valgt at inkludere omkostninger til patienttid. Dette er gjort på baggrund af lægemiddelmonitorerings besøg på hospitalet og inkluderer den effektive tid på hospitalet, ventetid og transporttid. Ansøgers estimerede patienttid kan ses i tabel 8.

Tabel 8: Ansøgers estimat af effektiv patienttid.

	Patienttid [minutter]
Lægebesøg	20
Sygeplejerskebesøg	20
CT-scanning	30
Vaginal ultralyd	30
Abdominal /pelvis MRI	30
Patient transporttid	90

Lægebesøg, sygeplejerskebesøg og vaginale ultralydsundersøgelser antages af ansøger at ske ved samme besøg i de tilfælde hvor det er muligt. CT-scanninger og MRI af abdomen og pelvis antages altid at kræve individuelle besøg. I tabel 9 er ansøgers estimerede patientomkostninger per måned vist.

Tabel 9: Ansøgers estimerede patientomkostninger per måned.

	Olaparib (Lynparza)	Placebo	Kemoterapi
Antal besøg per måned	1,33	0,66	1,66
Patienttid, besøg [timer]	0,93	0,49	1,10
Patienttid, transport [timer]	2,00	0,99	2,49
Patienttid, omkostning [DKK]	535	270	1.021
Transportomkostning [DKK]	133	66	166
Patientomkostning per måned [DKK]	**668**	**336**	**1.187**

Amgros' vurdering

Amgros ekskluderer omkostninger i forbindelse med kemoterapi fra Amgros' hovedanalysen.

2.2 Følsomhedsanalyser

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

- Diskonteringsrate 3 % og 5 %
- Lægemiddelpris for Olaparib (Lynparza) +/- 20 %
- Lægemiddelpris for kemoterapi +/- 20 %
- Monitoreringsomkostninger +/- 20 %
- Administrationsomkostninger +/-20 %

- Patienttid og transportomkostninger +/- 20 %
- Omkostninger til bivirkninger +/- 20 %

Amgros' vurdering

Da ansøger har inkluderet efterfølgende kemoterapi i alle følsomhedsanalyser, vælger Amgros derfor ikke at præsentere disse. Det skal dog nævnes, at det eneste parameter der har større indflydelse på resultaterne, er den pris olaparib (Lynparza) indkøbes til.

3 RESULTATER

3.2 Ansøgers hovedanalyse

Resultaterne fra ansøgers hovedanalyse præsenteres i tabel 10.

Ansøger estimerer i analysen de inkrementelle omkostninger per patient for olaparib (Lynparza) sammenlignet med placebo til at være ca. [redacted].

Tabel 10: Resultatet af ansøgers hovedanalyse hvor efterfølgende kemoterapi inkluderes, DKK.

	Olaparib (Lynparza)	Placebo	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	73.061	108.440	-35.379
Patientomkostninger	14.372	20.097	-5.724
Totale omkostninger	[redacted]	[redacted]	[redacted]

Amgros' vurdering

Amgros accepterer de antagelser der ligger til grund for ansøgers hovedanalyse, kun efterfølgende kemoterapi findes ikke i tråd med det kliniske spørgsmål. Ansøger har indsendt en scenarieanalyse hvor efterfølgende kemoterapi er ekskluderet, men bygger ellers på samme antagelse som i ansøgers hovedanalyse. Denne scenarieanalyse vil blive anvendt som Amgros' hovedanalyse.

3.1 Amgros' hovedanalyse

Amgros hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse, med undtagelse af, at Amgros ekskluderer af efterfølgende kemoterapi fra Amgros' hovedanalyse.
Resultaterne fra Amgros' hovedanalyse præsenteres i tabel 11.

Amgros' hovedanalyse resulterer i gennemsnitlige meromkostninger per patient for olaparib (Lynparza) sammenlignet med placebo på ca. [redacted].

Hvis analysen udføres på baggrund af AIP, bliver lægemiddelomkostningerne for olaparib (Lynparza) ca. 889.000 DKK, mens de total inkrementelle omkostninger bliver ca. 968.00 DKK per patient.

Tabel 11: Resultatet af Amgros' hovedanalyse ved sammenligning med placebo, DKK.

	Olaparib (Lynparza)	Placebo	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	74.339	6.632	67.707
Patientomkostninger	14.627	4.026	10.600
Totale omkostninger	[redacted]	[redacted]	[redacted]

4 BUDGETKONSEKVENSER

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

- Olaparib (Lynparza) bliver anbefalet som standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler
- Olaparib (Lynparza) bliver ikke anbefalet som standardbehandling

Budgetkonsekvenserne bliver differencen mellem budgetkonsekvenserne i de to scenarier.

4.1 Ansøgers estimater

4.1.1 Patientpopulation og markedsandel

Tabel 12 viser ansøgers estimat af antal patienter årligt. Ansøger har estimeret budgetkonsekvenserne samlet for placebo og bevacizumab.

Tabel 12: Ansøgers estimat af antal nye patienter per år.

	Anbefales som standardbehandling						Anbefales ikke som standardbehandling				
	År 1	År 2	År 3	År 4	År 5		År 1	År 2	År 3	År 4	År 5
Olaparib (Lynparza)	80	138	151	145	71		2	5	5	5	5
Placebo	103	109	92	93	147		173	216	212	213	204
Bevacizumab	23	13	13	13	27		31	39	38	38	37

Amgros' vurdering af estimeret antal patienter

Da Amgros og Medicinrådets fagudvalg som tidligere nævnt, ikke finder at sammenligning mellem olaparib (Lynparza) og bevacizumab kan laves på det datagrundlag ansøger har indsendt, vil Amgros udføre egen budgetkonsekvens analyse, hvor omkostningerne ved bevacizumab ikke medtages i analysen.

Ansøger har derudover også antaget, at der vil være mellem 71 og 151 patienter om året, der ved anbefaling vil modtage olaparib (Lynparza®). I Medicinrådet protokol er det angivet, at der er en forventning om 175 patienter per år vil være egent til behandling med olaparib (Lynparza) til den pågældende indikation. I ansøgers analyse er det antaget at 15 % af patienterne modtager bevacizumab hvis ikke olaparib (Lynparza) godkendes, på baggrund heraf reduceres patientantallet med 15 %. Det resterende 85 % af patienterne antages at modtage placebo eller olaparib (Lynparza).

På baggrund af dette udfører Amgros egen budgetkonsekvensanalyse, hvor bevacizumab ekskluderes fra analysen og patientantallet ændres til 149 patienter per år.

4.1.2 Estimat af budgetkonsekvenser

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som der er inkluderet i omkostningsanalysen.
Med de indlagte antagelser estimerer ansøger, at anvendelse af olaparib (Lynparza) vil resultere i budgetkonsekvenser på ca. [redacted] per år.
Ansøgers estimat af budgetkonsekvenserne fremgår af tabel 13.

Tabel 13: 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' vurdering

Ansøger har inkluderet omkostninger til patienttid og transport i budgetkonsekvensanalysen. Dette er ikke i overensstemmelse med Amgros' metodevejledning.

Ansøgers estimater inddrager som sagt omkostninger til bevacizumab og derfor udarbejder Amgros egen budgetkonsekvensanalyse, hvor disse omkostninger er ekskluderet. Derudover vil omkostninger til patienttid og transport ligeledes blive ekskluderet fra Amgros budgetkonsekvensanalyse.

4.2 Amgros' estimater af budgetkonsekvenser

Amgros har korrigeret følgende estimater i forhold til ansøgers analyse:

- Incidens af patienter, der vurderes at være kandidater til den pågældende indikation, er 149 personer per år.
- Omkostninger til bevacizumab er ekskluderes
- Omkostninger til patienttid og transport ekskluderes
- Efterfølgende kemoterapi ekskluderes, men inddrages i en scenarieanalyse

Med de indlagte antagelser estimerer Amgros, at anvendelse af olaparib (Lynparza) vil resultere i budgetkonsekvenser på ca. [redacted] per år efter første års anbefaling, ved et markedsoptag på 50 %, se tabel 14.

Hvis analysen udføres med AIP bliver budgetkonsekvenserne ca. 73 mio. per år efterfølgende første år.

Tabel 14: Amgros' analyse af totale budgetkonsekvenser ved et markedsoptag på 50 %, 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]

4.2.1 Amgros' følsomhedsanalyse af budgetkonsekvenserne

Ved samme antagelser som i Amgros' hovedanalyse for budgetkonsekvenser, men med efterfølgende kemoterapi inkluderet, vil de årlige budgetkonsekvenser være ca. [redacted] efter første års anbefaling, se tabel 15.

Tabel 15: Amgros' analyse af totale budgetkonsekvenser ved inklusion er efterfølgende kemoterapi, 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]

5 DISKUSSION

Behandling med olaparib (Lynparza) er forbundet med betydelige meromkostninger sammenlignet med behandling med placebo. Meromkostningerne er næsten udelukkende drevet af lægemiddelomkostningerne for olaparib (Lynparza).

Hvis efterfølgende kemoterapi inkluderes i analysen, reduceres meromkostningerne, men resulterer dog fortsat i betydelige meromkostninger.

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20.03 2019

Vedr.: Lynparza (olaparib) merværdi i BRCAwt/VUS ovarie cancer

EMA godkendte 8. maj 2018 en indikationsudvidelse for Lynparza tabletter, således at indikationen ikke længere var begrænset til patienter med påvist BRCA mutation. Til grund for denne indikationsudvidelse ligger kliniske data fra en post-hoc analyse fra fase II studiet Study 19. Grundet evidensniveau forpligtigede AstraZeneca sig til at generere yderligere data for den i ansøgningen behandlede patientpopulation. Denne forpligtigelse bliver mødt gennem studiet OPINION, som med dansk deltagelse har indrulleret 265 BRCAwt patienter. Data forventes offentliggjort i 2020. Med afsæt i ovennævnte indikationsudvidelse indsendte AstraZeneca den 19. marts 2018 foreløbig ansøgning til Medicinrådet og modtog 11. oktober 2018 en protokol fra Medicinrådet. Medicinrådet definerer i protokollen to kliniske spørgsmål, som ansøger (AstraZeneca) jævnfør Metodehåndbogen forventes at besvare.

Klinisk spørgsmål 1: Olaparib vs. bevacizumab:

Medicinrådet/Fagudvalget begrunder i deres vurdering, hvorfor de ikke mener, at en narrativ sammenligning kan foretages til besvarelse af det formulerede kliniske spørgsmål 1. Ligeledes noterer AstraZeneca sig, at Medicinrådet stiller sig enige med firmaet Tesaro, som ikke finder det muligt at foretage en statistisk sammenligning mellem niraparib og bevacizumab.

AstraZeneca er principielt enige i Fagudvalgets vurdering af muligheden for at lave sammenligningen, og anfører også i ansøgningen på olaparip, en række af de samme overvejelser, som Fagudvalget i forhold til besvarelsen af spørgsmål 1 i protokollen. I forbindelse med Fagudvalgets vurdering af niraparib ansøgningen modtog AstraZeneca en mundtlig orientering om, at Fagudvalget havde vurderet, at sammenligningen mellem PARPi og bevacizumab ikke var mulig i 2. linje BRCAwt og at det var op til AstraZeneca selv, om vi ville indsende en besvarelse af spørgsmål 1.

AstraZeneca finder det principielt ikke rigtigt, at det er ansøger selv, som skal vurdere om et klinisk spørgsmål kan besvares. Den forpligtigelse påhviler Fagudvalget/Medicinrådet, mens det er ansøgers forpligtigelse at besvare de kliniske spørgsmål. I stedet burde dette have været reflekteret i en ændring i protokollen eller som minimum, i en skriftlig orientering til ansøger.

Klinisk spørgsmål 2: Olaparib vs. placebo:

Medicinrådet anfører som konklusion på klinisk spørgsmål 2, at olaparib ikke giver en klinisk merværdi sammenlignet med placebo. AstraZeneca noterer sig ved en gennemgang af Medicinrådets begrundelse følgende for det kliniske spørgsmål vedrørende PFS:

"Den relative effektforskel (HR = 0.54 [0,34; 0,85] indplacerer olaparib i kategorien vigtig klinisk merværdi, da konfidensintervallets øvre grænse er <0,90. Fagudvalget bemærker, at den relative effektforskel aflæst på Kaplain-Meier kurven ikke ser ud til at være konstant over tid. Det kan betyde, at antagelsen om "proportional hazards" ikke er opfyldt, hvilket kan påvirke validiteten af effektestimatet. Hvorvidt antagelsen er opfyldt kan ikke afgøres med sikkerhed, da det kræver adgang til rådata. Fagudvalget vælger derfor at tillægge effektestimatet for den absolutte forskel mest værdi. Derfor vurderer Fagudvalget, at olaparib har ingen klinisk merværdi sammenlignet med placebo, hvad angår PFS."

Det er svært for AstraZeneca at vide, hvilken vægt Medicinrådet har tildelt henholdsvis den absolutte og relative effektforskel, men AstraZeneca tolker ovenstående i den retning, at Medicinrådets visuelle vurdering af Kaplan-Meier kurven får afgørende betydning for den samlede vurdering, hvad angår PFS. Den nævnte relative effektforskel er publiceret i et peer reviewed tidsskrift og derfor mener AstraZeneca, at dokumentationskravene fra Medicinrådets metodehåndbog følges, når den relative effektforskel fra publikationen i Lancet Oncology refereres i ansøgningen. Ligeledes undrer det os, at der i Medicinrådets begrundelse efterspørges adgang til rådata, da det efter AstraZenecas opfattelse kun er muligt at evaluere data publiceret i peer reviewed tidsskrifter og som tillige opfylder de opstillede krav til litteratursøgningen. Det er vigtig at få forståelse for de rammer angående dokumentation vi arbejder under, også for fremtidige ansøgninger.

Ved gennemlæsning af Medicinrådets vurdering af produktet niraparib til samme patientgruppe kan AstraZeneca læse følgende:

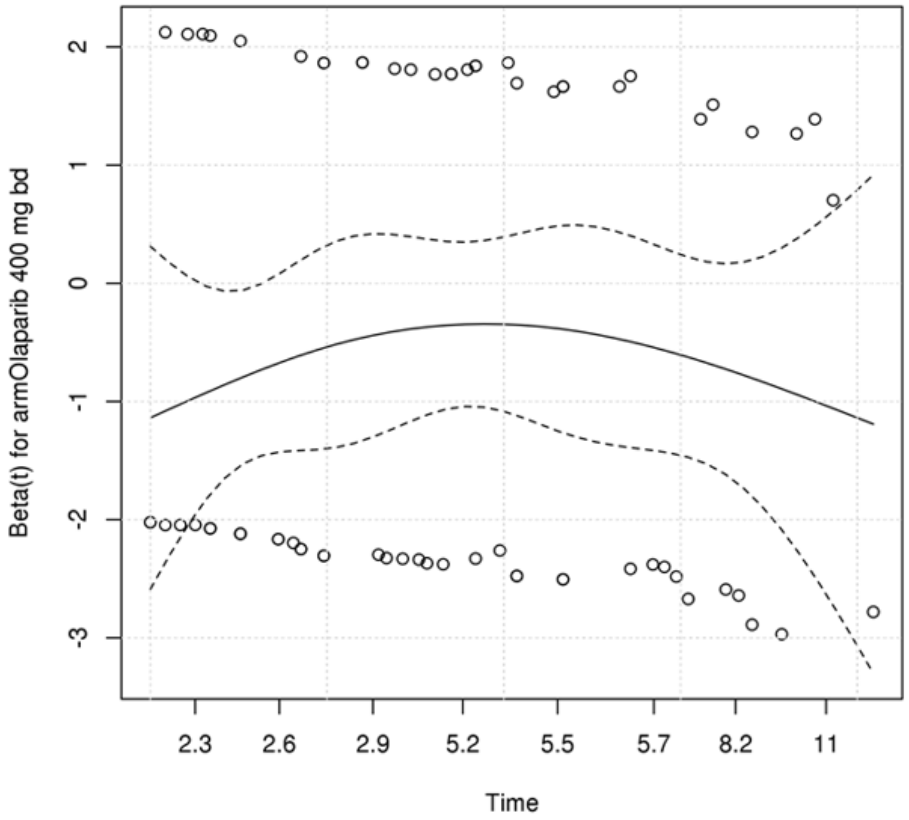
"Ansøger har udført en test for at vurdere, om PFS analysen i de tre studier overholder antagelsen om proprotionelle hazard'er (at den relative effekt er konstant over tid). Dette er en forudsætning for en formel indirekte sammenligning mellem studierne. Testen viste for alle tre studier, at den relative effekt ved effektmålet PFS ikke var konstant over tid, og at antagelsen om proportionelle hazard'er ikke er holdbar"

Det fremgår ikke hvilken test der er udført, men AstraZeneca kan konstatere, at referencen for ovennævnte angives til NICE Single Technology Appraisal dokument for niraparib. Anses et sådan dokument for at være sidestillet med peer reviewed artikler jævnfør metodehåndbogen? Ligeledes angives det i medicinrådsansøgningen for niraparib, at Kaplan-Meier kurver for olaparib er genereret digitalt. På baggrund af vurderingen af niraparib antager AstraZeneca, at Medicinrådet anser denne metode, som en valid metode til at estimere rå-data.

AstraZeneca mener, at vedrørende et så centralt punkt i ansøgningen som vurderingen af PFS, ville have været relevant, hvis Medicinrådet/Fagudvalget havde kontaktet os for at få adgang til ovennævnte rådata eller AstraZenecas analyse af, om proportionelle hazard'er - antagelsen er mødt i studiepopulationen inden man fældede afgørelsen. Vi har nedenfor præsenteret de efterspurgte data.

Schoenfeld residual plot er visuelt den bedste metode at illustrere PFS trenden i study 19 på, idet det viser den umiddelbare HR (den fuldoptrukne linje) i forhold til tid (figur 1). En nedadgående tendens over tid indikerer en forbedret HR. Figur 1 viser en tilsyneladende afvigelse fra antagelsen om proportionelle hazard'er. Dette understøttes af Therneau and Grambsch global test i tabel 1 (p=0.832). En tilsvarende analyse er som tidligere nævnt udført i NICE-dokumentet, for at demonstrere afvigelse af proportionelle hazard'er for niraparib. Af samme dokument fremgår det, at en visuel inspektion af HR over tid, ikke er en robust metode til at foretage denne vurdering.

Figur 1. Schoenfeld plot olaparib vs. placebo



Y-aksen i figuren er log-HR hvilket betyder at for værdier over værdien 0 er HR > 1 og HR er < 1 ved værdier under 0

Tabel 1. Therneau and Grambsch global test af non-proportional hazards

	rho	chisq	p
Olaparib 400 mg bd	0.025	0.045	0.832

Fra Schoenfeld residual plot kan HR udviklingen over tid udledes (tabel 2).

Tabel 2. PFS HR udvikling som funktion af tid i Study 19 BRCAwt/VUS

Time (months)	log(HR)	HR
2.3	-0.94	0.39
2.6	-0.66	0.52
2.9	-0.45	0.64
5.2	-0.35	0.70
5.5	-0.38	0.68
5.7	-0.56	0.57
8.2	-0.77	0.46
11.0	-1.05	0.35

Initialt stiger den øjeblikkelige HR til et maksimum omkring 0.7 omkring 5.3 måneder, for derefter at falde igen. Denne indikation af, at HR ikke overstiger 0.7 giver forhåbentlig Medicinrådet en vis forsikring om den relative effekt, uagtet at antagelsen om at proportionelle hazard'er ikke er mødt.

Ansøgningen er grundigt vurderet og bearbejdet af Fagudvalget, og de fejl vi har begået er kyndigt opfanget. På baggrund af ovenstående, udbeder vi os dog en revurdering af merværdien for det kliniske spørgsmål vedrørende PFS for olaparib vs. placebo.

Vi ser frem til at høre fra jer.

Med venlig hilsen

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Medicinrådet

Medicinrådets vurdering af klinisk merværdi for olaparib til behandling af kræft i æggestokkene, æggelederne eller primær kræft i bughinden

Versionsnr. 1.0

Medicinrådet

Om Medicinrådet

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

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

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

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

Om vurderingen af klinisk merværdi

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

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

Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	13. marts 2019
Ikrafttrædelsesdato	13. marts 2019
Dokumentnummer	43682
Versionsnummer	1.0

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

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Lynparza®
Generisk navn	Olaparib
Firma	AstraZeneca
ATC-kode	L01XX46
Virkningsmekanisme	Olaparib er en selektiv hæmmer af enzymerne poly (adenosine disphosphate [ADP]-ribose) polymerase (PARP) 1/2/3, der deltager i DNA-reparation. Blokering af PARP 1/2/3 i tumorceller, som i forvejen har mange genomiske skader, inducerer celledød.
Administration/dosis	2 tabletter á 150 mg, to gange dagligt.
EMA-indikation	"Lynparza is indicated as 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 or partial) to platinum-based chemotherapy."

2 Medicinrådets konklusion vedrørende klinisk merværdi

Medicinrådet vurderer, at olaparib til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende high-grade epitelialt karcinom i æggestokkene, æggelederne eller primær kræft i bughinden og respons på platinbaseret kemoterapi giver en **ikkedokumenterbar klinisk merværdi** sammenlignet med bevacizumab. Evidensens kvalitet er ikke vurderet.

Medicinrådet vurderer, at olaparib til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende high-grade epitelialt karcinom i æggestokkene, æggelederne eller primær kræft i bughinden og respons på platinbaseret kemoterapi giver en **ingen klinisk merværdi** sammenlignet med placebo. Evidensens kvalitet er meget lav.

Medicinrådet kategoriserer lægemidlers kliniske merværdi i en af følgende kategorier:

Kategori 1. Stor merværdi: Vedvarende og stor forbedring i effektforhold der ikke tidligere er opnået med et relevant behandlingsalternativ. Eksempler herpå er sygdomsremission, markant stigning i overlevelsestid, langvarigt fravær af alvorlige sygdomssymptomer eller udtalt fravær af alvorlige bivirkninger.

Kategori 2. Vigtig merværdi: Markant forbedring, eksempelvis lindring af sygdomstilstand, moderat stigning i overlevelsestid, lindring af alvorlige symptomer, fravær af alvorlige bivirkninger og væsentligt fravær af andre bivirkninger.

Kategori 3. Lille merværdi: Moderat forbedring, f.eks. reduktion i ikkealvorlige sygdomssymptomer eller fravær af bivirkninger.

Kategori 4. Ingen merværdi: Ingen merværdi sammenlignet med standardbehandling/andre behandlinger.

Kategori 5. Negativ merværdi: Negativ merværdi sammenlignet med standardbehandling/andre behandlinger.

Kategori 6. Ikkedokumenterbar merværdi: Ikkedokumenterbar merværdi sammenlignet med standardbehandling/ andre behandlinger. Effektforskellen kan ikke kvantificeres ud fra det videnskabelige datagrundlag.

3 Forkortelser

AR:	Bivirkning (*Adverse reaction)*
AE:	Uønsket hændelse *(Adverse event)*
BRCA1/2:	*BReast CAncer1/2* (tumorsuppressorgen)
CTCAE:	*Common Terminology Criteria for Adverse Events*
DGCD:	Dansk Gynækologisk Cancer Database
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency*)
EPAR:	*European Public Assessment Report*
GRADE:	*Grading of Recommendations Assessment, Development and Evaluation* (system til vurdering af evidens)
HGSC:	High-grade serøst adenokarcinom *(High-grade serous carcinoma)*
HR:	*Hazard ratio*
HRD:	Defekt homolog rekombination (*Homologous recombination deficiency*)
ITT:	*Intention-to-treat*
KRIS:	Koordineringsrådet for ibrugtagning af sygehusmedicin
MDS/AML:	Myelodysplastisk syndrom / akut myeloid leukæmi
OS:	Samlet overlevelse (*Overall survival*)
PARP:	Poly (adenosin disphosphat [ADP]-ribose) polymerase
PFS:	Progressionsfri overlevelse (*Progression free survival*)
RECIST:	*Response Evaluation Criteria In Solid Tumors*
RR:	Relativ risiko
SAE:	Alvorlig uønsket hændelse (*Serious adverse event*)

4 Formål

Formålet med Medicinrådets vurdering af klinisk merværdi af olaparib til platinsensitiv, recidiverende high-grade epitelialt karcinom i æggestokkene, herunder kræft i æggelederne og primær kræft i bughinden, er at vurdere den kliniske merværdi i forhold til et eller flere lægemidler til samme patientgruppe (komparatorer).

Med udgangspunkt i den kliniske merværdi og en omkostningsanalyse udarbejdet af Amgros vurderer Medicinrådet, om olaparib anbefales som mulig standardbehandling.

5 Baggrund

Kræft i æggestokkene

Kræft i æggestokkene, herunder kræft i æggelederne og primær kræft i bughinden er en heterogen gruppe med forskellige histologiske undertyper. Tumorer opstår overvejende i overfladeepitelceller. Serøst adenokarcinom, herunder undertypen high-grade serøst adenokarcinom (HGSC), er en af de hyppigste undertyper. I denne rapport bliver disse kræftformer fremadrettet kaldt for kræft i æggestokkene. Den komplekse histologiske klassifikation gør subklassificering og dermed behandlingsvalg til en kompleks proces, der kræver tæt samarbejde mellem gynækologer, patologer, billeddiagnostikere og kliniske onkologer [1,2].

Kræft i æggestokkene er den 4. hyppigste kræftdødsårsag hos kvinder i Danmark. Medianalder for sygdomsdebut er 63 år, og 80 % af patienterne er postmenopausale [2]. Der diagnosticeres omkring 550 nye tilfælde pr. år, og omkring 4600 kvinder lever med diagnosen i Danmark [3]. Kræft i æggestokkene har den højeste dødelighed blandt de gynækologiske kræftsygdomme, dels fordi kræften oftest bliver opdaget i stadium III-IV på grund af uspecifikke symptomer, hvor spredning udover æggestokkene allerede har fundet sted, men også på grund af høj frekvens af recidivudvikling (ca. 80 % af patienterne) [2]. Overlevelsen er bl.a. afhængig af sygdomsstadiet på diagnosepunktet. Ifølge Dansk Gynækologisk Cancer Database (DGCD) ligger 5-års overlevelsen for patienter med kræft i æggestokkene i stadie I, II, III eller IV på henholdsvis 87%, 70 %, 30 % og 15 % (tal fra 2005-2016) [2], og den samlede 5-års overlevelse er ca. 40 %.

Årsagen til kræft i æggestokkene er ikke kendt, men en række risikofaktorer har været beskrevet. Antal fødsler og brug af p-piller virker beskyttende og spiller en væsentlig rolle i livstidsrisikoen for at udvikle kræft i æggestokkene [1]. Desuden menes ca. 30 % af HGSC-tilfældene, som udgør ca. 75 % af de samlede high-grade epiteliale karcinomer, at være genetisk betinget med Brystkræft (BRCA) 1 eller 2 genmutationer (arvelige eller somatiske) som de mest kendte [2].

Nuværende behandling

Det overordnede mål med behandling af kræft i æggestokkene er helbredelse, alternativt at forlænge overlevelsen og øge livskvaliteten. Den primære behandling er kirurgisk, hvor målet er at få fjernet alt synligt kræftvæv (makroskopisk radikal operation) samt korrekt stadieinddeling [2]. Næsten alle patienter, der opereres makroskopisk radikalt, tilbydes efterfølgende adjuverende platinbaseret kombinations-kemoterapi i form af carboplatin og paclitaxel (6 serier). Patienter med efterladt makroskopisk tumorvæv (og alle stadium IV-patienter) tilbydes samme slags kemoterapi i kombination med bevacizumab efter operation (se nedenfor) [4]. Omkring 60-80 % af patienterne vil opnå komplet eller partielt respons efter 1. linjebehandling, men ca. 80 % af disse patienter vil få tilbagefald inden for 2-3 år efter afsluttet kemoterapi [2]. Patienter med tilbagefald har generelt en dårlig prognose og formålet med videre behandling er levetids-forlængelse og symptomlindring. Her er en af de vigtigste prognostiske faktorer det platinfrie interval, det vil sige tidsrummet fra afslutning af platinbaseret kemoterapi til recidiv. Dette tidsinterval er afgørende for valg

af efterfølgende behandling [4]. Nogle patienter, der primært blev makroskopisk radikalt opereret, vil også blive vurderet med henblik på mulighed for ny operation.

Patienter med recidiv ≥ 6 måneder fra endt platinholdig kemoterapi, som har haft primær effekt, betragtes som platinsensitive. For disse patienter anbefales der i 2. linjebehandling en platinbaseret kombinationskemoterapi i form af enten carboplatin og paclitaxel eller carboplatin og pegyleret liposomal doxorubicin. Behandlingen afhænger endvidere af patienternes BRCA1/2-mutationsstatus.

Patienter med BRCA1/2-mutation (arvelige eller somatiske)
Til patienter med mutation i BRCA1/2 og platinsensitivt recidiv tilbydes vedligeholdelsesbehandling med poly (adenosin disphosphat [ADP]-ribose) polymerase (PARP)-hæmmeren olaparib, såfremt de har respons på 2. linje platinbaseret kombinationskemoterapi [4].

Patienter uden BRCA1/2-mutation
Størstedelen af patienterne, der ikke får bevacizumab i 1. linjebehandling, tilbydes bevacizumab i kombination med ovenstående platinbaserede kombinationskemoterapi i 2. linjebehandling, efterfulgt af bevacizumab vedligeholdelsesbehandling, der fortsættes i alt 15 måneder eller til progression. Bevacizumab gives kun en gang i patientens behandlingsforløb [4].

Hvis patienten oplever platinsensitivt tilbagefald efter 2. linjebehandling, introduceres en ny linje platinbaseret kemoterapi. Hvis patienten ikke har fået bevacizumab tidligere, kan det tilbydes som beskrevet ovenfor. Nuværende behandlingsalgoritme efter 1.linjebehandling for patienter med platinsensitiv, recidiverende kræft i æggestokkene er opsummeret i tabel 1 nedenfor.

Anvendelse af det nye lægemiddel

Olaparib er en selektiv hæmmer af PARP 1/2/3. PARP 1/2/3 er cellekerneproteiner, der detekterer DNA-skader og fremmer deres reparation. Til forskel fra raske celler, har tumorceller tit defekter i deres DNA-reparationsmekanismer, såsom BRCA-mutationer eller defekt homolog rekombination (*homologous recombination deficiency* (HRD)), hvilket resulterer i genomisk ustabilitet og akkumulering af mutationer. Den celledræbende effekt af PARP-inhibition er særlig udtalt hos patienter med BRCA1/2-mutation eller positiv HRD. Platinsensitivitet vurderes også at være forbundet med PARP-hæmmersensitivitet på grund af høj prævalens af forandringer/mutationer i DNA-reparationsmekanismer i platinfølsom kræft i æggestokkene [5].

I 2014 godkendte det Europæiske Lægemiddelagentur (*European Medicines Agency* (EMA)) olaparib som vedligeholdelsesbehandling til patienter med BRCA1/2-mutation og recidiverende high-grade serøs karcinom i æggestokkene, herunder æggelederne og primær kræft i bughinden, som responderer på platinbaseret kemoterapi (komplet eller partiel respons). Den 11. juni 2015 anbefalede Koordineringsrådet for ibrugtagning af sygehusmedicin (KRIS) olaprib som standardbehandling til den pågældende population. I maj 2018 godkendte EMA en udvidelse af indikationen, som dækker over platinsensitive patienter med high-grade epitelial kræft i æggestokkene, herunder æggelederne og primær kræft i bughinden, uafhængigt af BRCA-mutationsstatus og histologisk undertype. Det er udelukkende indikationsudvidelsen fagudvalget tager stilling til i denne vurdering.

Indikationsudvidelsen inkluderer også en ændring i lægemiddelformuleringen, hvor olaparib gives i tabletform (150 mg, 2 tabletter ad gangen, 2 gange dagligt) indtil progression fremfor kapselform (50 mg, 8 kapsler ad gangen, 2 gange dagligt). Fagudvalget vurderer, at der i Danmark er 175 patienter per år, der er kandidater til behandling i henhold til EMA-godkendelsen af indikationsudvidelsen for olaparib. I tabel 1 er placering af olaparib efter indikationsudvidelsen i den nuværende behandlingsalgoritme markeret med rødt.

Fagudvalget vil gerne fremhæve, at indplacering af olaparib i behandlingsalgoritmen afhænger af anvendelse af bevacizumab. Bevacizumab kan gives i 1. linje, 2. linje eller senere i behandlingsforløbet. I klinisk praksis er valget baseret på en individuel vurdering i samarbejde med patienten.

Tabel 1. Behandlingsalgoritmen for patienter med platinsensitiv, recidiverende HGSC i æggestokkene efter 1. linjebehandling. Olaparibs potentielle placering i behandlingsalgoritmen er indikeret med rødt.

	Patienter med BRCA1/2-mutation	**Patienter uden BRCA1/2 mutation**	
2. linjebehandling*	Platinbaseret kombinationskemoterapi efterfulgt af olaparib vedligeholdelsesbehandling	Platinbaseret kombinationskemoterapi i kombination med bevacizumab efterfulgt af bevacizumab vedligeholdelsesbehandling	Platinbaseret kombinationsterapi efterfulgt af olaparib vedligeholdelsesbehandling
Efterfølgende behandlingslinjer**	Ny linje kemoterapi, eventuelt platinbaseret		

*1. linjebehandling er typisk carboplatin og paclitaxel (6 serier), eventuelt i kombination med bevacizumab (patienter med efterladt makroskopisk tumorvæv og/eller stadium IV-sygdom).
**Patienter kan få bevacizumab i forbindelse med deres platinbaserede kombinationskemoterapi, hvis de ikke har modtaget den før. Beslutningen er baseret på en individuel vurdering i samarbejde med patienten. Bevacizumab kan kun gives én gang.

6 Metode

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

Den endelige ansøgning fra AstraZeneca blev godkendt den 30. januar 2019. Ansøger har anvendt og fulgt den præspecificerede metode, jf. protokol, som blev godkendt i Medicinrådet den 9. oktober 2018.

Ansøgningen indeholder en narrativ sammenligning af olaparib og bevacizumab og en direkte sammenligning af olaparib og placebo.

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

Den kliniske merværdi kategoriseres først enkeltvis pr. effektmål, hvorefter der foretages en vurdering af den samlede kategori for lægemidlet på tværs af effektmålene. Kategoriseringen pr. effektmål foretages på baggrund af absolutte og relative værdier for det enkelte effektmål. Den relative effekt beskrives med et estimat og et konfidensinterval, der sammenholdes med generiske væsentlighedskriterier. Den absolutte effekt sammenholdes med den i protokollen beskrevne "mindste klinisk relevante forskel". Den endelige kategorisering af lægemidlets kliniske merværdi er en delvis kvalitativ proces, hvor der foretages en vurdering af det samlede datagrundlag på tværs af effektmålene.

Vurdering af evidensens kvalitet foretages med udgangspunkt i GRADE og udtrykker tiltroen til evidensgrundlaget for de enkelte effektstørrelser og den endelige kategori for klinisk merværdi. Evidensens kvalitet inddeles i fire niveauer: høj, moderat, lav og meget lav. GRADE-metoden er et internationalt anerkendt redskab til systematisk vurdering af evidens og udarbejdelse af anbefalinger. I denne vurdering er metoden anvendt til at vurdere evidensens kvalitet.

7 Litteratursøgning

Ansøger har søgt litteratur som beskrevet i protokollen. Ansøgers PRISMA-diagram og litteraturgennemgang fremgår af ansøgningen.

Ansøger har den 12. juni 2018 foretaget en systematisk litteratursøgning af olaparib og relevante komparatorer. Søgningen er udført som specificeret i protokollen. Ansøgers PRISMA-diagram og litteraturgennemgang fremgår af ansøgningen. Søgningen resulterede i identifikation af 10 publikationer fra to randomiserede dobbeltblindede kliniske studier. De kliniske studier opfylder Medicinrådets præspecificerede kriterier og kan således anvendes til at besvare de kliniske spørgsmål i protokollen. Publikationerne er listet nedenfor. Ansøger identificerede yderligere fem publikationer fra tre randomiserede dobbeltblindede kliniske studier (SOLO2/ENGOT Ov-21, ENGOT-OV16/NOVA og Studie 41). Disse studier opfylder ikke Medicinrådets præspecificerede kriterier og kan ikke anvendes til at besvare de kliniske spørgsmål. Derfor indgår de ikke i Medicinrådets vurdering af den kliniske merværdi af olaparib.

Tabel 2. Publikationer inkluderet i analysen af den kliniske merværdi af olaparib

Reference	Klinisk forsøg	NCT-nummer
Olaparib		
Ledermann J, Harter P, Gourley C, et al. Olaparib Maintenance Therapy in Platinum-Sensitive Relapsed Ovarian Cancer. N Engl J Med 2012. 366: 1382–1392 [6].	Studie 19	NCT00753545
Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in patients with platinumsensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomized phase 2 trial. Lancet Oncol 2014. 15: 852–861 [7].	Studie 19, retrospektiv analyse baseret på BRCA-mutationsstatus	NCT00753545
Ledermann JA, Harter P, Gourley C, et al. Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomized, placebo-controlled, double-blind, phase 2 trial. Lancet Oncol 2016. 17: 1579–1589 [8].	Studie 19, opdaterede overlevelsesdata	NCT00753545
Ledermann JA, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Quality of life during olaparib maintenance therapy in platinum-sensitive relapsed serous ovarian cancer. Br J Cancer. 2016;115(11):1313-20 [9].	Studie 19, livskvalitetsdata	NCT00753545
Matulonis UA, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in patients with platinum-sensitive, relapsed serous ovarian cancer and a BRCA mutation: Overall survival adjusted for postprogression poly (adenosine diphosphate ribose) polymerase inhibitor therapy. Cancer. 2016;122(12):1844-52 [10].	Studie 19, opfølgning	NCT00753545
Lheureux S, Lai Z, Dougherty BA, Runswick S, Hodgson DR, Timms KM, et al. Long-Term Responders on Olaparib Maintenance in High-Grade Serous Ovarian Cancer: Clinical and Molecular Characterization. Clin Cancer Res. 2017;23(15):4086-94 [11].	Studie 19, opfølgning	NCT00753545
Friedlander M, Matulonis U, Gourley C, du Bois A, Vergote I, Rustin G, 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;119(9):1075-85 [12].	Studie 19, opfølgning	NCT00753545
Bevacizumab		

Aghajanian C, Blank SV, Goff BA, 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 Off J Am Soc Clin Oncol 2012. 30: 2039–2045 [13].	OCEANS	NCT00434642
Aghajanian C, Goff B, Nycum LR, Wang Y, Husain A, Blank S. Independent radiologic review: bevacizumab in combination with gemcitabine and carboplatin in recurrent ovarian cancer. Gynecol Oncol. 2014;133(1):105-10 [14].	OCEANS, opfølgning	NCT00434642
Aghajanian C, Goff B, Nycum LR, et al. Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. Gynecol Oncol. 2015;139(1):10–6 [12].	OCEANS, opdaterede overlevelsesdata	NCT00434642

De overnævnte primærstudier samt European Product Assessment Report (EPAR) og produktresumé for olaparib [15,16] og bevacizumab [17–19] udgør datagrundlaget for de analyser, der benyttes til besvarelsen af de kliniske spørgsmål. Under hvert effektmål fremgår det, hvilke publikationer data er ekstraheret fra.

8 Databehandling

Klinisk spørgsmål 1

Til besvarelse af klinisk spørgsmål 1, hvor olaparib sammenlignes med bevacizumab til patienter uden BRCA1/2-mutation, har ansøger foretaget en narrativ sammenligning baseret på data for olaparib fra Studie 19 og data for bevacizumab fra OCEANS (se studiekarakteristika i bilag 1). Fagudvalget finder imidlertid ikke, at en sådan sammenligning kan gennemføres meningsfuldt på grund af følgende forskelle mellem studierne:

- BRCA1/2-mutationsstatus blev ikke analyseret i OCEANS, og dermed er frekvensen af patienter med og uden BRCA1/2-mutation ukendt. Som konsekvens foreligger der ikke noget data på patienter opgjort efter BRCA1/2-mutationsstatus. Dette afviger fra Studie 19, som indeholder to kohorter: patienter med BRCA1/2-mutation og patienter uden BRCA1/2-mutation. Fagudvalget vurderer, at disse forskelle i patientsammensætningen i de omtalte studier ikke tillader en narrativ sammenligning af studiedata.
- Behandling med bevacizumab gives *samtidigt* med kemoterapi, efterfulgt af bevacizumab vedligeholdelsesbehandling. Til gengæld gives olaparib som vedligeholdelsesbehandling *efter* endt kemoterapi. Dette vil medføre en forskel i opgørelsen af effektmålet PFS, som bliver målt over forskellige tidsintervaller i Studie 19 (fra afslutning af kemoterapi) og OCEANS (fra opstart af kemoterapi). Ansøger tillægger 5,6 måneder til PFS i Studie 19 baseret på en leveringstid af kemoterapi på 126 dage. Denne beregning er imidlertid ikke korrekt, idet kemoterapi (6 serier med 21 dages mellemrum) leveres på 105 dage. Desuden forbigår ansøger det faktum, at evaluering i OCEANS skete hver 9. uge sammenlignet med hver 12. uge i Studie 19. Dette vil kunne føre til en mindre undervurdering af PFS i OCEANS i forhold til Studie 19. En narrativ sammenligning er dermed ikke meningsfuld.

Derfor vurderer fagudvalget, at der ikke foreligger grundlag for en narrativ sammenligning.

Klinisk spørgsmål 2

Til besvarelse af klinisk spørgsmål 2, hvor olaparib sammenlignes med placebo til patienter uden BRCA1/2-mutation, har ansøger indsendt data fra den direkte sammenligning, der foreligger fra Studie 19. Medicinrådet har ikke fundet anledning til at foretage ændringer af beregninger foretaget af ansøger. Medicinrådets sekretariat og fagudvalget vurderer, at kategoriseringen kan basere sig på de indsendte analyser med følgende bemærkninger:

- Ansøger har ikke indsendt data opdelt på histologiske undertyper, som var 1) high-grade serøs adenokarcinom eller blandingstumorer med en serøs komponent og 2) patienter med anden epithelial histologi, som anført i protokollen.

- Ansøger har indsendt bivirkningsdata i form af uønskede hændelser (*adverse events* (AE'er)), som dækker over hændelser relateret til studiemedicinen (*adverse reactions* (AR'er)) og øvrige hændelser opstået under behandlingen. Fagudvalget vurderer, at dette ikke vil påvirke vurderingen af effektmålet.

- For effektmålene behandlingsophør på grund af uønskede hændelser og hændelser grad 3-4 har ansøger indsendt data for patienter uden BRCA1/2-mutation, som endnu ikke er publiceret i peer-reviewed tidsskrifter (*data on file*). Fagudvalget vil ikke basere vurderingen af olaparib herpå, men tager i stedet udgangspunkt i publicerede data for den samlede studiepopulation, hvor der både indgår patienter med og uden BRCA1/2-mutation med længst mulig opfølgningstid. Fagudvalget vurderer, at patienter med og uden BRCA1/2-mutation vil opleve samme type bivirkninger og med lignende frekvens. Data for den samlede population kan derfor godt anvendes til at besvare effektmålet for populationen uden BRCA1/2-mutation.

- For effektmålet livskvalitet målt ved FACT-O har sekretariatet foretaget en mindre justering i udregning af den absloutte effektforskel, hvor der tages højde for andelen af patienter, som ikke kunne evalueres, og beregnet den relative effektforskel.

9 Klinisk merværdi

Da størstedelen af patienter uden BRCA1/2-mutation tilbydes bevacizumab på et tidspunkt i deres behandlingsforløb, og da beslutningen er baseret på en individuel vurdering i samarbejde med patienten, ønsker fagudvalget at sammenligne olaparib både med bevacizumab (klinisk spørgsmål 1) og placebo (klinisk spørgsmål 2) til denne patientpopulation.

9.1 Konklusion klinisk spørgsmål 1

Hvilken klinisk merværdi tilbyder vedligeholdelsesbehandling med olaparib sammenlignet med bevacizumab hos patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende high-grade epitelialt karcinom og respons på platinbaseret kemoterapi?

På baggrund af de forskelle, som er fremhævet i afsnit 8, vurderer fagudvalget, at en narrativ sammenligning ikke er meningsfuld.

Fagudvalget vurderer, at olaparib til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende high-grade epitelialt karcinom i æggestokkene, æggelederne eller primær kræft i bughinden og respons på platinbaseret kemoterapi giver en **ikkedokumenterbar klinisk merværdi** sammenlignet med bevacizumab (evidensens kvalitet er ikke vurderet).

9.2 Konklusion klinisk spørgsmål 2

Hvilken klinisk merværdi tilbyder vedligeholdelsesbehandling med olaparib sammenlignet med placebo hos patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende high-grade epitelialt karcinom og respons på platinbaseret kemoterapi?

Fagudvalget vurderer, at olaparib til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende high-grade epitelialt karcinom i æggestokkene, æggelederne eller primær kræft i bughinden og respons på platinbaseret kemoterapi giver **ingen klinisk merværdi** sammenlignet med placebo (evidensens kvalitet er meget lav).

9.2.1 Gennemgang af studier

Karakteristika
I sammenligningen af olaparib og placebo indgår data fra Studie 19 [6–8,15]

Studie 19 er et randomiseret, dobbeltblindet, placebokontrolleret fase 2-studie. Det er et multicenterstudie (82 onkologiske centre), hvor 265 patienter (136 i olaparibarmen og 129 i placeboarmen) blev randomiseret (senest 8 uger efter endt platinbaseret kemoterapi) 1:1 til at modtage olaparib (800 mg dagligt som kapsler) eller placebo indtil sygdomsprogression eller forekomst af uacceptabel toksicitet. Patienterne i studiet havde platinsensitiv HGSC i æggestokkene, æggelederne eller primær kræft i bughinden og havde modtaget minimum 2 linjer platinbaseret kemoterapi tidligere. Patienter blev stratificeret efter herkomst (jødisk vs. ikkejødisk), tid til progression efter deres næstsidste platinbaserede kemoterapi (6-12 måneder vs. ≥ 12 måneder) og respons (komplet eller partiel) ved deres sidste platinbaserede kemoterapi. BRCA-mutationsstatus var kendt hos 36 % af patienterne i olaparibarmen og 37,2 % af patienterne i placeboarmen ved studiestart. Øvrige patienter blev analyseret for deres BRCA-mutationsstatus retrospektivt.

Studiets primære endepunkt var PFS, defineret som progression (målt radiologisk via RECIST-kriterierne) eller død, vurderet af investigator. Patienterne blev skannet hver 12. uge. Sekundære endepunkter var tid til progression (i henhold til RECIST-kriterierne eller CA-125-niveau), objektiv responsrate, sygdomskontrolrate (i henhold til RECIST-kriterierne, opgjort som andel patienter med komplet respons, partiel respons eller stabil sygdom i minimum 23 uger), procentvis ændring fra baseline i tumorstørrelsen ved 12 og 24 uger, OS, sikkerhed samt livskvalitet (Functional Assessment of Cancer Therapy-Ovary (FACT-O), FOSI og TOI).

Data-cutoff for den første primæranalyse af PFS var den 30. juni 2010 [6], efterfulgt af en planlagt retrospektiv analyse af data baseret på BRCA-mutationsstatus, som også inkluderede data for OS (data-cutoff: 26. november 2012) [7] samt opdateret opgørelse af data for OS (data-cutoff: 30. september 2015) [8]. Ved sidste data-cutoff (9. maj 2016) modtog 14 patienter i olaparibarmen og 1 patient i placeboarmen stadig behandling. Median opfølgningstid i ITT-populationen ved primær analyse af PFS (data-cutoff: 30. juni 2010) var 5,6 måneder (206,5 dage i olaparibarmen og 141 dage i placeboarmen). Effektanalyser blev udført på ITT-populationen. Sikkerhedsanalyser blev udført på alle patienter, der som minimum modtog én dosis studiemedicin (sikkerhedspopulation).

Population

Nedenfor rapporteres de relevante baselinekarakteristika for alle patienter og patienter uden BRCA1/2-mutation i placebo- og interventionsarmen.

Tabel 3. Baselinekarakteristika for alle patienter og patienter uden BRCA1/2-mutation

	Alle patienter		**Patienter uden BRCA1/2-mutation**	
	Olaparib (n = 136)	**Placebo (n = 129)**	**Olaparib (n = 57)**	**Placebo (n = 61)**
Median alder, år	58,0 (21-89)	59 (33-84)	62,0 (21-80)	63,0 (49-79)
Race, n (%)				
Kaukasiske	130 (95,6)	126 (97,7)	55 (96,5)	59 (96,7)
Afrikanske	2 (1,5)	1 (0,8)	0	1 (1,6)
Asiatiske	2 (1,5)	2 (1,6)	1 (1,8)	1 (1,6)
Andet	2 (1,5)	0	1 (1,8)	0
ECOG PS, n (%)				
0	110 (80,9)	95 (73,6)	45 (78,9)	45 (73,8)
1	23 (16,9)	30 (23,3)	10 (17,5)	14 (23,0)
2	1 (0,7)	2 (1,6)	1 (1,8)	1 (1,8)
Ukendt	2 (1,5)	2 (1,6)	1 (1,6)	1 (1,6)
Tumortype, n (%)				
Æggestokke	119 (87,5)	109 (84,5)	50 (87,7)	49 (80,3)
Æggeleder	3 (2,2)	3 (2,3)	2 (3,5)	1 (1,6)
Bughinden	14 (10,3)	16 (12,4)	5 (8,8)	10 (16,4)
Andet/ukendt	0	1 (0,8)	0	1 (1,6)
Tumor grad, n (%)				
Højt differentierende (G1)	0	0	0	0
Middelhøjt differentierende (G2)	36 (26,5)	34 (26,4)	15 (26,3)	16 (26,2)
Lavt differentierende (G3)	97 (71,3)	89 (69,0)	41 (71,9)	41 (67,2)
Ikke-differentierende (G4)	2 (1,5)	4 (3,1)	1 (1,8)	4 (6,6)
Kan ikke vurderes (GX)	1 (0,7)	2 (1,6)	0	0
Tid til progression efter forrige platinbaserede kemoterapi, n (%)				
> 6 til ≤ 12 måneder	53 (39,0)	54 (41,9)	23 (40,4)	24 (39,3)
> 12 måneder	83 (61,0)	75 (58,1)	34 (59,6)	37 (60,7)
Respons på seneste platinbaserede kemoterapi, n (%)				
Komplet	57 (41,9)	63 (48,8)	20 (35,1)	25 (41,0)
Partiel	79 (58,1)	66 (51,2)	37 (64,9)	36 (59,0)

Fagudvalget bemærker følgende forskelle i baselinekarakteristika mellem placebo- og interventionsarmen for patienter uden BRCA1/2-mutation:

- Patienter i gruppen behandlet med olaparib er overordnet set i bedre almen helbredstilstand (flere er i PS 0, og flere er lidt yngre).
- Flere patienter i gruppen behandlet med placebo har kræft i bughinden, hvilket kan være et udtryk for dissemineret sygdom og ikke primær sygdom.

Fagudvalget vurderer dog, at ovennævnte diskrete forskelle udgør små bidrag, og de skønnes ikke at påvirke effektestimaterne i væsentlig grad. Fagudvalget vurderer, at studiepopulationen er sammenlignelig med en tilsvarende dansk patientpopulation.

9.2.2 Resultater og vurdering

Resultater og vurdering af de effektmål, som fagudvalget har præspecificeret som henholdsvis kritiske og vigtige, følger nedenfor. Sammenligningen af olaparib med placebo baseres på en direkte sammenligning fra Studie 19 for patienter uden BRCA1/2-mutation. Den samlede kliniske merværdi af olaparib baseres på længst mulig opfølgningstid.

Fagudvalget bemærker, at resultaterne er baseret på en planlagt retrospektiv subgruppeanalyse, som undersøger patienter uden BRCA1/2-mutation, hvilket påvirker styrken af datagrundlaget. Data bør derfor tolkes med forsigtighed.

Overlevelse (OS) (kritisk)

OS ønskes opgjort som median OS. I analysen anvendes data for patienter uden BRCA1/2-mutation fra Studie 19 (data-cutoff 6. maj 2016) [12,15]. Den mediane opfølgningstid var 78 måneder.

Tabel 4. Vurdering af klinisk merværdi: Median overlevelse (OS) i antal måneder

	Forhåndsdefineret grundlag for vurdering		Resultater
Absolutte forskelle	3 måneder		- 2,1 måneder
Relative forskelle	Stor merværdi	Øvre konf.gr. < 0,85	
	Vigtig merværdi	Øvre konf.gr. < 0,95	
	Lille merværdi	Øvre konf.gr. < 1,00	
	Ingen merværdi	Øvre konf.gr. ≥ 1,00	HR = 0,84 [0,57;1,25]
	Negativ merværdi	Nedre konf.gr. > 1,00	
Evidensens kvalitet	Meget lav		

ANM: Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data på de absolutte og relative værdier fra resultatafsnittet, som indgår i Medicinrådets vurdering.

Median OS for olaparib er 24,5 måneder [19,8; 35,0] sammenlignet med 26,6 måneder [23,1; 32,5] for placebo. Forskellen på 2,1 måneder til fordel for placebo overstiger ikke den prædefinerede mindste klinisk relevante forskel på 3 måneder.

Den relative effektforskel (hazard ratio (HR) = 0,84 [0,57; 1,25]) indplacerer olaparib i kategorien ingen klinisk merværdi, da konfidensintervallets øvre grænse er ≥ 1,00. Fagudvalget bemærker, at OS ikke var den primære effektparameter i Studie 19, der ikke var dimensioneret til at detektere en forskel i OS.

Baseret på tilgængelige data vurderer fagudvalget, at olaparib har **ingen klinisk merværdi** sammenlignet med placebo, hvad angår OS.

Progressionsfri overlevelse (PFS) (kritisk)

PFS ønskes opgjort som median PFS. I analysen af PFS anvendes data for patienter uden BRCA1/2-mutation fra Studie 19 (data-cutoff 30. juni 2010). På tidspunktet for data-cutoff i 2010 var den mediane opfølgningstid 5,6 måneder [7].

Tabel 5. Vurdering af klinisk merværdi: Median progressionsfri overlevelse (PFS) i antal måneder

	Forhåndsdefineret grundlag for vurdering		Medicinrådets vurdering
Absolutte forskelle	3 måneder		1,9 måneder
Relative forskelle	Stor merværdi	Øvre konf.gr. < 0,75	
	Vigtig merværdi	Øvre konf.gr. < 0,90	HR = 0,54 [0,34;0,85]
	Lille merværdi	Øvre konf.gr. < 1,00	
	Ingen merværdi	Øvre konf.gr. ≥ 1,00	
	Negativ merværdi	Nedre konf.gr. > 1,00	
Evidensens kvalitet	Meget lav		

ANM: Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data på de absolutte og relative værdier fra resultatafsnittet, som indgår i Medicinrådets vurdering.

Median PFS for olaparib er 7,4 måneder [5,5; 10,3] sammenlignet med 5,5 måneder [3,7; 5,6] for placebo. Forskellen på 1,9 måneder til fordel for olaparib overstiger ikke den prædefinerede mindste klinisk relevante forskel på 3 måneder.

Den relative effektforskel (HR = 0,54 [0,34; 0,85]) indplacerer olaparib i kategorien vigtig klinisk merværdi, da konfidensintervallets øvre grænse er < 0,90. Fagudvalget bemærker, at den relative effektforskel aflæst på Kaplain-Meier kurven ikke ser ud til at være konstant over tid. Det kan betyde, at antagelsen om *"proportional hazards"* ikke er opfyldt, hvilket kan påvirke validiteten af effektestimatet. Hvorvidt antagelsen er opfyldt kan ikke afgøres med sikkerhed, da det kræver adgang til rådata. Fagudvalget vælger derfor at tillægge effektestimatet for den absolutte forskel mest værdi. Derfor vurderer fagudvalget, at olaparib har **ingen klinisk merværdi** sammenlignet med placebo, hvad angår PFS.

Bivirkninger (kritisk)

Udover en kvalitativ vurdering af bivirkninger ønskes bivirkninger opgjort som andel af patienter, der ophører behandling på grund af bivirkninger samt andel patienter, som oplever en eller flere grad 3-4 bivirkninger. Som beskrevet i afsnit 8 har ansøger indsendt bivirkningsdata i form af uønskede hændelser. Fagudvalget vurderer, at dette ikke vil påvirke vurderingen af effektmålet.

Data opgøres først separat for de to måleenheder, og til sidst udføres en samlet merværdikategorisering baseret på de opgjorte data samt den kvalitative vurdering af bivirkningsprofilen.

<u>*Behandlingsophør på grund af uønskede hændelser*</u>

I analysen anvendes data for hele studiepopulationen fra Studie 19 (data-cutoff 6. maj 2016) [12], da publiceret data for patienter uden BRCA1/2-mutation ikke er tilgængelig.

Tabel 6. Vurdering af klinisk merværdi: Andel af patienter, der ophører behandling pga. uønskede hændelser

	Forhåndsdefineret grundlag for vurdering		Medicinrådets vurdering
Absolutte forskelle	5 procentpoint		4,3 procentpoint
Relative forskelle	Stor merværdi	Øvre konf.gr. < 0,75	
	Vigtig merværdi	Øvre konf.gr. < 0,90	
	Lille merværdi	Øvre konf.gr. < 1,00	
	Ingen merværdi	Øvre konf.gr. ≥ 1,00	RR = 3,76 [0,81;17,4]
	Negativ merværdi	Nedre konf.gr. > 1,00	
Evidensens kvalitet	Lav		

ANM: Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data på de absolutte og relative værdier fra resultatafsnittet, som indgår i Medicinrådets vurdering.

I alt ophørte 10 patienter med behandling, fordi de oplevede uønskede hændelser, heraf 8 ud af 136 patienter (5,9 %) behandlet med olaparib og 2 ud af 128 patienter (1,6 %) behandlet med placebo. Den absolutte forskel mellem grupperne er 4,3 procentpoint og overstiger dermed ikke den mindste klinisk relevante forskel på 5 procentpoint.

Den relative effektforskel (relativ risiko (RR) = 3,76 [0,81; 17,4]) indplacerer olaparib i kategorien ingen klinisk merværdi, da konfidensintervallets øvre grænse er ≥ 1,00. Da der er ganske få hændelser, er der stor usikkerhed omkring estimatet, hvilket afspejles i det brede konfidensinterval.

Baseret på tilgængelige data vurderer fagudvalget, at olaparib har **ingen klinisk merværdi** sammenlignet med placebo, hvad angår behandlingsophør på grund af uønskede hændelser.

Uønskede hændelser grad 3-4

I analysen anvendes data for hele studiepopulationen fra Studie 19 (data-cutoff 6. maj 2016) [12], da publicerede data for patienter uden BRCA1/2-mutation ikke er tilgængelige.

Tabel 7. Vurdering af klinisk merværdi: Andel af patienter, som oplever en eller flere grad 3-4 uønskede hændelser

	Forhåndsdefineret grundlag for vurdering		Medicinrådets vurdering
Absolutte forskelle	10 procentpoint		21,5 procentpoint
Relative forskelle	Stor merværdi	Øvre konf.gr. < 0,75	
	Vigtig merværdi	Øvre konf.gr. < 0,90	
	Lille merværdi	Øvre konf.gr. < 1,00	
	Ingen merværdi	Øvre konf.gr. ≥ 1,00	
	Negativ merværdi	Nedre konf.gr. > 1,00	RR = 1,98 [1,36; 2,90]
Evidensens kvalitet	Lav		

ANM: Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data på de absolutte og relative værdier fra resultatafsnittet, som indgår i Medicinrådets vurdering.

59 patienter ud af 136 (43,4 %) behandlet med olaparib og 28 ud af 128 patienter (21,9 %) behandlet med placebo oplevede mindst en uønsket hændelse af grad 3-4. Den absolutte forskel mellem grupperne er 21,5 procentpoint til fordel for placebo, hvilket overstiger den mindste klinisk relevante forskel på 10 procentpoint. Fagudvalget bemærker, at dette er forventeligt i sammenligningen af en aktiv behandling med placebo.

Den relative effektforskel (RR = 1,98 [1,36; 2,90]) indplacerer olaparib i kategorien negativ klinisk merværdi, da konfidensintervallets nedre grænse er > 1,00.

Baseret på tilgængelige data vurderer fagudvalget, at olaparib har **negativ klinisk merværdi** sammenlignet med placebo, hvad angår grad 3-4 uønskede hændelser.

Kvalitativ gennemgang af bivirkninger

Fagudvalget ønskede i protokollen at lave en kvalitativ gennemgang af de konkrete bivirkninger forbundet med olaparib med henblik på at vurdere alvorlighed, hyppighed og håndterbarhed af bivirkningerne. Fagudvalget fremhævede, at de specifikt er interesserede i data vedrørende myelodysplastisk syndrom og akut myeloid leukæmi (MDS/AML). Ansøger har leveret bivirkningsdata fra de kliniske studier, der undersøger olaparib.

Bivirkningerne forbundet med behandling med olaparib er for størstedelen af let eller moderat sværhedsgrad (CTCAE grad 1-2) og kræver i en del tilfælde dosisreduktion men generelt ikke afbrydelse af behandling. De hyppigste bivirkninger observeret i kliniske forsøg er kvalme, opkastning, diarré, dyspepsi, træthed, hovedpine, smagsforstyrrelser , nedsat appetit, svimmelhed og anæmi. Anæmi er den mest almindelige CTCAE grad ≥ 3 bivirkning, som er rapporteret i kliniske studier [16].

Forekomsten af MDS/AML hos patienter, som blev behandlet med olaparib i kliniske studier, var < 1,5 %. Størstedelen af tilfældene havde dødelig udgang [16]. Frekvensen ligger inden for den rapporterede frekvens (0,15 % til 1,8 %) for udviklingen af sekundær MDS/AML hos patienter med kræft i æggestokkene [15]. Alle patienter behandlet med olaprib, som udvikler MDS/AML, har tidligere modtaget en række platinbaserede behandlinger. Kausaliteten mellem udviklingen af MDS/AML og behandling med olaparib er fortsat ukendt.

I Studie 19 var de hyppigste uønskede hændelser kvalme (70,6 % vs. 35,9 % i placebogruppen), træthed (63,2 % vs. 46,1 % i placebogruppen), opkastning (35,3 % vs. 14,1 % i placebogruppen), diarré (27,2 % vs. 24,2 % i placebogruppen) og anæmi (22,8 % vs. 7,0 % i placebogruppen) [12]. De hyppigste hændelser ≥ grad 3 i Studie 19 kan ses i tabel 8 [12]. Forekomsten af dosisafbrydelser, -reduktioner og -seponeringer på grund af uønskede hændelser var i Studie 19, henholdsvis 34,6 %, 25,7 % og 5,9 %. Dosisafbrydelserne og -reduktionerne forekom hyppigst i de første 3 måneder af behandlingen. De hyppigste bivirkninger, som førte til dosisafbrydelse eller dosisreduktion, var kvalme, anæmi, opkastning, neutropeni og træthed [16].

Tabel 8. Hyppigste hændelser ≥ grad 3 samt frekvensen af MDS og AML i Studie 19 [12]

	Olaparib (n = 136)	**Placebo (n = 128)**
Trombocytopeni, n (%)	1 (0,7)	0
Anæmi, n (%)	10 (7,4)	1 (0,8)
Neutropeni, n (%)	5 (3,7)	1 (0,8)
Træthed	12 (8,8)	4 (3,1)
Rygsmerter	4 (2,9)	0
Kvalme	3 (2,2)	0
Opkastning	3 (2,2)	1 (0,8)
MDS	NA	NA
AML	NA	NA

Samlet vurdering

Samlet vurderer fagudvalget, at olaparib har **negativ klinisk merværdi** sammenlignet med placebo, hvad angår bivirkninger. Fagudvalget vurderer dog, at bivirkningerne forbundet med behandling med olaparib generelt er acceptable og håndterbare i klinisk praksis.

Livskvalitet (vigtig)

Jævnfør protokollen ønskede fagudvalget livskvalitet opgjort som andel af patienter, der ikke viser statistisk signifikant forværring i livskvalitet. Fagudvalget ønskede data målt i prioriteret rækkefølge ved enten Functional Assessment of Cancer Therapy-Ovarian (FACT-O) [20], FACT Ovarian Symptom Index (FOSI) eller EQ-5D [21].

I Studie 19 blev livskvalitet vurderet ved brug af FACT-O, FOSI og trial outcome index (TOI). I analysen anvendes data for FACT-O for hele studiepopulationen fra Studie 19 (data-cutoff 30. juni 2010) [9], da publicerede data for patienter uden BRCA1/2-mutation ikke er tilgængelig. Data er opgjort som andel af patienter, der ikke viste forværring i livskvalitet, dvs summen af dem, der ikke oplevede en forskel, og dem, der oplevede bedring i livkvalitet.

Tabel 9. Vurdering af klinisk merværdi: Andel patienter, der ikke viser statistisk signifikant forværring i livskvalitet

	Forhåndsdefineret grundlag for vurdering		Medicinrådets vurdering
Absolutte forskelle	10 procentpoint		4,3 procentpoint
Relative forskelle	Stor merværdi	Øvre konf.gr. < 0,75	
	Vigtig merværdi	Øvre konf.gr. < 0,90	
	Lille merværdi	Øvre konf.gr. < 1,00	
	Ingen merværdi	Øvre konf.gr. ≥ 1,00	RR = 0,83 [0,49; 1,42]
	Negativ merværdi	Nedre konf.gr. > 1,00	
Evidensens kvalitet	Lav		

ANM: Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data på de absolutte og relative værdier fra resultatafsnittet, som indgår i Medicinrådets vurdering.

Andel patienter, der ikke viste forværring i livskvalitet (ingen ændring eller forbedring) målt med FACT-O, var 82,1 % i gruppen behandlet olaparib og 77,8 % i gruppen behandlet med placebo. Den absolutte forskel mellem grupperne er 4,3 procentpoint og overstiger dermed ikke den mindste klinisk relevante forskel på 10 procentpoint.

Den relative effektforskel (RR = 0,83 [0,49; 1,42]) indplacerer olaparib i kategorien ingen klinisk merværdi, da konfidensintervallets øvre grænse er ≥ 1,00.

Baseret på tilgængelige data, vurderer fagudvalget, at olaparib har **ingen klinisk merværdi** sammenlignet med placebo, hvad angår livskvalitet målt ved FACT-O.

9.2.3 Evidensens kvalitet

Evidensens kvalitet for klinisk spørgsmål 2 er samlet set vurderet som værende **meget lav**. Overvejelser vedrørende evidensens kvalitet kan ses i bilag 1.

Evidensens kvalitet er nedgraderet på baggrund af følgende GRADE-domæner:

- På samtlige effektmål er der nedgraderet for *"risk of bias"*. Opgørelsen af data efter BRCA1/2-mutationsstatus blev udført post-hoc, hvorfor randomiseringen ikke er opretholdt i subgruppen uden BRCA1/2-mutation. Dette kan have influeret effektmålene OS og PFS.

- På samtlige effektmål er der nedgraderet for *"inconsistency"*, da der kun er data fra ét studie, hvorfor det er usikkert, om studiet estimerer den sande størrelsesorden af effekten samt usikkerheden omkring effektestimatet.

- På samtlige effektmål er der nedgraderet for *"imprecission"*, da konfidensintervallet krydser den kliniske beslutningsgrænse for at anbefale eller ej, og/eller fordi kriteriet for *"optimal information size"* ikke er opfyldt.

9.2.4 Konklusion for klinisk spørgsmål 2

Fagudvalget vurderer, at olaparib til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende high-grade epitelialt karcinom i æggestokkene, æggelederne eller primær kræft i bughinden og respons på platinbaseret kemoterapi giver **ingen klinisk merværdi** sammenlignet med placebo (evidensens kvalitet er meget lav).

Nedenstående tabel viser en oversigt med konklusioner vedrørende klinisk merværdi af olaparib per effektmål til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende high-grade epitelialt karcinom i æggestokkene, æggelederne eller primær kræft i bughinden og respons på platinbaseret kemoterapi.

Tabel 10. Oversigt over merværdi og evidenskvalitet for kritiske og vigtige effektmål

Effektmål	Vigtighed	Merværdi	Evidenskvalitet
OS	Kritisk	Ingen	Meget lav
PFS	Kritisk	Ingen	Meget lav
Bivirkninger: - Ophør pga. AE'er - AE'er grad 3-4 - Kvalitativ gennemgang af bivirkninger	Kritisk	Negativ	Lav
Livskvalitet	Vigtig	Ingen	Lav
Samlet vurdering		**Ingen**	**Meget lav**

I den samlede vurdering har fagudvalget lagt vægt på, at olaparib:

- har ingen effekt sammenlignet med placebo, hvad angår de kritiske effektmål OS og PFS.
- har negativ merværdi, hvad angår det kritiske effektmål bivirkninger.

Fagudvalget bemærker desuden, at datagrundlaget for analysen er spinkelt, og at usikkerheden ved analysen er stor, idet der er tale om en planlagt retrospektiv subgruppeanalyse af intervention og komparator.

10 Fagudvalgets vurdering af samlet klinisk merværdi og samlet evidensniveau

Fagudvalget vurderer, at olaparib til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende high-grade epitelialt karcinom i æggestokkene, æggelederne eller primær kræft i bughinden og respons på platinbaseret kemoterapi giver en:

- **Ikkedokumenterbar klinisk merværdi** sammenlignet med bevacizumab. Evidensens kvalitet er ikke vurderet.

- **Ingen klinisk merværdi** sammenlignet med placebo. Evidensens kvalitet er meget lav

11 Rådets vurdering af samlet klinisk merværdi og samlet evidensniveau

Medicinrådet vurderer, at olaparib til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende high-grade epitelialt karcinom i æggestokkene, æggelederne eller primær kræft i bughinden og respons på platinbaseret kemoterapi giver en:

- **Ikkedokumenterbar klinisk merværdi** sammenlignet med bevacizumab. Evidensens kvalitet er ikke vurderet.

- **Ingen klinisk merværdi** sammenlignet med placebo. Evidensens kvalitet er meget lav

12 Relation til eksisterende behandlingsvejledning

Der findes ingen RADS-behandlingsvejledning for kræft i æggestokkene, æggelederne og primær kræft i bughinden. Medicinrådet vil i 2019 udarbejde en behandlingsvejledning på området.

Lægemidlet niraparib er også indiceret til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende high-grade epitelialt karcinom i æggestokkene, æggelederne eller primær kræft i bughinden og respons på platinbaseret kemoterapi. På det foreliggende datagrundlag vurderer fagudvalget, at det ikke er muligt at tage stilling til, om olaparib og niraparib kan ligestilles til denne patientgruppe. De nuværende data på niraparib er af en højere kvalitet end data på olaparib.

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14 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende kræft i æggestokkene

Formand	**Indstillet af**
Jørn Herrstedt Forskningsleder, professor, overlæge, dr.med.	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
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15 Versionslog

Version	Dato	Ændring
1.0	13.03.2019	Godkendt af Medicinrådet.

16 Bilag 1: OCEANS

OCEANS (NCT00434642)	
Studiedesign	OCEANS er et randomiseret, dobbeltblindet, placebokontrolleret multicenter fase 3-studie, der evaluerede effekten og sikkerheden af bevacizumab administreret i kombination med carboplatin og gemcitabin hos kvinder med platinsensitiv recidiverende epithelial kræft i æggestokkene, æggeledere eller primær kræft i bughinden. 484 patienter blev randomiseret 1:1 til carboplatin (areal under kurven [AUC] 4, dag 1 hver 21. dag) og gemcitabin (1000 mg/m2, dag 1 og dag 8 hver 21. dag) plus bevacizumab (15 mg/kg, dag 1 hver 21. dag) versus carboplatin og gemcitabin plus placebo. Patienterne blev stratificeret efter platinsensitiv sygdom (tilbagefald 6-12 måneder vs. ≥ 12 måneder efter sidste platinbaserede behandling) og cytoreduktiv kirurgi for reciverende epitelial kræft i æggestokkene, æggeledere eller primær kræft i bughinden.
Effektmål	Studiets primære endepunkt var PFS defineret som progression (målt radiologisk via RECIST retningslinjer) eller død, vurderet af investigator. Sekundære endepunkter var objektiv responsrate, responsvarighed, samlet overlevelse (OS), andel af patienter med gastrointestinal perforering (GIP) og andel af patienter med mindst 1 uønsket hændelse.
Opfølgning	Ved data-cutoff var median opfølgning for OS 58,2 måneder i forsøgsarmen og 56,4 måneder i kontrolarmen.
Subgruppeanalyser	For PFS blev der lavet analyser for subgrupper inddelt i forhold til alder, ECOG-status, platinfrit interval (6-12, 12-24, og >24 måneder) og cytoreduktiv kirurgi for recidiverende sygdom.

17 Bilag 2: GRADE-evidensprofiler

17.1 Cochrane Risk of Bias

Risiko for bias – Studie 19	Vurdering	Begrundelse
Random sequence generation (selection bias)	• Høj risiko for bias for OS og PFS • Lav risiko for bias for øvrige effektmål, hvor der tages udgangspunkt i den samlede population	Randomisering var udført via et interaktivt voice responssystem med et computer-genereret randomiseringsskema. Patienter blev stratificeret efter: • herkomst • tid til progression efter deres næstsidste platinbaserede kemoterapi • respons ved deres sidste platinbaserede kemoterapi. Patienter blev randomiseret 1:1 til olaparib- eller placeboarmen. Ingen cross-over var tilladt. Opgørelse af data efter BRCA1/2-mutationsstatus blev udført retrospektivt, hvorfor randomiseringen ikke er opretholdt i subgrupperne.
Allocation concealment (selection bias)	• Lav risiko for bias	
Blinding of participants and personnel (performance bias)	• Lav risiko for bias for OS and PFS • Uklar risiko for bias for øvrige effektmål	Både patienter og personale var blindede. Da behandling med olaparib er forbundet med bivirkninger, vil det i sammenligning med placebo sandsynligvis være tydeligt, hvilke patienter, som får aktiv behanding, og hvilke patienter, som får placebo. Dette kan influere alle effektmål på nær OS og PFS.
Blinding of outcome assessment (detection bias)	• Lav risiko for bias for OS and PFS • Uklar risiko for bias for øvrige effektmål	Behandlinger blev maskeret for de, der vurderede effektmål (site investigator) og udførte analyser ved brug af unikke identifiers genereret ved randomisering. Da behandling med olaparib er forbundet med bivirkninger, vil det i sammenligning med placebo sandsynligvis være tydeligt, hvilke patienter, som får aktiv behanding, og hvilke patienter, som får placebo. Dette kan influere alle effektmål på nær OS og PFS.
Incomplete outcome data (attrition bias)	• Lav risiko for bias	Alle effektmål blev analyseret i "intention-to-treat-population" og på prædefineret subgruppeniveau.
Selective reporting (reporting bias)	• Lav risiko for bias	De effektmål, der beskrives i metodeafsnittet, er rapporteret i studiet.
Other bias	-	-

17.2 GRADE-evaluering af evidenskvaliteten til vurdering af den kliniske merværdi af olaparib

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Olaparib	placebo	Relative (95% CI)	Absolute (95% CI)		
Samlet overlevelse (OS) (follow up: median 78 months)												
1	randomised trials	serious [a]	serious [b]	not serious	serious [c]	none	45/57 (78.9%)	57/61 (93.4%)	**HR 0.84** (0.57 to 1.25)	**36 fewer per 1.000** (from 146 fewer to 32 more)	⊕◯◯◯ VERY LOW	CRITICAL
Progressionsfri overlevelse (PFS) (follow up: median 5,6 months)												
1	randomised trials	serious [a]	serious [b]	not serious	serious [d]	none	32/57 (56.1%)	44/61 (72.1%)	**HR 0.54** (0.34 to 0.85)	**223 fewer per 1.000** (from 369 fewer to 59 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Behandlingsophør på grund af uønskede hændelser												
1	randomised trials	not serious	serious [b]	not serious	serious [c]	none	8/136 (5.9%)	2/128 (1.6%)	**RR 3.76** (0.81 to 17.40)	**43 more per 1.000** (from 3 fewer to 256 more)	⊕⊕◯◯ LOW	CRITICAL
Uønskede hændelser grad 3-4												
1	randomised trials	not serious	serious [b]	not serious	serious [c]	none	59/136 (43.4%)	28/128 (21.9%)	**RR 1.98** (1.36 to 2.90)	**214 more per 1.000** (from 79 more to 416 more)	⊕⊕◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Olaparib	placebo	Relative (95% CI)	Absolute (95% CI)		
Livskvalitet												
1	randomised trials	not serious	serious [b]	not serious	serious [c]	none	92/112 (82.1%)	84/108 (77.8%)	**RR 0.8300** (0.4893 to 1.4193)	**132 fewer per 1.000** (from 397 fewer to 326 more)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **HR:** Hazard Ratio; **RR:** Risk ratio

Explanations

a. Der nedgraderes, da resultatet er baseret på en planlagt retrospektiv subgruppeanalyse, hvorfor randomiseringen ikke er opretholdt.

b. Der nedgraderes, da der kun er et studie, og det derfor er usikkert, om dette estimerer størrelsesordenen på effekten korrekt.

c. Der nedgraderes, da CI krydser den kliniske beslutningsgrænse for at anbefale eller ej.

d. CI krydser ikke den kliniske beslutningsgrænse for at anbefale eller ej, men der nedgraderes, da kriteriet for OIS ikke er opfyldt.

Application for the assessment of clinically added value of Lynparza (olaparib) as 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.

Contents

1 Basic information

Table 1 Contact information

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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 x daily
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	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)
Other approved therapeutic indications	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)
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
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BARD1	BRCA1-associated ring domain 1 (gene)
BICR	Blinded independent central review
BIM	Budget impact model
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; for patients who had best response of complete response or partial response, calculated as (i) date of randomisation until date of documented disease progression (derived from central read RECIST assessments) or death in the absence of documented progression; (ii) date of first documented response until date of documented disease progression or death in the absence of documented progression (provided death was within 3 months of last evaluable central read RECIST assessment)
EMA	European Medicines Agency
ENGOT	European Network of Gynaecological Oncological Trials
EOC	Epithelial ovarian cancer
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer life questionnaire 30
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

Abbreviations	
EU	European Union
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
HER2	Human epidermal growth factor receptor 2
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
HTA	Health technology assessment
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; percentage of patients with a best objective response of complete response or partial response. Best objective response was determined based on data up to the point of the first RECIST progression according to all available central read RECIST assessments
OS	Overall survival
PARP	Poly (ADP-ribose) polymerase
PARPi	Poly (ADP-ribose) polymerase inhibitor
PD	Progressed disease
PF	Progression-free
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
RCT	Randomised clinical trial

Abbreviations	
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
SPP	Survival post progression
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) – The TNM Classification of Malignant Tumours is a cancer staging system that describes the extent of cancer in a patient's body
TSST	Time from randomisation to second subsequent therapy or death
TTP	Time to progression
TWiST	Time without symptoms of disease or treatment toxicity
VUS	Variants of unknown significance
Wt	Wild-type

3 Summary

Lynparza achieved CHMP positive opinion on February 22nd, 2018 and the CHMP recommended approval of a broader indication and new tablet formulations: Lynparza 100 mg and 150 mg.

Lynparza tablet formulation is indicated:

- as "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 or partial) to platinum-based chemotherapy".

The indication for the capsule formulation will remain:

- "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."

EU approval was granted May 8th, 2018, and this application to Medicinrådet concerns the treatment of the *BRCAwt/VUS* patient group with the tablet formulation.

The tablet formulation was launched in Medicinpriser.dk in June 2018 and is currently used for the newly relapsed patients with *BRCAm*. Olaparib is also under investigation as 1st line treatment of *BRCAm* ovarian cancer and the first data was presented at ESMO 2018. EMA approval in 1st line *BRCAm* is expected May 2019.

The protocol from fagudvalget is divided into two main areas/questions 1) added benefit vs. placebo in *BRCAwt/VUS* and 2) added benefit vs. bevacizumab both in two separate OC histology populations. It has not been possible for AstraZeneca to do the histology split and this has been accepted by Medicinrådet.

No direct comparison to bevacizumab exists and indirect comparison is very difficult to do as the populations in Study 19 is not exactly identical to bevacizumab studies (OCEANS). Medicinrådet is currently also evaluating Zejula (niraparib) and during that process it became evident for Fagudvalget that an indirect comparison between niraparib and bevacizumab is not possible. We received the information from Medicinrådet that AstraZeneca also did not need to answer that part of the protocol (vs bevacizumab). We have however found it possible to do a narrative and indirect comparison with conclusions for some parts of the clinical question. Compared with placebo a 3.0 months benefit of olaparib vs. placebo can be shown for *BRCAwt/VUS* patients following their first platinum sensitive relapse. Compared with bevacizumab in the OCEANS study, the numerical benefit of olaparib was 1.7 months, however the BRCAm status in OCEANS was unknown. It was not possible to demonstrate a three months benefit in OS however it should be highlighted that around 10% of *BRCAwt/VUS* patients were treated with olaparib for more than six years, resulting in the median OS underestimating the mean benefit on OS. These results indicate that platinum sensitivity is associated with long term response to olaparib, which is currently incompletely defined by *BRCAm* status only.

The indirect comparison has shown that treatment with olaparib tablets is associated with a lower risk of discontinuation compared to bevacizumab, while we could not demonstrate any difference towards placebo. Compared with placebo, the number of patients experiencing grade 3 or higher adverse events was higher for olaparib, while it was not feasible to do a comparison with bevacizumab due to the nature of the study designs.

If Medicinrådet approve the use of olaparib in PSR/*BRCAwt/VUS* ovarian cancer around 100 patients a year will be candidates for olaparib in 2nd line treatment (figure 1).

Figure 1. Patient candidates for olaparib BRCAm + BRCA*wt*

First Line					
Ovarian Cancer Incidence Denmark(1)				553	
Epithelial Ovarian Cancer (2)		90%		498	
High-grade(3)		90%		448	
Stage II-IV		75%		336	
Receiving 1st Line platinum based CTX (4)		95%		319	
	Platinum Resistant (5)		10%	32	
	Platinum Sensitive (5)		75%	239	
	Longterm responders (5)		15%	48	
Second Line					
Number of Patients with 1st Platinum Sensitive relapse				239	
Patients with known BRCA status (6)		90%		215	
Patients with unknown BRCA status		10%		24	
				BRCAm	BRCAwt/Unknown
	BRCAmut (4)		23%	50	
	BRCAwt (4)		77%		190
	Responding to Pl based ctx (6)		80/60	40	114

1. Nordcan - http://www-dep.iarc.fr/NORDCAN/DK/frame.asp
2. Based on DGCG Database Annual report 2015-16 (Tabel A3.3.2) estimated that ~75% present with Stage II-IV disease
3. Romero I et al. Endocrinology 2012; 153: 1593-1602 [1]
4. Lynparza LRP 2017
5. Perren et al, NEJM 2011 [2]
6. Questionnaire Advisory Board 2018. 20 Nordic KEE asked. TBD if other ref should be used since it potential changes model

4 Literature search

Olaparib literature search Denmark

Literature search

Search profile

The literature search was conducted as instructed in the protocol and as detailed through dialogue with Medicinrådet.

Search strategy

The search was conducted in PubMed, which included MEDLINE, and in Cochrane Central Register of Controlled Trials (CENTRAL).

The searches were not limited by time or language.

Search process

The PubMed search was conducted on the 2018-12-06 and the CENTRAL search on the 2018-12-06. Obtained results are described and evaluated in the following.

Information sources

- MEDLINE (included in PubMed)
- Cochrane Database of Controlled Trials (CENTRAL) via Cochrane Library

Guidelines used

DGCG Database Annual report 2015-16

http://www.dgcg.dk/index.php/guidelines/ovariecancer-guidelines

Other sources

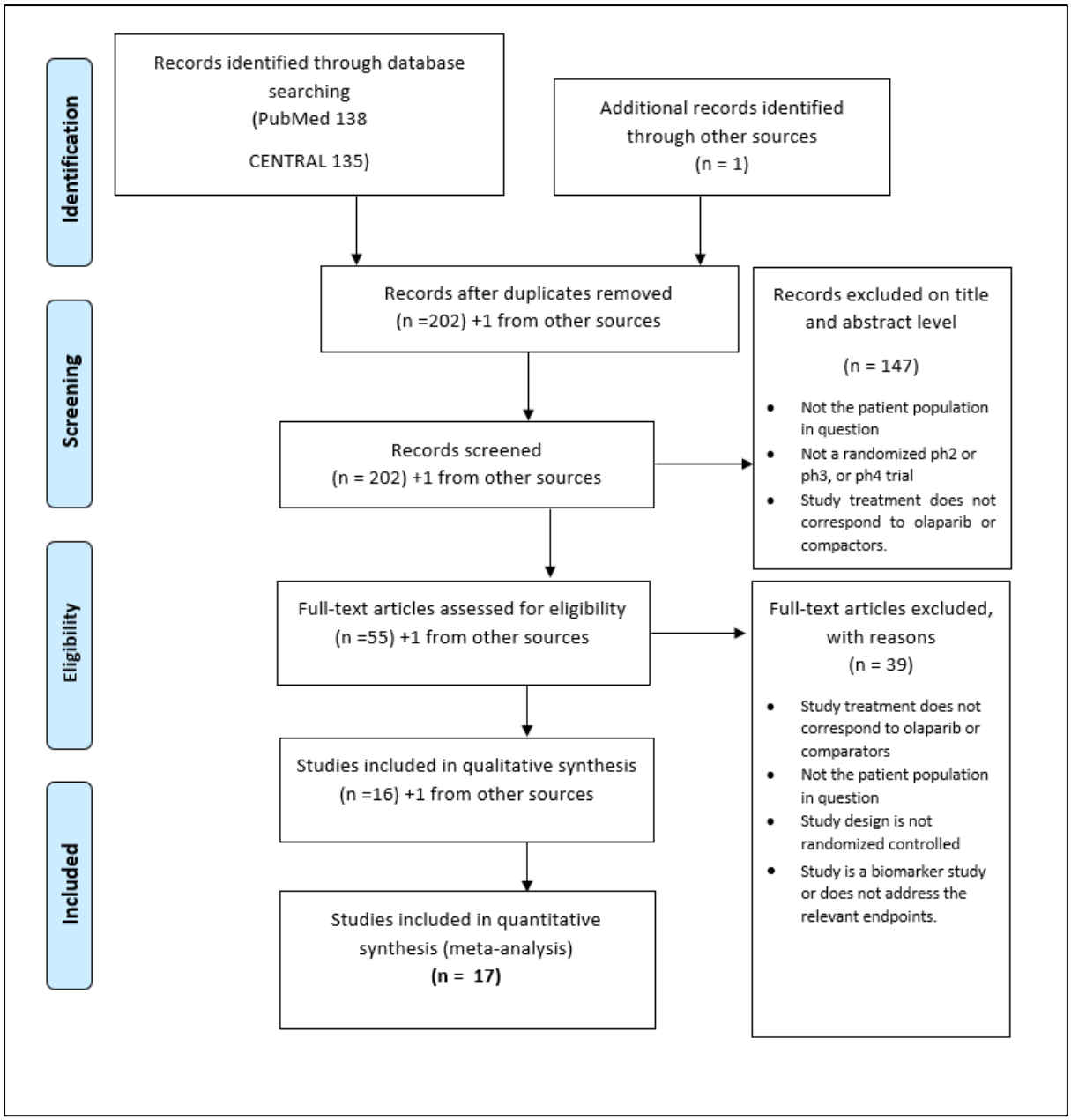
Lynparza EPAR, available from: https://www.ema.europa.eu/en/medicines/human/EPAR/lynparza

Flow diagram illustrating the search strategy underlying the literature search

Table 3 search strategy

PubMed (incl. MEDLINE)			CENTRAL			Comment
#1	("ovarian cancer" OR "ovarian neoplasms"[MeSH Terms])	91 934	#1	("ovarian cancer"):ti,ab,kw OR ("*ovary cancer"):ti,ab,kw OR [mh "Ovarian Neoplasms"]	4382	Search for disease term using the appropriate MeSH term supplemented with a general search for
#2	olaparib OR lynparza OR bevacizumab OR avastin	16971	#2	olaparib OR lynparza OR bevacizumab OR avastin	4279	Search for olaparib or bevacizumab OR Lynparza (commercial brand name) OR Avastin (commercial brand name) in all search fields.
#3	#1 AND #2	963	#3	#1 AND #2	365	
#4	(("clinical trial, phase ii"[Publication Type] or "clinical trial, phase iii"[Publication Type] or "clinical trial, phase iv"[Publication Type] or "controlled clinical trial"[Publication Type] or "randomized controlled trial"[Publication Type]))	582992	#4	("phase 2 clinical trial" or "phase 3 clinical trial" or "randomized controlled trial"):kw	248953	Search terms to identify phase 2, phase 3, or phase 4 clinical studies.
#5	((randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR randomly[tiab] OR controlled[tiab] OR trial[ti] OR single-blind[tiab] OR single-blinded[tiab] OR double-blind[tiab] OR double-blinded[tiab]))	1331121	#5	(randomized OR randomised OR placebo OR randomly OR single-blind* OR double-blind*):ti,ab or trial.ti	770171	Additional serach terms to identify randomized, controlled clinical studies.
#6	#3 AND (#4 OR #5)	213	#6		292	
#7	((Review[ptyp] OR Editorial[ptyp] OR Comment[ptyp] OR Meta-Analysis[ptyp] OR Case Reports[ptyp] OR case[ti] OR review[ti] or "clinical trial, phase i"[ptyp] or "phase I"[ti] OR "phase 1"[ti]))	5722867	#7	conference abstract:pt OR review:pt or nct*:au	256841	Search terms to identify publication types to be excluded in #9
#8	(("Animals"[mh] NOT "Humans"[mh]))	4520285	#8			Search terms to identify studies on animals (not humans) to be excluded in #9 from PubMed.
#9	#6 NOT (#7 OR #8)	138	#9	#6 NOT #7	135	Result

Flow diagram



*Full list of **PubMed and CENTRAL** search results. Used literature is listed in the reference list, the remaining listed here are excluded, based on grounds stated in the flow diagram and noted in com*

SEARCH QUERY PubMed:

#1 ("ovarian cancer" OR "ovarian neoplasms"[MeSH Terms])

#2 lynparza OR olaparib OR bevacizumab OR avastin

#3 #1 AND #2

#4 (("clinical trial, phase ii"[Publication Type] or "clinical trial, phase iii"[Publication Type] or "clinical trial, phase iv"[Publication Type] or "controlled clinical trial"[Publication Type] or "randomized controlled trial"[Publication Type]))

#5 ((randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR randomly[tiab] OR controlled[tiab] OR trial[ti] OR single-blind[tiab] OR single-blinded[tiab] OR double-blind[tiab] OR double-blinded[tiab]))

#6 #3 AND (#4 OR #5)

#7 ((Review[ptyp] OR Editorial[ptyp] OR Comment[ptyp] OR Meta-Analysis[ptyp] OR Case Reports[ptyp] OR case[ti] OR review[ti] or "clinical trial, phase i"[ptyp] or "phase I"[ti] OR "phase 1"[ti]))

#8 (("Animals"[mh] NOT "Humans"[mh]))

#9 #6 NOT (#7 OR #8)

SEARCH QUERY CENTRAL:

#1 ("ovarian cancer"):ti,ab,kw OR ("*ovary cancer"):ti,ab,kw OR [mh "Ovarian Neoplasms"]

#2 lynparza OR olaparib OR bevacizumab OR avastin

#3 #1 AND #2

#4 ("phase 2 clinical trial" or "phase 3 clinical trial" or "randomized controlled trial"):kw

#5 (randomized OR randomised OR placebo OR randomly OR single-blind* OR double-blind*):ti,ab or trial.ti

#6 #3 AND (#4 OR #5)

#7 conference abstract:pt OR review:pt or nct*:au

#8 #6 NOT #7

See appendix A1 for included and excluded publications

4.1 Relevant studies

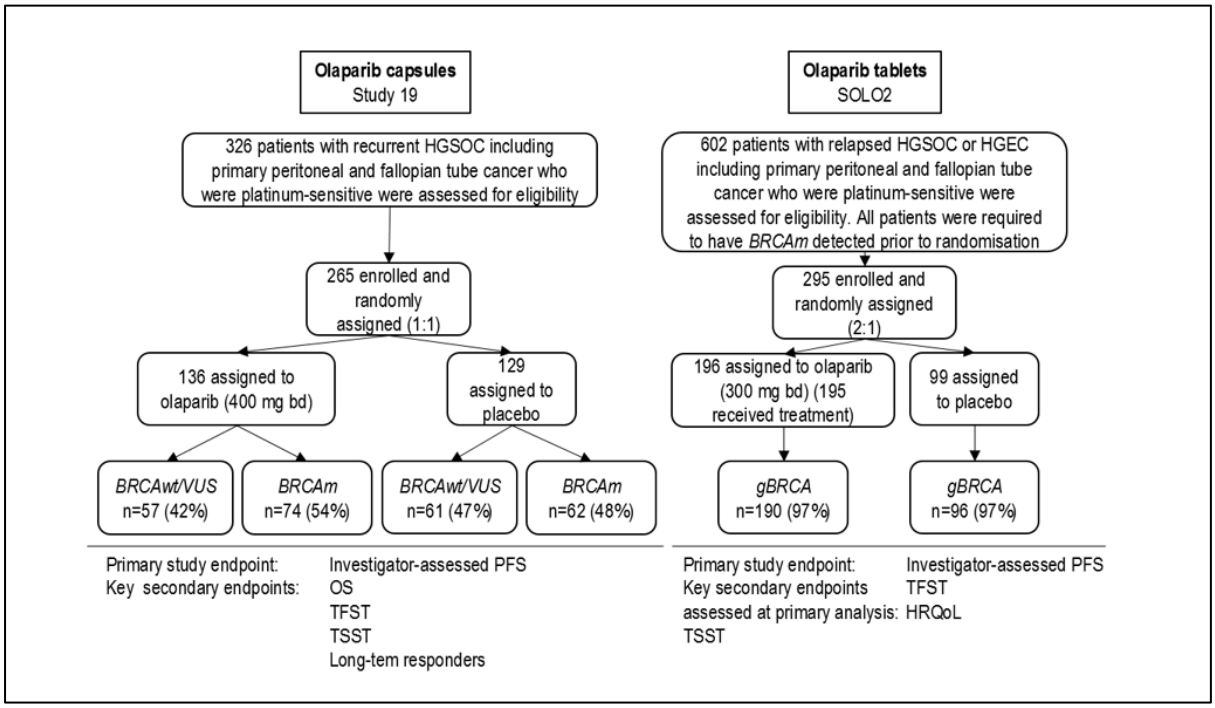
Table 4. Relevant studies. Only main publications

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer.Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, Scott C, Meier W, Shapira-Frommer R, Safra T, Matei D, Macpherson E, Watkins C, Carmichael J, Matulonis U. N Engl J Med. 2012 Apr 12;366(15):1382-92.	Phase II Randomised, Double Blind, Multicentre Study to Assess the Efficacy of AZD2281 in the Treatment of Patients with Platinum Sensitive Relapsed Serous Ovarian Cancer Following Treatment with Two or More Platinum Containing Regimens	NCT00753545	Enrolment between Aug 28, 2008 and Feb 9, 2010. Capsules Table 11: Data analyses of Study 19 Data cutoff / Primary analysis and reported secondary endpoints / Median follow-up (data maturity) 30 June 2010 / Investigator-assessed PFS and HRQoL / 5.6 months (PFS 58%) 31 October 2011 / Interim analysis of OS / Not stated (OS 38%) 26 November 2012 / Interim analysis of OS / 37.3 months (OS 58%) 30 September 2015 / Interim analysis of OS / 71.0 months (OS 77%) 9 May 2016 / Final analysis of OS / 78.0 months (OS 79%)	Overall Survival, Progression Free Survival, Discontinuations, AE grade 3 or more and HQoL.
Pujade-Lauraine E, Ledermann JA, Selle F, Gebski V, Penson RT, Oza AM, 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.	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.	NCT01874353	Enrolment between Sept 3, 2013, and Nov 21, 2014 Tablets	Overall Survival, Progression Free Survival, Discontinuations, AE grade 3
Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, Fabbro M, Ledermann JA, Lorusso D, Vergote I, Ben-Baruch NE, Marth C, Mądry R, Christensen RD, Berek JS, Dørum A, Tinker AV, du Bois A, González-Martín A,	A Phase 3 Randomized Double-blind Trial of Maintenance with Niraparib Versus Placebo in Patients with Platinum Sensitive Ovarian Cancer.	NCT01847274	Enrolment between Aug 28, 2008 and Feb 9, 2010. Between Aug 28, 2013, and June 1, 2015	Progression Free Survival, Discontinuations, AE grade 3

Follana P, Benigno B, Rosenberg P, Gilbert L, Rimel BJ, Buscema J, Balser JP, Agarwal S, Matulonis UA; N Engl J Med. 2016 Dec 1;375(22):2154-216				
Oza AM, Cibula D, Benzaquen AO, Poole C, Mathijssen RH, Sonke GS, et al. Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial. Lancet Oncol. 2015;16(1):87-97.	A Phase II Open Label Randomised Comparative Multicentre Study to Compare the Efficacy and Tolerability of Olaparib in Combination with Paclitaxel and Carboplatin Versus Paclitaxel and Carboplatin Alone in Patients With Platinum Sensitive Advanced Serous Ovarian Cancer	NCT01081951	Enrolment between Feb 12 and July 30, 2010. Primary data cutoff Oct 10, 2011. OS cutoff Jan 31, 2014	Overall Survival, Progression Free Survival, Discontinuations and AE grade 3
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. Aghajanian C, Blank SV, Goff BA, Judson PL, Teneriello MG, Husain A, Sovak MA, Yi J, Nycum LR. J Clin Oncol. 2012 Jun 10;30(17):2039-45.	A Phase III, Multicenter, Randomized, Blinded, Placebo-controlled Trial of Carboplatin and Gemcitabine Plus Bevacizumab in Patients with Platinum-sensitive Recurrent Ovary, Primary Peritoneal, or Fallopian Tube Carcinoma (OCEANS)	NCT00434642	Enrolment. April 2007 through January 2010. OS cutoff August 29, 2011	Progression Free Survival, Discontinuations, AE grade 3

4.2 Main characteristics of included studies

Figure 2. Design of olaparib studies in 2nd line OC



5 Clinical questions vs placebo *BRCAwt*

5.1 Overall Survival vs placebo *BRCAwt/VUS*

5.1.1 Presentation and results of relevant studies

Study 19

At the final analysis for OS (data cut-off: 12 May 2016), maturity had increased 2% since the previous data cut-off (30 September 2015) to 79% maturity (210 deaths out of 265 patients [7 further deaths since the last data cut-off]). The median duration of follow-up for the OS analysis was 6.5 years, representing the longest follow-up of patients treated with a PARPi to date [3, 4].

In the overall population, median OS was 2 months longer for olaparib-treated patients compared with placebo (29.8 months vs 27.8 months).

A retrospective, pre-planned subgroup analysis in Study 19 (table 5) evaluated the efficacy of olaparib in the *BRCAwt/vus* patient population, indicates that patients without *BRCAm* benefit from olaparib maintenance therapy. This subgroup analysis is important in establishing that the benefit seen in the overall patient population is not solely due to improved outcomes in the *BRCAm* population.

Patients were retrospectively assigned to the BRCA*wt/VUS* subgroup (n=118) if they had no deleterious *BRCA* mutation detected in the blood and/or the tumour, and data were available via a local test and/or retrospective testing using the BRACAnalysis assay (Myriad Genetics Laboratories) [3, 5].

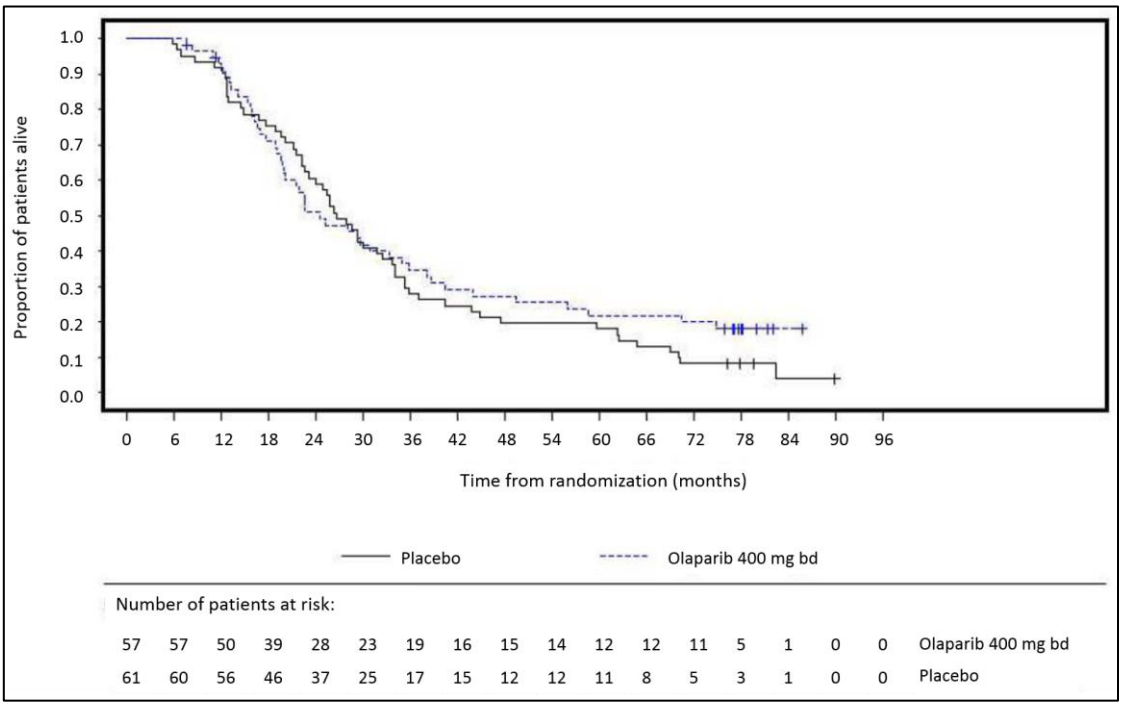
TABLE 5: OS BY *BRCA* MUTATION STATUS STUDY 19

	Full analysis set (n=265)		***BRCAm* (n=136)**		***BRCAwt/VUS* (n=118)**		***gBRCA* (n=96)**	
	O	**P**	**O**	**P**	**O**	**P**	**O**	**P**
Number of events: total number of patients (%)	98:136 (72)	112:129 (87)	49:74 (66)	50:62 (81)	45:57 (79)	57:61 (93)	35:53 (66)	34:43 (79)
Median, months	29.8	27.8	34.9	30.2	24.5	26.6	32.9	27.3
HR (95% CI)	0.73 (0.55, 0.95)		0.62 (0.42, 0.93)		0.84 (0.57, 1.25)		0.68 (0.42, 1.10)	
P value (2-sided)	*P*=0.02138		*P*=0.02140		*P*=0.39749		*P*=0.11363	

Source: Study 19 [3]

Kaplan-Meier survival curves (figure 3) showed some separation between treatment groups at the tail end of the curve for patients with BRCA*wt/VUS* ovarian cancer, suggesting that there may be a subset of patients with BRCA*wt/VUS* who receive long-term benefit from olaparib treatment (HR 0.84; 95% CI 0.57, 1.25; *P*=0.397 [data cut off: 9 May 2016] [3]).

FIGURE 3: KAPLAN-MEIER CURVE FOR OVERALL SURVIVAL IN THE *BRCAWT/VUS* PATIENT POPULATION (DATA CUT-OFF: 9 MAY 2016) (REF)



Source: Study 19 [3]

5.1.2 Long term responder's vs placebo

In Study 19 at the final analysis (9 May 2016), 15 patients (11%) received olaparib maintenance monotherapy for ≥6 years compared to only 1 patient (0.8%) who received placebo for ≥6 years. Five of these 15 patients (33%) treated for ≥6 years in the olaparib group were *BRCAwt*, providing further evidence that patients without *BRCA* mutation can derive substantial benefit from olaparib maintenance therapy. Biomarker analysis for deficiencies in the HRR pathway were performed in the long-term responder patient population using the Myriad MyChoice HRD and Foundation Medicine T5 genetic tests. Of the 15 patients who received olaparib for ≥6 years, 9 had *BRCAm*, of which 3 had *sBRCAm,* and there was a slight preponderance for *BRCA2* mutation. Of the *BRCAwt* patients, 1 patient had a RAD51B mutation (a gene involved in HRR); however, HRR mutations were not detected in all patients, and 1 patient tested negative for HRD. One patient was germline *BRCAwt,* but the tumour *BRCA* status was not determined [4].

A clinical and molecular analysis of patients with relapsed or PSR HGSOC who participated in Studies 19 and 41 was also performed to identify patients with a durable response to olaparib (patients who received olaparib for >2 years). Table 6 summarises characteristics of short-term and long-term responders by clinical and *BRCA* status. For olaparib, a higher proportion of durable response to short-term response (60.4%) was observed compared with placebo (11.1%; *P*<0.0001). *TP53*, *BRCA1*, and *BRCA2* mutations were most common in the group of long-term responders who received olaparib. Although no significant difference was observed

between long-term and short-term responders based on HRD score, there was a greater proportion of patients with a high HRD score (defined as ≥42) in the long-term responder population (96% vs 76% in the short-term responder population). This study indicates that long-term response to olaparib is related to HRD, including *BRCA* mutation. However, HRD status was not predictive of patient response, indicating that response to olaparib is multifactorial and is incompletely defined by current measures of HRD and *BRCA* status. In contrast, complete response to platinum-based chemotherapy at the time of olaparib maintenance was associated with long-term response to olaparib [6].

TABLE 6: PATIENTS ACHIEVING >2 YEARS OR <6 MONTHS OF THERAPY WITH OLAPARIB BY *BRCA* MUTATION STATUS FROM STUDIES 19 AND 41

Treatment duration	**Clinical status**				***BRCA* status**		
	Number of lines of prior chemotherapy, median (range)	**Initial FIGO state, n**	**RECIST at baseline, n**	**Platinum sensitivity status, n**	***BRCAm* (n=74)**	***BRCAwt* (n=57)**	***BRCA* missing (n=5)**
Olaparib arm (n=136)							
ST responders: <3 months 21 pts (15%)	2.8 (2-5)	1II/19III/1IV	PR: 16 CR: 5	6–12 months: 9 12 months: 12	10 (14%) 7=*BRCA1*	9 (16%)	2
LT responders: >2 years 32 pts (24%)	2.9 (2-8)	3I/II25III/3IV Missing: 1	PR: 14 CR: 18	6–12 months: 11 >12 months: 21	22 (30%) 10=*BRCA1*	10 (18%)	0
Placebo arm (n=129)							
ST responders: <3 months 40 pts (31%)	2.8 (2-8)	3I/II27III/8IV Missing: 2	PR: 25 CR: 15	6–12 months: 22 >12 months: 18	19 (31%) 16=*BRCA1*	18 (30%)	3
LT responders: >2 years 5 pts (4%)	2 (2)	5 III	PR: 1 CR: 4	6–12 months: 1 >12 months: 4	5 (8%) 4=*BRCA1*	0	0

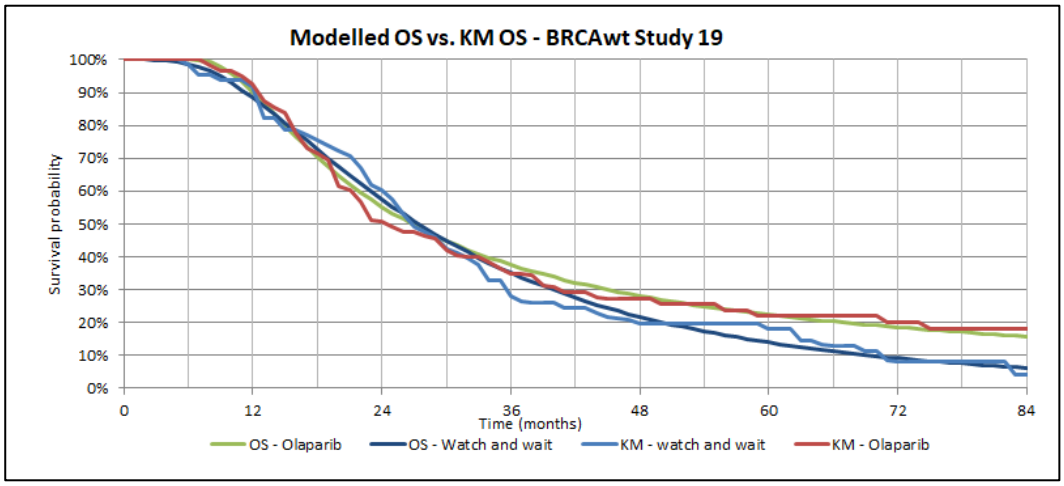
Source: [6]

5.1.3 Comparative OS analyses vs placebo *BRCAwt/VUS*

Modelled OS extrapolations (Generalized Gamma distribution) predict that treatment with olaparib will lead to a mean OS of approximately 51 months versus 36 months for watch and wait in BRCA*wt* patients (figure 4, AZ data-on-file). The incremental gain in average life expectancy is 15 months.

The long-term benefit from olaparib is highlighted by the right skewed OS curve with long tails for the BRCAwt/VUS population in Study 19 (FIGURE 3). The mean OS serve as a more adequate marker to describe the long-term benefit of olaparib since median parameters will underestimate the benefit of right skewed data [18].

Figure 4: Generalized gamma model for OS and the Kaplan-Meier plot for OS in Study 19 (*BRCAwt/VUS*):



Source: KM data:[7]. Generalized Gamma modelling: AZ data-on-file.

5.1.4 Conclusion OS analyses vs placebo *BRCAwt/VUS*

As mentioned in the EPAR, study 19 is not powered to show OS benefit in the BRCAwt/VUS population. Long-term follow-up (median 6.5 years) of OS in Study 19 demonstrated that olaparib generates a trend towards improved OS.[4] Median OS was 2 months longer for olaparib compared with placebo (29.8 months vs 27.8 months; HR 0.73; 95% CI 0.55, 0.95; P<0.02138) in the overall population Based on study 19 the OS result for the subset of patients with BRCAwt/VUS cannot meet the target of 3 months set by Medicinrådet/Fagudvalget. The median OS was 24.5 vs. 26.6 months(olaparib vs. placebo) with HR= 0.84; 95% CI 0.57, 1.25 and P=0.397 in favour of olaparib.

However, Kaplan-Meier survival curves (figure 3) showed some separation between treatment groups at the tail end of the curves for patients with *BRCAwt/VUS*, suggesting that there may be a subset of *BRCAwt/VUS* patients with who received long-term benefit from olaparib treatment.

EPAR:

The Study 19 was not powered and designed to show OS benefit. The descriptive final analysis (DCO: 09 May 2016) was performed at 79% maturity in the FAS (210 deaths out of 265 patients). Even if statistical significance was not reached, OS data were numerically in favour of the olaparib arm in terms of reduced risk of death (HR 0.73; 95% CI: 0.55, 0.95; p=0.02138) in the overall population.

In the *BRCAwt/VUS group*, the estimate for the median OS was 24.5 months in the olaparib arm and 26.6 months in the placebo arm, with 95%CI for HR exceeding 1 (HR 0.84 95%CI 0.57-1.25, p=0.3975), but as highlighted previously this patient population is highly heterogeneous and a larger sample size or analysis in specific subgroups would be more informative.

To identify patients who are likely to benefit to a greater extent, the MAH(AstraZeneca) should investigate predictive biomarkers within this patient group in the context of the OPINION study. Analysis of exploratory efficacy endpoints showed a reduction in the risk of discontinuation of study treatment or death, in the olaparib group, compared with the placebo group in overall population (FAS): HR of 0.39, 95% CI 0.30 to 0.51, p<0.00001, and a lengthening of time until the first subsequent anti-cancer therapy and the second subsequent therapy or death, compared with placebo: HR of 0.39, 95% CI 0.30 to 0.52, p<0.00001 and HR of 0.53, 95% CI 0.40 to 0.69, p<0.00001 for TFST and TSST respectively. These exploratory efficacy outcomes support the PFS results, by showing that the treatment benefit of olaparib is maintained beyond the treatment period. This beneficial effect of maintenance therapy was found whatever the subgroup. However, it was more pronounced in BRCA mutated patients.

5.2 Discontinuations due to adverse events vs. placebo. *BRCAwt*

5.2.1 Comparative analysis

Study 19

In Study 19, no single AE was the reason for discontinuation of more than 1 patient in either treatment group. The percentage of patients reported with AEs leading to discontinuation of study(FAS) treatment was low (5.9% and 1.6% of patients receiving olaparib and placebo, respectively). The proportion of patients experiencing an AE leading to permanent treatment discontinuation was also low in SOLO2 (only *BRCAm* patients); 10.8%.[4, 8]

5.2.2 Conclusion discontinuations AE vs. placebo. *BRCAwt/VUS*

In study 19, AEs leading to discontinuation occurred in eight (6%) olaparib-arm patients and two (2%) placebo-arm patients in the overall population. Four of the olaparib-arm patients had received two prior lines of chemotherapy, and four had received three prior lines; both placebo-arm patients had received two prior lines of chemotherapy. Three of the patients who discontinued olaparib due to an AE did so after 2 years of treatment; one due to grade 4 pancytopenia and grade 1 pharyngitis, one due to grade 2 bronchiectasis, and one with a new primary squamous cell carcinoma of the oral cavity.

Figure 5. Summary of number (%) of *BRCA wt/VUS* patients who had an AE leading to discontinuation of study treatment by preferred term, arranged by system organ class.

System organ class / MedDRA preferred term	Number (%) of patients [a] Olaparib 400 mg bd (N=57)		Placebo (N=61)	
Patients with an AE leading to discontinuation [b]	2	(3.5)	2	(3.3)
GASTROINTESTINAL DISORDERS	1	(1.8)	1	(1.6)
NAUSEA	1	(1.8)	1	(1.6)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1	(1.8)	0	
BRONCHIECTASIS	1	(1.8)	0	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0		1	(1.6)
RASH PRURITIC	0		1	(1.6)

AstraZeneca data on file DCO 09MAY2016

Figure 6a. Study 19. AE's leading to discontinuations (FAS)

	Olaparib 400 mg bd (N=136)		Placebo (N=128)				
	n	Number (%) of patients with events [a]	n	Number (%) of patients with events [a]	Statistic [b]	Estimate (95% CI)	p-value
SAE SOC: RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	136	5 (3.7)	128	1 (0.8)	Relative Risk	4.71 (0.56, 39.74)	0.1548
					Risk Difference	0.03 (-0.01, 0.06)	0.1061
SAE SOC: VASCULAR DISORDERS	136	1 (0.7)	128	1 (0.8)	Odds Ratio [c]	0.85 (0.05, 14.50)	0.9076
					Relative Risk	0.94 (0.06, 14.89)	0.9657
					Risk Difference	-0.00 (-0.02, 0.02)	0.9657
Common SAE: ANAEMIA	136	3 (2.2)	128	0		Not calculable	
Common SAE: CONSTIPATION	136	2 (1.5)	128	0		Not calculable	
Common SAE: DYSPNOEA	136	2 (1.5)	128	0		Not calculable	
Common SAE: FEMUR FRACTURE	136	2 (1.5)	128	0		Not calculable	
Common SAE: GASTRITIS	136	0	128	2 (1.6)		Not calculable	
Common SAE: PANCYTOPENIA	136	2 (1.5)	128	0		Not calculable	
Common SAE: SMALL INTESTINAL OBSTRUCTION	136	2 (1.5)	128	3 (2.3)	Odds Ratio [c]	0.70 (0.11, 4.35)	0.7029
					Relative Risk	0.63 (0.11, 3.69)	0.6064
					Risk Difference	-0.01 (-0.04, 0.02)	0.6052
AE with outcome=death	136	2 (1.5)	128	0		Not calculable	
AE leading to discontinuation of olaparib/placebo	136	8 (5.9)	128	2 (1.6)	Odds Ratio [c]	3.92 (0.81, 19.05)	0.0901
					Relative Risk	3.76 (0.81, 17.40)	0.0896

[a] Patients with multiple events in the same category are counted only once in that category.Patients with events in more than one category are counted once in each of those categories. [b] Odds ratio and relative risk <1, and risk difference <0 favours olaparib. [c] Odds ratio obtained from logistic regression adjusted for stratification variables. [d] Odds ratio obtained from unadjusted logistic regression (unadjusted due to sparse data). Source: Number of events Friedlander 2018 supplementary appendix [10]. OR and RR calculated by AstraZeneca

Figure 6b. Study 19. AE's leading to discontinuations (*BRCAwt/VUS*)

	Olaparib 400 mg bd (N=57)		Placebo (N=61)				
	n	Number (%) of patients with events [a]	n	Number (%) of patients with events [a]	Statistic [b]	Estimate (95% CI)	p-value
Common SAE: PAPILLARY THYROID CANCER	57	1 (1.8)	61	0		Not calculable	
Common SAE: SMALL INTESTINAL OBSTRUCTION	57	2 (3.5)	61	2 (3.3)	Odds Ratio [c]	1.20 (0.16, 9.12)	0.8612
					Relative Risk	1.07 (0.16, 7.35)	0.9450
					Risk Difference	0.00 (-0.06, 0.07)	0.9450
AE with outcome=death	57	0	61	0		Not calculable	
AE leading to discontinuation of olaparib/placebo	57	2 (3.5)	61	2 (3.3)	Odds Ratio [c]	1.12 (0.15, 8.53)	0.9101
					Relative Risk	1.07 (0.16, 7.35)	0.9450
					Risk Difference	0.00 (-0.06, 0.07)	0.9450
AE of CTCAE grade 3 or higher	57	26 (45.6)	61	17 (27.9)	Odds Ratio [c]	2.29 (1.06, 4.98)	0.0361
					Relative Risk	1.64 (1.00, 2.68)	0.0503
					Risk Difference	0.18 (0.01, 0.35)	0.0424

Odds ratio and relative risk <1, and risk difference <0 favours olaparib. Odds ratio obtained from logistic regression adjusted for stratification variables.

The target set by Fagudvalget/Medicinrådet is 5 % absolute difference. Only 2 patients(8 and 2 in FAS) in each group in the BRCAwt/VUS subpopulations discontinued treatment with RR 1.07 and with a very large CI (figure 6). We cannot meet/answer the target set for this clinical question mainly due to very low event rate.

5.3 Grade 3 or more events vs. placebo. *BRCAwt/VUS*

5.3.1 Comparative analysis

Study 19

In the overall study population, the proportion of patients that had a grade ≥3 AE was greater in the olaparib arm than the placebo arm (43% and 22%, respectively) (table 7,8). The most frequently reported AE of grade ≥3 was anaemia, which occurred at a higher rate than all other grade ≥3 events. Grade 3 events of anaemia were mainly managed through temporary reduction or cessation of olaparib and through blood transfusions[9]

Table 7: AEs (grade ≥3)

	Overall population			
n (%)	Olaparib *n* = 136	Placebo *n* = 128	Olaparib *n* = 136	Placebo *n* = 128
Preferred term	**All grades**		**Grade ≥3**	
Total episodes	**1796**	**1002**	**102**	**45**
Patients with any AE	**132 (97)**	**119 (93)**	**59 (43)**	**28 (22)**

Source: Friedlander 2018 supplementary appendix [10]

TABLE 8: COMMON AES AND HEMATOLOGICAL AES OF INTEREST IN STUDY 19

	All grades		Grade ≥3	
	Olaparib 400 mg bd (n=136)	**Placebo (n=128)**	**Olaparib 400 mg bd (n=136)**	**Placebo (n=128)**
Any AE	132 (97.1)	119 (93.0)	59 (43.4)	28 (21.9)
Nausea	96 (70.6)	46 (35.9)	3 (2.2)	0
Fatigue/asthenia	86 (63.2)	59 (46.1)	12 (8.8)	4 (3.1)
Vomiting	48 (35.3)	18 (14.1)	3 (2.2)	1 (0.8)
Diarrhoea	37 (27.2)	31 (24.2)	3 (2.2)	3 (2.3)
Anaemia*	31 (22.8)	9 (7.0)	10 (7.4)	1 (0.8)
Neutropenia	7 (5.1)	5 (3.9)	5 (3.7)	1 (0.8)
Thrombocytopenia	5 (3.7)	3 (2.3)	1 (0.7)	0

*Includes patients with anaemia, haemoglobin decreased, red blood cell count decreased, and haematocrit decreased
Source: Friedlander 2018 supplementary appendix [10]

SOLO2 (*BRCAm* and tablet formulation)

The proportion of patients that had a grade ≥3 AE was greater in the olaparib arm than the placebo arm (36.9% and 18.2%, respectively) (table 9 and appendix A6). The most frequently reported AE of grade ≥3 was anaemia, which occurred at a higher rate than all other grade ≥3 events (19.5% in the olaparib group and 2.0% in the placebo group). Grade 3 events of anaemia were mainly managed through temporary reduction or cessation of olaparib and through blood transfusions; patients treated with olaparib received more blood transfusions than the placebo group (17.9% and 1.0%, respectively) [8].

TABLE 9: AEs (GRADE ≥3) BY SYSTEM ORGAN CLASS AND PREFERRED TERM. SOLO2

	Number of patients (%)	
System organ class/MedDRA preferred term	**Olaparib 300 mg bd (n=195)**	**Placebo (n=99)**
Patients with AE of grade ≥3	72 (36.9)	18 (18.2)
Blood and lymphatic system disorders	43 (22.1)	5 (5.1)
Anaemia	38 (19.5)	2 (2.0)
Neutropenia	5 (2.6)	4 (4.0)
Leukopenia	3 (1.5)	0
GI disorders	16 (8.2)	6 (6.1)
Abdominal pain	5 (2.6)	3 (3.0)
Nausea	5 (2.6)	0
Vomiting	5 (2.6)	1 (1.0)
Diarrhoea	2 (1.0)	0
Intestinal obstruction	2 (1.0)	1 (1.0)
Mouth ulceration	2 (1.0)	0
Stomatitis	2 (1.0)	0
General disorders and administration site conditions	11 (5.6)	3 (3.0)
Asthenia	6 (3.1)	2 (2.0)
Fatigue	2 (1.0)	0
Investigations	9 (4.6)	3 (3.0)
Neutrophil count decreased	5 (2.6)	0
Platelet count decreased	2 (1.0)	0
White blood cell count decreased	2 (1.0)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (2.6)	1 (1.0)
Gastric cancer	2 (1.0)	0
Respiratory, thoracic and mediastinal disorders	3 (1.5)	0
Dyspnoea	2 (1.0)	0
Vascular disorders	2 (1.0)	1 (1.0)
Deep vein thrombosis	2 (1.0)	1 (1.0)

Source: [8]

EPAR

Overall, the most common AEs reported for both tablet and capsule pool were nausea, asthenia/fatigue, vomiting, diarrhoea and anaemia. Proportions of patients with AE of CTCAE Grade 3 or higher and SAE were lower in the tablet pool than in the capsule pool (respectively 45.3% and 26.4% vs. 36.1% and 19.7%). Anaemia was reported at an increased frequency with the tablet formulation as compared to the capsule formulation. However, anaemia remained manageable by interrupting or reducing the olaparib dose or giving blood transfusions, when indicated; treatment discontinuation was rarely required. Proportion of patients reporting events of CTCAE Grade ≥3 was lower in the tablet pool (36.1%) compared to the capsule pool (45.3%). The most commonly reported event of CTCAE Grade ≥3 was anaemia in all 4 populations; the proportion of patients with Grade ≥3 anaemia was higher in SOLO2 (19.5%) than in Study 19 (5.9%).

The incidence of AEs leading to discontinuation of olaparib was low. The only AE leading to discontinuation that occurred at ≥2% difference between any of the treatment groups was anaemia, which led to discontinuation in 3.1% patients in SOLO2 compared with no patients in Study 19. Discontinuations due to anaemia was also higher in the tablet pool than in the capsule pool, the difference was <2%). There was a similar broad range of time to onset of MDS/AML in both the olaparib- and placebo-treated patients, with no obvious difference in the median time to onset of events.

5.3.2 Conclusion Grade 3 or more adverse events vs. placebo *BRCAwt/VUS*

Long-term maintenance therapy with olaparib, evaluated in Study 19, resulting in 43% of patients experiencing grade 3/4 AEs vs. 22 % in the placebo arm(figure 8) [4].

At the final analysis (median follow-up >6 years) 72% of patients receiving olaparib had died while on treatment, in the 30 days follow-up period, and post follow-up, compared to 87% in the placebo group. Most deaths were considered to be related to ovarian cancer. 2 patients in the olaparib group had treatment-related AEs with an outcome of death [3].

Overall in Study 19, 3 patients had MDS/AML, 2 in the olaparib group and 1 in the placebo group [4].

The AE profile, severity and incidence are similar in the overall study population and *BRCAm* in Study 19. Although the study does not report AE results from the *BRCAwt/VUS* subgroup it can be estimated that incidence in this group is similar to the overall study population.

Figure 7. Study 19. AE leading to discontinuations and Grade 3 or more AE. FAS

	Olaparib 400 mg bd (N=136)		Placebo (N=128)				
	n	Number (%) of patients with events [a]	n	Number (%) of patients with events [a]	Statistic [b]	Estimate (95% CI)	p-value
AE leading to discontinuation of olaparib/placebo	136	8 (5.9)	128	2 (1.6)	Risk Difference	0.04 (-0.00, 0.09)	0.0599
AE of CTCAE grade 3 or higher	136	59 (43.4)	128	28 (21.9)	Odds Ratio [c]	2.74 (1.59, 4.70)	0.0003
					Relative Risk	1.98 (1.36, 2.90)	0.0004
					Risk Difference	0.22 (0.11, 0.32)	0.0001

Odds ratio and relative risk <1, and risk difference <0 favours olaparib. Odds ratio obtained from logistic regression adjusted for stratification variables. Source: Ledermann 2018 supplementary appendix[10]

Findings from Study 19(capsules) and SOLO2(tablets) indicate that there is a consistent safety and tolerability profile for olaparib monotherapy between the capsule and tablet formulation. In both Study 19 and SOLO2, the safety and AE profiles were similar between olaparib and placebo treatment groups. The majority of AEs reported in SOLO2 and Study 19 were grade ≤2 [4, 8].The most commonly reported AEs for patients in the olaparib group in both studies

were nausea, fatigue/asthenia, vomiting, and diarrhoea[4, 8]. These events were manageable by either treatment interruption, dose reduction, or therapeutic intervention [9]. There was a higher frequency of grade ≥3 AEs of anaemia reported in SOLO2 compared with Study 19 (19.5% vs 7.4% respectively).

Long-term data from Study 19 suggest that olaparib tolerability was acceptable, predictable and non-cumulative and considered suitable for the maintenance setting [3]. The tolerability observed in SOLO2 was consistent with previous studies of olaparib monotherapy [8, 9].

The target set by Medicinrådet/Fagudvalget is 10 % absolute difference. The difference in the FAS population is 21,5 % with a RR of 1.98. For the BRCAwt/VUS subgroup the corresponding numbers (figure 7) are 17,7 % and a RR of 1.64 CI (1.00, 2.68). Olaparib vs. placebo do not meet the target for this clinical question.

5.3.3 AE of special interest and indirect comparison of AEs vs. other PARPi's

Indirect comparison vs. other PARPi's

Indirect treatment comparisons, using data from SOLO2 and Study 19, suggest that olaparib has an improved safety profile vs niraparib, with a reduced Odds Ratio(OR) of grade ≥3 AEs and drug interruption in patients with *gBRCA* mutation, and reduced OR of grade ≥3 AEs in patients who are *gBRCAwt*

ITCs of safety data from SOLO2 and ENGOT-OV16/NOVA has been used to compare the safety profiles of olaparib and niraparib in the *gBRCAm* patient population (table 10 and figure 8). In comparison to niraparib, olaparib had statistically significant reduced OR of grade 3/4 AEs, and incidences of required dose interruptions and dose reductions due to AEs. Compared to niraparib, olaparib also had, non-statistically significant, numerically lower odds of incidences of any AE, grade 3/4 AEs, and discontinuation of treatment due to an AE [11, 12].

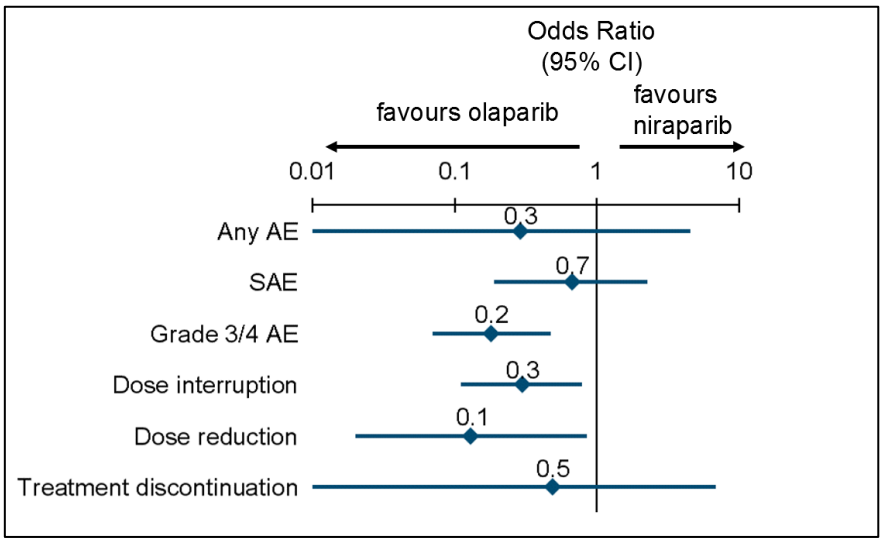
TABLE 10: RESULTS OF INDIRECT TREATMENT COMPARISONS FOR SAFETY ENDPOINTS IN THE *GBRCAM* PATIENT POPULATION

	Comparison	**Risk ratio (95% CI)**	**Odds ratio (95% CI)**
Any AE	Olaparib vs niraparib	0.99 (0.95, 1.02)	0.29 (0.01, 4.52)
SAEs	Olaparib vs niraparib	0.73 (0.29, 1.85)	0.67 (0.19, 2.25)
Grade 3/4 AEs	Olaparib vs niraparib	0.51 (0.34, 0.74)	0.18 (0.07, 0.47)
Dose interruption due to an AE	Olaparib vs niraparib	0.60 (0.38, 0.90)	0.30 (0.11, 0.79)
Dose reduction due to an AE	Olaparib vs niraparib	0.39 (0.15, 0.93)	0.13 (0.02, 0.85)
Discontinuation of treatment due to an AE	Olaparib vs niraparib	0.53 (0.03, 5.38)	0.49 (0.01, 6.91)

Source: Systematic literature review and meta-analysis of maintenance with a PARPi after response to two or more lines of chemotherapy in patients with platinum-sensitive relapsed ovarian cancer. Technical report. October 2017. Tables 27-32 [11].
R Hettle, A Sackeyfio et al. Value in Health. 20 (9) October 2017 [12].

See appendix (A2 and A6) for detailed AE overview per study.

FIGURE 8: INDIRECT TREATMENT COMPARISON RESULTS OF THE SAFETY AND TOLERABILITY OF OLAPARIB VS NIRAPARIB IN *GBRCAM* PSR OVARIAN CANCER



Source: data compiled from: Systematic literature review and meta-analysis of maintenance with a PARPi after response to two or more lines of chemotherapie in patients with platinum-sensitive relapsed ovarian cancer. Technical report. October 2017.[11]
R Hettle, A Sackeyfio et al. Value in Health. 20 (9) October 2017 [12].

Treatment with olaparib was associated with a significantly lower risk of the following any grade events: constipation (OR 0.32; 95% CI 0.12, 0.79), insomnia (OR 0.20; 95% CI 0.05, 0.77), and thrombocytopenia (OR 0.03; 95% CI 0.00, 0.26); and the following grade 3/4 events: neutropenia (OR 0.06; 95% CI 0.01, 0.45) and thrombocytopenia (OR 0.001, 95% CI 0.00, 0.09) in comparison to niraparib.[11]

5.4 PFS vs placebo Study 19 *BRCAwt/VUS*

5.4.1 Presentation and results of relevant studies

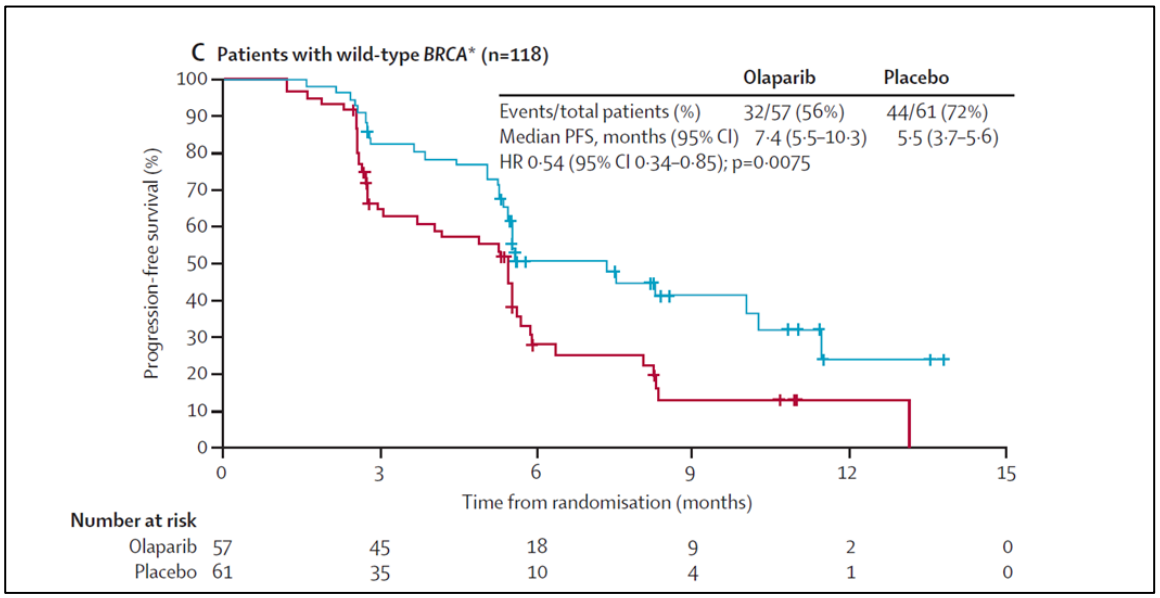
Olaparib treatment resulted in a significantly longer investigator-assessed PFS than placebo in the overall study population (8.4 vs 4.8 months, respectively; HR 0.35; 95% CI 0.25, 0.49; *P*<0.00001). BICR-assessed PFS was consistent with the investigator-assessed PFS (HR 0.39; 95% CI 0.27, 0.55; *P*<0.001).[3, 13] Evaluation of PFS based on patient *BRCA* status was also performed following retrospective *BRCA* genetic testing of trial participants. PFS was longest in the olaparib treatment arm of the *BRCAm* and *gBRCA* subgroups (11.2 months) and was also extended in the overall population and in the *BRCAwt/VUS* subgroup (table 11 and figure 9).[3, 5]

TABLE 11: SUBGROUP ANALYSIS OF PFS IN STUDY 19

	Overall population (n=265)		*BRCAm* (n=136)		*BRCAwt/VUS* (n=118)		*gBRCA* (n=96)	
Median PFS, months	8.4	4.8	11.2	4.3	7.4	5.5	11.2	4.1
HR (95% CI)	0.35 (0.25, 0.49)		0.18 (0.10, 0.31)		0.54 (0.34, 0.85)		0.17 (0.09, 0.31)	
P value (2-sided)	<0.00001		<0.00001		0.00745		<0.00001	

Data are from the cut off of 30 June 2010. Source: [5]

FIGURE 9: SUBGROUP ANALYSIS OF PFS IN BRCA*WT/VUS* IN STUDY 19



*Includes patients with BRCA mutation with unknown significance. Source: [5]

A careful evaluation of Study 19 dataset reveals a feature with impact on assessment of absolute difference in median PFS (Δ of 3 months). The median PFS for the control arm in the ITT population was 4.8 months. Taking the positive prognostic value of a harbouring a BRCA mutation into account, it is striking that the median PFS in the control arm for the *BRCAwt/VUS* subgroup (5.5 months) is longer than the observed median PFS for the control arm in the *BRCAm* subgroup (4.3 month).

Other RCT investigating PARPi in a broad group of platinum sensitive relapsed ovarian cancer reveals the opposite relationship. In the NOVA study, a median PFS of 3.7 months was observed for the non-gBRCA HRD+ subgroup and corresponding value being 3.8 months for the non-gBRCA HRD÷ subgroup and 5.5 months for the *gBRCAm* cohort [14].

The 1.7 months difference in control arm between actual comparable subgroups in Study 19 and NOVA have major implications on assessment of minimum clinical relevant difference per Medicinråds protocol.

The absolute difference observed in Study 19 *BRCAwt/VUS* was 1.9 months, not reaching the target of 3 months set by Medicinrådet. However, with a shorter median PFS for the control arm as could have been expected based on the observation in the NOVA study, the target of 3 months would have been reached.

In addition, a 3-month median PFS difference between olaparib and control arm was observed for the subgroup of 2L patients only, within the *BRCAwt/VUS* population (8.3 months vs 5.3 months) (table 13).

The observed median PFS value for the olaparib arm in Study 19 BRCAwt/VUS was 7.4 months. A median PFS comparable to median PFS observed in the NOVA study for the non-gBRCA HRD+ subgroup (excluding sBRCA mutated patients) (9.3 months) and the non-gBRCA HRD÷ group excluding sBRCA mutated (6.9 months). Since the HRD status in the Study 19 *BRCAwt/VUS* subgroup was unknown, it is reasonable to expect a median PFS between the two HRD+/HRD- subgroups in the NOVA study. The potential impact of a larger proportion of patients having had 3 or more prior lines of chemotherapy in Study 19 however impairs additional comparison [5, 14].

5.4.2 Comparative analyses

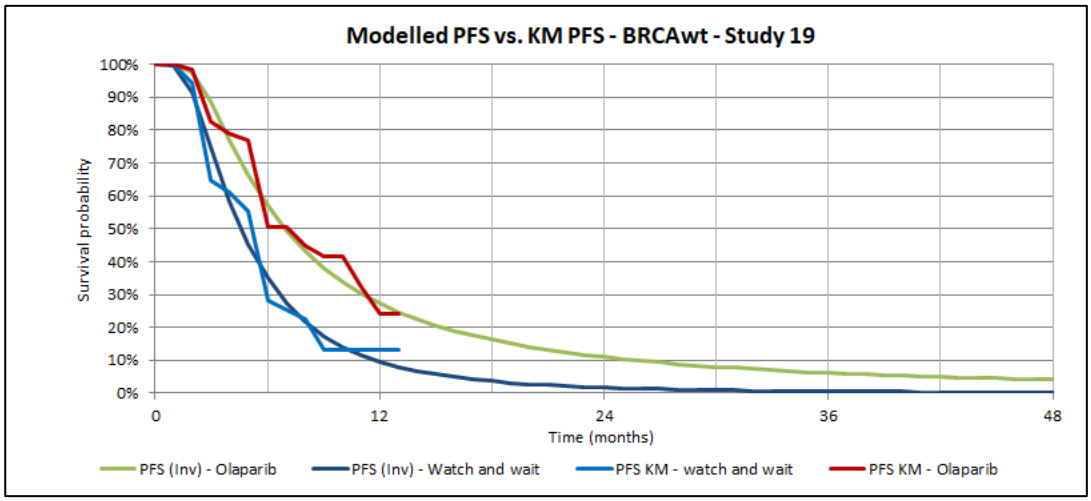
TABLE 12: DETAILED SUBGROUP ANALYSIS OF PFS IN STUDY 19

	Olaparib 400 mg bd (N=136)			Placebo (N=129)					
Subgroup	n	Number (%) of patients with events	Median time (months) [a]	n	Number (%) of patients with events	Median time (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Age group									
<65	91	36 (39.6)	10.8	94	68 (72.3)	4.1	0.31	0.20, 0.46	<0.0001
>=65	45	24 (53.3)	8.0	35	26 (74.3)	5.5	0.57	0.32, 1.00	0.0481
Number of lines of prior chemotherapy									
2 prior regimens	59	28 (47.5)	10.0	63	45 (71.4)	5.3	0.41	0.25, 0.65	0.0002
>=3 prior regimens	77	32 (41.6)	8.4	66	49 (74.2)	4.4	0.35	0.22, 0.55	<0.0001
BRCA status 1									
gBRCA	53	17 (32.1)	11.2	43	33 (76.7)	4.1	0.20	0.11, 0.36	<0.0001
sBRCA	8	3 (37.5)	NE	10	6 (60.0)	7.7	0.62	0.13, 2.34	0.4842
tBRCA	13	6 (46.2)	12.4	9	7 (77.8)	4.8	0.38	0.12, 1.16	0.0875
BRCA wt/VUS	57	32 (56.1)	7.4	61	44 (72.1)	5.5	0.52	0.33, 0.83	0.0054
BRCA status 2									
BRCA 1/2	74	26 (35.1)	11.2	62	46 (74.2)	4.3	0.26	0.16, 0.43	<0.0001
BRCA wt/VUS	57	32 (56.1)	7.4	61	44 (72.1)	5.5	0.52	0.33, 0.83	0.0054

Source: [5]. DCO 30JUN2010.

The long-term benefit from olaparib is highlighted by the right skewed PFS curve with long tails for the BRCAwt/VUS population in Study 19 (figure 10). The mean PFS serve as a more adequate marker to describe the long-term benefit of olaparib since median parameters will underestimate the benefit of right skewed data [18]. Modelled PFS extrapolations (Generalized Gamma distribution) predict that treatment with olaparib will lead to a mean PFS of approximately 13.3 months versus 6.2 months for watch and wait in *BRCAwt/VUS* patients. The incremental gain in **mean** PFS is 7.1 months.

Figure 10. Generalized gamma model for PFS and the Kaplan-Meier plot for PFS in Study 19 (BRCAwt/VUS).



Source: KM PFS data: [5]. Generalized Gamma modelling: AZ data-on-file

It is up to Fagudvalget to consider whether modelling should be part of the evaluation of olaparib vs. placebo for the clinical question PFS.

5.4.3 Conclusion PFS vs. placebo BRCA*wt/VUS*

Data from study 19 show that for the *BRCAwt/VUS* group (table 12) an absolute value of 1.9 months difference was seen for olaparib vs. placebo, HR 0.54 with 95% CI 0.34, 0.85. In the overall study population, the investigator-assessed PFS showed an absolute difference of 4 months (8.4 vs 4.8 months, respectively; HR 0.35; 95% CI 0.25, 0.49; *P*<0.00001). However, in the subset of BRCAwt/VUS group treated in 2nd line the numerical benefit of olaparib compared with placebo was 3.0 months (8.3 vs 5.3 months, respectively; HR 0.51; 95% CI 0.28, 0.92; P = 0.0265). For subgroup analysis (not BRCA status) see table 13.

Table 13. Study 19. Summary of subgroup analysis of PFS (investigator) . FAS

	Olaparib 400 mg bd (N=57)			Placebo (N=61)					
Subgroup	n	Number (%) of patients with events	Median time (months) [a]	n	Number (%) of patients with events	Median time (months) [a]	Hazard ratio [b]	95% CI [b]	2-sided p-value [b]
Age group									
<65	30	14 (46.7)	7.5	38	26 (68.4)	4.0	0.43	0.22, 0.81	0.0089
>=65	27	18 (66.7)	5.6	23	18 (78.3)	5.5	0.68	0.35, 1.33	0.2593
Response to final platinum chemotherapy									
Complete response	20	8 (40.0)	10.0	25	13 (52.0)	5.5	0.48	0.19, 1.14	0.0968
Partial response	37	24 (64.9)	5.5	36	31 (86.1)	4.0	0.54	0.31, 0.92	0.0235
Time to PD for penultimate platinum chemo									
> 6 - < 12 months	23	13 (56.5)	5.6	24	16 (66.7)	5.5	0.65	0.31, 1.36	0.2554
>12 months	34	19 (55.9)	7.5	37	28 (75.7)	5.5	0.48	0.26, 0.85	0.0126
Ethnic descent									
Jewish	6	1 (16.7)	NE	3	2 (66.7)	5.7	NC	NC	NC
Non Jewish	51	31 (60.8)	5.6	58	42 (72.4)	5.5	NC	NC	NC
Number of lines of prior chemotherapy									
2 prior regimens	32	19 (59.4)	8.3	35	26 (74.3)	5.3	0.51	0.28, 0.92	0.0265
>=3 prior regimens	25	13 (52.0)	5.5	26	18 (69.2)	5.5	0.58	0.28, 1.17	0.1264

Source: [5]. DCO 30JUN2010. HR calcaled by AstraZeneca

The target set by Medicinrådet/Fagudvalget is 3 months and is achieved for olaparib vs. placebo for the overall population but not in the subset of 118 patients with BRCAwt/VUS olaparib. The absolute difference observed in Study 19, BRCAwt/VUS was 1.9 months not reaching the target of 3 months. However as mentioned above, with a shorter median PFS for the control arm as observed in NOVA study the target of 3 months would have been reached for the BRCAwt/VUS subgroup. In addition, a 3.0 months median PFS difference between active and control arm were observed for the subgroup of 2nd line patients in the BRCAwt/VUS population (8.3 months vs 5.3 months)

Long term responders

In Study 19 at the final analysis (9 May 2016), 15 patients (11%) received olaparib maintenance monotherapy for ≥6 years compared to only 1 patient (0.8%) who received placebo for ≥6 years. Five patients out of 15 (33%) treated for ≥6 years in the olaparib group were *BRCAwt*, providing further evidence that patients without *BRCA* mutation can derive substantial benefit from olaparib maintenance therapy.

EPAR

The PFS improvement in the overall population was clinically relevant and observed regardless the sub-groups (BRCAm and non-mutated BRCA population). All analyses of PFS, including sensitivities (eg, evaluation time bias, attrition bias, and those adjusted for ECOG PS) demonstrated a consistent and favourable treatment benefit for olaparib.

However, magnitude of PFS improvement was distinct depending on the BRCA mutation status (HR of 0.18 in BRCAm and HR of 0.54 in non-BRCAm). This difference explains why the HR of the overall population is pulled upward (HR 0.39; 95% CI: 0.28, 0.56; p<0.00001). In order to better estimate the magnitude of benefit in patients without germline BRCA1/2 mutations, the MAH(AstraZeneca) should conduct and submit the results of the OPINION study, a phase IIIb single-arm, open-label, multicentre study of maintenance therapy in PSR non-germline BRCA mutated ovarian cancer patients who are in complete or partial response following platinum-based chemotherapy.

5.5 QoL vs. placebo FAS.

5.5.1 Comparative analyses

The impact of olaparib on HRQoL was evaluated as a secondary endpoint in Study 19(table 14), the results of which were used to inform the HRQoL assessments in the subsequent confirmatory phase 3 trial, SOLO2 [15]. The QoL question was the focus of the publication by Ledermann et al, BJC 2016.The primary analysis of HRQoL was performed using the Trial Outcome Index of the Functional Assessment of Cancer Therapy−Ovarian (FACT−O), with secondary analyses performed with the entire FACT-O questionnaire and the Functional Assessment of Cancer Therapy/National Comprehensive Cancer Network Ovarian Symptom Index (FOSI) assessment [15]. Patients completed the FACT-O questionnaire at baseline and monthly thereafter from randomisation until confirmed disease progression or until the primary data cut-off date (30 June 2010) [15].

Data by BRCA status from the publication is shown below. Data for *BRCAwt/VUS* is not available in the publication and the questions will be answered based on the overall population.

Table 14a: HRQoL best response for the overall population and by *BRCA* status

	Overall population, *n* (%)		*BRCA*m, *n* (%)		g*BRCA*m, *n* (%)	
	Olaparib	Placebo	Olaparib	Placebo	Olaparib	Placebo
TOI	*n*=115	*n*=111	*n*=64	*n*=53	*n*=45	*n*=37
Baseline score, mean (s.d.)	81.7 (11.8)	81.5 (11.6)	79.9 (12.1)	79.5 (12.1)	79.5 (12.3)	81.0 (11.0)
Improved	23 (20.0)	20 (18.0)	16 (25.0)	10 (18.9)	12 (26.7)	3 (8.1)
No change	72 (62.6)	67 (60.4)	38 (59.4)	30 (56.6)	27 (60.0)	22 (59.5)
Worsened	16 (13.9)	20 (18.0)	7 (10.9)	10 (18.9)	4 (8.9)	9 (24.3)
Non-evaluable	4 (3.5)	4 (3.6)	3 (4.7)	3 (5.7)	2 (4.4)	3 (8.1)
FOSI	*n*=117	*n*=115	*n*=66	*n*=56	*n*=46	*n*=39
Baseline score, mean (s.d.)	26.1 (3.4)	25.4 (3.8)	25.9 (3.4)	24.8 (4.1)	25.8 (3.3)	25.1 (4.1)
Improved	20 (17.1)	17 (14.8)	14 (21.2)	9 (16.1)	12 (26.1)	5 (12.8)
No change	74 (63.2)	74 (64.3)	39 (59.1)	36 (64.3)	26 (56.5)	23 (59.0)
Worsened	20 (17.1)	21 (18.3)	11 (16.7)	9 (16.1)	6 (13.0)	9 (23.1)
Non-evaluable	3 (2.6)	3 (2.6)	2 (3.0)	2 (3.6)	2 (4.3)	2 (5.1)
FACT-O	*n*=114	*n*=111	*n*=63	*n*=53	*n*=45	*n*=37
Baseline score, mean (s.d.)	121.9 (17.3)	119.7 (17.4)	118.9 (18.1)	115.9 (18.9)	119.5 (18.5)	118.6 (17.2)
Improved	24 (21.1)	21 (18.9)	17 (27.0)	11 (20.8)	13 (28.9)	4 (10.8)
No change	68 (59.6)	63 (56.8)	35 (55.6)	26 (49.1)	25 (55.6)	19 (51.4)
Worsened	20 (17.5)	24 (21.6)	10 (15.9)	14 (26.4)	6 (13.3)	12 (32.4)
Non-evaluable	2 (1.8)	3 (2.7)	1 (1.6)	2 (3.8)	1 (2.2)	2 (5.4)
Nausea	*n*=115	*n*=113	*n*=64	*n*=54	*n*=44	*n*=37
Improved	5 (4.3)	11 (9.7)	0 (0)	6 (11.1)	0 (0)	4 (10.8)
No change	69 (60.0)	77 (68.1)	43 (67.2)	38 (70.4)	31 (70.5)	24 (64.9)
Worsened	37 (32.2)	19 (16.8)	18 (28.1)	5 (9.3)	12 (27.3)	4 (10.8)
Non-evaluable	4 (3.5)	6 (5.3)	3 (4.7)	5 (9.3)	1 (2.3)	5 (13.5)
Vomiting	*n*=115	*n*=111	*n*=65	*n*=54	*n*=46	*n*=38
Improved	6 (5.2)	5 (4.5)	2 (3.1)	2 (3.7)	2 (4.3)	1 (2.6)
No change	95 (82.6)	94 (84.7)	54 (83.1)	45 (83.3)	38 (82.6)	31 (81.6)
Worsened	7 (6.1)	6 (5.4)	3 (4.6)	3 (5.6)	3 (6.5)	2 (5.3)
Non-evaluable	7 (6.1)	6 (5.4)	6 (9.2)	4 (7.4)	3 (6.5)	4 (10.5)

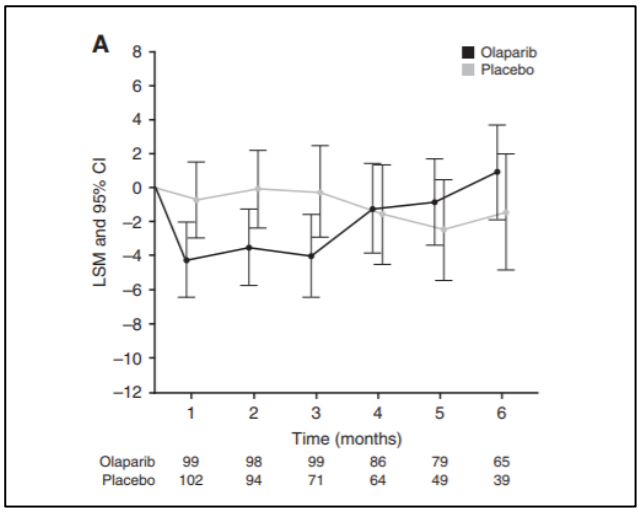
Source: [15]

Table 14b: Time to worsening of TOI, FOSI and FACT-O overall population, patients with *BRCA*m, and g*BRCA*m

	TOI						FOSI						FACT-O					
	Overall population		*BRCA*m		g*BRCA*m		Overall population		*BRCA*m		g*BRCA*m		Overall population		*BRCA*m		g*BRCA*m	
	Olap (n=115)	Pla (n=111)	Olap (n=64)	Pla (n=53)	Olap (n=45)	Pla (n=37)	Olap (n=117)	Pla (n=115)	Olap (n=66)	Pla (n=56)	Olap (n=46)	Pla (n=39)	Olap (n=114)	Pla (n=111)	Olap (n=63)	Pla (n=53)	Olap (n=45)	Pla (n=37)
Events, n (%)	64 (55.7)	56 (50.5)	33 (51.6)	29 (54.7)	21 (46.7)	23 (62.2)	77 (65.8)	67 (58.3)	45 (68.2)	35 (62.5)	28 (60.9)	28 (71.8)	72 (63.2)	63 (56.8)	39 (61.9)	31 (58.5)	27 (60.0)	24 (64.9)
Median time to worsening, months[a]	3.8	4.6	5.7	3.7	7.4	3.6	2.8	3.7	2.8	3.7	3.7	3.3	2.8	4.6	3.2	4.4	3.2	3.7
Treatment effect[b]																		
Hazard ratio (95% CI)	1.08 (0.75, 1.55)		0.80 (0.48, 1.34)		0.54 (0.30, 0.99)		1.22 (0.88, 1.71)		1.15 (0.74, 1.81)		0.71 (0.42, 1.22)		1.16 (0.83, 1.64)		1.04 (0.65, 1.69)		0.84 (0.48, 1.48)	
2-sided p-value	0.68		0.4		0.05		0.23		0.53		0.21		0.39		0.87		0.55	

[a]Calculated using the Kaplan-Meier technique; [b]analysis was performed using a Cox proportional hazards model with factors for treatment, ethnic descent, platinum sensitivity and response to final platinum therapy; HR <1 favours olaparib. Source Ledermann 2016 suppl. [15]

Table 15: FACT-O total score change from baseline to 6 months for the overall population



Worsening of FACT-O indicated with a negative score. Olaparib/Placebo indicates the number of patients who completed the assessment at each time point. Abbreviations: CI ¼ confidence interval; LSM ¼ least squares mean. Source Ledermann 2016 [15]

Conclusion adopted from source 15 and based on the overall population "No statistically significant differences were observed between treatment groups for improvement in the FACT-O score in the overall population. The FACT-O total score remained consistent with baseline and comparable between groups and over time. Time to FACT-O score worsening in the overall population was numerically shorter with olaparib vs placebo (2.8 vs 4.6 months, respectively; HR 1.16; 95% CI 0.83, 1.64; P=0.39)".

Target from Fagudvalget/Medicinrådet is a difference of 10 percentage points in number of patients that do not show a significant deterioration of OoL. No statistically significant differences were observed between treatment groups (21% vs 19% for olaparib vs placebo) for improvement in the FACT-O score in the overall population (OR 1.17; 95% CI 0.60, 2.27; P ¼ 0.65)([15]). *80.7 % showed no change or improvement in the durvalumab group vs. 75,7% in the placebo arm (table 14a and* [15]) an absolute difference of 5 %. The target is not met.

5.6 Other endpoints olaparib vs. placebo *BRCAwt/VUS*

There was a statistically significant extension of PFS, TFST, and TSST in patients on olaparib maintenance treatment compared to the placebo group in the *BRCAwt/VUS* subgroup, although the treatment benefit was smaller than for the *BRCAm* population (table 16)[3].

TABLE 16: EFFICACY OUTCOMES BY *BRCA* MUTATION STATUS

	PFS (DCO 30 June 2010)				**TFST (DCO 9 May 2016)**				**TSST (DCO 9 May 2016)**			
	***BRCAwt/ VUS* n=118**		***BRCAm* n=136**		***BRCAwt/ VUS* n=118**		***BRCAm* n=136**		***BRCAwt/ VUS* n=118**		***BRCAm* n=136**	
	O	**Pbo**	**O**	**Pbo**	**O**	**Pbo**	**O**	**Pbo**	**O**	**Pbo**	**O**	**Pbo**
Median, months	7.4	5.5	11.2	4.3	12.9	6.9	15.6	6.2	17.0	14.7	21.4	15.3
HR (95% CI)	0.54 (0.34, 0.85)		0.18 (0.10, 0.31)		0.45 (0.30, 0.66)		0.33 (0.22, 0.49)		0.63 (0.43, 0.94)		0.43 (0.29, 0.64)	
P value (2-sided)	0.00745		<0.00001		0.00006		<0.00001		0.02263		0.00003	
Kaplan-Meier plot	NA		NA		NA		NA		NA		NA	

TFST=time to first subsequent treatment or death; TSST=time to second subsequent treatment or death.Source:[3]

5.7 Overall conclusion vs. placebo BRCA*wt/VUS*

Study 19 was not designed to evaluate the efficacy of olaparib by *BRCA* status. However, a pre-planned, retrospective, exploratory analysis of efficacy endpoints was performed according to *BRCA* status, which further characterised the clinical efficacy of olaparib (capsules). Following local and central testing of blood and tumour samples, *BRCA* mutational data was available for 254 (96%) patients. For the efficacy endpoints, a HR (95% CI) of 0.54 (0.34, 0.85) were demonstrated for *BRCAwt/VUS* subgroup in Study 19. The magnitude of risk reduction is comparable with observation from other RCTs investigating the clinical impact of PARPi's in a maintenance setting in *BRCA*wt/*VUS* patients. However, we have not been able to meet the numerical target of 3 months benefit of olaparib compared to placebo for *BRCAwt/VUS* set by Medicinrådet. Surprisingly the mPFS control arm in Study 19 *BRCAwt/VUS* were longer than the control arm in *BRCAm* subgroup in Study19. In addition, the comparable mPFS for the control arms in the NOVA study were 1.7 months shorter, potential indicating that delta mPFS in Study 19 *BRCAwt/VUS* were underestimated due to a relative longer mPFS in the control arm. Despite these findings a 3 months gain were demonstrated for the subset of *BRCAwt/VUS* group treated in 2nd line the numerical benefit of olaparib compared with placebo was 3.0 months (8.3 vs 5.3 months, respectively; HR 0.51; 95% CI 0.28, 0.92; P = 0.0265).

Regarding OS, a HR of 0.84 (0.57, 1.25) were demonstrated indicating a long-term benefit from olaparib treatment in *BRCAwt/VUS* patients. However, the numerical target of 3 months benefit for m OS were not meet for this subgroup. Study 19 was not powered to show an OS benefit however a proportion of patients was shown to obtain long term benefit of olaparib regardless of their BRCA mutation status. In Study 19, >20% of the overall patient cohort remained on olaparib maintenance therapy for ≥2 years, and >10% remain on therapy for ≥6 years. A substantial proportion of long-term responders to olaparib were *BRCAwt* (33%) patients. Long-term follow-up (median 6.5 years) of OS in Study 19 demonstrated that olaparib generates a trend towards improved OS in the overall population. Median OS was 2 months longer for olaparib compared with placebo.

The fact that a number of BRCAwt/VUS patients in study 19 have long term benefit of olaparib treatment highlight that while BRCA mutation is a prognostic marker for olaparib, platinum sensitivity can identify patients with long term benefit of olaparib that are not harbouring a BRCA mutation. For PFS, the target of 3 months benefit set by Medicinrådet was met if only evaluating the BRCAwt/VUS patients treated at their first platinum sensitive relapse.

Regarding side effects, it was not possible to show a difference in rate of discontinuations due to a low event rate. Treatment with olaparib was associated with a higher rate of grade 3 or higher adverse events compared with placebo (no treatment) and did not meet the target of 10 percentage point difference set by Medicinrådet. The most frequent grade 3 or higher adverse event associated with olaparib treatment was anemia. Anaemia was mainly managed through temporary reduction or cessation of olaparib and through blood transfusions. Treatment with PARP inhibitors is associated with hematologic toxicity, however comparing clinical trials investigating PARP inhibitors indicate that the frequency is lower for olaparib. The most frequent adverse event of any grade associated with olaparib was nausea and fatigue. It is difficult for AstraZeneca to address the manageability and weight of these adverse events. But as olaparib has been recommended and used for the treatment of BRCAm PSR ovarian cancer since 2015, it implies that the side effects in fact is manageable.

In Study 19, patient HRQoL was assessed using the Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O) HRQoL scale. Patient scores were high at baseline (patient randomisation), remained consistent over time, and were similar between the treatment groups.

EPAR:

Analysis of exploratory efficacy endpoints showed a reduction in the risk of discontinuation of study treatment or death, in the olaparib group, compared with the placebo group in overall population (FAS): HR of 0.39, 95% CI 0.30 to 0.51, p<0.00001, and a lengthening of time until the first subsequent anti-cancer therapy and the second subsequent therapy or death, compared with placebo: HR of 0.39, 95% CI 0.30 to 0.52, p<0.00001 and HR of 0.53, 95% CI 0.40 to 0.69, p<0.00001 for TFST and TSST respectively. These exploratory efficacy outcomes support the PFS results, by showing that the treatment benefit of olaparib is maintained beyond the treatment period. This beneficial effect of maintenance therapy was found whatever the subgroup. However, it was more pronounced in BRCA mutated patients.
Efficacy in non-mutated BRCA patients has only been provided based on Study 19 results, for patients with high grade serous ovarian cancer. However, consistent results have been reported in the SOLO2 study for patients with high grade serous or endometrioid cancer. In addition, the mechanism of action of olaparib and recent evidence on the biologic features of high grade epithelial ovarian tumors support an extension of the indication from “serous” to other histological types.
Given an existing uncertainty in regard to magnitude of benefit in patients with gBRCAwt which should be balanced against known toxicity, and a potential for reduced benefit in subset of patients without HRD, the MAH(AstraZeneca) should provide additional evidence specifically in this group of patients. Moreover, further investigation of biomarkers of HRD, such as TP53 disruptive status, that would allow to identify patients that benefit the most and optimise the target population. The OPINON study is expected to provide additional data

6 Clinical questions vs bevacizumab (indirect comparison)

6.1 Introduction

DGCG Guidelines 5th Edition 2016 – recommendation for patients with platinum sensitive relapse

"Patients with platinum sensitive relapse should be treated with platinum-based chemotherapy combined with bevacizumab (only approved for first relapse). That is if they have not previously been treated with bevacizumab or other VEGFi"

This recommendation in DGCG Guidelines 5th Edition 2016 are based on findings in the placebo-controlled OCEANS study, in which addition of bevacizumab to the combination of carboplatin + gemcitabine followed by maintenance bevacizumab was investigated [16].

Indirect treatment comparison between Study 19 and OCEANS is impaired by a key difference in Study design with randomization point in Study 19 being within 8 weeks after last dose of chemotherapy unlike OCEANS with randomization prior to initiation of chemotherapy (table 16) [13, 16].

In order to perform a narrative comparison of the olaparib maintenance dataset (Study 19) and treatment with bevacizumab (OCEANS) the following will be applied

- Median numbers of cycles of carboplatin + gemcitabine in OCEANS was 6 for both control and active arm with cycles being repeated every 21 days. For calculations adding length of initial chemotherapy (table 17 and table 18) in Study 19 the assumption of patients receiving 6 cycles of platinum chemotherapy (q3w) is applied thereby adding a total of 126 days ~4.2 months
- Time from completion of final platinum chemotherapy to randomization in Study 19 is set to 42 days ~1.4 months (ref EPAR)
- In total 5.6 months being added to survival results from Study 19 in order to perform a narrative comparison with OCEANS.

In addition, there is a significant imbalance between the studies in terms of two important prognostic markers, both of which favors the OCEANS study in comparison with the *BRCAwt/VUS* cohort in Study 19. Firstly, OCEANS enrolled a pure cohort of patients at 1st platinum sensitive relapse. This in contrast to Study19 where only 49% in the control arm and 44% in the olaparib arm were patients at 1st platinum sensitive relapse [13, 16].

Secondly, the proportion of BRCA mutated patients in OCEANS are unknown, although it must be anticipated that a sizeable proportion of enrolled patients in OCEANS harbour a BRCA mutation. BRCA1/2 mutations are known to be positive prognostic markers for ovarian cancer patients. This finding was confirmed in a retrospective analysis of the GOG218 study investigating bevacizumab as 1st line maintenance treatment. However, BRCA mutation status did not predict outcome of bevacizumab treatment in this retrospective analysis.

In order to perform an indirect comparison between bevacizumab treatment and olaparib maintenance treatment a narrative description of the datasets is undertaken, due to the above described negative prognostic markers and variation in randomization point.

Added to this narrative description is a subgroup analysis of the study population in Study 19 displaying data from the subgroup of patients enrolled after 1st platinum sensitive relapse.

This in addition to two meta analyses performed in order to calculate the relative risk of discontinuing treatment on olaparib capsules (data from Study 19 and maintenance phase in Study 41) and on olaparib tablets (SOLO2 + SOLO1 dataset), where similar discontinuations rates have been observed. Indirect comparison (Bucher method) between

either of the combined dataset for capsules and tablets and the OCEANS dataset is performed in order to determine potential significant differences in relative and absolute risk of discontinuing treatment.

TABLE 17: DESIGN AND POPULATION OVERVIEW KEY STUDIES OLAPARIB VS. BEVACIZUMAB

	Olaparib: Study 19	**Olaparib: Study 19 – BRCAwt subgroup**	**Bevacizumab: OCEANS**
Design	A double-blind, randomised, placebo-controlled, multicentre, phase 2 international study	A double-blind, randomised, placebo-controlled, multicentre, phase 2 international study	A randomized, multicenter, blinded, placebo-controlled phase III trial
N	265	118	484
Population	Patients with platinum sensitive recurrent HGSOC, who had received ≥2 platinum-based regimens and were in objective response (PR or CR) to their most recent platinum-based chemotherapy	Patients with platinum sensitive recurrent HGSOC, who had received ≥2 platinum-based regimens and were in objective response (PR or CR) to their most recent platinum-based chemotherapy	Patients with platinum-sensitive recurrent ovarian cancer (recurrence ≥6 months after first-line platinum-based therapy)
Timepoint for Randomization	Within 8 weeks after last dose of platinum-based therapy (average 44 days according to CSR S19)		Before initiation of chemotherapy
Proportion of 2nd line patients	49% in control arm 44% in olaparib arm		100%
Proportion of BRCA mutated patients	51 %	0 %	Unknown

Source: [5], [17].

6.2 Overall Survival vs. bevacizumab

6.2.1 Comparative analyses

In both Study 19 and OCEANS study OS were assessed as a secondary endpoint in the overall ITT population [7, 17]. In addition, OS analysis was performed for the *BRCAm* and the *BRCAwt/VUS* subgroups identified as a result of the pre-planned retrospective analysis of BRCA mutation status of subjects enrolled in Study 19.

Table 18 describes OS data and relative risk reduction (HR) for the overall ITT population of Study 19 and OCEANS in addition to data for the *BRCAwt/VUS* subgroup in Study 19.

TABLE 18: OS OVERVIEW OLAPARIB VS. BEVACIZUMAB

	Olaparib: Study 19[a]		**Olaparib: Study 19 - BRCAwt subgroup[a]**		**Bevacizumab: OCEANS**	
	Overall ITT population		***BRCAwt/ VUS* n=118**		**Overall ITT population**	
	Olaparib	**Placebo**	**Olaparib**	**Placebo**	**Bevacizumab**	**Placebo**
Median, months	29.8 (26.9-35.7)	27.8 (24.9-33.7)	24.5 (19.8-35.0)	26.6 (23.1-40.7)	33.6	32.9
Median (mo) + initial CTX + randomization period b)	35.4	33.4	30.1	32.2		
HR (95% CI)	0,73 (0.55, 0.95)		0.84 (0.57, 1.25)		0.952 (0.771, 1.176)	
P value (2-sided)	0.02138		0.39749		0.6479	

a) DCO: May 2016; data maturity 79%; b) Calculated by adding 5.6 months to median PFS as described in introduction.

Although the OS data in Study 19 was immature at the final analysis (79% maturity), the results after a median follow-up duration of 6.5 years suggest that there was a trend towards improved survival (median OS: 29.8 months vs. 27.8 months in the olaparib and placebo groups, respectively) for the ITT population in Study 19, which despite a low p-value, was not considered statistically significant due to loss of alpha as a consequence of multiple testing (HR 0.73; 95% CI 0.73, 0.95; nominal P=0.02138). The data suggest that there is a favourable survival advantage for patients with platinum-sensitive relapsed ovarian cancer treated with olaparib in comparison to patients on placebo ('watch and wait') across the overall population.

The results compare favourably with those of a pure 2nd line population treated with bevacizumab as represented by the ITT population of the OCEANS, where BRCA status is unknown.

As previously discussed in section 5.1.2, Kaplan-Meier survival curves indicate separation between treatment groups at the tail-end of the curve for patients with *BRCAwt/VUS* ovarian cancer, suggesting that there may be a subset of patients with *BRCAwt/VUS* who receive long-term benefit from olaparib treatment (HR 0.84; 95% CI 0.57, 1.25; P=0.40) (table 18).

Indeed, data from Study 19 shows that 12 % of *BRCAwt/VUS* patients receive long-term benefit from olaparib (7 out of 57 had received olaparib for more than 5 years). Overall, 18 (13%) of 136 patients had received olaparib for 5 years or more; 11 of these patients had a *BRCAm* (15% of 74 patients) and 7 were in the *BRCAwt/VUS* subgroup (12% of 57 patients with *BRCAwt/VUS*).

6.2.2 Conclusion OS olaparib vs. bevacizumab

As mentioned in the EPAR, study 19 is not powered to show OS benefit in the ITT/*BRCAwt/VUS population. As previously described, BRCAwt/VUS subgroup in Study 19 failed to demonstrate a 3 month gain in median OS compared to placebo with a HR of 0.84* (0.57, 1.25), *thereby resembling the OS result demonstrated in OCEANS*.

Numerically the ITT population in Study 19 demonstrate a longer mOS compared to mOS in OCEANS when including the initial chemotherapy phase plus phase from end of chemotherapy to randomization. This is despite the higher number of previous line of chemotherapy in Study 19.

6.3 PFS vs. bevacizumab

6.3.1 Comparative analyses

Investigator assessed PFS was the primary endpoint in both Study 19 and OCEANS. As previously discussed, the *BRCAwt/VUS* subgroup in Study 19 demonstrated a 46% relative reduction in risk of progression or death compared to placebo with an absolute PFS improvement of 1.9 months. For the subgroup of patients at 1st platinum sensitive relapse the corresponding benefit was demonstrated to be an absolute improvement of 3.0 months with a 49% relative risk reduction (table 19).

The ITT population demonstrated a mPFS of 8.4 months vs 4.8 months in the placebo arm. The total median length from initiation chemotherapy to progression were 14.0 months for the ITT population and 15.6 months for the subgroup of patients at 1st platinum sensitive relapse compared with 12.4 months in the OCEANS study. As previously discussed, the proportion of BRCA mutated patients in OCEANS is unknown, but numerically comparison of the 2nd line cohorts of patients, demonstrates an absolute difference of 3.2 month in favor of olaparib treated patients vs. bevacizumab for the ITT population. Matching number for the *BRCAwt/VUS* 2nd line population yields an absolute difference of 1.7 months vs bevacizumab maintenance treatment.

Relative risk reduction observed in Study 19 was 65% for the ITT population with corresponding number being 52% in OCEANS. For the *BRCAwt/VUS* cohort a reduction in risk of progression or death of 46% was observed with 49% for the subgroup of Patients at 1st platinum sensitive relapse.

TABLE 19: POPULATION AND PFS OVERVIEW KEY STUDIES OLAPARIB VS. BEVACIZUMAB

	Olaparib: Study 19		**Olaparib: Study 19 - BRCAwt subgroup**		**Bevacizumab: OCEANS**	
	Overall ITT population		***BRCAwt/ VUS* n=118**		**Overall ITT population**	
	Olaparib	**Placebo**	**Olaparib**	**Placebo**	**Bevacizumab**	**Placebo**
Median, months	8,4 (7.4 – 11.5)	4.8 (4.0 – 5.5)	7.4 (5.5 – 10.3)	5.5 (3.7 – 5.6)	12.4	8.4
Median (mo) + initial CTX + randomization period	14.0	10.4	13.0	11.1		
HR (95% CI)	0.35 (0.25, 0.49)		0.54 (0.34, 0.85)		0.484 (0.388; 0.605)	
P value (2-sided)	<0,0001		0.0075		P<0.0001	
Patients at 1st platinum sensitive relapse[a]						

Subgroup: 2 Line of prior regimens	10,0 (n=59)	5.3 (n=63)	8.3 (n=32)	5.3 (n=35)	12,4	8,4
Median (mo) + initial CTX + randomization period	15.6	10,9	14,1	11,1		
HR (95% CI)	0.41 (0.25;0.65)		0.51 (0.28; 0.51)		0.484 (0.388; 0.605)	
P value (2-sided)	0.0002		0.0265		P<0.0001	

Source: 1) Friedlander et al 2018 [10] 2) Oza et al 2015 [19] 3) Pujade-Lorraine et al 2017 [8] 4) Aghajanian et al 2015 [17] a) Data on file. AstraZeneca

The long-term benefit from olaparib is highlighted by the right skewed PFS curve with long tails for the *BRCAwt/VUS* population in Study 19. The mean PFS serve as a more adequate marker to describe the long-term benefit of olaparib since median parameters will underestimate the benefit of right skewed data [18]. Modelled PFS extrapolations (Generalized Gamma distribution) predict that treatment with olaparib will lead to a mean PFS of approximately 13.3 months versus 6.2 months (figure 11) for watch and wait *in BRCAwt* patients. The incremental gain in mean PFS is 7.1 months.

Bevacizumab Kaplan-Meier curves has often been described to have a "banana-shape", thereby indicating a less pronounced long-term benefit. If so the difference between the mean PFS and median PFS should be smaller indicated by a ratio closer to 1 compared to compounds with more pronounced long-term benefit, i.e. "right skewed data" as previously discussed in section 5.1.3 and 5.5.2. When applying the Weibull survival function to the PFS curves in the OCEANS study, the mean PFS for placebo arm is 10.4 months with a mean PFS estimated to be 14.2 months for the olaparib arm.

A numerically higher mean/median ratio was observed for the olaparib arm in Study 19 BRCAwt/VUS when compared to both the placebo arm in Study 19 and to both arms in the OCEANS study. This support the finding of long-term treatment benefit for a subgroup of *BRCAwt/VUS* patients in Study 19 (table 20).

While these data are not statistically significant they are supportive of the clinically meaningful and statistically significant PFS and TSST treatment benefit observed at the primary analysis. The data suggest that there is a favorable survival advantage for patients with platinum-sensitive relapsed ovarian cancer treated with olaparib in comparison to patients on placebo ('watch and wait') across the overall population [5].

Table 20: Median and modelled mean PFS values in Study 19 and OCEANS

	Study 19 BRCAwt/VUS		OCEANS	
	Olaparib	Placebo	Bevacizumab	Placebo
Median PFS (months)	7.4	5.5	12.4	8.4
Mean PFS (months)	13.3	6.2	14.6	10.4
Δ mean – median (months)	5.9	0.7	1.8	1.5
Ratio mean PFS/median PFS	1.8	1.1	1.2	1.2

6.3.2 Conclusion

Major limitations exist when comparing data from OCEANS and Study19. The target of 3 months absolute gain in median PFS set by Medicinrådet/Fagudvalgetis numerically demonstrated when comparing the 2nd line subgroup of the ITT population in Study 19 with the OCEANS (15.6 months vs 12.4 months)

For the BRCAwt subgroup a gain of 1.7 months is demonstrated when comparing with an expected mixed population of BRCA mutated and BRCAwt in OCEANS.

A proportion of BRCAwt/VUS patients similar to the proportion in the BRCAm cohort became long-term responders to olaparib treatment also indicated by the right skewed PFS curve. This finding is in contrast to the finding in OCEANS study with a banana shaped PFS curve also supported by a difference in mean/median ratio numerically favoring treatment with olaparib.

6.4 Olaparib vs. bevacizumab ≥CTCAE Grade 3 AEs

6.4.1 Comparative analyses

Key differences between Study 19 and OCEANS were discussed in the section 6.1. The difference in study design and randomization point reflects the concomitant use of bevacizumab in addition to maintenance treatment. The proportion of patients that experience an AE ≥CTCAE Grade 3 in the OCEANS study is therefore expected to be numerically higher, due to the contribution from concomitant chemotherapy. Literature search have not revealed data describing separate AE data for the concomitant phase and maintenance phase in the OCEANS study.

Study 41, a Phase II, open-label, randomised, comparative, multicentre study that compared the efficacy and tolerability of olaparib in combination with paclitaxel and carboplatin followed by maintenance olaparib vs. paclitaxel and carboplatin alone followed by placebo in patients with platinum-sensitive advanced serous ovarian cancer, indeed demonstrated that a higher proportion of patients experienced AE ≥CTCAE Grade 3 in the concomitant phase (65% vs 57%, table 21) compared to the maintenance phase (29% vs 16%) [19].

Although Study 41 was not designed to measure the contribution of each treatment phase, the late separation of the PFS curves and improvement in objective response during combination phase suggest that the maintenance phase was probably the key contributor to the improvement in progression-free survival. On the basis of these findings, the combination of olaparib plus chemotherapy with the schedule applied in Study 41 is not believed to provide an advantage over olaparib maintenance alone.

6.4.2 Conclusion ≥CTCAE Grade 3 AEs

The target set by Medicinrådet/Fagudvalget is 10 % absolute difference. AstraZeneca is not able to do an indirect comparison vs. bevacizumab for this clinical question.

Although the AE outcomes of Study 41 and Study 19 are complementary, their outcome cannot be compared directly, but together the safety and efficacy results from those studies provide a solid rationale for only utilizing olaparib as maintenance treatment thereby improving the risk-benefit ratio.

As a consequence, validity of potential comparison between OCEANS and Study 19 in terms of proportion of patients who experienced AE ≥CTCAE Grade 3, is judged to be limited by AstraZeneca due to variation in phases from which data is collected.

TABLE 21: AE, ≥CTCAE GRADE 3. OLAPARIB VS. BEVECIZUMAB

	Study 19		Study 41				SOLO2		OCEANS	
	Maintenance Phase		Concomitant phase		Maintenance Phase		Maintenance Phase		Concomitant + Maintenance	
	Olaparib Capsules	Placebo	Olaparib Capsules	Placebo	Olaparib Capsules	Placebo	Olaparib Tablets	Placebo	Bevacizumab IV	Placebo
N	136	129	81	75	66	55	196	99	242	242
Proportion of patients with AE, ≥CTCAE Grade 3	35%	20%	65%	57%	29%	16%	36%	18%	89.5%	82.4%
	Δ15%		Δ8%		Δ13%		Δ18%		Δ7%	

Source: 1) Friedlander et al 2018 [10] 2) Oza et al 2015 [19] 3) Pujade-Lorraine et al 2017 [8] 4) Aghajanian et al 2015 [17]

6.5 Olaparib vs.bevacizumab discountinuations

6.5.1 Comparative analysis

The proportion of patients experiencing an AE leading to permanent treatment discontinuation was low in both SOLO2 and Study 19 (10.8% vs 5.9%, respectively) when numerically compared to data from OCEANS study, where a more than 22% of patients discontinue bevacizumab treatment vs 4.7% in the control arm (table 22).

Table 22. Discontinuation rates from Study 19, SOLO2, Study 41 and OCEANS is displayed

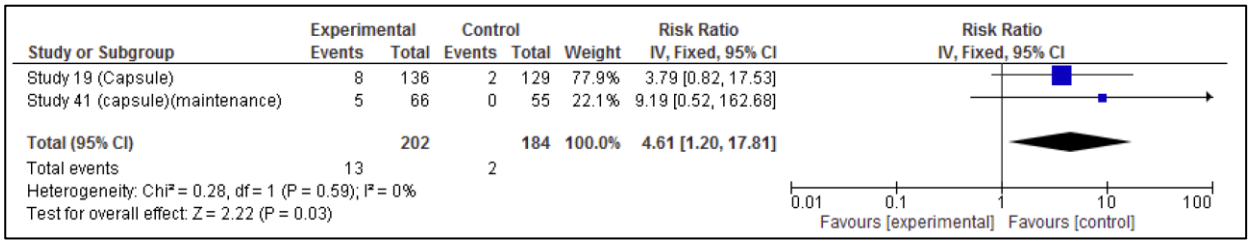
	Study 19		Study 41		SOLO2		SOLO1		OCEANS	
	Maintenance Phase		Maintenance Phase		Maintenance Phase		Maintenance Phase		Concomitant + Maintenance	
	Olaparib Capsules	Placebo	Olaparib Capsules	Placebo	Olaparib Tablets	Placebo	Olaparib Tablets	Placebo	Bevacizumab IV	Placebo
N	136	129	66	55	196	99	260	131	242	242
number of patients discontinued	8	2	5	0	21	2	30	11	55	11
	6%	2%	8%	0%	11%	2%	11.5%	2.3%	22.3%	4.7%
	Δ4%		Δ8%		Δ9%		Δ9.2%		Δ17.6%	
Relative risk (RR) vs placebo	4.61 (CI 95% 1.20; 17.81) p=0.03				1.74 (CI 95% 0.96; 3.16) p=0.07				5.00 (CI 95% 2.68; 9.32) p<0.00001	
Risk reduction vs bevacizumab (Bucher method)	RR 0.922 (CI 95% 0.209; 4.074); p=0.9147 Absolute risk reduction (ARR): 1.8%				RR 0.348 (CI 95% 0.147; 0.824); p=0.016 Absolute risk reduction (ARR): 14.8%				NA	

Source: 1) Friedlander et al 2018 [10] 2) Oza et al 2015 [19] 3) Pujade-Lorraine et al 2017 [8] 4) Moore et al 2018 [20] 5) Aghajanian et al 2015 [17].

As previous discussed comparison of AE ≥CTCAE Grade 3 is impaired by lack of separate data from the concomitant and maintenance phase in OCEANS study. However, AstraZeneca finds it relevant to perform an indirect comparison of difference in number of patients (represented by delta %-point between active and control arm) that discontinue treatment due to additional intervention represented by either bevacizumab (concomitant + maintenance) or olaparib (maintenance).

Firstly, an assessment of the potential added risk of discontinuation due to maintenance treatment with olaparib capsule. Pooled data from Study 19 and Study 41 (maintenance phase only). Meta-analysis (figure 11) demonstrated an increased risk of discontinuing treatment with a Risk Ratio of 4.61 (CI 95% 1.20; 17.81) with p=0.03

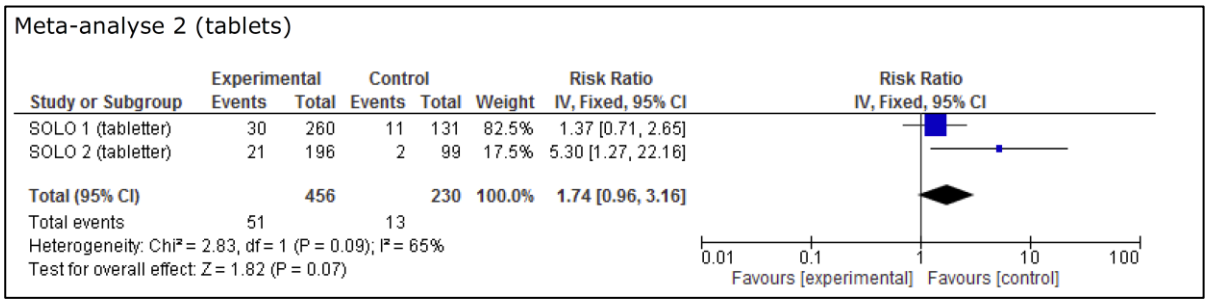
Figure 11. Pooled data from study 19 and study 41



Secondly, an assessment, with pooled data from SOLO2 and SOLO1, of the potential added risk of discontinuation due to maintenance treatment with olaparib tablets with pooled data from SOLO2 and SOLO1. The assumptions applied being that the AE profile is identical in *BRCAm* and *BRCAwt/VUS* patient group. The safety profile observed in SOLO2 were consistent with the profile observed in SOLO1, including identical discontinuations rates, for which reason AstraZeneca finds it relevant to perform a meta-analysis.

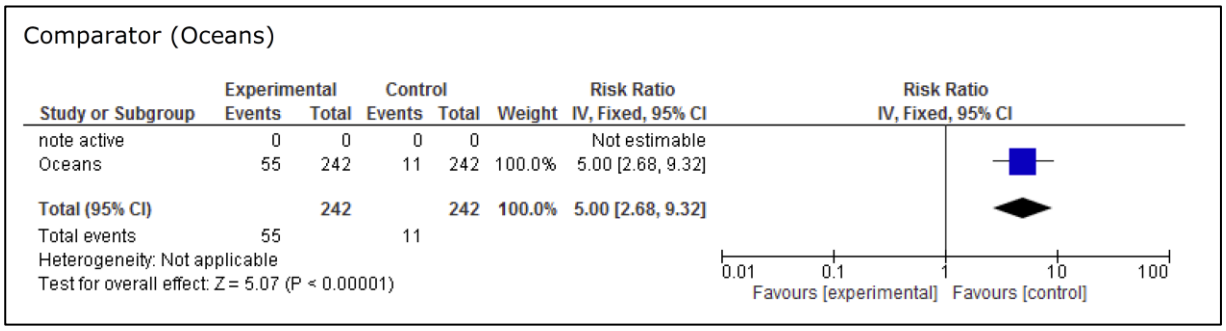
The meta-analysis (figure 12) demonstrated a numerical increased risk of discontinuing treatment with a Risk Ratio of 1.74 (CI 95% 0.96; 3.16) with p=0.07.

Figure 12. Meta-analysis SOLO2 and SOLO1



Thirdly, an assessment of the potential added risk of discontinuation due to bevacizumab treatment were performed on the dataset from OCEANS. Due to differences in design (secondary surgery) GOG 213 has been left out of this analysis. Data from AGO-OVAR 2.21 have not yet been published.
The meta-analysis (figure 13) demonstrated an increased risk of discontinuing treatment with a Risk Ratio of 5.00 (CI 95% 2.68; 9.32) with p<0.00001.

Figure 13. Risk of discontinuations OCEANS.



6.5.2 Conclusion discontinuations olaparib vs. bevacizumab

Two indirect comparisons (Bucher method) were then performed in order to test for potential differences in risk of discontinuing treatment between olaparib capsules and olaparib tablets treatment respectively and bevacizumab.

No differences were detected between olaparib capsules and bevacizumab(figure 14) with an Relative Risk (RR) of 0.922 (CI 95% 0.209; 4.074); p=0.9147 and an absolute risk reduction (ARR) of 1.8%

Figure 14. Bucher capsules

Result Bucher
Indirect 1 (capsules)

Result of meta-analysis	ln RR	SE-ln RR	RR	lower95% CI	upper95% CI
Study 19 + study 41 meta (capsules)	1.528	0.688	4.6100	1.200	17.8100
Oceans	1.609	0.318	5.000	2.680	9.3200

Indirect MA using Bucher method

	ln RR	SE-ln RR	RR	lower95% CI	upper95% CI	Z: SE = estimate / Z. (z=estimate/SE)	P-value (two sided)
Study 19 + study 41 meta (capsules) vs Oceans	-0.081210	0.758	0.9220	0.209	4.074	0.107	0.9147

Absolute risk reduction (ARR)	RR	RR-1	Event rate (control)	ARR
RR	0.9220	-0.0780	22.7%	-1.8%
Lower CI	0.2087	-0.7913	22.7%	-18.0%
Upper CI	4.0736	3.0736	22.7%	69.9%

However, indirect comparison of olaparib tablets and bevacizumab revealed RR of 0.348 (CI 95% 0.147; 0.824); p=0.016 and an absolute risk reduction (ARR): 14.8% favoring patients on olaparib (figure 15).

Figure 15. Bucher tablets vs. OCEANS

Indirect MA using Bucher method							
	ln RR	SE-ln RR	RR	lower95% CI	upper95% CI	Z: SE = estimate / Z. (z=estimate/ SE)	P-value (two sided)
SOLO2 and SOLO1 (tabletter) vs Oceans	-1.056	0.440	0.348	0.147	0.824	2.400	0.016
Absolute risk reduction (ARR)	RR	RR-1	Event raten kontrol				
RR	0.3480	-0.6520	22.7%	-14.8%			
Lower CI	0.1470	-0.8530	22.7%	-19.4%			
Upper CI	0.8241	-0.1759	22.7%	-4.0%			

In conclusion, analysis revealed a statistically significant increased risk of discontinuing treatment for olaparib capsules and bevacizumab and a numerically increased risk for olaparib tablets compared to placebo. Indirect comparison between maintenance treatment with olaparib capsules/tablets and bevacizumab demonstrated an absolute risk reduction of 14.8% when comparing olaparib tablets and bevacizumab, which meets the criteria for minimum clinical differences.

6.5.3 Qualitative assessment of AEs related to olaparib (tablets) and bevacizumab

Findings from Study 19 and SOLO2 indicate that there is a consistent safety and tolerability profile for olaparib monotherapy across the capsule and tablet formulation. The majority of AEs reported in SOLO2 and Study 19 were grade ≤2. The most commonly reported AEs for patients in the olaparib group in both studies were nausea, fatigue/asthenia, vomiting, and diarrhoea.

24% of patients in Study 19 received maintenance olaparib for over 2 years with 11% receiving for over 6 years. The long follow up time in Study 19 provides a solid basis for an evaluation of potential cumulative increase in toxicity being a consequence of the long treatment exposure.

Based on DCO sept 2015 (77% OS data maturity) [7] no new safety findings were reported compared with those that have previously been reported. For patients who received olaparib treatment for 2 years or more, the frequencies of previously reported common adverse events such as low-grade nausea, fatigue, vomiting and anaemia were consistent with the frequencies that were previously reported in the overall population. A finding that was confirmed at the final DCO May 2016 (79% OS data maturity) [10]. However, there was a higher frequency of grade ≥3 AEs of anaemia reported in SOLO2 compared with Study 19 (19.5% vs 5.9%, respectively). For this reason, and due to convenience for patients (2x2 tablets daily vs 8x2 capsules daily) and inclusion in update label, SOLO2 study is chosen as comparator study for the qualitative assessment in this section (table 23).

Table 23. AEs of special interest SOLO2 and OCEANS

	OCEANS Study[a] Treatment-emergent AE Bevacizumab			SOLO2 Study Treatment-emergent AE olaparib		
	GC + Placebo (n = 233)	GC + bevacizumab (n = 247)	Manageability	Placebo (n=99)	Olaparib tablets (n=195)	Manageability
	n (%)	n (%)		n (%)	n (%)	
Hematological Adverse events -						
Myelosuppression						General guidance for PARPi: For olaparib and rucaparib myelosuppression should be monitored with monthly complete blood count for the first year and periodically thereafter. For niraparib patients should have blood counts drawn weekly but more frequently if platelets are trending down
Anemia • Any Grade • gr≥3				• 8 (8.0) • 2 (2.0)	• 85 (43.6) • 38 (19.5)	Grade ≥3 Anemia were reported at a higher frequency with the tablet formulation compared to the capsule formulation (19.5% vs 5.9% respectively) and in line with PARPi class. Grade 1&2 Anemia may be managed by transfusions without interruptions of treatment, however Grade gr≥3 toxicities should be managed by dose interruptions. If toxicity resolves to ≤1 within a maximum of 28 days patients can restart treatment on a lower dose
Thrombocytopenia (gr≥3)	• 79 (33.9)	• 99 (40.1)	Grade ≥3 Thrombocytopenia was observed at a higher incidence for patients treated with bevacizumab, with an absolute difference 6.2 %-point	• 1 (1.0)	• 2 (1.0)	Grade ≥3 thrombocytopenia was rarely observed in either SOLO2 (tablets) nor Study 19 (Capsules) (1.0% & 0.7% respectively) unlike other PARPi which have reported incidence of Grade ≥3 above 30%
Neutropenia (gr≥4)	• 51 (21.9)	• 52 (21.1)		• 4 (4.0)	• 10 (5.1)	Grade ≥3 neutropenia was observed in SOLO2 (tablets) and S19 (capsules) at an incidence of 5,1% vs 4.0% in SOLO2 and 3,7% vs 0.8% in S19.
Non-Hematological Adverse events						
Cardiovascular • Hypertension (any grade) • Hypertension (gr≥3) • Bleeding (CNS) (any Grade) • Bleeding (non-CNS) (gr≥3) • Arterial thromboembolic event (any Grade) • Venous thromboembolic event (gr≥3) • Wound healing complication	• 20 (8.6) • 2 (0.9) • 2 (0.9) • 2 (0.9) • 1 (0,4) • 6 (2.6) • 0	• 104 (42.1) • 45 (18.2) • 2 (0.8) • 14 (5.7) • 6 (2,4) • 6 (2.6) • 2 (0.8)	Hypertension (HTN) is the most common AE associated with bevacizumab. In OCEANS 42.1% vs 8.6 of patients reports HTN with 18.2% vs 0.9% being Grade ≥3. Management includes risk profile assessment, Blood Pressure (BP) monitoring and potential use of anti-HTN agents. NCI recommends that the goal of BP management should be 140/90 mmHg. Arterial (strokes, transient ischemic attacks, angina and myocardial infarctions) and venous thrombotic events may occur with bevacizumab use. Increased risk of hemorrhage and treatment should be stooped if bleeding is severe. Care should be taken in patients with brain metastases given the risk of intracerebral hemorrhage. Bevacizumab is known to impair wound healing in humans, and package insert states that bevacizumab should not be started at least 28 days following surgery	• 1 (1.0)	• 2 (1.0)	Besides 2 cases of DVT (1.0%) no other vascular disorders mentioned in olaparib EPAR No data are available about the impact of olaparib on wound healing
Gastrointestinal (GI) • Nausea (any Grade) • Vomiting (any Grade) • Diarrhea (gr≥3) • GI perforations (any Grade) • Fistulae/abscess (any Grade)	• 153 (65,7) • NA • 4 (1.7) • 1 (0.4) • 0	• 179 (72.5) • NA • 7 (2.8) • 2 (0.8) • 2 (0.8)	Nausea and vomiting were frequently reported in OCEANS, but the difference between active and control arm were low compared to observation from PARPi trials, thereby suggesting this to be related to the chemotherapy component in the treatment. GI perforations (GIP) were reported in 2 cases (0,8%), but have been reported at higher frequencies, and it is suggested that risk differ with level of level of platinum sensitivity and prior lines of chemotherapy. GIP is one of the most severe AE occurring with bevacizumab treatment given the high mortality rate suggesting a high need of suspicion for abdominal pain in these patients to enable early detection (Diaz et al 2009)	• 33 (33.0) • 19 (19.1) • 0 • 0 • 0	• 148 (75.9) • 73 (37.4) • 2 (1.0) • 0 • 0	Nausea is very common in SOLO2 with an absolute difference of 42.9 %-point consistent with findings in the PARPi class. Long-term safety data from S19 suggest that nausea and vomiting is an early event. A decreased frequency of nausea (17%) amongst patient who continue therapy for more than 2 years were observed compared to 70.6% in the safety population (n=136).Being amongst some of the most feared consequences of cancer treatment, even low-grade nausea and vomiting can be of considerable distress, thus this must be addressed at each encounter. According to MASCC/ESMO guidelines olaparib is classified to have a low emetogenic potential albeit demonstrating an emetic risk >30% for both formulations. MASCC/ESMO guidelines suggest that single antiemetic agent may be considered for prophylaxis in these patients. Minimizing the risk for anticipatory nausea and vomiting could suggest that emphasize should be put on sufficient prophylactic anti-emetic treatment prior to initiation of platinum-based chemotherapy. This in addition to individualized monitoring of CINV related risk factors for candidates for olaparib treatment

Renal • Proteinuria (gr≥3)	• 2 (0.9)	• 27 (10.9)	The most common renal toxicities of bevacizumab are proteionuria observed in more than 10% of patients in the active arm in OCEANS and has been reported in all phase II and III studies of bevacizumab in gynecological cancer patients.Few studies have examined the effect of long-term bevacizumab on renal function after the agents has been discontinued. Proteinura has been linked to adverse cardiovascular outcomes and progression to end stage renal disease for which reason it should be monitored closely with bevacizumab use	NA	NA	
General disorders • Fatigue (Any Grade) • Fatigue (gr≥3)	• 175 (75.1) • 10 (4.3)	• 202 (81.8) • 16 (6.5)		• 39 (39.4) • 2 (2.0)	• 128 (65.6) • 8 (4.1)	Fatigue is one of the most predominant side effects noted with PARPi and unfortunately can have negative impact on QoL during and and after cancer treatment given the myriad of effects on work, relationships, mood and functional status. It may be related to prior chemotherapy but observed to be increase with olaparib Of concern, considering the length of treatment, would be an increased prevalence of fatigue. Data from Study 19 do not suggest this to be the case. It could be suggested to screen all PARPi patients for fatigue at each visit, but also patients should be advised to monitor, and self-report perceived level of fatigue. Interventions may be simple e.g. task prioritization to more complex interventions potential involving pharmacologic and non-pharmacologic approaches
Neurologic • Headache (gr≥3) • PRES (Any Grade)	• 2 (0.9) • 0	• 9 (3.6) • 2 (0.8)	Headache is the most common neurologic AE observed with bevacizumab reported at 48.6% (any grade) of patients receiving bevacizumab.	• 2 (0.5) • 0	• 0 • 0	
Respiratory, thoracic and mediastinal disorders • Dyspnea (any Grade) • Epistaxis (any Grade) • Cough (Any Grade) • Pneumonitis*	• 56 (24.0) • 33 (14.2) • 43 (18.5) • NA	• 74 (30.0) • 135 (54.7) • 64 (25.9) • NA		• 1 (1.0) • NA • 5 (5.1) • See text	• 23 (11.8) • NA • 33 (16.9) • See text	Two cases of pneumonitis were reported during S19 one in the olaparib <3 months into treatment, and one in the placebo arm, both of grade 1 severity. In SOLO2 3 cases (grade 1) occurred in the olaparib arm and none in the control arm. The frequency observed within the olaparib clinical program continues to appear consistent with expected rates for cancer patients based on published data for patients with lung cancer Advise patient to report new onset of shortness of breath, cough, wheezing or fever. Interrupt olaparib and investigate patients with new or worsening respiratory symptoms or a radiological abnormality consistent with pneumonitis
Secondary Malignancies • AML • MDS • CML • Gastric cancer • Breast Carcinoma	• NA • NA • NA • NA • NA	• NA • NA • NA • NA • NA		• 1 (1.0) • 3 (3.0) • 0 • 0 • 1 (1.0)	• 2 (1.0) • 1 (0.5) • 1 (0.5) • 2 (1.0) • 0	MDS/AML are rare but potential fatal AEs with PARP inhibitors use and occur in 1-2 % of patients across large phase 3 trials. Of note, these patients have previously received platinum and other DNA damaging agents. MDS/AML were reported in both olaparib arm as well as in the placebo arm, and at an incidence broadly consistent with that seen in SOLO2. Shenolikar et al (2018) reported Real-World data on more than 23.000 patients with Ovarian Cancer and 280.000 Breast Cancer patients, with findings that suggests a likely background risk of secondary MDS/AML associated with use of DNA-damaging therapies in earlier lines of chemotherapy. Of note, new malignancies that occurred in S19 were unrelated to duration of exposure to olaparib. If these conditions are suspected, olaparib should be discontinued during the process of evaluation

[a] Aghajanian et al 2015 [17]; [b] All reported events were included regardless of relationship to study drug *see text

6.6 Overall conclusion olaparib vs.bevacizumab

For the efficacy endpoints, OS and PFS, we have not been able to meet the numerical target of 3 months benefit of olaparib compared to bevacizumab for *BRCAwt/VUS* set by Medicinrådet. A number of factors makes it challenging to

compare study 19 and OCEANS. Firstly, the randomization time was at initiation of chemotherapy in OCEANS while it was after chemotherapy and a subsequent time to randomization calculated to 5.6 months on average. Secondly, OCEANS included only patients treated at their first platinum sensitive relapse, compared to only 44% of patients treated with olaparib. Finally, BRCA mutation status was unknown for OCEANS, and since this is a positive prognostic marker, this challenges the comparison further. Nonetheless, we have shown that in the overall population of Study 19, when adding 5.6 months for chemotherapy and randomization time, there was a numerical benefit of olaparib over bevacizumab, not considering the pure second line population in OCEANS. For PFS, we have been able to compare the pure second line population of study 19 with the corresponding population in OCEANS. This resulted in a 3.2 months benefit in the overall population and a 1.7 months benefit in the BRCAwt/VUS population. In addition to this numerical benefit, we have demonstrated that a subset of patients derives long term benefit from olaparib treatment. This results in the median PFS underestimating the mean benefit of olaparib as evident from the ratio of mean-to-median PFS of 1.8. For both control arms in study 19 and OCEANS and for the bevacizumab arm in OCEANS, the ratios were 1.1-1.2, indicating that there was not a similar long-term benefit for these treatments.

For the adverse event endpoints, we have not been able to do an indirect comparison between olaparib and bevacizumab, since OCEANS evaluated both active and maintenance phase, while study 19 only evaluated maintenance phase. Treatment with bevacizumab was associated with a higher proportion of patients experiencing grade 3 or higher adverse events compared with olaparib, while the numerical difference from placebo was lower for bevacizumab compared with olaparib.

Through indirect comparisons, we have shown that there is no difference in discontinuation between olaparib capsules and bevacizumab. However, treatment with olaparib tablets was associated with a 14.8% reduction in risk of discontinuation compared with bevacizumab, which meets the criteria set by Medicinrådet.

6.7 Overall conclusion olaparib vs. placebo and bevacizumab

For the survival endpoints, OS and PFS, medicinrådet had set a target of three months benefit for olaparib compared to both placebo and bevacizumab in *BRCAwt/VUS* patients following their first platinum sensitive relapse. In study 19, these patients did derive a 3.0 months benefit in PFS compared to placebo. When comparing to patients treated with bevacizumab in the OCEANS study, the numerical benefit of olaparib was 1.7 months. The comparison with OCEANS was challenging due to the *BRCAm* status being unknown in OCEANS and consequently it is expected that a number of patients must have had a *BRCAm* which is a positive prognostic marker. For OS, we were not able to demonstrate a three months benefit of olaparib compared to placebo or bevacizumab for *BRCAwt/VUS*. We have however highlighted that around 10 % of these patients were treated with olaparib for more than six years, which results in the median OS underestimating the mean benefit on OS. This was not the case for neither placebo nor bevacizumab. Despite having a *BRCAm* is a prognostic marker for the benefit of olaparib treatment, it does not identify all patients that experience long term benefit of olaparib in a similar manner as platinum sensitivity.

Compared to placebo we could not demonstrate any difference in discontinuation. In contrast we have shown through indirect comparison that treatment with olaparib tablets was associated with a lower risk of discontinuation compared to bevacizumab.

Regarding number of patients experiencing adverse events of grade 3 or higher, olaparib was not able to meet the target of ten percentage points difference set by Medicinrådet, when comparing olaparib with placebo (watch and wait). Comparison with bevacizumab was not feasible due to the nature of the different study designs, where olaparib is evaluated as maintenance treatment following platinum-based chemotherapy, while bevacizumab is administered concurrently with platinum-based chemotherapy followed by maintenance treatment. This results in the absolute number of patients experiencing adverse events of grade 3 or higher in OCEANS was higher than for both olaparib capsules and tablets, while the numerical difference from placebo was lower for bevacizumab.

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8 Appendices

Literature search

See appendix for included and excluded literature.

8.1.1 Main characteristics of included studies

Table A2 Study and baseline characteristics Study 19

Trial name	Phase II Randomised, Double Blind, Multicentre Study to Assess the Efficacy of AZD2281 in the Treatment of Patients With Platinum Sensitive Relapsed Serous Ovarian Cancer Following Treatment With Two or More Platinum Containing Regimens
NCT number	NCT00753545
Objective	To evaluate the efficacy of olaparib mono-therapy as maintenance treatment in patients with platinum-sensitive, relapsed, high-grade serous ovarian cancer who had a complete or partial response to their most recent platinum-based chemotherapy.
Publications – title, author, journal, year	Friedlander M, Matulonis U, Gourley C, du Bois A, Vergote I, Rustin G, 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;119(9):1075-85. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med. 2012;366(15):1382-92. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, 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. Lancet Oncol. 2014;15(8):852-61. Ledermann J, Harter P, Gourley C. Correction to Lancet Oncol 2014; 15: 856. 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. Lancet Oncol. 2015;16(4):e158. Ledermann JA, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Quality of life during olaparib maintenance therapy in platinum-sensitive relapsed serous ovarian cancer. Br J Cancer. 2016;115(11):1313-20. Ledermann JA, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial. The Lancet Oncology. 2016;17(11):1579-89.

	Lheureux S, Lai Z, Dougherty BA, Runswick S, Hodgson DR, Timms KM, et al. Long-Term Responders on Olaparib Maintenance in High-Grade Serous Ovarian Cancer: Clinical and Molecular Characterization. Clin Cancer Res. 2017;23(15):4086-94. Matulonis UA, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in patients with platinum-sensitive, relapsed serous ovarian cancer and a BRCA mutation: Overall survival adjusted for postprogression poly(adenosine diphosphate ribose) polymerase inhibitor therapy. Cancer. 2016;122(12):1844-52.
Study type and design	A multicenter, double-blind, placebo-controlled, phase 2 trial at 82 study sites across 16 countries between Aug 28, 2008 and Feb 9, 2010. A total of 265 Patients were randomly assigned in a 1:1 ratio to receive olaparib capsules (n=136), at a dose of 400 mg twice daily (the monotherapy dose shown to be the maximum dose associated with acceptable adverse-event rates), or matching placebo (n=129) within 8 weeks after completion of the last dose of platinum-based chemotherapy. Eligible patients were stratified according to the interval between disease progression and completion of their penultimate platinum-based regimen (from 6 to 12 months vs. more than 12 months), objective response to their most recent regimen (complete response vs. partial response), and ancestry (Jewish vs. non-Jewish), to help balance the distribution.of *BRCA1/2* germline mutations (which are found more frequently in Jewish populations). A prespecified exploratory analysis of all efficacy endpoints was done according to *BRCA* status. Germline *BRCA* mutation status was either reported on case report forms after local testing or it was established retrospectively using the Integrated BRAC*Analysis* assay (Myriad Genetics Laboratories, Salt Lake City, UT, USA), with DNA extracted from blood samples obtained before randomization. *BRCA* genes were sequenced and examined for mutations and rearrangements (deletions and duplications) in the coding regions and 10–20 base pairs of flanking intronic sequence. Tumour *BRCA*status was established retrospectively using DNA extracted from formalin-fixed, paraffin-embedded archival tumour samples using a previously validated next-generation sequencing protocol (Foundation Medicine, Cambridge, MA, USA).
Follow-up time	At the final analysis of Study 19, the median OS follow-up time was 78 months.
Population (inclusion and exclusion criteria)	Inclusion and exclusion criteria related to NCT number from www.clinicaltrials.gov: **Inclusion criteria:** Female patients with histologically diagnosed serous ovarian cancer or recurrent serous ovarian cancer. Patients must have completed at least 2 previous courses of platinum containing therapy; the patient must have been platinum sensitive to the penultimate chemo regimen. For the last chemotherapy course prior to enrolment on the study, patients must have demonstrated an objective stable maintained response (partial or complete response) and this response needs to be maintained until completion of chemotherapy. Patients must be treated on the study within 8 wks of completion of their final dose of the platinum containing regimen **Exclusion criteria:** Previous treatment with PARP inhibitors including olaparib. Patients with low grade ovarian carcinoma.

	Patients who have had drainage of their ascites during the final 2 cycles of their last chemotherapy regimen prior to enrolment on the study. Patients receiving any chemotherapy, radiotherapy (except for palliative reasons), within 2 weeks from the last dose prior to study entry (or a longer period depending on the defined characteristics of the agents used).
Intervention	With the use of an interactive voice response system, 265 patients were randomly assigned in a 1:1 ratio to receive olaparib capsules, at a dose of 400 mg twice daily or matching placebo within 8 weeks after completion of the last dose of platinum-based chemotherapy. Study treatment was blinded with the use of unique identifiers generated during randomization. Patients continued the assigned study treatment until objective disease progression, as defined by RECIST guidelines, provided that they did not meet any criteria for discontinuation (any grade 3 or 4 adverse event that did not resolve completely or to grade 1 within 28 days after onset, according to the National Cancer Institute's Common Terminology Criteria for Adverse Events [CTCAE], version 3.0). All the trial agents were provided by AstraZeneca.
Baseline characteristics	Germline or tumour testing established the *BRCA* status of 254 (96%) patients, of whom 136 (74 [56%] in the olaparib group and 62 [50%] in the placebo group) had a known or suspected deleterious *BRCA1/2* mutation. Germline *BRCA* mutation was detected in 36% of all patients. Somatic *BRCA* mutation, in the absence of *gBRCA* mutation was detected in 18 patients, representing 13% of all patients with a known *BRCA* mutation (n=136). The randomisation of patients with *BRCAm* between the treatment groups was fairly balanced. The two treatment groups were well matched for baseline characteristics including age, number of prior courses of platinum-containing chemotherapy, site of cancer (ovarian vs fallopian tube vs peritoneal). The characteristics of patients with *BRCAm* were similar to the overall patient population except that they were slightly younger (approximately 26% aged under 50 years in the *BRCAm* population compared with 19% in the overall patient population.
Primary and secondary endpoints	The primary endpoint was investigator assessed PFS as measured by RECIST 1.0 criteria. Secondary endpoints included PFS by Blinded independent central review (BICR), OS, TFST, TSST, best overall response, health-related quality of life (trial outcome index [TOI], functional assessment of cancer therapy for ovarian cancer [FACT-O], FACT-O symptom index [FOSI]), and safety and tolerability.
Method of analyzis	The primary objective of this study was to assess the efficacy of olaparib compared to the efficacy of placebo alone. This objective was assessed by the primary variable of PFS. Secondary efficacy variables included OS, best overall response, duration of response, CA-125 response (GCIG criteria), time to progression by CA125 (GCIG criteria), or RECIST, QoL and disease related symptoms. Efficacy data was summarized and analysed on an intention-to-treat (ITT) basis using randomised treatment. The primary analysis population was based on the Full Analysis Set (FAS) and included all randomised patients. This compared the treatment groups on the basis of randomised treatment, regardless of the treatment actually received or protocol deviations/violations. PFS was analysed using a Cox proportional hazards model with factors for time to progression (6-12 months and >12 months, after the penultimate platinum therapy before study enrolment), objective response (CR or PR, after the last platinum therapy before enrolment on the study) and Jewish decent (yes or no) in accordance with the stratification used at randomisation. The effect of treatment was estimated by the adjusted HR together with its corresponding 80% and 95% confidence intervals (CIs). The existence of any treatment-by-covariate interactions was investigated and the assumption of proportionality was assessed. The primary analysis was programmatically derived from the objective RECIST assessments. Subsequently, a pre-planned exploratory analysis of secondary endpoints TFST, TSST that includes BRCA status in the COX model was performed. Sensitivity analyses was performed to assess potential censoring bias and possible time assessment bias. In order to assess

	symptomatic progression a further sensitivity analysis that censors RECIST progressions (not deaths) was performed for the analysis of OS, TFST, and TSST used the same methodology and model as described for PFS.
Subgroup analyses	Based on germline or tumour testing, a pre-planned subsequent exploratory analysis grouped the patients according to BRCA mutation status.

Demographics and baseline characteristics

Table 1. Demographic and Baseline Characteristics of the Patients.

Characteristic	Olaparib (N=136)	Placebo (N=129)
Age — yr		
Median	58.0	59.0
Range	21–89	33–84
Ancestry — no. (%)*		
Non-Jewish	116 (85.3)	112 (86.8)
Jewish	20 (14.7)	17 (13.2)
Ashkenazi	16 (11.8)	12 (9.3)
Sephardi or Mizrahi	3 (2.2)	2 (1.6)
Other or unknown	1 (0.7)	3 (2.3)
ECOG performance status — no. (%)†		
0	110 (80.9)	95 (73.6)
1	23 (16.9)	30 (23.3)
2	1 (0.7)	2 (1.6)
Unknown	2 (1.5)	2 (1.6)
Primary tumor location — no. (%)		
Ovary	119 (87.5)	109 (84.5)
Fallopian tube	3 (2.2)	4 (3.1)
Peritoneum	14 (10.3)	16 (12.4)
Time to progression with penultimate platinum-based regimen — no. (%)		
>6–12 mo	53 (39.0)	54 (41.9)
>12 mo	83 (61.0)	75 (58.1)
Objective response to most recent platinum-based regimen — no. (%)		
Complete	57 (41.9)	63 (48.8)
Partial	79 (58.1)	66 (51.2)
BRCA-germline-mutation status — no. (%)		
BRCA 1 or *BRCA 2* mutation	31 (22.8)	28 (21.7)
BRCA1 mutation	25 (18.4)	20 (15.5)
BRCA2 mutation	6 (4.4)	7 (5.4)
Both *BRCA1* and *BRCA2* mutations	0	1 (0.8)
Negative	18 (13.2)	20 (15.5)
Unknown	87 (64.0)	81 (62.8)
Previous chemotherapy regimens — no.		
Median	3‡	3
Range	0–11	2–8
Previous platinum-based chemotherapy regimens — no.		
Median	2‡	2
Range	0–7	2–8

* Ancestry was self-reported. Data on race or ethnic group, which was determined by the investigators, were as follows: more than 95% of the patients in each study group were white (95.6% in the olaparib group and 97.7% in the placebo group). Data for the remaining patients were as follows: black (1.5% in the olaparib group and 0.8% in the placebo group), Asian (1.5% and 1.6%, respectively), and other (1.5% and 0%, respectively).

† The Eastern Cooperative Oncology Group (ECOG) performance status is measured on a scale from 0 to 4, with 0 indicating normal activity, 1 restricted in strenuous activity but ambulatory and able to carry out light work, 2 ambulatory more than 50% of the time, 3 ambulatory 50% of the time or less and nursing care is required, and 4 bedridden and possibly requiring hospitalization.

‡ One patient received two regimens of platinum-based chemotherapy that were not recorded because the data were not entered into the database before it was locked. This patient was therefore classified as having received no chemotherapy regimens.

Study 19. Demographics and baseline characteristics by BRCA mutation status.

	All patients				Patients on treatment ≥2 years			
	Patients with *BRCA*m (n=136)		Patients with *BRCA*wt (n=118)		Patients with *BRCA*m (n=26)[‡]		Patients with *BRCA*wt (n=11)[†]	
	Olaparib (*n* = 74)	Placebo (*n* = 62)	Olaparib (*n* = 57)	Placebo (*n* = 61)	Olaparib (*n* = 21)	Placebo (*n* = 5)	Olaparib (*n* = 11)	Placebo (*n* = 0)
Age (years)	57.5 (38–89)	55.0 (33–84)	62.0 (21–80)	63.0 (49–79)	60.0 (43–80)	59.0 (48–71)	63.0 (44–79)	–
Ancestry								
Non-Jewish	60 (81)	48 (77)	51 (89)	58 (95)	16 (76)	5 (100)	10 (91)	–
Jewish	14 (19)	14 (23)	6 (11)	3 (5)	5 (24)	0	1 (9)	–
Number of previous lines of chemotherapy								
2	26 (35)	28 (45)	32 (56)	35 (57)	9 (43)	3 (60)	5 (45)	–
3	28 (38)	18 (29)	14 (25)	14 (23)	7 (33)	2 (40)	4 (36)	–
4	9 (12)	10 (16)	6 (11)	9 (15)	4 (19)	0	1 (9)	–
≥5	11 (15)	6 (10)	5 (9)	3 (5)	1 (5)	0	1 (9)	–
Primary tumour location								
Ovary	65 (88)	54 (87)	50 (88)	49 (80)	18 (86)	5 (100)	10 (91)	–
Fallopian tube or primary peritoneal	9 (12)	8 (13)	7 (12)	12 (20)	3 (14)	0	1 (9)	–
Time to progression after completion of penultimate platinum-based regimen								
>6 to ≤12 months	28 (38)	26 (42)	23 (40)	24 (39)	7 (33)	1 (20)	4 (36)	–
>12 months	46 (62)	36 (58)	34 (60)	37 (61)	14 (67)	4 (80)	7 (64)	–
Objective response to most recent platinum-based regimen								
Complete response	36 (49)	34 (55)	20 (35)	25 (41)	12 (57)	4 (80)	6 (55)	–
Partial response	38 (51)	28 (45)	37 (65)	36 (59)	9 (43)	1 (20)	5 (45)	–
Secondary debulking ≤1 month prior to randomisation	12 (16)	7 (11)	10 (18)	6 (10)	6 (29)	0	2 (18)	–
Metastatic disease at baseline								
Any site	27 (36)	16 (26)	24 (42)	30 (49)	5 (24)	2 (40)	5 (45)	–
Lymph nodes	14 (19)	5 (8)	11 (19)	4 (7)	2 (10)	1 (20)	2 (18)	–
Peritoneum	11 (15)	6 (10)	8 (14)	5 (8)	0	1 (20)	2 (18)	–
Hepatic	11 (15)	5 (8)	7 (12)	7 (11)	2 (10)	0	3 (27)	–

Table A2: Study and baseline characteristics SOLO2

Trial name	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.
NCT number	NCT01874353
Objective	To assess the efficacy of olaparib (tablets) maintenance monotherapy in relapsed high grade serous ovarian cancer (HGSOC) patients (including patients with primary peritoneal and / or fallopian tube cancer) or high grade endometrioid 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 platinum based chemotherapy.
Publications – title, author, journal, year	Friedlander M, Gebski V, Gibbs E, Davies L, Bloomfield R, Hilpert F, et al. Health-related quality of life and patient-centred outcomes with olaparib maintenance after chemotherapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT Ov-21): a placebo-controlled, phase 3 randomised trial. Lancet Oncol. 2018;19(8):1126-34. Pujade-Lauraine E, Ledermann JA, Selle F, Gebski V, Penson RT, Oza AM, 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):1274-84.
Study type and design	A Phase III, randomised, double-blind, placebo-controlled, multi-centre study to assess the efficacy of olaparib maintenance monotherapy in relapsed high grade serous ovarian cancer (HGSOC) patients (including patients with primary peritoneal and / or fallopian tube cancer) or high grade endometrioid 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 platinum based chemotherapy. Patients were randomised in a 2:1 ratio to the treatments as specified below: olaparib tablets p.o. 300 mg twice daily or placebo tablets p.o. twice daily. Randomisation was stratified by response to previous platinum chemotherapy (complete response (CR) or partial response (PR)) and time to disease progression in the penultimate platinum based chemotherapy prior to enrolment (>6 - 12 months and >12 months). Patients were randomised within 8 weeks after their last dose of chemotherapy (last dose is the day of the last infusion). Patients in both treatment arms had tumour assessments according to RECIST at baseline and every 12 weeks (±1week) up to 72 weeks and then every 24 weeks (±1week) relative to date of randomisation, until objective radiological disease progression according to RECIST. All CT/MRI scans were 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 were no longer be required. Patients continued to receive study treatment until objective radiological disease progression as per RECIST as assessed by the investigator or as long as in the investigator's opinion they were benefiting from treatment and they did not meet any other discontinuation criteria. Patients continued with therapy to RECIST progression despite rises in cancer antigen-125 (CA-125). All patients continued to be assessed for radiological tumour assessments according to the study schedule until objective radiological disease progression, irrespective of their continuation on study treatment. Once a patient had progressed the patient was followed as per local clinical practice, but assessment was made every 12 weeks for second progression and then survival until the final analysis.
Follow-up time	At the primary data cutoff (19 September 2016) the median follow-up time was approximately 22 months.
Population (inclusion and exclusion criteria)	Inclusion and exclusion criteria related to NCT number from www.clinicaltrials.gov: **Inclusion criteria:** Patients must be ≥ 18 years of age. Female patients with histologically diagnosed relapsed high grade serous ovarian cancer (including primary peritoneal and / or fallopian tube cancer) or high grade endometrioid cancer. 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 received at least 2 previous lines of platinum containing therapy prior to randomisation For the penultimate chemotherapy course prior to enrolment on the study: Patients defined as platinum sensitive after this treatment; defined as disease progression greater than 6 months after completion of their last dose of platinum chemotherapy For the last chemotherapy course immediately prior to randomisation on the study:

	Patients must be, in the opinion of the investigator, in response (partial or complete radiological response), or may have no evidence of disease (if optimal cytoreductive surgery was conducted prior to chemotherapy), and no evidence of a rising CA-125, following completion of this chemotherapy course Patients must have received a platinum based chemotherapy regimen (e.g. carboplatin or cisplatin) and have received at least 4 cycles of treatment Patients must be randomized within 8 weeks of their last dose of chemotherapy Maintenance treatment is allowed at the end of the penultimate platinum regimen, including bevacizumab **Exclusion criteria:** Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site). BRCA 1 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 who have had drainage of their ascites during the final 2 cycles of their last chemotherapy regimen prior to enrolment on the study.
Intervention	With the use of an interactive voice response system, 265 patients were randomly assigned in a 2:1 ratio to receive olaparib tablets, at a dose of 300 mg twice daily or matching placebo within 8 weeks after completion of the last dose of platinum-based chemotherapy. Study treatment was blinded with the use of unique identifiers generated during randomization. Patients continued to receive study treatment until objective radiological disease progression as per RECIST as assessed by the investigator or as long as in the investigator's opinion they were benefiting from treatment and they did not meet any other discontinuation criteria. All the trial agents were provided by AstraZeneca.
Baseline characteristics	Demographic and baseline characteristics seemed to be well balanced between the two groups. 33 (17%) of 196 patients in the olaparib group and 20 (20%) of 99 patients in the placebo group had received treatment with bevacizumab before their final platinum regimen prior to randomisation in this study. 153 (78%) patients in the olaparib group and 83 (84%) patients in the placebo group had a *BRCA1/2*mutation previously determined by local testing and could be enrolled on the basis of this information. All patients received a confirmatory *BRCA* test as part of the trial, which confirmed a germline *BRCA1/2* mutation in 190 (97%) patients in the olaparib group and 96 (97%) in the placebo group. The Myriad Genetics *BRCA* test did not determine a *BRCA1/2* mutation either to be deleterious or suspected deleterious in nine cases (six in the olaparib group and three in the placebo group): four of these nine patients had variants of unknown significance, two patients were *BRCA1/2*wildtype according to the Myriad Genetics *BRCA* test, and three had a missing confirmatory Myriad Genetics *BRCA* test (because the *BRCA1/2* mutation status of all nine patients had previously been determined by local testing before randomisation, they were still eligible for inclusion). No patients had a confirmed somatic *BRCA1/2* mutation.
Primary and secondary endpoints	The primary endpoint was investigator assessment of PFS, defined as the time from randomisation until objective radiological disease progression or death using modified RECIST version 1.1. Secondary endpoints included: PFS by blinded independent central review (BICR), OS, time from randomisation to second progression (PFS2), time from randomisation to first subsequent therapy or death (TFST), time from randomisation to second subsequent therapy or death (TSST), time from randomisation to study treatment discontinuation or death (TDT).

	The Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian Cancer (FACT-O) was used to determine change from baseline in TOI score
Method of analyzis	The aim was to analyse a higher number of events than required for a powered superiority analysis for both progression-free survival and time to second progression; therefore, the power to show superiority for both endpoints was greater than 90%. In total, 192 events of progression or death (~65% maturity) were required to provide sufficient precision of the estimated hazard ratio. PFS was tested at a two-sided significance level of 5% and analysed with a log-rank test, using the randomisation stratification factors. The sensitivity analysis of progression-free survival by blinded independent central review used the same methods and model as for the primary analysis of progression-free survival. Time to second progression and overall survival was analysed at the time of primary analysis of progression-free survival, using the same methods. At this initial analysis, statistical significance would be declared for time to second progression if one-sided p<0·0125 and for overall survival if one-sided p<0·0001. SAS version 9.1.3 was used for all analyses. Efficacy data and patient-reported outcomes were analysed in the intention-to-treat population, which included all randomised patients (full analysis set). Safety was analysed in all patients from the intention-to-treat population who received at least one dose of study treatment (safety analysis set). Patients were required to have both an evaluable score at baseline and at least one evaluable follow-up form to be assessable for health-related quality of life. An evaluable form was defined as one having at least one subscale that could be measured, or a form that was not completed because the patient was deemed too heavily affected by symptoms of disease. Patients who did not fulfil these requirements were deemed as not assessable for health-related quality of life.
Subgroup analyses	Subgroup analyses were conducted comparing PFS between treatments in the following subgroups of the full analysis set: Response to previous platinum chemotherapy (Complete Response or Partial Response), Time to disease progression in the penultimate platinum based chemotherapy prior to enrolment (>6-12 months and >12 months), gBRCAm status-confirmed by Myriad test vs gBRCA wt or missing by Myriad gBRCA test, ECOG performance status at baseline (0 or 1), Prior cytoreductive surgery (Yes or No), Lines of prior platinum therapy (2, 3 or 4+), Baseline CA 125 value (≤ ULN vs > ULN), BRCA mutation type eg BRCA1, BRCA2 or BRCA1/2 (both) and Age at randomization (<65 vs. ≥65).

Demographics and baseline characteristics

	Olaparib (n=196)	Placebo (n=99)
Age (years)	56 (51–63)	56 (49–63)
ECOG performance status*		
0	162 (83%)	77 (78%)
1	32 (16%)	22 (22%)
Missing	2 (1%)	0
Primary tumour location		
Ovary	164 (84%)	86 (87%)
Fallopian tubes or primary peritoneal	31 (16%)	13 (13%)
Missing	1 (1%)	0
Histology type		
Serous	183 (93%)	86 (87%)
Endometrioid	9 (5%)	8 (8%)
Mixed	3 (2%)	5 (5%)
Missing	1 (1%)	0
Patients with >2 cm target lesions at baseline	30 (15%)	18 (18%)
Confirmed germline *BRCA* mutation		
BRCA1	132 (67%)	61 (62%)
BRCA2	58 (30%)	35 (35%)
Both	0	0
Missing†	6 (3%)	3 (3%)
Response to previous platinum therapy		
Complete	91 (46%)	47 (47%)
Partial	105 (54%)	52 (53%)
Number of previous platinum-based regimens‡		
Two	110 (56%)	62 (63%)
Three	60 (31%)	20 (20%)
Four	18 (9%)	12 (12%)
Five or more	7 (4%)	5 (5%)
Platinum-free interval		
>6–12 months	79 (40%)	40 (40%)
>12 months	117 (60%)	59 (60%)

Table 1. Demographic and Baseline Characteristics of the Patients.

Characteristic	Olaparib (N = 136)	Placebo (N = 129)
Age — yr		
Median	58.0	59.0
Range	21–89	33–84
Ancestry — no. (%)*		
Non-Jewish	116 (85.3)	112 (86.8)
Jewish	20 (14.7)	17 (13.2)
Ashkenazi	16 (11.8)	12 (9.3)
Sephardi or Mizrahi	3 (2.2)	2 (1.6)
Other or unknown	1 (0.7)	3 (2.3)
ECOG performance status — no. (%)†		
0	110 (80.9)	95 (73.6)
1	23 (16.9)	30 (23.3)
2	1 (0.7)	2 (1.6)
Unknown	2 (1.5)	2 (1.6)
Primary tumor location — no. (%)		
Ovary	119 (87.5)	109 (84.5)
Fallopian tube	3 (2.2)	4 (3.1)
Peritoneum	14 (10.3)	16 (12.4)
Time to progression with penultimate platinum-based regimen — no. (%)		
>6–12 mo	53 (39.0)	54 (41.9)
>12 mo	83 (61.0)	75 (58.1)
Objective response to most recent platinum-based regimen — no. (%)		
Complete	57 (41.9)	63 (48.8)
Partial	79 (58.1)	66 (51.2)
BRCA-germline-mutation status — no. (%)		
BRCA 1 or *BRCA 2* mutation	31 (22.8)	28 (21.7)
BRCA1 mutation	25 (18.4)	20 (15.5)
BRCA2 mutation	6 (4.4)	7 (5.4)
Both *BRCA1* and *BRCA2* mutations	0	1 (0.8)
Negative	18 (13.2)	20 (15.5)
Unknown	87 (64.0)	81 (62.8)
Previous chemotherapy regimens — no.		
Median	3‡	3
Range	0–11	2–8
Previous platinum-based chemotherapy regimens — no.		
Median	2‡	2
Range	0–7	2–8

* Ancestry was self-reported. Data on race or ethnic group, which was determined by the investigators, were as follows: more than 95% of the patients in each study group were white (95.6% in the olaparib group and 97.7% in the placebo group). Data for the remaining patients were as follows: black (1.5% in the olaparib group and 0.8% in the placebo group), Asian (1.5% and 1.6%, respectively), and other (1.5% and 0%, respectively).

† The Eastern Cooperative Oncology Group (ECOG) performance status is measured on a scale from 0 to 4, with 0 indicating normal activity, 1 restricted in strenuous activity but ambulatory and able to carry out light work, 2 ambulatory more than 50% of the time, 3 ambulatory 50% of the time or less and nursing care is required, and 4 bedridden and possibly requiring hospitalization.

‡ One patient received two regimens of platinum-based chemotherapy that were not recorded because the data were not entered into the database before it was locked. This patient was therefore classified as having received no chemotherapy regimens.

Table A2: Study and baseline characteristics NOVA

Trial name	A Phase 3 Randomized Double-blind Trial of Maintenance With Niraparib Versus Placebo in Patients With Platinum Sensitive Ovarian Cancer.
NCT number	NCT01847274
Objective	The primary objective of the study is to evaluate efficacy of niraparib as maintenance therapy in patients who have platinum sensitive ovarian cancer as assessed by the prolongation of progression free survival (PFS).
Publications – title, author, journal, year	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. Oza AM, Matulonis UA, Malander S, Hudgens S, Sehouli J, Del Campo JM, et al. Quality of life in patients with recurrent ovarian cancer treated with niraparib versus placebo (ENGOT-OV16/NOVA): results from a double-blind, phase 3, randomised controlled trial. Lancet Oncol. 2018;19(8):1117-25.
Study type and design	A multicenter, double-blind, placebo-controlled, phase 3 trial at 107 study sites across 16 countries between Aug 28, 2008 and Feb 9, 2010. Between Aug 28, 2013, and June 1, 2015, 553 patients were enrolled and randomly assigned to receive niraparib or placebo. Two independent cohorts were enrolled on the basis of the presence or absence of a germline *BRCA* mutation (g*BRCA* cohort and non-g*BRCA* cohort), as determined on BRACAnalysis testing (Myriad Genetics). Not later than 8 weeks after completing their last dose of platinum-based therapy, patients were randomly assigned in a 2:1 ratio to receive niraparib (300 mg) or placebo once daily in 28-day cycles (with no treatment breaks) until disease progression. Randomization within each cohort was stratified according to the time to progression after completion of the penultimate platinum regimen (6 to <12 months vs. ≥12 months), the use of bevacizumab in conjunction with the penultimate or last platinum regimen, and the best response (complete or partial) during the last platinum regimen.
Follow-up time	At the data cut-off, the median OS follow-up time was 17 months.
Population (inclusion and exclusion criteria)	Inclusion and exclusion criteria related to NCT number from www.clinicaltrials.gov: **Inclusion criteria:** • Female, age at least 18 years • Patient agrees to undergo analysis of their germline BRCA status. (Testing must be completed prior to randomization with sample submitted up to 3 months prior to randomization if it appears patient is likely to meet other eligibility requirements.) • Histologically diagnosed ovarian cancer, fallopian tube cancer or primary peritoneal cancer • High grade (or grade 3) serous histology or known to have gBRCAmut • Patients must have completed at least 2 previous courses of platinumcontaining therapy (e.g. carboplatin, oxaliplatin or cisplatin):

	○ For the penultimate (next to last) platinum based chemotherapy course prior to enrollment on the study: i. A patient must have platinum sensitive disease after this treatment; defined as achieving a response (CR or PR) and having a CFI of ≥6 months (document 6- 12m or >12m). Chemotherapy-free interval is defined as the time from last dose of platinum until initiation of subsequent therapeutic chemotherapy (excluding maintenance therapy; source documentation required and may include physician or clinic notes) ○ For the last chemotherapy course prior to enrollment on the study: i. Patients must have received a platinum-containing regimen for a minimum of 4 cycles ii. Patients must have achieved a partial or complete tumor response. iii. Following the last regimen, patients must have either 1. CA125 in the normal range OR 2. CA125 decrease by more than 90% during their last platinum regimen which is stable for at least 7 days (i.e., no increase >15%) iv. Following the last regimen, patients must have no measurable disease >2cm at the time of study entry c. Patients must be started on study treatment between 3 and 8 weeks after completion of their final dose of the platinumcontaining regimen. • The patient agrees to complete PROs during study. • Formalin fixed, paraffin embedded archival tumor available from the primary or recurrent cancer required for all non-gBRCAmut patients (and strongly encouraged for gBRCAmut patients). • ECOG performance status 0-1. • Adequate organ function • Able to take oral medications • Women of childbearing potential must use adequate birth control for the duration of study participation **Exclusion criteria:** • Known hypersensitivity to the components of niraparib • Invasive cancer other than ovarian cancer within 2 years (except basal or squamous cell carcinoma of the skin that has been definitely treated) • Symptomatic uncontrolled brain metastasis • Is pregnant or breast feeding • Immunocompromised patients • Known active hepatic disease • Prior treatment with a known PARP inhibitor
Intervention	Patients were randomly assigned in a 2:1 ratio to receive niraparib (300 mg) or placebo once daily in 28-day cycles (with no treatment breaks) until disease progression. Study treatment was administered orally once daily continuously. Three capsules of 100 mg strength were to be taken at each dose administration. Dose interruption (no longer than 28 days) was allowed. In addition, dose reduction was allowed based on treatment side effects.

	Dose reductions to 2 capsules daily (200 mg) and subsequently to 1 capsule daily (100 mg) were allowed. No further dose reductions were allowed.
Baseline characteristics	Demographic and clinical characteristics were well balanced in the two cohorts at baseline. The median age ranged from 57 to 63 years, and the majority of the patients had stage III or IV ovarian cancer at the time of diagnosis. Approximately half the patients in the g*BRCA*cohort and one third of those in the non-g*BRCA*cohort had received three or more lines of chemotherapy. See also Table 1 below (1.1.1.1)
Primary and secondary endpoints	The primary endpoint was PFS as measured by by RECIST v.1.1 criteria using blinded central review (BICR). Secondary endpoints included Patient Reported Outcomes (PRO) by Functional Assessment of Cancer therapy - Ovarian Symptom Index (FOSI) EQ-5D-5L Neuropathy Questionnaire, chemotherapy free interval (CFI), overall survival (OS), safety and tolerability, BRCA diagnostic test and HRD diagnostic test.
Method of analysis	For each primary efficacy population, progression-free survival was analyzed with a stratified log-rank test using randomization stratification factors, and summarized using the Kaplan-Meier methodology. Hazard ratios with 95% confidence intervals were estimated using a 13 stratified Cox proportional hazards model, with the stratification factors used in randomization. For each group, the Cox proportional hazards model was fitted and a table showing the hazard ratios and 95% confidence intervals within each subgroup category was provided. A statistical test for the presence of a treatment-by-subgroup interaction was performed by including the interaction term in the primary analysis model using Cox regression. If the treatment-bysubgroup interaction was found to be statistically significant at the 10% level (P<0.10) this may have been taken as evidence of heterogeneity of the treatment effect across the subgroup categories. Secondary time-to-event end points were analyzed in the same manner as progression-free survival. Primary efficacy populations were explored for progression-free survival based on age, race, geographic region, time to progression after the penultimate platinum therapy before study enrollment, use of bevacizumab in conjunction with the penultimate or last platinum regimen, best response during the last platinum regimen, number of prior platinum regimens, and number of prior chemotherapy regimens.
Subgroup analyses	Exploratory analyses were performed on subgroups in the non-gBRCAmut cohort. These included tumors with somatic BRCA mutations (HRD-positive/sBRCAmut), those with wild-type BRCA genes (HRD-positive/BRCAwt), and those that were HRD-negative. Results for tumors with an undetermined HRD status were analyzed separately. Formal hypothesis testing was not performed for the exploratory analyses.

Demographics and baseline characteristics

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Germline *BRCA* Mutation		No Germline *BRCA* Mutation	
	Niraparib (N=138)	Placebo (N=65)	Niraparib (N=234)	Placebo (N=116)
Median age (range) — yr	57 (36–83)	58 (38–73)	63 (33–84)	61 (34–82)
Eastern Cooperative Oncology Group performance status — no. (%)				
0	91 (65.9)	48 (73.8)	160 (68.4)	78 (67.2)
1	47 (34.1)	17 (26.2)	74 (31.6)	38 (32.8)
Cancer stage — no. (%)†				
I or II	23 (16.7)	10 (15.4)	22 (9.4)	5 (4.3)
III	95 (68.8)	46 (70.8)	173 (73.9)	86 (74.1)
IV	20 (14.5)	9 (13.8)	38 (16.2)	24 (20.7)
Time to progression after penultimate platinum therapy — no. (%)				
6 to <12 mo	54 (39.1)	26 (40.0)	90 (38.5)	44 (37.9)
≥12 mo	84 (60.9)	39 (60.0)	144 (61.5)	72 (62.1)
Best response to most recent platinum therapy — no. (%)				
Complete	71 (51.4)	33 (50.8)	117 (50.0)	60 (51.7)
Partial	67 (48.6)	32 (49.2)	117 (50.0)	56 (48.3)
Previous bevacizumab use — no. (%)	33 (23.9)	17 (26.2)	62 (26.5)	30 (25.9)
Germline *BRCA* mutation — no. (%)				
BRCA1	85 (61.6)	43 (66.2)	NA	NA
BRCA2	51 (37.0)	18 (27.7)	NA	NA
BRCA1, *BRCA2* rearrangement, or both	9 (6.5)	4 (6.2)	NA	NA
Previous lines of chemotherapy — no. (%)‡				
1	1 (0.7)	0	0	0
2	70 (50.7)	30 (46.2)	155 (66.2)	77 (66.4)
≥3	67 (48.6)	35 (53.8)	79 (33.8)	38 (32.8)

* There were no significant differences between the niraparib group and the placebo group. NA denotes not applicable.
† Staging was performed with the use of the International Federation of Gynecology and Obstetrics system. Among the patients without a germline *BRCA* mutation, data with respect to staging were not available for one patient in the placebo group, and one patient in the niraparib group had stage 0 disease at the time of diagnosis.
‡ Among the patients without a germline *BRCA* mutation, data with respect to previous lines of therapy were not available for one patient in the placebo group.

Table A2: Study and baseline characteristics OCEANS

Trial name	A Phase III, Multicenter, Randomized, Blinded, Placebo-controlled Trial of Carboplatin and Gemcitabine Plus Bevacizumab in Patients With Platinum-sensitive Recurrent Ovary, Primary Peritoneal, or Fallopian Tube Carcinoma (OCEANS)
NCT number	NCT00434642
Objective	To evaluate the safety and efficacy of bevacizumab, administered in combination with carboplatin with gemcitabine, in women with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube carcinoma.
Publications – title, author, journal, year	Aghajanian C, Blank SV, 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. 2012;30(17):2039-45. Aghajanian C, Goff B, Nycum LR, Wang Y, Husain A, Blank S. Independent radiologic review: bevacizumab in combination with gemcitabine and carboplatin in recurrent ovarian cancer. Gynecol Oncol. 2014;133(1):105-10. Aghajanian C, Goff B, Nycum LR, Wang YV, Husain A, Blank SV. Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. Gynecol Oncol. 2015;139(1):10-6.
Study type and design	This was a placebo-controlled, randomized, double-blind multicenter Phase III study evaluating the efficacy and safety of bevacizumab (15 mg/kg, Day 1, every 21 days), administered in combination with carboplatin (area under the curve [AUC] 4, Day 1, every 21 days) with gemcitabine (1000 mg/m2 , Day 1 and Day 8, every 21 days) in women with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube carcinoma. A total of 484 patients were enrolled over a period of approximately 2.5 years. Patients who met the eligibility criteria and gave consent to participate were randomized 1:1 to carboplatin and gemcitabine + placebo versus carboplatin and gemcitabine+ bevacizumab. At randomization, patients were stratified by platinum-sensitive disease (recurrence 6–12 months from last platinum-based treatment vs. recurrence > 12 months from last platinum-based treatment) and cytoreductive surgery for recurrent epithelial ovarian, primary peritoneal, or fallopian tube carcinomas (surgery was performed vs. was not performed).
Follow-up time	At the data cut-off, median follow-up for OS was 58.2 months in the experimental arm and 56.4 months in the control arm.
Population (inclusion and exclusion criteria)	Inclusion and exclusion criteria related to NCT number from www.clinicaltrials.gov: **Inclusion criteria:** • Signed Informed Consent Form • Age≥ 18 years • Histologically documented ovarian, primary peritoneal, or fallopian tube carcinoma that has recurred> 6 months after platinum-based chemotherapy • The patient must have recurrent epithelial ovarian, primary peritoneal, or fallopian tube carcinoma. This must be the first recurrence of epithelial ovarian, primary peritoneal, or fallopian tube carcinoma. • Examples of eligible histological cell types include: serous adenocarcinoma, endometrioid adenocarcinoma, mucinous adenocarcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, transitional cell carcinoma, malignant Brenner's Tumor, or adenocarcinoma not otherwise specified

	• No prior chemotherapy in the recurrent setting • Measurable disease according to modified RECIST with at least one lesion that can be accurately measured in at least one dimension (longest dimension recorded) • Each measurable lesion must be ≥20 mm when measured by conventional techniques, CT and magnetic resonance imaging (MRI), or 10 mm when measured by spiral CT • Greater than 28 days from and recovered from prior radiation therapy or surgery • ECOG performance status 0 or 1 • Use of an effective means of contraception (for women of childbearing potential) • Ability to comply with study and follow-up procedures **Exclusion criteria:** • Prior chemotherapy treatment for recurrent ovarian, primary peritoneal, or fallopian tube carcinoma • History of abdominal fistula, gastrointestinal perforation (GIP), or intra-abdominal abscess • Patients with clinical symptoms or signs of gastrointestinal (GI) obstruction or who require parenteral hydration, parenteral nutrition, or tube feeding • Patients with evidence of abdominal free air not explained by paracentesis or recent surgical procedure • Current, recent, or planned participation in an experimental drug study • History of systemic bevacizumab (Avastin) or other vascular endothelial growth factor (VEGF) or VEGF receptor-targeted agent use • Inadequately controlled hypertension • Prior history of hypertensive crisis or hypertensive encephalopathy • New York Heart Association Class II or greater congestive heart failure (CHF) • History of myocardial infarction or unstable angina • History of stroke or transient ischemic attack (TIA) • Known central nervous system (CNS) disease except for treated brain metastasis • Significant vascular disease or recent peripheral arterial thrombosis • History of hemoptysis • Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation)
Intervention	Patients received gemcitabine 1,000 mg/m^2 on days 1 and 8 and carboplatin area under the curve 4 mg/mL/min on day 1 (based on the Calvert formula). Cycles were repeated every 21 days. The trial was designed so that patients would receive six cycles of gemcitabine-carboplatinbut would be allowed to receive up to 10 cycles if continued response was documented. Bevacizumab or placebo 15 mg/kg was administered intravenously on day 1 of each cycle, before gemcitabine-carboplatin. After completion of the 6-10 cycles of gemcitabine-carboplatin, either bevacizumab or placebo, respectively, was continued until PD or unacceptable toxicity
Baseline characteristics	From April 2007 through January 2010, 484 patients were randomly assigned. Patient disposition is shown below in Figure 1. The treatment arms were well balanced for baseline patient and disease characteristics (See Table 1 below).
Primary and secondary endpoints	**Primary endpoint:** Progression Free Survival (PFS) as Determined by the Investigator, Per Response Evaluation Criteria for Solid Tumors (RECIST) **Secondary endpoints:**

	Percentage of Patients with an Objective Response as Determined by the Investigator, Per Response Evaluation Criteria for Solid Tumors (RECIST) Duration of Objective Response (OR) as Determined by the Investigator, Per Response Evaluation Criteria for Solid Tumors (RECIST) Overall Survival Percentage of Patients Who Had a Gastrointestinal Perforation (GIP) Percentage of Patients Who Had at Least 1 Adverse Event
Method of analysis	The primary outcome measure was PFS, as determined by investigators. Secondary outcome measures were ORR, OS, and DOR. A sensitivity analysis was performed for PFS determined by an independent review committee (IRC). PFS was defined as the time from random assignment to PD or death as a result of any cause. For patients alive without documented PD at the time of the analysis, PFS was censored at the time of the last tumor assessment. If no postbaseline assessment was performed, the date of random assignment plus 1 day was used as the censor date. OS was defined as the time from random assignment until death as a result of any cause, and patients alive at the time of the analysis were censored at the date of last contact. In the ORR analysis, patients without a postbaseline assessment were considered to be nonresponders. In the IRC-determined analysis, PFS was defined as the time from random assignment until PD (IRC determined) or on-study death (ie, death within 9 weeks of the last dose of protocol treatment). To detect an HR of 0.73 for PFS in the Bevacizumab-arm relative to the PL arm, approximately 317 events were required. A two-sided log-rank test at the .05 level of significance with 80% power was assumed in the calculation. Per agreement with regulatory authorities, two interim OS analyses were planned: one at the time of final PFS analysis and the other at approximately 214 deaths. The final OS analysis was conducted at 353 deaths. Kaplan-Meier methodology was applied to estimate the median PFS and DOR for each treatment group. Brookmeyer-Crowley methodology was used to construct 95% CIs for median values. The stratified HR was estimated using a Cox regression model. Stratification factors were time to recurrence since the last platinum therapy (6 to 12 vs > 12 months) and cytoreductive surgery for recurrent disease (yes *vs* no). A two-sided stratified log-rank test was used to compare the two groups. ORRs were compared by the Cochran-Mantel-Haenszel test. Efficacy analyses were performed on the intent-to-treat population, and the safety population consisted of all randomly assigned patients who received at least one partial dose of any component of protocol treatment.
Subgroup analyses	Subgroup analyses on clinically relevant treatment groups examining age, baseline Eastern Cooperative Oncology Group performance status, platinum-free interval (6 to 12, 12 to 24, and > 24 months), and cytoreductive surgery for recurrent disease was performed for PFS.

Patient disposition

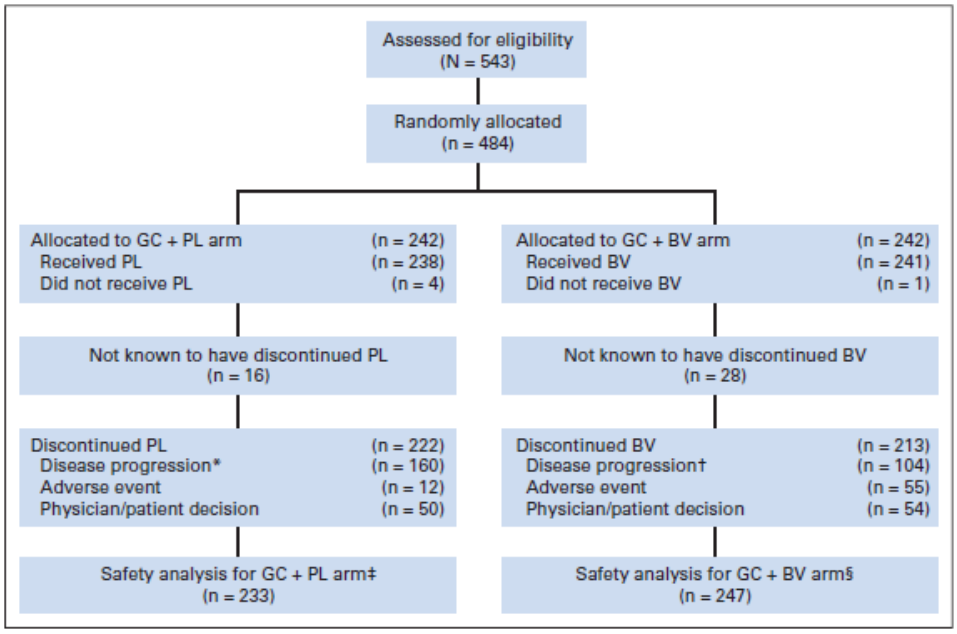

Fig 1. CONSORT diagram of all randomly assigned patients (represents intent-to-treat population). BV, bevacizumab; GC, gemcitabine plus carboplatin; PL, placebo. (*) Includes 158 patients with disease progression per RECIST and two patients with clinical disease progression. (†) Includes 100 patients with disease progression per RECIST and four patients with clinical disease progression. (‡) Five patients who were randomly assigned to the GC plus PL arm received one or two doses of BV in error and were assigned to the GC plus BV arm for all safety analyses. Four patients who were randomly assigned to the GC plus PL arm did not receive any protocol treatment and thus were not included in the safety analyses. (§) Five patients who were randomly assigned to the GC plus PL arm received one or two doses of BV in error and were assigned to the GC plus BV arm for all safety analyses.

Baseline patient and disease characteristics

Table 1. Baseline Patient Demographics and Disease Characteristics*

Characteristic	GC + PL (n = 242) No.	%	GC + BV (n = 242) No.	%
Age, years				
Mean	61.6		60.5	
SD	10.2		9.8	
Median	61.0		60.0	
Percentile				
25th	55.0		53.0	
75th	68.0		68.0	
Range	28.0-86.0		38.0-87.0	
Age group, years				
< 40	2	0.8	2	0.8
40-64	147	60.7	155	64.0
≥ 65	93	38.4	85	35.1
Race				
American Indian or Alaska Native	0	0.0	2	0.8
Asian	6	2.5	9	3.7
Black or African American	7	2.9	8	3.3
Native Hawaiian or other Pacific Islander	1	0.4	1	0.4
White	222	91.7	218	90.1
Not available	6	2.5	4	1.7
ECOG PS				
0	185	76.4	182	75.2
1	57	23.6	59	24.4
2	0	0.0	1	0.4
Primary site				
Fallopian tube	15	6.2	14	5.8
Ovarian	207	85.5	200	82.6
Primary peritoneal	20	8.3	28	11.6
Histology subtype				
Serous	202	83.5	189	78.1
Mucinous	1	0.4	3	1.2
Endometrioid	16	6.6	13	5.4
Transitional cell	2	0.8	2	0.8
Clear cell	6	2.5	9	3.7
Mixed	5	2.1	6	2.5
Other	10	4.1	20	8.3
Cytoreductive surgery for recurrent disease				
Yes	24	9.9	30	12.4
No	218	90.1	212	87.6
Time to recurrence since last platinum-based therapy, months				
6-12	102	42.1	100	41.3
> 12	140	57.9	142	58.7

Abbreviations: BV, bevacizumab; ECOG PS, Eastern Cooperative Oncology Group performance status; GC, gemcitabine plus carboplatin; PL, placebo; SD, standard deviation.
*Randomly assigned patients.

Table A2: Study and baseline characteristics Study 41

Trial name	A Phase II Open Label Randomised Comparative Multicentre Study to Compare the Efficacy and Tolerability of Olaparib in Combination With Paclitaxel and Carboplatin Versus Paclitaxel and Carboplatin Alone in Patients With Platinum Sensitive Advanced Serous Ovarian Cancer
NCT number	NCT01081951
Objective	The primary objective of this study is: • To compare the efficacy of olaparib when given in combination with paclitaxel and carboplatin to paclitaxel and carboplatin alone, by assessment of Progression Free Survival (PFS). (Independent Central Review) The secondary objectives of this study are: • To compare the efficacy of olaparib when given in combination with paclitaxel and carboplatin to paclitaxel and carboplatin alone, by assessment of Overall Survival (OS), percent change in tumour size, Objective Response Rate (ORR), Ovarian Cancer Response Rate (a composite of CA-125 Response Rate [Gynecologic Cancer InterGroup GCIG criteria] and/or RECIST Response Rate), and CA-125 response rate (GCIG criteria).
Publications – title, author, journal, year	Oza AM, Cibula D, Benzaquen AO, Poole C, Mathijssen RH, Sonke GS, et al. Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial. Lancet Oncol. 2015;16(1):87-97.
Study type and design	A multicentre, multinational phase 2, open-label study at 43 investigational sites across 12 countries between Feb 12 and July 30, 2010. A total of 173 patients were enrolled into the study, of whom 162 were eligible and were randomly assigned in a 1:1 ratio to the two treatment groups. In this randomised, open-label, phase 2 study, adult patients with platinum-sensitive, recurrent, high-grade serous ovarian cancer who had received up to three previous courses of platinum-based chemotherapy and who were progression free for at least 6 months before randomisation received either olaparib (200 mg capsules twice daily, administered orally on days 1-10 of each 21-day cycle) plus paclitaxel (175 mg/m(2), administered intravenously on day 1) and carboplatin (area under the curve [AUC] 4 mg/mL per min, according to the Calvert formula, administered intravenously on day 1), then olaparib monotherapy (400 mg capsules twice daily, given continuously) until progression (the olaparib plus chemotherapy group), or paclitaxel (175 mg/m(2) on day 1) and carboplatin (AUC 6 mg/mL per min on day 1) then no further treatment (the chemotherapy alone group). Randomisation was done by an interactive voice response system, stratified by number of previous platinum-containing regimens received and time to disease progression after the previous platinum regimen. Prespecified exploratory analyses included efficacy by BRCA mutation status, assessed retrospectively.
Follow-up time	At the final analysis of overall survival (Jan 31, 2014), the median duration of follow-up was 33·4 months (IQR 20·4–42·9) in the olaparib plus chemotherapy group and 32·2 months (19·5–43·6) in the chemotherapy alone group.
Population (inclusion and exclusion criteria)	The key inclusion and exclusion criteria related to NCT number from www.clinicaltrials.gov: **Inclusion Criteria:** • Diagnosed with serous ovarian cancer • Patients who have received no more than 3 previous platinum containing treatments and were progression free for at least 6 months following the end of the last platinum treatment

	• At least one lesion that is suitable for accurate repeated measurements **Exclusion Criteria:** • Patients receiving any systemic anticancer chemotherapy, radiotherapy (except palliative) within two weeks from the last dose prior to study treatment • Hypersensitivity to pre medications required for treatment with paclitaxel/carboplatin
Intervention	**The patients were randomized 1:1 to one of the two treatment arms:** **A. Investigational product, dosage and mode of administration** Olaparib p.o. (200 mg bid on day 1 –10 of a 21 day cycle), in combination with paclitaxel i.v. (175 mg/m2 on day 1 of a 21 day cycle) and carboplatin i.v. (AUC 4 day 1 of a 21 day cycle). Olaparib will be in capsule form. Following 6 cycles of combined treatment, patients may continue on olaparib monotherapy 400 mg bid continuous dosing, days 1-21. **B. Comparator, dosage and mode of administration** Paclitaxel i.v. (175 mg/m2 on day 1 of a 21 day cycle) and carboplatin i.v. (AUC 6 day 1 of a 21 day cycle) for 6 cycles. **Duration of treatment** It is expected all patients will receive 6 cycles (18 weeks) of paclitaxel and carboplatin. Following cycle 6, patients randomised to receive olaparib in combination (Arm A) will continue on olaparib monotherapy at a dose of 400 mg bid continuously, days 1-21. Patients will continue to receive treatment until objective disease progression as per RECIST v1.1 or for as long as receiving clinical benefit.
Baseline characteristics	Baseline characteristics were generally well balanced between the treatment groups (See Table 1 below). Based on germline *BRCA* mutation status at baseline and retrospective tumour BRCA testing, *BRCA* mutation status was known for 107 (66%) of 162 patients, of whom 41 (38%) had *BRCA* mutations. The proportion of *BRCA*mutation-positive patients was well balanced between treatment groups (20 [25%] of 81 in the olaparib plus chemotherapy group, and 21 [26%] of 81 in the chemotherapy alone group).
Primary and secondary endpoints	**Primary endpoint:** The primary endpoint was Progression Free Survival (PFS), defined as the time from randomisation until objective disease progression as defined by RECIST v1.1 or death (by any cause in the absence of progression). **Secondary endpoints:** **Overall Survival (OS)** Overall survival is defined as the time from randomisation until death by any cause. Patients who have not died at the time of the statistical analysis of OS will be censored at the time they were last known to be alive. **Percentage Change in Total Tumour Size** The total tumour size is defined as the sum of the longest diameters of the target lesions. For each post-baseline tumour assessment, the percentage change in tumour size will be calculated from the ratio of the post-baseline size over the baseline total tumour size for each patient.

	Objective Response Rate (ORR) ORR is defined as the percentage of patients who have at least one visit response of CR or PR prior to any evidence of progression (as defined by RECIST v1.1). A visit response of CR is defined when all TL and NTL lesions present at baseline have disappeared (with the exception of lymph nodes which must be <10mm to be considered nonpathological) and no new lesions have developed since baseline. A visit response of PR is defined when the sum of diameters of the TLs has decreased by 30% or more compared to baseline (with no evidence of progression) and the NTLs are at least stable with no evidence of new lesions. **Ovarian Cancer Response Rate** Ovarian Cancer Response Rate will be defined as the proportion patients with a response based on either the RECIST criteria (PRs or CRs only) or CA-125 response criteria.
Method of analysis	PFS and OS was analyzed on an intention-to-treat basis by a stratified log-rank test that used the same stratification factors as those used at randomisation. Predictive and prognostic factors were explored for progression-free survival using pre-planned subgroup analyses, including number of previous platinum-based treatments, time to disease progression following the previous platinum-containing therapy, and *BRCA* mutation status. Objective response, and CA-125 and ovarian cancer responses were analysed by logistic regression, with adjustment for the same stratification factors as for progression-free survival. The least-squares mean percentage change in tumour size were assessed using an analysis of covariance, which included covariates for baseline tumour size, previous platinum treatments, and time to disease progression after the previous platinum-containing therapy. SAS version 8.1 was used for all analyses. Since the primary overall survival analysis used a stratified log-rank test, an exploratory post-hoc analysis of overall survival using a Cox proportional hazards model was performed that adjusted for these imbalances.
Subgroup analyses	Prespecified exploratory subgroup analysis included efficacy by *BRCA* mutation status, assessed retrospectively. For consenting patients, archival tumour samples were analysed for deleterious, or suspected deleterious, mutations in *BRCA* with use of next-generation sequencing (performed by Foundation Medicine, Cambridge, MA, USA); the sequence variants were classified in accordance with the American College of Medical Genetics and Genomics' recommendations using the Breast Cancer Information Core database.

Demographics and baseline characteristics

	Olaparib plus chemotherapy (n=81)	Chemotherapy alone (n=81)
Age (years)	59 (27–78)	62 (31–79)
Ethnic origin		
White	70 (86%)	69 (85%)
Asian	8 (10%)	8 (10%)
Black	0	2 (2%)
Other	3 (4%)	2 (2%)
ECOG performance status		
0	58 (72%)	63 (78%)
1	21 (26%)	15 (19%)
2	2 (2%)	1 (1%)
Unknown	0	2 (2%)
Germline *BRCA* mutation status at study entry*		
Germline *BRCA1* mutation	7 (9%)	10 (12%)
Germline *BRCA2* mutation	5 (6%)	2 (2%)
Wild type	3 (4%)	8 (10%)
Missing	66 (81%)	61 (75%)
Previous platinum-containing chemotherapy regimens†		
1	58 (72%)	53 (65%)
>1	23 (28%)	28 (35%)
Time to disease progression after previous platinum therapy†		
>6 to ≤12 months	39 (48%)	40 (49%)
>12 months	42 (52%)	41 (51%)
Primary tumour location		
Ovary	69 (85%)	72 (89%)
Peritoneum	7 (9%)	4 (5%)
Fallopian tube	4 (5%)	2 (2%)
Other‡	1 (1%)	2 (2%)
Unknown	0	1 (1%)

Data are median (range) or n (%). ECOG=Eastern Cooperative Oncology Group. *Germline *BRCA* mutation status at baseline was recorded on case report forms; germline *BRCA* testing procedures can vary, so patients defined as wild type at study entry might not have undergone comprehensive *BRCA* testing. †Stratification factor for patient randomisation. ‡Other primary tumour locations were as follows: olaparib plus chemotherapy group: pelvis (n=1); chemotherapy alone group: bilateral ovary (n=1), and synchronous ovarian and fallopian tube (n=1).

Table 1: **Patient demographics and baseline characteristics**

8.1.2 A3. Results per study Study 19

Trial name:	Study 19									
NCT number:	NCT00753545									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	
OS *ITT*	Olaparib	136	29.8	2.0	NA	NA	HR=0.73	0.55-0.95	0.002138	
	Placebo	129	27.8							
OS *BRCAwt*	Olaparib	57	24.5	-2.1	NA	NA	HR=0.84	0.57 - 1.25	0.39749	*Median time to event based on the Kaplan Meier estimate. HR Estimated from Cox proportional hazards model including treatment, subgroup and the treatment by subgroup interaction. Efron method for handling ties. 95% CI from profile likelihood estimation. P-value for HR from comparing difference in -2 log likelihood from this model and a model without the treatment term, against a chi-squared distribution. HR% <1 favours olaparib.*
	Placebo	61	26.6							
PSF *ITT (Inv)*	Olaparib	136	8.4	3.6 m	NA	NA	HR=0.35	0.25-0.49	<0.00001	*PFS was analyzed using a Cox proportional hazards model with factors for time to progression (6–12 months, and >12 months, after the penultimate platinum therapy prior to study enrolment).See Also table A"BICR-assessed PFS was consistent with the investigator-assessed PFS (HR 0.39; 95% CI 0.27, 0.55; P<0.001)*
	Placebo	129	4.8							
PFS *BRCAwt*	Olaparib	57	7.4	1.9 m	NA	NA	HR=0.54	0.34-0.85	0.00745	*PFS was analyzed using a Cox proportional hazards model with factors for time to progression (6–12 months, and >12 months, after the penultimate platinum therapy*
	Placebo	61	5.5							
Discontinuations *ITT*	Olaprib	136	5,9 %	4.3 %	NA	NA	RD=-0.04	-0.00 – 0.09	0.0599	*Odds ratio and relative risk <1, and risk difference <0 favours olaparib. Odds ratio obtained from logistic regression adjusted for stratification variables.*
	Placebo	128	1.6%							

Trial name:	Study 19 (capsules)									
NCT number:	NCT00753545									
				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	HR/OR/RR	95% CI	*P* value	
Discontinuations 1)FAS (Ledermann 18 suppl.) *2)BRCAwt* (DCO May 16. Data on file. Extracted from Study 19)	Olaparib Placebo	57 61	1)5.9% 2)3.5% 1)1.6% 2)3.3%	1) 4.3% 2) 0.2%	NA NA	NA NA	Calculated AZ 1) OR=3.92 1) RR=3.76 2) OR=1.12 2) RR=1.07	Calculated AZ 1) 0.81-19.05 1) 0.81-17.4 2) 0.15-8.53 2) 0.16-7.35	Calculated AZ 1) 0.0901 1) 0.0896 2) 0.9101 2) 0.9450	*Odds ratio and relative risk <1, and risk difference <0 favours olaparib. Odds ratio obtained from logistic regression adjusted for stratification variables.*
AE of CTCAE grade 3 or Higher. ITT (Ledermann 18 suppl.). Calculated OR/RR	Olaparib Placebo	136 128	43.4% 21.9%	21.5%	NA NA	NA NA	OR=2.74 RR=1.98	1.59-4.70 1.36-2.90	0.0003 0.0004	*Odds ratio and relative risk <1, and risk difference <0 favours olaparib. Odds ratio obtained from logistic regression adjusted for stratification variables.*
AE of CTCAE grade 3 or Higher. *BRCAwt*	Olaparib Placebo	57 61	45.6% 27.9%	17.7%	NA NA	NA NA	OR=2.29 RR=1.64	1.06-4.98 1.00-2.68	0.0361 0.0503	*Odds ratio and relative risk <1, and risk difference <0 favours olaparib. Odds ratio obtained from logistic regression adjusted for stratification variables.*
HQoL *ITT. Patient with improved or unchanged FACT-O* Ledermann 2016 BJO[15]	Olaparib Placebo	114 111	80.7% 75,7%	5 %	NA NA	NA NA	RR=0.94	NA	NA	*Derived from table 14a*

HQoL *FACT-O and FOSI improvement rate* Ledermann 2016 suppl. [15]	Olaparib	114	21.1%	1.2%	NA	NA	OR=1.17	0.60-2.27	0.65	*See Ledermann suppl.* [15] *for statistical methods*
	Placebo	111	19.9%							

8.1.3 A3. Results per study SOLO2

Trial name:	SOLO2 (tablets)									
NCT number:	NCT01874353									
				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.) BRCAm	Olaparib	196	19.1m (16.3-25.7)	13.6m	NA	NA	HR=0.3	(0.22-0.41)	p<0.0001	*Defined as the time from randomisation until objective radiological disease progression or death using modified RECIST version 1.1.*
	Placebo	99	5.5m (5.2-5.8)							
PFS(BICR) BRCAm	Olaparib	196	30.2m (19.8-NC)	24.7m	NA	NA	HR=0.25	(0.18-0.35)	p<0.0001	*Defined as the time from randomisation until objective radiological disease progression or death using modified RECIST version 1.1.*
	Placebo	99	5.5m (4.8-5.6)							

Discontinuations	Olaparib Placebo	196 99	11% 2%	9%	NA	NA	NA	NA	NA	*See section 6.5.1*
AE of CTCAE grade 3 or Higher. ITT	Olaparib Placebo	196 99	36% 18%	18%	NA	NA	NA	NA	NA	*See section 6.5.2*
OS *Events*	Olaparib Placebo	196 99	45 (23%) 27 (27%)	NA	NA	NA	HR 0.80	0·50–1·31	0·43	*24% maturity*

8.1.4 A3. Results per study NOVA

Trial name:	NOVA										
NCT number:	NCT01847274										
					Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N(gBRCA)	N(non-gBRCA	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	
PFS (Inv)	Niraparib	138	234	21.0 in gBRCA, 9,3 in non-BRCA	15.5 and 5.4 m	NA	NA	HR=0.27 HR= 0.45	0.17-0.41 0.34-0.61	P<0.001	Consult the Medicinråd application for niraparib for more info
	Placebo	65	116	5.5 in gBRCA, 3.9 in non-BRCA							
Discontinuations	Niraparib	138	234	14.7%	12.5%	NA	NA	NA	NA	NA	Consult the Medicinråd application for niraparib for more info
	Placebo	65	116	2.2%							
AE of CTCAE grade 3 or Higher. ITT	Niraparib	138	234	74,1%	51.2%	NA	NA	NA	NA	NA	Consult the Medicinråd application for niraparib for more info
	Placebo	65	116	22.9%							
Median OS Event	Niraparib	138	234	16.1%	NA	NA	NA	NA	NA	NA	Consult the Medicinråd application for niraparib for more info
	Placebo	65	116	19.3%							

8.1.5 A3. Results per study OCEANS

Trial name:	OCEANS									
NCT number:	NCT00434642									
				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)	GC + Bev	242	12.4m (11.4-12.7)	4.0m	NA	NA	HR= 0.484	(0.388-0.605)	<0.0001	Kaplan-Meier estimates of progression-free survival (PFS) based on investigator assessment, censoring for non–protocol-specified therapy (randomly assigned patients)
	GC + Placebo	242	8.4m (8.3-9.7)							
PFS (BIRC)	GC + Bev	242	12.3m (10.7-14.6)	3.7m	NA	NA	HR=0.451	(0.351-0.580)	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).
	GC + Placebo	242	8.6m (8.3-10.2)							
AE of CTCAE grade 3 or Higher. *BRCAwt*	GC + Bev	242	29.1%	8.9%	NA	NA	NA	NA	NA	RR calculated by AstraZeneca. See section 6.5.1
	GC + Placebo	242	20.2%							
Median OS	GC + Bev	242	35.2 (29.9-40.4)	1.9m	NA	NA	HR=1.027	(0.792-1.331)	NA	*See publication for statistical methods*
	GC + Placebo	242	33.3 (29.8-35.5)							
Discontinuations	GC + Bev	242	19.8	15.1%	NA	NA	RR=5.0	(2.68; 9.32)	p<0.00001	*RR calculated by AstraZeneca. See section 6.5.1*
	GC + Placebo	242	4.7							

8.1.6 A3. Results per study Study 41

Trial name:	Study 41(capsules) open label									
NCT number:	NCT01081951									
				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 ITT	Olaparib + chemo	81	12.2m (9·7–15·0)	2.6m	NA	NA	HR= 0,51	(0,34–0,77)	0·0012	*See table A2*
	Chemo + placebo	81	9.6m (9·1–9·7)							
OS ITT	Olaparib + chemo	81	33·8 months (95% CI 26·9–38·5	-3.6m	NA	NA	HR= 1.17	0·79–1·73)	p=0·44	*See table A2*
	Chemo + placebo	81	37·6 months (95% CI 27·8–44·6)							
AE Grade 3 or more (maintenance phase)	Olaparib + chemo	81	65%(29%)	8%(13%)	NA	NA	NA	NA	NA	*CTCAE grade 3 or higher events occurring in 3% or more of patients in either group*
	Chemo + placebo	81	57%(16%)							
Discontinuations	Olaparib + chemo	81	19%	3%	NA	NA	NA	NA	NA	
	Chemo + placebo	81	16%							

8.1.7 Results per PICO (ITT and *BRCAwt/VUS*)

Table A4 Results referring to olaparib vs placebo

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	Hazard/Odds/Risk ratio	CI	*P* value	
Overall survival *1)FAS* *2)BRCAwt/VUS* *3)BRCAwt/VUS maintenance*	Study 19 DCO: May 2016; data maturity 79%;	1) 2,0 months(m) 2) 24.5m vs. 26.6m 3) 22.5 vs. 28.5	NA NA NA	NA NA NA	1) HR= 0.73 2) HR= 0.84 3) HR= 0.88	1) 0.55 - 0.95 2) 0.57 - 1.25 3) 0.52 - 1.48	1) 0.02138 2) 0.39749 3) 0.6334	*2) and 3) Estimated from Cox proportional hazards model including treatment, subgroup and the treatment by subgroup interaction. Efron method for handling ties. 95% CI from profile likelihood estimation. P-value for HR from comparing difference in -2 log likelihood from this model and a model without the treatment term, against a chi-squared distribution.*
AEs leading to Discontinuation *1)FAS* *2)BRCAwt/VUS*	1) Friedlander 2018 supplementary material 2) AstraZeneca data on file DCO 09MAY2016	1) 4,3 % 2) 0,2 %	NA NA	NA NA	1) OR=3.92 RR=3.76 2) RR=1.07 OR=1.12	1) 0.81-19.05 0.81-17.4 2) 0.16-7.35 0.15-8.53	1) 0.0901 0.0896 2) 0.9450 0.0361	*1) OR obtained from unadjusted logistic regression (unadjusted due to sparse data). 2)Odds ratio and relative risk <1, and risk difference <0 favours olaparib. OR obtained from logistic regression adjusted for stratification variables.*
Grade 3 or more AEs: *1)FAS* *2)BRCAwt/VUS*	1) Friedlander 2018 supplementary material 2) DCO 09MAY2016, Study 19	1) ARR = 21,5 % 2) ARR = 17,7 %	NA NA	NA NA	1) RR = 1.98. 2) RR = 1.64 0R = 2.29	1) 1.36 - 2.90 2)1.00 – 2.68 and 0.15 – 8.53	1) 0.004 2) 0.0503 0.0361	*Odds ratio and relative risk <1, and risk difference <0 favours olaparib.* *Odds ratio obtained from logistic regression adjusted for stratification variables.*
HQoL *ITT. Patient with improved or unchanged FACT-O*	*See Ledermann 2016*[15]	5 %	NA NA	NA NA	RR=0.94	NA	NA	*Derived from table 14a*

Ledermann 2016 BJO[15]								
HQoL *FACT-O improvement rate*	Ledermann 2016[15]	1.2 %	NA	NA	OR=1.17	0.60-2.27	0.65	*See Ledermann suppl.2016 For statistical methods*[15]
Progression Free survival(PFS invest): *1)FAS 2)BRCAwt/VUS*	Study 19 DCO 30 June 2010.	1) 4 months 2) 1.9 months	NA NA	NA NA	1) HR= 0.35 2) HR= 0.54	1) 0.25-0.49 2) 0.34-0.85	1)<0.00001 2) 0.00745	*Median time to event based on the Kaplan Meier estimate. HR estimated from Cox proportional hazards model including treatment, subgroup and the treatment by subgroup interaction. Efron method for handling ties. 95% CI from profile likelihood estimation. P-value for HR from comparing difference in -2 log likelihood from this model and a model without the treatment term, against a chi-squared distribution. HR <1 favours olaparib.*

Appendix

A1 Litterature search excluded and included studies

SEARCH QUERY PubMed:

#1 ("ovarian cancer" OR "ovarian neoplasms"[MeSH Terms])

#2 lynparza OR olaparib OR bevacizumab OR avastin

#3 #1 AND #2

#4 (("clinical trial, phase ii"[Publication Type] or "clinical trial, phase iii"[Publication Type] or "clinical trial, phase iv"[Publication Type] or "controlled clinical trial"[Publication Type] or "randomized controlled trial"[Publication Type]))

#5 ((randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR randomly[tiab] OR controlled[tiab] OR trial[ti] OR single-blind[tiab] OR single-blinded[tiab] OR double-blind[tiab] OR double-blinded[tiab]))

#6 #3 AND (#4 OR #5)

#7 ((Review[ptyp] OR Editorial[ptyp] OR Comment[ptyp] OR Meta-Analysis[ptyp] OR Case Reports[ptyp] OR case[ti] OR review[ti] or "clinical trial, phase i"[ptyp] or "phase I"[ti] OR "phase 1"[ti]))

#8 (("Animals"[mh] NOT "Humans"[mh]))

#9 #6 NOT (#7 OR #8)

SEARCH QUERY CENTRAL:

#1 ("ovarian cancer"):ti,ab,kw OR ("*ovary cancer"):ti,ab,kw OR [mh "Ovarian Neoplasms"]

#2 lynparza OR olaparib OR bevacizumab OR avastin

#3 #1 AND #2

#4 ("phase 2 clinical trial" or "phase 3 clinical trial" or "randomized controlled trial"):kw

#5 (randomized OR randomised OR placebo OR randomly OR single-blind* OR double-blind*):ti,ab or trial.ti

#6 #3 AND (#4 OR #5)

#7 conference abstract:pt OR review:pt or nct*:au

#8 #6 NOT #7

Color coding for evaluation of literature search:

Included

Excluded on basis of title/abstract

Excluded on basis full text reading

1.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. Metaregister of controlled trials. 2006. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

2.Correction to Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial. Lancet oncology. 2015;16(2):e55. Erratum

3.The role of cediranib in ovarian cancer: current status and further investigation. Expert opinion on orphan drugs 4 (8) (pp 855-865), 2016 Date of publication: 02 aug 2016. 2016. Review article

4.The status of poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors in ovarian cancer, part 1: olaparib. Clinical advances in hematology and oncology 14 (8) (pp 619-627), 2016 Date of publication: august 2016. 2016. Review article

5.Aghajanian C, Blank SV, Goff BA, Judson PL, Nycum LR, Sovak MA. An updated safety analysis of OCEANS, a randomized, double-blind, phase III trial of gemcitabine (G) and carboplatin (C) with bevacizumab (BV) or placebo (PL) followed by BV or PL to disease progression (PD) in patients with platinum-sensitive (Plat-S) recurrent ovarian cancer. Journal of clinical oncology. 2012;30:5054. Conference abstract.

6.Aghajanian C, Blank SV, 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. 2012;30(17):2039-45. Included.

7.Aghajanian C, Goff B, Nycum LR, Wang Y, Husain A, Blank S. Independent radiologic review: bevacizumab in combination with gemcitabine and carboplatin in recurrent ovarian cancer. Gynecol Oncol. 2014;133(1):105-10. Included.

8.Aghajanian C, Goff B, Nycum LR, Wang YV, Husain A, Blank SV. Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. Gynecol Oncol. 2015;139(1):10-6. Included.

9.Aghajanian C, Nycum L, Chan JK, Husain A, Yi J, Blank SV. CA-125 in oceans: phase 3 randomized study of gemcitabine/carboplatin + bevacizumab (GC+BV) or placebo (GC+PL) in platinum-sensitive recurrent ovarian cancer. International journal of gynecological cancer. 2012;Conference:14th Biennial Meeting of the International Gynecologic Cancer Society. Conference abstract

10.Al Rawahi T, Lopes AD, Bristow RE, Bryant A, Elattar A, Chattopadhyay S, et al. Surgical cytoreduction for recurrent epithelial ovarian cancer. Cochrane Database Syst Rev. 2013(2):CD008765. Review.

11.Am O, Tj P, Am S, W S, E P-L, H H. ICON7: final overall survival results in the GCIG phase III randomized trial of bevacizumab in women with newly diagnosed ovarian cancer. European journal of cancer. 2013;49(Supplement 3 (September 2013)):LBA6. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

12.Audeh MW, Carmichael J, Penson RT, Friedlander M, Powell B, Bell-McGuinn KM, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. Lancet (London, England). 2010;376(9737):245-51. Not a randomized controlled phase II or phase III clinical trial.

13.Auranen A, Grenman S. Radiation therapy and biological compounds for consolidation therapy in advanced ovarian cancer. Int J Gynecol Cancer. 2008;18 Suppl 1:44-6. Review.

14.Backen A, Renehan AG, Clamp AR, Berzuini C, Zhou C, Oza A, et al. The combination of circulating Ang1 and Tie2 levels predicts progression-free survival advantage in bevacizumab-treated patients with ovarian cancer. Clin Cancer Res. 2014;20(17):4549-58. Biomarker study, not relevant for addressing the endpoints in this application.

15.Backes FJ, Richardson DL, McCann GA, Smith B, Salani R, Eisenhauer EL, et al. Should bevacizumab be continued after progression on bevacizumab in recurrent ovarian cancer? Int J Gynecol Cancer. 2013;23(5):833-8. Oppinion/comment article

16.Bais C, Mueller B, Brady MF, Mannel RS, Burger RA, Wei W, et al. Tumor Microvessel Density as a Potential Predictive Marker for Bevacizumab Benefit: GOG-0218 Biomarker Analyses. J Natl Cancer Inst. 2017;109(11). Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

17.Bakrin N, Tempfer C, Scambia G, De Simone M, Gabriel B, Grischke EM, et al. PIPAC-OV3: a multicenter, open-label, randomized, two-arm phase III trial of the effect on progression-free survival of cisplatin and doxorubicin as Pressurized Intraperitoneal Chemotherapy (PIPAC) vs. Chemotherapy alone in patients with platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer. Pleura and peritoneum. 2018;3(3) (no pagination). Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

18.Ball G, Xie F, Tarride JE. Economic Evaluation of Bevacizumab for Treatment of Platinum-Resistant Recurrent Ovarian Cancer in Canada. PharmacoEconomics - open. 2018;2(1):19-29. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

19.Bamias A, Gibbs E, Khoon Lee C, Davies L, Dimopoulos M, Zagouri F, et al. Bevacizumab with or after chemotherapy for platinum-resistant recurrent ovarian cancer: exploratory analyses of the AURELIA trial. Ann Oncol. 2017;28(8):1842-8. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

20.Barni S, Labianca R, Agnelli G, Bonizzoni E, Verso M, Mandala M, et al. Chemotherapy-associated thromboembolic risk in cancer outpatients and effect of nadroparin thromboprophylaxis: results of a retrospective analysis of the PROTECHT study. J Transl Med. 2011;9(1):179. Study does not address any of the relevant endpoints for this appliocation (Study investigates risk of thromboembolism associated with chemotherapy).

21.Bauersfeld SP, Kessler CS, Wischnewsky M, Jaensch A, Steckhan N, Stange R, et al. The effects of short-term fasting on quality of life and tolerance to chemotherapy in patients with breast and ovarian cancer: a randomized cross-over pilot study. BMC Cancer. 2018;18(1):476. . Study does not address any of the relevant endpoints for this appliocation (Study investigates the effects of short term fasting on QoL).

22.Bertelli G, Drews F, Lutchman-Singh K. Bevacizumab for Ovarian Cancer at High Risk of Progression: Reproducibility of Trial Results in 'Real-world' Patients. Anticancer research. 2016;36(9):4947-50. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

23.Brown J, Brady WE, Schink J, Van Le L, Leitao M, Yamada SD, et al. Efficacy and safety of bevacizumab in recurrent sex cord-stromal ovarian tumors: results of a phase 2 trial of the Gynecologic Oncology Group. Cancer. 2014;120(3):344-51. Not a randomized controlled phase II or phase III clinical trial.

24.Bruckner HW, Hirschfeld A, Schwartz M. Targeted Therapy for Resistant Cholangiocarcinoma with Bevacizumab or Cetuximab Added to Failed Cytotoxic Drug Cores. Anticancer research. 2016;36(1):399-402. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$ ovarian cancer)

25.Burger R, Brady M, Bookman M. Prospective investigation of risk factors for gastrointestinal adverse events in a phase III randomized trial of bevacizumab in first-line therapy of advanced epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer: a Gynecologic Oncology Group study. Gynecologic oncology. 2011;120(1 suppl 1):S5 Abstract 7. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

26.Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med. 2011;365(26):2473-83. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

27.Burger RA, Brady MF, Bookman MA, Monk BJ, Walker JL, Homesley HD, et al. Risk factors for GI adverse events in a phase III randomized trial of bevacizumab in first-line therapy of advanced ovarian cancer: A Gynecologic Oncology Group Study. J Clin Oncol. 2014;32(12):1210-7. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

28.Burger RA, Brady MF, Rhee J, Sovak MA, Kong G, Nguyen HP, 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):21-6. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

29.Burger RA, Sill MW, Monk BJ, Greer BE, Sorosky JI. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group Study. J Clin Oncol. 2007;25(33):5165-71. Study treatment does not correspond to olaparib or relevant comparators. (Bevacizumab is given as single agent without chemotherapy)

30.Callata-Carhuapoma HR, Garcia-Foncillas Lopez J. Is there a place for immunotherapy in colorectal cancer? Cancer and chemotherapy reviews. 2016;11(1):12-20. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

31.Cannistra SA, Matulonis UA, Penson RT, Hambleton J, Dupont J, Mackey H, et al. Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. J Clin Oncol. 2007;25(33):5180-6. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

32.Chakravarthy U, Harding SP, Rogers CA, Downes S, Lotery AJ, Dakin HA, et al. A randomised controlled trial to assess the clinical effectiveness and cost-effectiveness of alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation (IVAN). Health Technol Assess. 2015;19(78):1-298. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

33.Chambers SK, Clouser MC, Baker AF, Roe DJ, Cui H, Brewer MA, et al. Overexpression of tumor vascular endothelial growth factor A may portend an increased likelihood of progression in a phase II trial of bevacizumab and erlotinib in resistant ovarian cancer. Clin Cancer Res. 2010;16(21):5320-8. Study treatment does not correspond to olaparib or relevant comparators. (bevacizumab is given combined with erlotinib)

34.Chan JK, Brady MF, Penson RT, Huang H, Birrer MJ, Walker JL, et al. Weekly vs. Every-3-Week Paclitaxel and Carboplatin for Ovarian Cancer. N Engl J Med. 2016;374(8):738-48. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

35.Chappell NP, Miller CR, Fielden AD, Barnett JC. Is FDA-Approved Bevacizumab Cost-Effective When Included in the Treatment of Platinum-Resistant Recurrent Ovarian Cancer? J Oncol Pract. 2016;12(7):e775-83. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

36.Chase DM, Chaplin DJ, Monk BJ. The development and use of vascular targeted therapy in ovarian cancer. Gynecol Oncol. 2017;145(2):393-406. Review.

37.Chase DM, Huang H, Foss CD, Wenzel LB, Monk BJ, Burger RA. Neurotoxicity in ovarian cancer patients on Gynecologic Oncology Group (GOG) protocol 218: characteristics associated with toxicity and the effect of substitution with docetaxel: an NRG Oncology/Gynecologic Oncology Group study. Gynecol Oncol. 2015;136(2):323-7. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

38.Chase DM, Sill MW, Monk BJ, Chambers MD, Darcy KM, Han ES, et al. Changes in tumor blood flow as measured by Dynamic Contrast-Enhanced Magnetic Resonance Imaging (DCE-MRI) may predict activity of single agent bevacizumab in recurrent epithelial ovarian (EOC) and primary peritoneal cancer (PPC) patients: an exploratory analysis of a Gynecologic Oncology Group Phase II study. Gynecol Oncol. 2012;126(3):375-80. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$). Patients are in part platinum resistant.

39.Coleman RL, Brady MF, Herzog TJ, Sabbatini P, Armstrong DK, Walker JL, et al. A phase III randomized controlled clinical trial of carboplatin and paclitaxel alone or in combination with bevacizumab followed by bevacizumab and secondary cytoreductive surgery in platinumsensitive, recurrent ovarian, peritoneal primary and fallopian tube cancer (Gynecologic Oncology Group 0213). Gynecologic oncology. 2015;137(SUPPL. 1):3-4. The study investigates the role of secondary cytoreduction before initiation of chemotherapy.

40.Coleman RL, Brady MF, Herzog TJ, Sabbatini P, Armstrong DK, Walker JL, et al. Bevacizumab and paclitaxel-carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2017;18(6):779-91. The study investigates the role of secondary cytoreduction before initiation of chemotherapy.

41.Collinson F, Hutchinson M, Craven RA, Cairns DA, Zougman A, Wind TC, et al. Predicting response to bevacizumab in ovarian cancer: a panel of potential biomarkers informing treatment selection. Clin Cancer Res. 2013;19(18):5227-39. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

42.Daniele G, Lorusso D, Scambia G, Cecere SC, Nicoletto MO, Breda E, et al. Feasibility and outcome of interval debulking surgery (IDS) after carboplatin-paclitaxel-bevacizumab (CPB): A subgroup analysis of the MITO-16A-MaNGO OV2A phase 4 trial. Gynecol Oncol. 2017;144(2):256-9. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

43.del Carmen MG, Micha J, Small L, Street DG, Londhe A, McGowan T. A phase II clinical trial of pegylated liposomal doxorubicin and carboplatin plus bevacizumab in patients with platinum-sensitive recurrent ovarian, fallopian tube, or primary peritoneal cancer. Gynecol Oncol. 2012;126(3):369-74. The study is not a randomized controlled study.

44.Delgado-Balderas JR, Garza-Rodriguez ML, Gomez-Macias GS, Barboza-Quintana A, Barboza-Quintana O, Cerda-Flores RM, et al. Description of Genetic Variants in BRCA Genes in Mexican Patients with Ovarian Cancer: A First Step towards Implementing Personalized Medicine. Genes. 2018;9(7). Biomarker study, not relevant for addressing the endpoints in this application.

45.Dirix L, Swaisland H, Verheul HM, Rottey S, Leunen K, Jerusalem G, et al. Effect of Itraconazole and Rifampin on the Pharmacokinetics of Olaparib in Patients With Advanced Solid Tumors: Results of Two Phase I Open-label Studies. Clin Ther. 2016;38(10):2286-99. Study is not a phase 2 or phase 3 randomized controlled clinical trial.

46.DiSilvestro P, Moore K. 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. Https://clinicaltrialsgov/ct2/show/nct01844986. 2013. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$).

47.Dockery LE, Tew WP, Ding K, Moore KN. Tolerance and toxicity of the PARP inhibitor olaparib in older women with epithelial ovarian cancer. Gynecol Oncol. 2017;147(3):509-13. Meta-anaysis.

48.Domchek SM, Aghajanian C, Shapira-Frommer R, Schmutzler RK, Audeh MW, Friedlander M, et al. Efficacy and safety of olaparib monotherapy in germline BRCA1/2 mutation carriers with advanced ovarian cancer and three or more lines of prior therapy. Gynecol Oncol. 2016;140(2):199-203. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

49.Dougherty BA, Lai Z, Hodgson DR, Orr MCM, Hawryluk M, Sun J, et al. Biological and clinical evidence for somatic mutations in BRCA1 and BRCA2 as predictive markers for olaparib response in high-grade serous ovarian cancers in the maintenance setting. Oncotarget. 2017;8(27):43653-61. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

50.Duska LR, Java JJ, Cohn DE, Burger RA. Risk factors for readmission in patients with ovarian, fallopian tube, and primary peritoneal carcinoma who are receiving front-line chemotherapy on a clinical trial (GOG 218): an NRG oncology/gynecologic oncology group study (ADS-1236). Gynecol Oncol. 2015;139(2):221-7. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

51.Eisenhauer EL, Zanagnolo V, Cohn DE, Salani R, O'Malley DM, Sutton G, et al. A phase II study of gemcitabine, carboplatin and bevacizumab for the treatment of platinum-sensitive recurrent ovarian cancer. Gynecol Oncol. 2014;134(2):262-6. Study treatment does not correspond to olaparib or relevant comparators. Bevacizumab is not given as maintenance treatment after combination with chemotherapy in this study.

52.Elies A, Riviere S, Pouget N, Becette V, Dubot C, Donnadieu A, et al. The role of neoadjuvant chemotherapy in ovarian cancer. Expert Rev Anticancer Ther. 2018;18(6):555-66. Review

53.Elit L, Hirte H. Palliative systemic therapy for women with recurrent epithelial ovarian cancer: current options. OncoTargets and therapy. 2013;6:107-18. Review

54.Endris V, Stenzinger A, Pfarr N, Penzel R, Mobs M, Lenze D, et al. NGS-based BRCA1/2 mutation testing of high-grade serous ovarian cancer tissue: results and conclusions of the first international round robin trial. Virchows Archiv : an international journal of pathology. 2016;468(6):697-705. Biomarker study, not relevant for addressing the endpoints in this application.

55.Eskander RN, Kauderer J, Tewari KS, Mannel RS, Bristow RE, O'Malley DM, et al. Correlation between Surgeon's assessment and radiographic evaluation of residual disease in women with advanced stage ovarian cancer reported to have undergone optimal surgical cytoreduction: An NRG Oncology/Gynecologic Oncology Group study. Gynecol Oncol. 2018;149(3):525-30. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

56.Fagotti A, Ferrandina G, Vizzielli G, Fanfani F, Gallotta V, Chiantera V, et al. Phase III randomised clinical trial comparing primary surgery versus neoadjuvant chemotherapy in advanced epithelial ovarian cancer with high tumour load (SCORPION trial): Final analysis of peri-operative outcome. Eur J Cancer. 2016;59:22-33. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

57.Falchook GS, Wheler JJ, Naing A, Jackson EF, Janku F, Hong D, et al. Targeting hypoxia-inducible factor-1alpha (HIF-1alpha) in combination with antiangiogenic therapy: a phase I trial of bortezomib plus bevacizumab. Oncotarget. 2014;5(21):10280-92. Not a phase 2 or phase 3 randomized controlled trial.

58.Ferriss JS, Java JJ, Bookman MA, Fleming GF, Monk BJ, Walker JL, et al. Ascites predicts treatment benefit of bevacizumab in front-line therapy of advanced epithelial ovarian, fallopian tube and peritoneal cancers: an NRG Oncology/GOG study. Gynecol Oncol. 2015;139(1):17-22. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

59.Fleming ND, Coleman RL, Tung C, Westin SN, Hu W, Sun Y, et al. Phase II trial of bevacizumab with dose-dense paclitaxel as first-line treatment in patients with advanced ovarian cancer. Gynecol Oncol. 2017;147(1):41-6. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

60.Foote J, Secord AA, Liang M, Cohn DE, Jewell E, Havrilesky LJ. ASCO Value Framework Highlights the Relative Value of Treatment Options in Ovarian Cancer. J Oncol Pract. 2017;13(12):e1030-e9. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

61.Francis J, Coakley N, Elit L, Mackay H, Gynecologic Cancer Disease Site G. Systemic therapy for recurrent epithelial ovarian cancer: a clinical practice guideline. Current oncology (Toronto, Ont). 2017;24(6):e540-e6. Guidelines publication for Canada, not relevant for this application.

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150.Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade Lauraine E, Kristensen G. A phase 3 trial of bevacizumab in ovarian cancer. New england journal of medicine. 2011;365(26):2484-96. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$).

151.Pham E, Birrer MJ, Eliasof S, Garmey EG, Lazarus D, Lee CR, et al. Translational impact of nanoparticle-drug conjugate CRLX101 with or without bevacizumab in advanced ovarian cancer. Clin Cancer Res. 2015;21(4):808-18. Study treatment does not correspond to olaparib or relevant comparators. (bevacizumab is given combined with nanoparticle-drug conjugate CRLX101)

152.Phippen NT, Leath CA, Havrilesky LJ, Barnett JC. Bevacizumab in recurrent, persistent, or advanced stage carcinoma of the cervix: is it cost-effective? Gynecologic oncology. 2015;136(1):43-7. Study does not address any of the relevant endpoints for this application (Study is a health economic analysis).

153.Plummer R, Swaisland H, Leunen K, van Herpen CM, Jerusalem G, De Grève J, et al. Olaparib tablet formulation: effect of food on the pharmacokinetics after oral dosing in patients with advanced solid tumours. Cancer chemotherapy and pharmacology. 2015;76(4):723-9. Study is not a phase 2 or phase 3 randomized controlled trial.

154.Poveda AM, Selle F, Hilpert F, Reuss A, Savarese A, Vergote I, et al. Bevacizumab Combined With Weekly Paclitaxel, Pegylated Liposomal Doxorubicin, or Topotecan in Platinum-Resistant Recurrent Ovarian Cancer: analysis by Chemotherapy Cohort of the Randomized Phase III AURELIA Trial. Journal of clinical oncology. 2015;33(32):3836-8. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

155.Pujade L. Errata: bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial (J Clin Oncol 32: 1302-1308, 2014). Journal of clinical oncology. 2014;32(35):4025. Erratum

156.Pujade-Lauraine E. Phase III randomised, double blind, placebo controlled study of olaparib maintenance monotherapy in platinum sensitive relapsed BRCA mutated ovarian cancer patients with a complete or partial response following platinum based chemotherapy. Https://clinicaltrialsgov/nct01874353. 2013. Not a peer-reviewed publication (Only a link to clinicaltrialsgov)

157.Pujade-Lauraine E, Hilpert F, Weber B. AURELIA: a randomized phase III trial evaluating bevacizumab (BEV) plus chemotherapy (CT) for platinum (PT) resistant recurrent ovarian cancer (OC). Journal of clinical oncology: ASCO annual meeting proceedings. 2012;30(Suppl):Abstract LBA5002. . Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

158.Pujade-Lauraine E, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. J Clin Oncol. 2014;32(13):1302-8. . Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

159.Pujade-Lauraine E, Ledermann JA, Selle F, Gebski V, Penson RT, Oza AM, 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):1274-84. ncluded due relevant safety data on olaparib tablets.

160.Pujade-Lauraine E, Oza AM, Perren TJ, Swart AM, Mahner S, Gourley C. ICON7: final overall survival results in the gcig phase III randomised trial of bevacizumab in newly diagnosed ovarian cancer. International journal of gynecological cancer. 2013;Conference:18th International Meeting of the European Society of Gynaecological Oncology. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

161.Randall LM, Sill MW, Burger RA, Monk BJ, Buening B, Sorosky JI. Predictive value of serum CA-125 levels in patients with persistent or recurrent epithelial ovarian cancer or peritoneal cancer treated with bevacizumab on a Gynecologic Oncology Group phase II trial. Gynecol Oncol. 2012;124(3):563-8. Patient population is in part platinum resistant

162.Richardson DL, Sill MW, Coleman RL, Sood AK, Pearl ML, Kehoe SM, et al. Paclitaxel with and without pazopanib for persistent or recurrent ovarian cancer: a randomized clinical trial. JAMA oncology. 2018;4(2):196-202. Study treatment does not correspond to olaparib or relevant comparators (paclitaxel with or without pazopanib is not standard of care).

163.Rody A, Loibl S, Kaufmann M. [Molecular diagnostic and targeted therapy--"Barking dogs are going to bite": presentations from the 42nd Annual Meeting of the American Society of Clinical Oncology, Atlanta

2006]. Zentralblatt fur Gynakologie. 2006;128(5):233-41. Congress summary, not relevant for addressing any of the endpoints in the application.

164.Roncolato FT, Gibbs E, Lee CK, Asher R, Davies LC, Gebski VJ, et al. Quality of life predicts overall survival in women with platinum-resistant ovarian cancer: an AURELIA substudy. Ann Oncol. 2017;28(8):1849-55. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

165.Ross JA, Miller MM, Rojas Hernandez CM. Comparative effectiveness and safety of direct oral anticoagulants (DOACs) versus conventional anticoagulation for the treatment of cancer-related venous thromboembolism: A retrospective analysis. Thromb Res. 2017;150:86-9. Study does not address any of the relevant endpoints.

166.Rouzier R, Gouy S, Selle F, Lambaudie E, Floquet A, Fourchotte V, et al. Efficacy and safety of bevacizumab-containing neoadjuvant therapy followed by interval debulking surgery in advanced ovarian cancer: results from the ANTHALYA trial. European journal of cancer. 2017;70:133-42. Study treatment does not correspond to olaparib og relevant comparator (bevacizumab is given neoadjuvant).

167.Sato S, Itamochi H. Neoadjuvant chemotherapy in advanced ovarian cancer: latest results and place in therapy. Therapeutic advances in medical oncology. 2014;6(6):293-304. Review.

168.Schaffer EM, Coles TM, Wysham WZ, Roque DR, Kim KH, Wheeler SB. Adding Bevacizumab To Single-Agent Chemotherapy For The Treatment Of Platinum-Resistant Recurrent Ovarian Cancer: A Cost-Effectiveness Analysis Of The Aurelia Trial. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2015;18(7):A461. . Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

169.Schultheis AM, Lurje G, Rhodes KE, Zhang W, Yang D, Garcia AA, et al. Polymorphisms and clinical outcome in recurrent ovarian cancer treated with cyclophosphamide and bevacizumab. Clin Cancer Res. 2008;14(22):7554-63. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$). Treatment is neither olaparib or relevant comparator.

170.Seagle BL, Shahabi S. Cost-effectiveness analysis of dose-dense versus standard intravenous chemotherapy for ovarian cancer: An economic analysis of results from the Gynecologic Oncology Group protocol 262 randomized controlled trial. Gynecol Oncol. 2017;145(1):9-14. Study does not address any of the relevant endpoints for this application (Study is a health economic analysis).

171.Secord AA, Barnett JC, Ledermann JA, Peterson BL, Myers ER, Havrilesky LJ. Cost-effectiveness of BRCA1 and BRCA2 mutation testing to target PARP inhibitor use in platinum-sensitive recurrent ovarian cancer. Int J Gynecol Cancer. 2013;23(5):846-52. Study does not address any of the relevant endpoints for this application (Study is a health economic analysis).

172.Shoji T, Komiyama S, Kigawa J, Tanabe H, Kato K, Itamochi H, et al. An open-label, randomized, phase II trial evaluating the efficacy and safety of standard of care with or without bevacizumab in platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer patients previously treated with bevacizumab for front-line or platinum-sensitive ovarian cancer: rationale, design, and methods of the Japanese Gynecologic Oncology Group study JGOG3023. BMC Cancer. 2018;18(1):771. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$).

173.Sorio R, Roemer-Becuwe C, Hilpert F, Gibbs E, García Y, Kaern J, et al. Safety and efficacy of single-agent bevacizumab-containing therapy in elderly patients with platinum-resistant recurrent ovarian cancer:

subgroup analysis of the randomised phase III AURELIA trial. Gynecologic oncology. 2017;144(1):65-71. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$).

174.Stark D, Nankivell M, Pujade-Lauraine E, Kristensen G, Elit L, Stockler M, et al. Standard chemotherapy with or without bevacizumab in advanced ovarian cancer: quality-of-life outcomes from the International Collaboration on Ovarian Neoplasms (ICON7) phase 3 randomised trial. Lancet Oncol. 2013;14(3):236-43. . Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

175.Stehman FB, Brady MF, Thigpen JT, Rossi EC, Burger RA. Cytokine use and survival in the first-line treatment of ovarian cancer: a Gynecologic Oncology Group Study. Gynecol Oncol. 2012;127(3):495-501. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$).

176.Stewart J, George A, Banerjee S. Olaparib for the treatment of relapsed ovarian cancer with a BRCA1/2 mutation. Expert Rev Anticancer Ther. 2018;18(10):947-58. . Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

177.Stockler MR, Hilpert F, Friedlander M, King MT, Wenzel L, Lee CK, et al. Patient-reported outcome results from the open-label phase III AURELIA trial evaluating bevacizumab-containing therapy for platinum-resistant ovarian cancer. Journal of clinical oncology. 2014;32(13):1309-16. . Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

178.Sugiyama T. [Second-line treatment using novel chemotherapeutic and biologic agents]. Gan to kagaku ryoho Cancer & chemotherapy. 2009;36(5):730-5. Review.

179.Sugiyama T, Kumagai S, Hatayama S. [Treatments of epithelial ovarian cancer by histologic subtype]. Gan to kagaku ryoho Cancer & chemotherapy. 2009;36(2):187-92. Review.

180.Sugiyama T, Takeuchi S, Fukagawa T. [Gynecologic cancer]. Gan to kagaku ryoho Cancer & chemotherapy. 2014;41(2):157-61. Review.

181.Suh DH, Kim JW, Kim K, Kim HJ, Lee KH. Major clinical research advances in gynecologic cancer in 2012. Journal of gynecologic oncology. 2013;24(1):66-82. Review.

182.Sui H, Shi C, Yan Z, Li H. Combination of erlotinib and a PARP inhibitor inhibits growth of A2780 tumor xenografts due to increased autophagy. Drug design, development and therapy. 2015;9:3183-90. Study is a xenograft-based study (Not a clinical trial with human patients).

183.Tanyi JL, McCann G, Hagemann AR, Coukos G, Rubin SC, Liao JB, et al. Clinical predictors of bevacizumab-associated gastrointestinal perforation. Gynecol Oncol. 2011;120(3):464-9. Study does not address any of the relevant endpoints for this application.

184.Tappenden P, Harnan S, Ren S, Thokala P, Wong R, Mukuria C, et al. Olaparib for Maintenance Treatment of BRCA 1 or 2 Mutated, Relapsed, Platinum-Sensitive Ovarian, Fallopian Tube and Peritoneal Cancer in People Whose Relapsed Disease has Responded to Platinum-Based Chemotherapy: an Evidence Review Group Perspective of a NICE Single Technology Appraisal. Pharmacoeconomics. 2017;35(1):97-109. . Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

185.Tew WP, Sill MW, Walker JL, Secord AA, Bonebrake AJ, Schilder JM, et al. Randomized phase II trial of bevacizumab plus everolimus versus bevacizumab alone for recurrent or persistent ovarian, fallopian tube or peritoneal carcinoma: An NRG oncology/gynecologic oncology group study. Gynecol Oncol.

2018;151(2):257-63. Study treatment does not correspond to olaparib or relevant comparators. (bevacizumab is not given in combination with chemotherapy).

186.Tewari KS, Java JJ, Eskander RN, Monk BJ, Burger RA. Early initiation of chemotherapy following complete resection of advanced ovarian cancer associated with improved survival: NRG Oncology/Gynecologic Oncology Group study. Ann Oncol. 2016;27(1):114-21. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$).

187.Tillmanns TD, Lowe MP, Walker MS, Stepanski EJ, Schwartzberg LS. Phase II clinical trial of bevacizumab with albumin-bound paclitaxel in patients with recurrent, platinum-resistant primary epithelial ovarian or primary peritoneal carcinoma. Gynecol Oncol. 2013;128(2):221-8. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$).

188.Trillsch F, Mahner S, Hilpert F, Davies L, Garcia-Martinez E, Kristensen G, et al. Prognostic and predictive effects of primary versus secondary platinum resistance for bevacizumab treatment for platinum-resistant ovarian cancer in the AURELIA trial. Ann Oncol. 2016;27(9):1733-9. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

189.Vatsa R, Kumar L, Kumar S, Roy KK, Singh N, Meena J. Frontline use of bevacizumab in ovarian cancer: Experience from India. The National medical journal of India. 2018;31(1):15-8. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

190.Vergote IB, Smith DC, Berger R, Kurzrock R, Vogelzang NJ, Sella A, et al. A phase 2 randomised discontinuation trial of cabozantinib in patients with ovarian carcinoma. Eur J Cancer. 2017;83:229-36. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$). Treatment is neither olaparib or relevant comparator.

191.Verschraegen CF, Czok S, Muller CY, Boyd L, Lee SJ, Rutledge T, et al. Phase II study of bevacizumab with liposomal doxorubicin for patients with platinum- and taxane-resistant ovarian cancer. Ann Oncol. 2012;23(12):3104-10. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$).

192.Wenham RM, Lapolla J, Lin HY, Apte SM, Lancaster JM, Judson PL, et al. A phase II trial of docetaxel and bevacizumab in recurrent ovarian cancer within 12 months of prior platinum-based chemotherapy. Gynecol Oncol. 2013;130(1):19-24. Study treatment does not correspond to olaparib or relevant comparators. (bevacizumab is not given in combination with platinum chemotherapy).

193.Wiggans AJ, Cass GK, Bryant A, Lawrie TA, Morrison J. Poly(ADP-ribose) polymerase (PARP) inhibitors for the treatment of ovarian cancer. Cochrane Database Syst Rev. 2015(5):CD007929. Review.

194.Witteveen P, Lortholary A, Fehm T, Poveda A, Reuss A, Havsteen H. Final overall survival (OS) results from AURELIA, an open-label randomised phase III trial of chemotherapy (CT) with or without bevacizumab (BEV) for platinum-resistant recurrent ovarian cancer (OC). European journal of cancer. 2013;Conference:European Cancer Congress 2013. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

195.Wuntakal R, Seshadri S, Montes A, Lane G. Luteinising hormone releasing hormone (LHRH) agonists for the treatment of relapsed epithelial ovarian cancer. Cochrane Database of Systematic Reviews. 2016(6). Review.

196.Wysham WZ, Schaffer EM, Coles T, Roque DR, Wheeler SB, Kim KH. Adding bevacizumab to single agent chemotherapy for the treatment of platinum-resistant recurrent ovarian cancer: A cost effectiveness

analysis of the AURELIA trial. Gynecol Oncol. 2017;145(2):340-5. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

197.Yi S, Zeng L, Kuang Y, Cao Z, Zheng C, Zhang Y, et al. Antiangiogenic drugs used with chemotherapy for patients with recurrent ovarian cancer: a meta-analysis. OncoTargets and therapy. 2017;10:973-84. Metaanalysis focuses on bevacizumab and other angiogenesis inhibitors in recurrent ovarian cancer. The analysis addresses relative benefit of chemotherapy + bevacizumab compared with chemotherapy only and thus does not provide new information useful for comparing bevacizumab to olaparib other than what is already known from the original trial publications.

198.Yin J, Qin R, Sargent DJ, Erlichman C, Shi Q. A hierarchical Bayesian design for randomized Phase II clinical trials with multiple groups. J Biopharm Stat. 2018;28(3):451-62. Study adresses trial design in general and does not investigate any of the endpoints relevant for this application.

199.Zhang Y, Guo J, Zhang XL, Li DP, Zhang TT, Gao FF, et al. Antibody fragment-armed mesoporous silica nanoparticles for the targeted delivery of bevacizumab in ovarian cancer cells. International journal of pharmaceutics. 2015;496(2):1026-33. Study is not a phase 2 or phase 3 randomized controlled trial.

200.Zhao H, Li X, Chen D, Cai J, Fu Y, Kang H, et al. Intraperitoneal administration of cisplatin plus bevacizumab for the management of malignant ascites in ovarian epithelial cancer: results of a phase III clinical trial. Medical oncology (northwood, london, england). 2015;32(2):292. Study treatment does not correspond to olaparib or relevant comparators. (Study investigates bevacizumab given intraperitoneal).

201.Zhong L, Tran AT, Tomasino T, Nugent E, Smith JA. Cost-Effectiveness of Niraparib and Olaparib as Maintenance Therapy for Patients with Platinum-Sensitive Recurrent Ovarian Cancer. Journal of managed care & specialty pharmacy. 2018;24(12):1219-28. Study does not address any of the relevant endpoints for this application (Study is a health economic analysis).

202.Zhou C, Clamp A, Backen A, Berzuini C, Renehan A, Banks RE, et al. Systematic analysis of circulating soluble angiogenesis-associated proteins in ICON7 identifies Tie2 as a biomarker of vascular progression on bevacizumab. British journal of cancer. 2016;115(2):228-35. Not the patient population in question (Platinum-sensitive recurrent, $BRCA_{wt}$)

Publications for use in qualitative analysis

The list of included publications for use in the analysis thus originates from 5 randomized controlled clinical trials:

OCEANS

Aghajanian C, Blank SV, 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. 2012;30(17):2039-45.

Aghajanian C, Goff B, Nycum LR, Wang Y, Husain A, Blank S. Independent radiologic review: bevacizumab in combination with gemcitabine and carboplatin in recurrent ovarian cancer. Gynecol Oncol. 2014;133(1):105-10.

Aghajanian C, Goff B, Nycum LR, Wang YV, Husain A, Blank SV. Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. Gynecol Oncol. 2015;139(1):10-6.

NOVA

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.

Oza AM, Matulonis UA, Malander S, Hudgens S, Sehouli J, Del Campo JM, et al. Quality of life in patients with recurrent ovarian cancer treated with niraparib versus placebo (ENGOT-OV16/NOVA): results from a double-blind, phase 3, randomised controlled trial. Lancet Oncol. 2018;19(8):1117-25.

SOLO2

Friedlander M, Gebski V, Gibbs E, Davies L, Bloomfield R, Hilpert F, et al. Health-related quality of life and patient-centred outcomes with olaparib maintenance after chemotherapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT Ov-21): a placebo-controlled, phase 3 randomised trial. Lancet Oncol. 2018;19(8):1126-34.

Pujade-Lauraine E, Ledermann JA, Selle F, Gebski V, Penson RT, Oza AM, 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):1274-84.

Study 19

Friedlander M, Matulonis U, Gourley C, du Bois A, Vergote I, Rustin G, 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;119(9):1075-85.

Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med. 2012;366(15):1382-92.

Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, 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. Lancet Oncol. 2014;15(8):852-61.

Ledermann J, Harter P, Gourley C. Correction to Lancet Oncol 2014; 15: 856. 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. Lancet Oncol. 2015;16(4):e158.

Ledermann JA, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Quality of life during olaparib maintenance therapy in platinum-sensitive relapsed serous ovarian cancer. Br J Cancer. 2016;115(11):1313-20.

Ledermann JA, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial. The Lancet Oncology. 2016;17(11):1579-89.

Lheureux S, Lai Z, Dougherty BA, Runswick S, Hodgson DR, Timms KM, et al. Long-Term Responders on Olaparib Maintenance in High-Grade Serous Ovarian Cancer: Clinical and Molecular Characterization. Clin Cancer Res. 2017;23(15):4086-94.

Matulonis UA, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in patients with platinum-sensitive, relapsed serous ovarian cancer and a BRCA mutation: Overall survival adjusted for postprogression poly (adenosine diphosphate ribose) polymerase inhibitor therapy. Cancer. 2016;122(12):1844-52.

Study 41

Oza AM, Cibula D, Benzaquen AO, Poole C, Mathijssen RH, Sonke GS, et al. Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial. Lancet Oncol. 2015;16(1):87-97.

A2 Adverse events and Grade 3 or more Study 19 ITT and *BRCAwt/VUS*

***n* (%)**	**Olaparib *n* = 136**	**Placebo *n* = 128**	**Olaparib *n* = 136**	**Placebo *n* = 128**
Preferred term	**All grades**		**Grade ≥3**	
Total episodes	**1796**	**1002**	**102**	**45**
Patients with any AE	**132 (97)**	**119 (93)**	**59 (43)**	**28 (22)**
Nausea	96 (71)	46 (36)	3 (2)	0
Fatigue/asthenia	86 (63)	59 (46)	12 (9)	4 (3)
Vomiting	48 (35)	18 (14)	3 (2)	1 (1)
Diarrhoea	37 (27)	31 (24)	3 (2)	3 (2)
Abdominal pain	35 (26)	34 (27)	3 (2)	4 (3)
Constipation	30 (22)	14 (11)	1 (1)	0
Anaemia*	31 (23)	9 (7)	10 (7)	1 (1)
Decreased appetite	29 (21)	17 (13)	0	0
Headache	29 (21)	17 (13)	0	1 (1)
Dyspepsia	27 (20)	11 (9)	0	0

***n* (%)**	**Olaparib *n* = 136**	**Placebo *n* = 128**	**Olaparib *n* = 136**	**Placebo *n* = 128**
Preferred term	**All grades**		**Grade ≥3**	
Back pain	25 (18)	14 (11)	4 (3)	0
Upper abdominal pain	25 (18)	11 (9)	0	1 (1)
Arthralgia	24 (18)	18 (14)	1 (1)	0
Cough	24 (18)	13 (10)	0	0
Dysgeusia	22 (16)	8 (6)	0	0
Dizziness	21 (15)	9 (7)	0	0
Nasopharyngitis	21 (15)	14 (11)	0	0
Abdominal distension	21 (15)	11 (9)	0	0
Upper respiratory tract infection	19 (14)	8 (6)	0	0
Dyspnoea	18 (13)	8 (6)	2 (2)	0
Urinary tract infection	16 (12)	7 (6)	0	1 (1)
Pyrexia	14 (10)	4 (3)	1 (1)	0
Neuropathy peripheral	12 (9)	3 (2)	0	0
Depression	11 (8)	9 (7)	0	0
Neutropenia	7 (5)	5 (4)	5 (4)	1 (1)
Abdominal pain, lower	7 (5)	10 (8)	0	0
Hot flush	5 (4)	16 (13)	0	0
Thrombocyto-penia	5 (4)	3 (2)	1 (1)	0

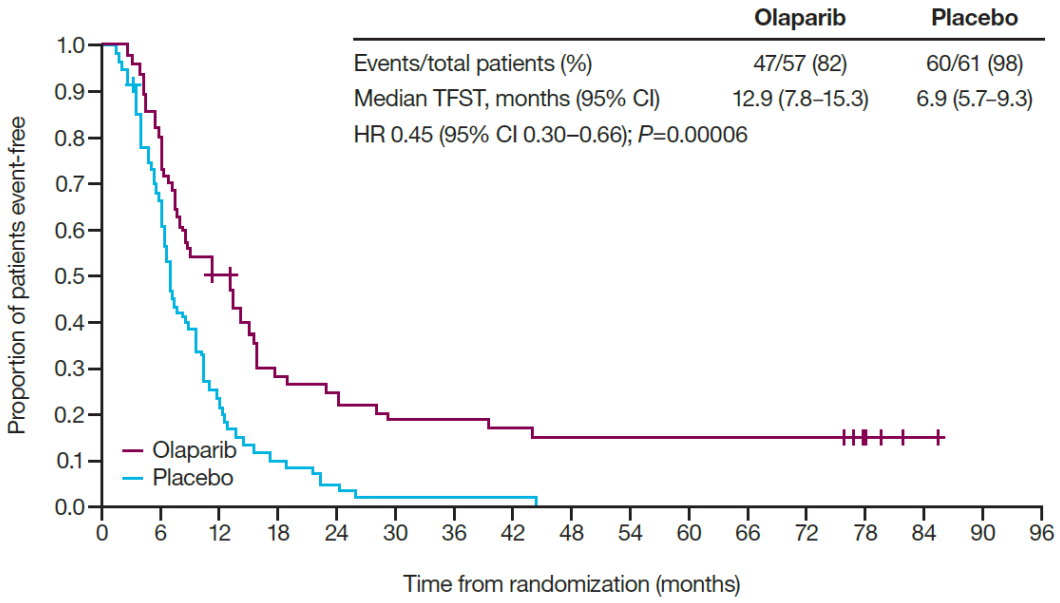
*Includes patients with anaemia, haemoglobin decreased, red blood cell count decreased and haematocrit decreased

Supplementary material. Friedlander 2018. AEs of all grades (frequency >10%), of grade ≥3 (frequency ≥5%), and of haematological interest for the overall population.

Summary of number (%) of patients with at least one AE of CTCAE grade 3 or higher by preferred term, arranged by system organ class - DCO 09MAY2016, BRCA wt/VUS Study 19

System organ class / MedDRA preferred term	Number (%) of patients [a] Olaparib 400 mg bd (N=57)		Placebo (N=61)	
Patients with AE of CTCAE grade 3 or higher	26	(45.6)	17	(27.9)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	5	(8.8)	1	(1.6)
ANAEMIA	2	(3.5)	0	
FEBRILE NEUTROPENIA	0		1	(1.6)
LEUKOPENIA	1	(1.8)	0	
NEUTROPENIA	2	(3.5)	0	
PANCYTOPENIA	1	(1.8)	0	
GASTROINTESTINAL DISORDERS	8	(14.0)	7	(11.5)
ABDOMINAL PAIN	2	(3.5)	2	(3.3)
ABDOMINAL PAIN UPPER	0		1	(1.6)
CONSTIPATION	1	(1.8)	0	
DIARRHOEA	1	(1.8)	2	(3.3)
GASTRITIS	0		1	(1.6)
NAUSEA	1	(1.8)	0	
RECTAL HAEMORRHAGE	1	(1.8)	0	
SMALL INTESTINAL OBSTRUCTION	2	(3.5)	2	(3.3)
VOMITING	1	(1.8)	1	(1.6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	4	(7.0)	3	(4.9)
FATIGUE	4	(7.0)	3	(4.9)
IMMUNE SYSTEM DISORDERS	1	(1.8)	0	
IODINE ALLERGY	1	(1.8)	0	
INFECTIONS AND INFESTATIONS	0		1	(1.6)
ENDOPHTHALMITIS	0		1	(1.6)
INVESTIGATIONS	5	(8.8)	3	(4.9)
ACTIVATED PARTIAL THROMBOPLASTIN TIME PROLONGED	0		1	(1.6)
AMYLASE INCREASED	1	(1.8)	0	
BLOOD CREATINE PHOSPHOKINASE INCREASED	2	(3.5)	0	
GAMMA-GLUTAMYLTRANSFERASE INCREASED	0		1	(1.6)
HAEMOGLOBIN DECREASED	1	(1.8)	0	
LIPASE INCREASED	1	(1.8)	0	
WHITE BLOOD CELLS URINE POSITIVE	0		1	(1.6)
METABOLISM AND NUTRITION DISORDERS	0		3	(4.9)
HYPERCALCAEMIA	0		1	(1.6)
HYPONATRAEMIA	0		2	(3.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	3	(5.3)	0	
BACK PAIN	1	(1.8)	0	
BURSITIS	1	(1.8)	0	
MYALGIA	1	(1.8)	0	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0		2	(3.3)
BLADDER CANCER	0		1	(1.6)
MALIGNANT ASCITES	0		1	(1.6)
NERVOUS SYSTEM DISORDERS	1	(1.8)	0	
DYSAESTHESIA	1	(1.8)	0	
PSYCHIATRIC DISORDERS	1	(1.8)	0	
CONFUSIONAL STATE	1	(1.8)	0	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1	(1.8)	0	
DYSPNOEA	1	(1.8)	0	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1	(1.8)	1	(1.6)
PRURITUS	1	(1.8)	0	
RASH PRURITIC	0		1	(1.6)
URTICARIA	1	(1.8)	0	
VASCULAR DISORDERS	1	(1.8)	1	(1.6)
DEEP VEIN THROMBOSIS	0		1	(1.6)
HYPERTENSION	1	(1.8)	0	

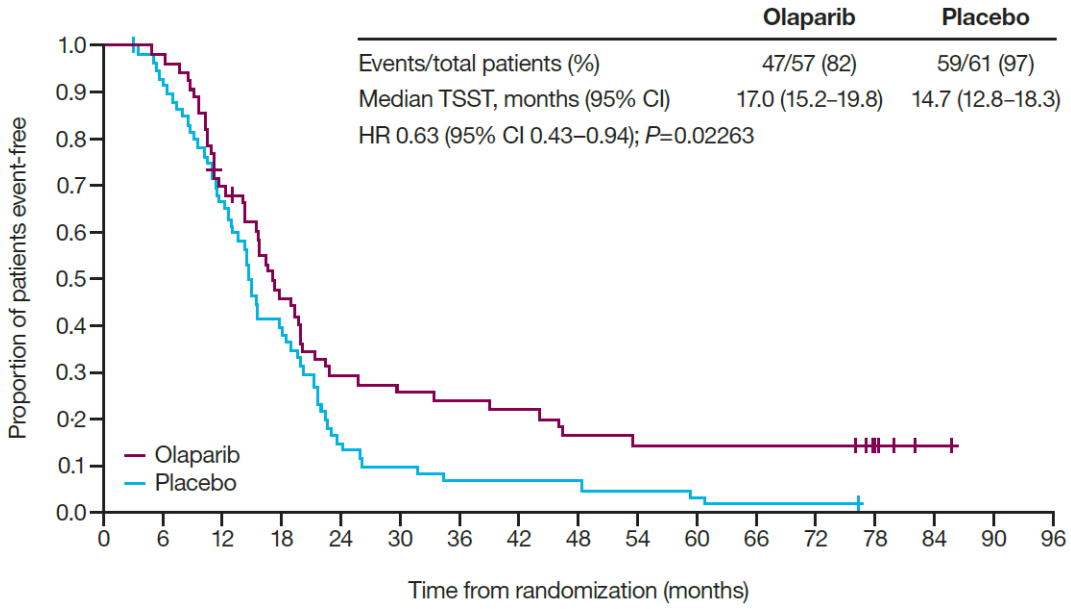
A3: TFST in *BRCA*wt subgroup



Number of patients at risk (number censored)																
Olaparib 400 mg bid	57 (0)	42 (0)	28 (1)	15 (2)	13 (2)	10 (2)	10 (2)	9 (2)	8 (2)	8 (2)	8 (2)	8 (2)	8 (2)	4 (6)	1 (9)	0 (10)	0 (10)
Placebo	61 (0)	37 (1)	13 (1)	6 (1)	3 (1)	1 (1)	1 (1)	1 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)

Source: Pujade-Lauraine et al, 2017. Figure 3A, 3C.(1)

A4: TSST in *BRCA*wt subgroup Study 19



Number of patients at risk (number censored)																
Olaparib 400 mg bid	57 (0)	56 (0)	38 (1)	25 (2)	16 (2)	14 (2)	13 (2)	12 (2)	9 (2)	8 (2)	8 (2)	8 (2)	8 (2)	4 (6)	1 (9)	0 (10)	0 (10)
Placebo	61 (0)	55 (1)	40 (1)	24 (1)	9 (1)	6 (1)	4 (1)	4 (1)	4 (1)	3 (1)	2 (1)	1 (1)	1 (1)	0 (2)	0 (2)	0 (2)	0 (2)

A5 Studies with olaparib

Clinical trial	Design	Setting	Patient population	Primary endpoint	Status
ORZORA NCT02476968	Single arm	Olaparib capsule maintenance in PSR ovarian cancer patients in response to prior platinum chemotherapy	*tBRCAm* (n=180) *BRCAwt*/HRRm (n=35)	PFS	Ongoing
OReO NCT03106987	RCT	Olaparib tablet maintenance in PSR ovarian cancer patients in response to prior platinum chemotherapy Re-challenge after prior PARPi	*gBRCAm*/*sBRCAm* (n=136) *BRCAwt* (n=280)	PFS	FSI 2Q2017
LIGHT NCT02983799	Single arm	Olaparib tablet treatment at relapse or PSR ovarian cancer patients	*gBRCAm* (n=30-90) *sBRCAm* (n=30-90) *BRCAwt*/HRD positive (n=30-90) *BRCAwt*/HRD negative (n=30-90)	ORR	Ongoing
GY004 NCT02446600	RCT	Randomized treatment at relapse for PSR ovarian cancer cediranib+olaparib; single agent olaparib tablet or platinum-based chemotherapy	*BRCAm* and *BRCAwt* (n=450)	PFS	Ongoing, recruitment to complete 3Q-4Q2017

A6. Toxicity profiles of olaparib (Study 19 and SOLO2) and niraparib (NOVA)

	Study 19				SOLO2				NOVA			
	Olaparib (n=136)		Placebo (n=128)		Olaparib (n=195)		Placebo (n=99)		Niraparib (n=367)		Placebo (n=179)	
	All Grades	Gr≥3	All Grades	Gr≥3	All Grades	Gr≥3	All Grades	Gr≥3	All Grades	Gr≥3	All Grades	Gr≥3
Anemia	21.3%	5.9%	5.5%	0.8%	43.1%	19.5%	7.1%	2.0%	50.1%	25.3%	6.7%	0%
Neutropenia	5.1%	3.7%	3.9%	0.8%	11.8%	2.5%	5.1%	4.0%	30.2%	19.6%	6.1%	1.7%
Thrombocytopenia	3.7%	0.7%	2.3%	0%	8.2%	0%	3.0%	1.0%	61.3%	33.8%	5.6%	0.6%
MDS/AML	1.5%		0.8%		1.5%		4%		1.4%		1.1%	
Nausea	70.6%	2.2%	35.9%	0%	75.9%	2.6%	33.1%	0%	73.6%	3.0%	35.2%	1.1%
Vomiting	35.3%	2.2%	14.1%	0.8%	37.4%	2.6%	19.2%	1.0%	34.3%	1.9%	16.2%	0.6%
Diarrhea	27.2%	2.2%	24.2%	2.3%	32.8%	1.0%	20.2%	0%	19.1%	0.3%	20.7%	1.1%
Fatigue	53.7%	7.4%	39.1%	3.1%	37.9%	1.0%	15.2%	0%	59.4%	8.2%	41.3%	0.6%
Asthenia	14%	0.7%	9.4%	0%	31.3%	3.1%	27.3%	2.0%				
Hypertension	7.4%	0.7%	3.1%	0%	2.6%	0%	1.0%	0%	19.3%	8.2%	4.5%	2.2%
Any G3 or higher	43.4%		21.9%		36.9%		18.2%		74.1%		22.9%	
% with AE leading to dose interruption	34.6%		10.2%		45.1%		18.2%		68.9%		5.0%	
% with AE leading to dose reduction	25.7%		3.9%		25.1%		3.0%		66.5%		14.5%	
AE leading to Discontinuation	5.9%		1.6%		10.8%		2.0%		14.7%		2.2%	

A7 Data analysis of Study 19

Data cutoff	Primary analysis and reported secondary endpoints	Median follow-up (data maturity)
30 June 2010	Investigator-assessed PFS and HRQoL	5.6 months (PFS 58%)
31 October 2011	Interim analysis of OS	Not stated (OS 38%)
26 November 2012	Interim analysis of OS	37.3 months (OS 58%)
30 September 2015	Interim analysis of OS	71.0 months (OS 77%)
9 May 2016	Final analysis of OS	78.0 months (OS 79%)

Source: Ledermann et al, 2012,[13] Ledermann et al, 2014,[32] Ledermann et al, 2016,[25] Gourley et al, 2017,[26] AstraZeneca data on file, 2016.[27]

References (appendix only)

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Medicinrådet

Medicinrådets protokol for vurdering af klinisk merværdi for olaparib til behandling af kræft i æggestokkene, æggelederne eller primær kræft i bughinden

Handelsnavn	Lynparza®
Generisk navn	Olaparib
Firma	AstraZeneca
ATC-kode	L01XX46
Virkningsmekanisme	Olaparib er en selektiv hæmmer af enzymerne poly (adenosine disphosphate [ADP]-ribose) polymerase (PARP) 1/2/3, der deltager i DNA-reparation. Blokering af PARP 1/2/3 i tumorceller, som i forvejen har mange genomiske skader, inducerer celledød.
Administration/dosis	Pr. oral tablet, 150 mg, 2 tabletter ad gangen, to gange dagligt
EMA-indikation	"Lynparza is indicated as 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 or partial) to platinum-based chemotherapy."
Godkendelsesdato Offentliggørelsesdato Dokumentnummer Versionsnummer	09.10.2018 11.10.2018 27262 1.0

Indhold

Forkortelser

AR:	Bivirkning (*Adverse reaction)*
ARR:	Absolut risikoreduktion
BRCA1/2:	*BReast CAncer1/2* (tumorsuppressorgen)
CFI:	Det kemoterapifrie interval (*chemotherapy-free interval*)
CTCAE:	*Common Terminology Criteria for Adverse Events*
DGCD:	Dansk Gynækologisk Cancer Database
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency*)
EPAR:	*European Public Assessment Report*
HGSC:	High-grade serøst adenokarcinom *(high-grade serous carcinoma)*
HR:	*Hazard Ratio*
HRD:	Defekt homolog rekombination (*homologous recombination deficiency*)
ITT:	*Intention-to-treat*
OR:	*Odds Ratio*
ORR:	Overordnet responsrate
OS:	Overlevelse (*overall survival*)
PFS:	Progressionsfri overlevelse (*Progression free survival*)
PFS2:	Progressionsfri overlevelse 2 (*Progression free survival 2*)
PICO:	Fokuserede forskningsspørgsmål baseret på Population, Intervention, Komparator og Outcome (effektmål)
RECIST:	*Response Evaluation Criteria In Solid Tumors*
RR:	Relativ Risiko
SAE:	Alvorlig uønsket hændelse (s*erious adverse event*)
TFST:	Tid til første efterfølgende behandling (*time to first subsequent treatment*)
TSST:	Tid til efterfølgende behandling nummer 2 (*time to second subsequent treatment*)
SMD:	Standardized mean difference

1 Formål

Protokollen har til formål at definere de kliniske spørgsmål, der ønskes belyst i vurderingen af olaparib som mulig standardbehandling af patienter med platinsensitiv, recidiverende high-grade epitelialt karcinom i æggestokkene, herunder kræft i æggelederne og primær kræft i bughinden (peritoneal cancer). I protokollen angives en definition af populationer, komparator og effektmål, der skal præsenteres i den endelige ansøgning, samt de metoder der ønskes anvendt til den komparative analyse. Arbejdet med protokollen er igangsat på baggrund af den foreløbige ansøgning vedrørende olaparib modtaget den 19. marts 2018.

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

2 Baggrund

Kræft i æggestokkene, herunder kræft i æggelederne og primær kræft i bughinden, opstår i epitelceller. Fremadrettet bliver disse kræftformer kaldt for kræft i æggestokkene. Kræft i æggestokkene er en heterogen gruppe med forskellige histologiske undertyper. High-grade serøst adenokarcinom (HGSC) er en af de hyppigste undertyper. Dette gør subklassificering og dermed behandlingsvalg til en kompleks proces, der kræver tæt samarbejde mellem gynækologer, patologer, billeddiagnostikere og kliniske onkologer [1,2]. Kræft i æggestokkene er den 4. hyppigste kræftdødsårsag hos kvinder i Danmark. Medianalder for sygdomsdebut er 63 år, og 80 % af patienterne er postmenopausale [2]. Der diagnosticeres omkring 550 nye tilfælde pr. år, og omkring 4600 kvinder lever med diagnosen i Danmark [3]. Kræft i æggestokkene har den højeste dødelighed blandt de gynækologiske kræftsygdomme, dels fordi kræften oftest bliver opdaget i stadium III-IV på grund af uspecifikke symptomer, hvor spredning udover æggestokkene allerede har fundet sted, men også på grund af høj frekvens af recidivudvikling (ca. 80 % af patienterne) [2]. Overlevelsen er bl.a. afhængig af sygdomsstadiet på diagnosepunktet. Ifølge Dansk Gynækologisk Cancer Database (DGCD) ligger 5-års overlevelsen for patienter med kræft i æggestokkene i stadie I, II, III eller IV på henholdsvis 87%, 70 %, 30 % og 15 % (tal fra 2005-2016) [2] og den samlede 5-års overlevelse på ca. 40%.

Årsagen til kræft i æggestokkene er ikke kendt, men en række risikofaktorer har været beskrevet. Antal fødsler og brug af p-piller (beskyttende), spiller en væsentlig rolle i livstidsrisikoen for at udvikle kræft i æggestokkene [1]. Desuden menes ca. 30 % af HGSC tilfældene, som udgør ca. 75 % af de samlede high-grade epiteliale karcinomer, at være genetisk betinget, med breast cancer (BRCA) 1 eller 2 genmutationer (arvelige eller somatiske) som de mest kendte [2].

2.1 Nuværende behandling

Det overordnede mål med behandling af kræft i æggestokkene er helbredelse, alternativt at forlænge overlevelsen og øge livskvaliteten. Den primære behandling er kirurgisk, hvor målet er at få fjernet alt synligt kræftvæv (makroskopisk radikal operation) samt korrekt stadieinddeling [2]. Næsten alle patienter, der opereres makroskopisk radikalt, tilbydes efterfølgende adjuverende platinbaseret kombinationskemoterapi i form af carboplatin og paclitaxel (6 serier). Patienter med efterladt makroskopisk tumorvæv (og alle stadium IV patienter) tilbydes samme slags kemoterapi i kombination med bevacizumab efter operation (se nedenfor) [4]. Omkring 60-80 % af patienterne vil opnå komplet eller partielt respons

efter 1. linje behandling, men ca. 80 % af disse patienter vil få tilbagefald inden for 2-3 år efter afsluttet kemoterapi [2]. Patienter med tilbagefald har generelt en dårlig prognose og formålet med videre behandling er symptomlindring og levetidsforlængelse. Her er en af de vigtigste prognostiske faktorer det platinfrie interval, det vil sige tidsrummet fra afslutning af platinbaseret kombinationskemoterapi til recidiv. Dette tidsinterval er afgørende for valg af efterfølgende behandling [4]. Nogle patienter, der primært blev makroskopisk radikalt opereret, vil også blive vurderet med henblik på mulighed for ny operation.

Patienter med recidiv ≥ 6 måneder fra endt platinholdig kemoterapi, som har haft primær effekt, betragtes som platinsensitive. For disse patienter anbefales der i 2. linje behandling en platinbaseret kombinationskemoterapi i form af enten carboplatin og paclitaxel, eller carboplatin og pegyleret liposomal doxorubicin. Behandlingen afhænger endvidere af patienternes BRCA1/2 mutationsstatus.

Patienter med BRCA1/2-mutation (arvelige eller somatiske)
Til patienter med mutation i BRCA1/2 og platinsensitivt recidiv tilbydes vedligeholdelsesbehandling med poly (adenosin disphosphat [ADP]-ribose) polymerase (PARP)-hæmmeren olaparib såfremt de har respons på 2. linje platinbaseret kombinationskemoterapi [4].

Patienter uden BRCA1/2-mutation
Størstedelen af patienterne, der ikke fik bevacizumab i 1. linje behandling, tilbydes bevacizumab i kombination med ovenstående platinbaserede kombinationskemoterapi i 2. linje behandling, efterfulgt af bevacizumab vedligeholdelsesbehandling der fortsættes i alt 15 måneder eller til progression. Bevacizumab gives kun en gang i patientens behandlingsforløb [4].

Hvis patienten oplever platinsensitivt tilbagefald efter 2. linje behandling, introduceres en ny linje platinbaseret kemoterapi. Hvis patienten ikke har fået bevacizumab tidligere, kan det tilbydes som beskrevet ovenfor. Nuværende behandlingsalgoritme efter 1.linje behandling for patienter med platinsensitiv, recidiverende kræft i æggestokkene er opsummeret i tabel 1 nedenfor.

2.2 Olaparib

Olaparib er en selektiv hæmmer af PARP 1/2/3. PARP 1/2/3 er cellekerneproteiner, der detekterer DNA-skader og fremmer deres reparation. Tumorceller har tit defekter i deres DNA-reparationsmekanismer, såsom BRCA-mutationer eller defekt homolog rekombination (*homologous recombination deficiency* (HRD)), hvilket resulterer i genomisk ustabilitet og akkumulering af mutationer. Rationalet er at den celledræbende effekt af PARP-inhibition er særlig udtalt hos patienter med BRCA1/2 mutation eller positiv HRD. Celledøden sker primært i tumorcellerne, da normale celler ikke har samme mængder af genomiske skader som tumorceller [5].

Olaparib blev godkendt af det Europæiske Lægemiddelagentur (*European Medicines Agency* (EMA)) i 2014 som vedligeholdelsesbehandling til patienter med BRCA1/2-mutation og recidiverende HGSC i æggestokkene, herunder æggelederne og primær kræft i bughinden, som responderer på platinbaseret kemoterapi (komplet eller partiel respons). Koordineringsrådet for ibrugtagning af sygehusmedicin (KRIS) godkendte den 11. juni 2015 olaparib som standardbehandling til patienter dækket af den oprindelige EMA-indikation.

Platinsensitivitet vurderes at være forbundet med PARP-hæmmersensitivitet pga. høj prævalens af forandringer/mutationer i DNA-reparationsmekanismer i platinfølsom kræft i æggestokkene. På baggrund af dette har ansøger søgt EMA om udvidelse af indikationen til at dække platinsensitive patienter med high-grade epitelial kræft i æggestokkene, herunder æggelederne og primær kræft i bughinden, *uafhængigt af BRCA-mutationsstatus og histologisk undertype*. Dermed tager denne protokol kun udgangspunkt i den

udvidede patientpopulation, dvs. patienter uden BRCA1/2-mutation. Indikationsudvidelsen medfører også en ændring i administrationsformen, hvor olaparib gives i tabletform (150 mg, 2 tabletter ad gangen, 2 gange dagligt) indtil progression fremfor kapselform (50 mg, 8 kapsler ad gangen, 2 gange dagligt). Fagudvalget vurderer, at der i Danmark diagnosticeres omkring 175 patienter pr. år, der vil være egnet til behandling ved EMA-godkendelse af indikationsudvidelsen for olaparib. I tabel 1 er placering af olaparib efter indikationsudvidelsen i den nuværende behandlingsalgoritme indikeret med rødt. Fagudvalget vil gerne fremhæve, at indplacering af olaparib i behandlingsalgoritmen afhænger af anvendelse af bevacizumab. Bevacizumab kan gives i 1. linje, 2. linje eller senere i behandlingsforløbet. I klinisk praksis er valget baseret på en individuel vurdering i samarbejde med patienten.

Tabel 1. Behandlingsalgoritmen for patienter med platinsensitiv, recidiverende HGSC i æggestokkene efter 1. linje behandling. Olaparibs placering i behandlingsalgoritmen er indikeret med rødt.

	Patienter med BRCA1/2-mutation	**Patienter uden BRCA1/2 mutation**	
2. linje behandling*	Platinbaseret kombinationskemoterapi efterfulgt af olaparib vedligeholdelsesbehandling	Platinbaseret kombinationskemoterapi i kombination med bevacizumab efterfulgt af bevacizumab vedligeholdelsesbehandling eller olaparib vedligeholdelsesbehandling	Platinbaseret kombinationsterapi efterfulgt af olaparib vedligeholdelsesbehandling
Efterfølgende behandlingslinjer**	Ny linje kemoterapi, eventuelt platinbaseret		

*1. linje behandling er typisk carboplatin og paclitaxel (6 serier), eventuelt i kombination med bevacizumab (patienter med efterladt makroskopisk tumorvæv og/eller stadium IV sygdom).
**Patienter kan få bevacizumab i forbindelse med deres platinbaserede kombinationskemoterapi, hvis de ikke har modtaget den før. Beslutningen er baseret på en individuel vurdering i samarbejde med patienten. Bevacizumab kan kun gives én gang.

3 Kliniske spørgsmål

De kliniske spørgsmål skal indeholde specifikation af patientgruppen, interventionen, alternativet/-erne til interventionen og effektmål. Da størstedelen af patienter uden BRCA1/2-mutation tilbydes bevacizumab på et tidspunkt i deres behandlingsforløb, og da beslutningen er baseret på en individuel vurdering i samarbejde med patienten, ønsker fagudvalget at sammenligne olaparib både med bevacizumab og placebo til denne patientpopulation.

3.1 Klinisk spørgsmål 1

1. *Hvilken klinisk merværdi tilbyder vedligeholdelsesbehandling med olaparib sammenlignet med bevacizumab hos patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende high-grade epitelialt karcinom og respons på platinbaseret kemoterapi?*

Population

Patienter uden BRCA1/2-mutation og med recidiverende high-grade epitelialt karcinom i æggestokkene, herunder æggeleder eller primær kræft i bughinden som vurderes at være kandidater til bevacizumab. Patienterne skal være platinsensitive, dvs. have responderet (komplet eller partiel respons) på platinbaseret kemoterapi. Fagudvalget ønsker data opgjort separat for:

- patienter med high-grade serøs adenokarcinom eller blandingstumorer med en serøs komponent
- patienter med anden epitelial histologi

Intervention
Olaparib[1]

Komparator
Bevacizumab[2]

Effektmål
Tabel 2 i afsnit 3.3 summerer de valgte effektmål, deres vigtighed, mindste kliniske relevante forskel og kategori.

3.2 Klinisk spørgsmål 2

2. *Hvilken klinisk merværdi tilbyder vedligeholdelsesbehandling med olaparib sammenlignet med placebo hos patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende high-grade epitelialt karcinom og respons på platinbaseret kemoterapi?*

Population
Patienter uden BRCA1/2-mutation og med recidiverende high-grade epitelialt karcinom i æggestokkene, herunder æggeleder eller primær kræft i bughinden. Patienterne skal være platinsensitive, dvs. have responderet (komplet eller partiel respons) på platinbaseret kemoterapi. Fagudvalget ønsker data opgjort separat for:

- patienter med high-grade serøs adenokarcinom eller blandingstumorer med en serøs komponent
- patienter med anden epitelial histologi

Intervention
Olaparib

Komparator
Placebo

Effektmål
Tabel 2 i afsnit 3.3 summerer de valgte effektmål, deres vigtighed, mindste kliniske relevante forskel og kategori.

3.3 Valg af effektmål

Tabel 2 summerer de valgte effektmål, deres vigtighed, mindste klinisk relevante forskel og kategori. For alle effektmål ønskes både absolutte og relative værdier, jævnfør ansøgningsskemaet. For de relative værdier vurderes den kliniske relevans (merværdi), jævnfør væsentlighedskriterierne beskrevet i Medicinrådets metodehåndbog for vurdering af nye lægemidler. De relative effektestimater kan angives i relativ risiko (RR), odds ratio (OR) eller hazard ratio (HR). Det skal begrundes i ansøgningen, hvis der afviges fra de ønskede effektmål.

[1] Data for intervention ønskes opgjort fra start af kemoterapi efterfulgt af olaparib vedligeholdelsesbehandling.
[2] Data for komparator ønskes opgjort fra start af kemoterapi i kombination med bevacizumab efterfulgt af bevacizumab vedligeholdelsesbehandling.

Tabel 2 Oversigt over valgte effektmål. For hvert effektmål er angivet deres vigtighed. For kritiske og vigtige effektmål er desuden angivet den mindste klinisk relevante forskel, samt indplacering i de fire kategorier (overlevelse, alvorlige symptomer og bivirkninger, livskvalitet og ikke-alvorlige symptomer og bivirkninger). Alle kritiske og vigtige effektmål skal besvares med en sammenlignende analyse af både absolutte og relative værdier for de udspecificerede populationer i de angivne måleenheder.

Effektmål*	**Vigtighed**	**Kategori**	**Måleenhed**	**Mindste klinisk relevante forskelle (absolutte værdier)**
Overlevelse (OS)	Kritisk	Dødelighed	Median OS i antal måneder	En forskel på 3 måneder
Progressionsfri overlevelse (PFS)	Kritisk	Alvorlige symptomer og bivirkninger	Median PFS i antal måneder	En forskel på 3 måneder
Bivirkninger	Kritisk	Alvorlige symptomer og bivirkninger	Andel af patienter der ophører behandling pga. bivirkninger	En forskel på 5 %-point
			Andel af patienter, som oplever en eller flere grad 3-4 bivirkninger	En forskel på 10 %-point
			Kvalitativ gennemgang af bivirkningstyperne med henblik på at vurdere alvorlighed, håndterbarhed og tyngde af bivirkningerne	Narrativ vurdering
Livskvalitet	Vigtig	Helbredsrelateret livskvalitet	Andel patienter der ikke viser statistisk signifikant forværring i livskvalitet	En forskel på 10 %-point
PFS2	Mindre vigtig	Alvorlige symptomer og bivirkninger		
Tid til første efterfølgende behandling (TFST)	Mindre vigtig	Alvorlige symptomer og bivirkninger		
Det kemoterapifrie interval (CFI)	Mindre vigtig	Alvorlige symptomer og bivirkninger		
Tid til sekundær efterfølgende behandling (TSST)	Mindre vigtig	Alvorlige symptomer og bivirkninger		

* For alle effektmål ønskes data med længst mulig opfølgningstid.

Den samlede kliniske merværdi af olaparib ønskes baseret på en så lang opfølgningstid som muligt.

Kritiske effektmål

Overlevelse (OS)

Overlevelse defineres som tiden fra behandlingsstart til død, uafhængigt af årsag. Fagudvalget vurderer OS som et kritisk effektmål, fordi æggestokkræft er en livstruende sygdom.

Fagudvalget vurderer, at en forskel i forbedring på 3 måneder på median OS mellem olaparib og komparator for patienter uden BRCA1/2-mutation er klinisk relevant.

Progressionsfri overlevelse (PFS)
PFS anvendes til vurdering af behandlingseffekt og defineres som tiden fra start af behandling til første dokumentation af progression i henhold til Response Evaluation Criteria i Solid Tumors (RECIST)-kriterierne [6] eller til død. Fagudvalget fremhæver, at PFS tillige med OS vælges som kritisk endepunkt, fordi PFS ikke påvirkes af akkumulerede effekter af efterfølgende behandlinger på samme måde som OS. Desuden fremhæver fagudvalget, at PFS ved olaparib vedligeholdelsesbehandling også afspejler, at der går længere tid til næste linje med platinbaseret kemoterapi, som er forbundet med patientbelastende bivirkninger. Det understreges desuden, at de forskellige kategorier for OS og PFS på hhv. "dødelighed" og "alvorlige symptomer og bivirkninger" reflekterer, at der stilles højere krav til effekt på PFS end OS iht. til Medicinrådets væsentlighedskriterier [7]. Korrelation mellem PFS og OS i studier omfattende kræft i æggestokkene er ukendt.

Fagudvalget finder, at en forskel på 3 måneder på median PFS mellem olaparib og komparator er klinisk relevant.

Bivirkninger
Fagudvalget finder det relevant at definere bivirkninger (adverse reactions (AR)) som et effektmål, da det belyser, hvorvidt olaparib tolereres sammenlignet med komparator. På den baggrund vurderer fagudvalget bivirkninger som et kritisk effektmål og ønsker data på nedenstående måleenheder.

Behandlingsophør på grund af bivirkninger
Fagudvalget ønsker en opgørelse over forskellen i andel af patienter, som ophører behandling grundet bivirkninger. Mindste klinisk relevante forskel sættes til 5 %-point.

Bivirkninger grad 3/4
Det er fagudvalgets betragtning, at andelen af patienter, som oplever en eller flere bivirkninger af grad 3 og/eller 4, i henhold til National Cancer Institute CTCAE version 4.03 [8], er relevant for vurderingen. Mindste klinisk relevante forskel sættes til 10 %-point.

Da der ikke foreligger kliniske studier, der direkte sammenligner effekten af olaparib og bevacizumab, bør ansøger lave en vurdering af, om sammenligning af ophør på grund af bivirkninger og andel patienter med grad 3/4 bivirkninger kan foretages på forsvarlig vis på baggrund af studiedesign, median opfølgningstid og dataindsamling. Overvejelser omkring dette skal indgå i den endelige ansøgning.

Kendte bivirkninger
Fagudvalget ønsker derudover en kvalitativ gennemgang af de konkrete bivirkninger forbundet med olaparib samt komparator med henblik på at vurdere alvorlighed, hyppighed samt håndterbarhed af bivirkningerne. Ansøger bedes derfor bidrage med bivirkningsdata fra både kliniske studier samt produktresuméet for lægemidlerne. Fagudvalget fremhæver, at de specifikt er interesserede i data vedrørende myelodysplastisk syndrom og akut myeloid leukæmi. Ansøger bedes derfor fremsende deres nyeste data herom.

Vigtige effektmål

Livskvalitet

Ændring i livskvalitet er et patientrelevant effektmål, som kan give indblik i, hvordan lægemidlets fordele og ulemper samlet set påvirker patienten. På baggrund af dette betragter fagudvalget livskvalitet som et vigtigt effektmål.

Fagudvalget ønsker livskvalitet opgjort som andel patienter, der ikke viser statistisk signifikant forværring i livskvalitet. Livskvalitet kan for patienter med kræft i æggestokkene måles med forskellige instrumenter (spørgeskemaer). Fagudvalget vurderer, at følgende validerede spørgeskemaer er relevante, i prioriteret rækkefølge: Functional Assessment of Cancer Therapy-Ovarian (FACT-O) [9], FACT Ovarian Symptom Index (FOSI) og EQ-5D [10]. Hvis der foreligger data fra flere spørgeskemaer for både olaparib og komparator, vil vurderingen baseres på det instrument med højest prioritet. Nedenfor omtales de ovennævnte spørgeskemaer:

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) [9]. En høj samlet score repræsenterer høj livskvalitet.

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).

EQ-5D: EQ-5D spørgeskemaet er et velvalideret generisk spørgeskema, som anvendes til vurdering af helbredsrelateret livskvalitet (EuroQol Group) [10]. Spørgeskemaet består af fem dimensioner (bevægelighed, personlig pleje, sædvanlige aktiviteter, smerte/ubehag og angst/depression). Spørgeskemaet indeholder desuden en visuel analog skala (VAS), der får fra 0 (værst tænkelige helbred) til 100 (bedst tænkelige helbred).

Fagudvalget vurderer, at en forskel på 10 %-point i andel patienter der, ikke viser statistik signifikant forværring i livskvalitet mellem olaparib og komparator, er klinisk relevant.

Mindre vigtige effektmål

Under udarbejdelsen af protokollen har fagudvalget vurderet, at nedenstående effektmål er mindre vigtige set i forhold til effektmålene i kategorierne ”Kritiske effektmål” og ”Vigtige effektmål”. Disse effektmål vil ikke indgå i vurderingen af den kliniske merværdi.

Progressionsfri overlevelse 2 (PFS2)

PFS2 defineres som tiden fra start af behandling til første dokumenterede progression eller dødsfald på efterfølgende behandlingslinje efter endt vedligeholdelsesbehandling. Da tiden fra progression frem til start af næste behandlingslinje kan variere af hensyn til patientpræferencer, vurderer fagudvalget, at dette effektmål klassificeres som mindre vigtigt.

Tid til første efterfølgende behandling (*time to first subsequent treatment* (TFST))

TFST defineres som tiden fra start af behandling til start af den første platinbaserede kemoterapi efter endt vedligeholdelsesbehandling. Med samme argumentation som for PFS2 vurderer fagudvalget, at effektmålet er mindre vigtigt.

Det kemoterapifrie interval (*chemotherapy-free interval* (CFI))
CFI defineres som tiden fra sidste behandling med platinbaseret kemoterapi til start af næste antineoplastiske behandling. Med samme argumentation som for PFS2 vurderer fagudvalget, at effektmålet er mindre vigtigt.

Tid til efterfølgende behandling nummer 2 (*time to second subsequent treatment* (TSST))
TSST defineres som tiden fra start af behandling til start af den anden antineoplastiske behandling efter endt vedligeholdelsesbehandling. Med samme argumentation som for PFS2 vurderer fagudvalget, at effektmålet er mindre vigtigt.

4 Litteratursøgning

Databaser for søgningen
Relevant litteratur søges i databaserne MEDLINE (via PubMed eller Ovid) og CENTRAL (via Cochrane Library).

Derudover skal EMAs European public assessment reports (EPAR) konsulteres for både det aktuelle lægemiddel og dets komparator(er).

Søgetermer
Søgningen skal inkludere det generiske navn og handelsnavnet for både det aktuelle lægemiddel og dets komparator(er), som kombineres med termer for indikationen.

Søgningen skal som minimum indeholde termer, som er beskrivende for de områder, der angivet i tabellen herunder. Både indekseret (f.eks. Medical Subject Headings, MeSH) og fritekstsøgning skal anvendes.

[Olaparib, LYNPARZA] *Termer for det generiske navn, handelsnavn og alternative stavemåder og eventuelle MeSH/Supplementary Concepts kombineres med **OR**. AND kan bruges, hvor flere termer skal forekomme samtidigt for at beskrive lægemidlet korrekt, f.eks. ved coformuleringer.*	*Blokkene til venstre og højre kombineres med **AND***	**[Kræft i æggestokkene]** *Termer for indikationen, alternative stavemåder og eventuelle MeSH kombineres med **OR**. AND kan bruges, hvor flere termer skal forekomme samtidigt for at beskrive indikationen korrekt.*
*Ovenstående og nedenstående blokke kombineres med **OR***		
[Bevacizumab, AVASTIN] *Termer for de(t) generiske navn(e), handelsnavn(e), alternative stavemåder og eventuelle MeSH/Supplementary Concepts kombineres med **OR**. AND kan bruges, hvor flere termer skal forekomme samtidigt for at beskrive lægemidlet korrekt, f.eks. ved coformuleringer.*		

De anvendte søgetermer, og hvordan de er blevet kombineret, dokumenteres separat for hver af de to databaser.

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

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

Inklusions- og eksklusionskriterier: Andre studiedesign end randomiserede kontrollerede studier ekskluderes, fase I og fase IIa studier ekskluderes. Derudover ekskluderes studier med andre populationer end de valgte og studier, som ikke rapporterer mindst et af de kritiske eller vigtige effektmål.

Vurderingen af klinisk merværdi baseres i udgangspunktet på data fra publicerede fuldtekstartikler og data fra EMAs EPAR – Public assessment report. Data skal derudover stemme overens med protokollens beskrivelser.

5 Databehandling/analyse

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

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

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

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

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

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

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

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

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

6 Andre overvejelser

Fagudvalget vil gerne fremhæve, at datagrundlaget for indikationsudvidelsen til patienter uden BRCA 1/2-mutation, specielt de patienter som ikke har high-grade serøst adenokarcinom, er begrænset. Dette vil formentlig påvirke vurderingen af den kliniske merværdi.

7 Referencer

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8 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende kræft i æggestokkene

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