Medicinrådet

Baggrund for Medicinrådets anbefaling vedrørende niraparib 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 lægemidlets samlede pris er rimelig, når man sammenligner den med lægemidlets værdi for patienterne.

Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	30. januar 2019
Ikrafttrædelsesdato	30. januar 2019
Dokumentnummer	40729
Versionsnummer	1.0

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 30. januar 2019

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Zejula®
Generisk navn	Niraparib
Firma	Tesaro
ATC-kode	L01XX54
Virkningsmekanisme	Niraparib er en selektiv hæmmer af enzymerne poly (adenosin diphosphat [ADP]-ribose) polymerase (PARP) 1/2, der deltager i DNA-reparation. Blokering af PARP 1/2 i tumorceller, som i forvejen har mange genomiske skader, inducerer celledød.
Administration/dosis	Peroral kapsel, 100 mg, 3 kapsler dagligt
EMA-indikation	Zejula is indicated as monotherapy for the maintenance treatment of adult patients with platinum sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

2 Medicinrådets anbefaling

Medicinrådet **anbefaler** niraparib som mulig standardbehandling til patienter med BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, æggelederne eller primær kræft i bughinden og respons på platinbaseret kemoterapi.

- Medicinrådet finder, at der er et rimeligt forhold mellem lægemidlets kliniske merværdi og omkostningerne ved behandling med niraparib sammenlignet med olaparib, som er dansk standardbehandling.

Medicinrådet **anbefaler ikke** niraparib som mulig standardbehandling til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC 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 niraparib sammenlignet med ingen behandling (placebo).

- Datagrundlaget for den kliniske merværdi ved behandling med niraparib sammenlignet med bevacizumab er utilstrækkeligt. Derfor kan forholdet mellem den kliniske merværdi og meromkostningerne ikke vurderes.

Medicinrådet anbefaler, at patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, æggelederne eller primær kræft i bughinden og respons på platinbaseret kemoterapi, som allerede er i behandling med niraparib, kan færdiggøre behandlingsperioden.

Medicinrådet har besluttet, at der i 2019 udarbejdes en behandlingsvejledning for kræft i æggestokkene. Indtil der foreligger en behandlingsvejledning anbefaler Medicinrådet, at regionerne, under hensyntagen til den godkendte indikation og population, vælger det lægemiddel, der er forbundet med de laveste omkostninger.

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

1. Hvilken klinisk merværdi tilbyder vedligeholdelsesbehandling med niraparib sammenlignet med olaparib hos patienter med BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC og respons på platinbaseret kemoterapi?

2. Hvilken klinisk merværdi tilbyder vedligeholdelsesbehandling med niraparib sammenlignet med bevacizumab hos patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC og respons på platinbaseret kemoterapi?

3. Hvilken klinisk merværdi tilbyder vedligeholdelsesbehandling med niraparib sammenlignet med placebo hos patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC og respons på platinbaseret kemoterapi?

3 Formål

Formålet med baggrundsrapporten for Medicinrådets anbefaling vedrørende niraparib 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 4. hyppigste kræftdødsårsag hos kvinder i Danmark. Der diagnosticeres omkring 550 nye tilfælde pr. år, og omkring 4.600 kvinder lever med diagnosen.

High-grade serøst adenokarcinom (HGSC) i æggestokkene (herunder kræft i æggelederne og primær kræft i bughinden) udgør ca. 75 % af de samlede high-grade epiteliale karcinomer og er dermed en af de hyppigste histologiske undertyper. 30 % af HGSC-tilfældene menes at være genetisk betinget med *breast cancer 1* eller *2* genmutationer (arvelige eller somatiske) som de mest kendte. Dette benævnes BRCA1/2-mutation.

Omkring 60-80 % af patienterne vil opnå komplet eller partielt respons efter 1. linjebehandling med platinbaseret kombinationskemoterapi, 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 med BRCA1/2-mutation og platinsensitivt recidiv tilbydes vedligeholdelsesbehandling med olaparib, såfremt de har respons på 2. linje platinbaseret kombinationskemoterapi. Størstedelen af patienter uden BRCA1/2-mutation, der ikke får 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.

Det vurderes, at der i Danmark er 250 patienter pr. år, der vil være kandidater til behandling med niraparib. Heraf vil omkring 30 % bære en BRCA1/2-mutation.

4.1 Sagsbehandlingstid og proces for Medicinrådets vurdering

Medicinrådet modtog den foreløbige ansøgning vedrørende niraparib den 20. september 2017 og den endelige ansøgning (bilag 5) den 19. september 2018.

Fagudvalgets vurdering af klinisk merværdi blev godkendt af Medicinrådet den 12. december 2018. Medicinrådet har gennemført vurderingen af niraparib på 19 uger.

5 Medicinrådets vurdering af samlet værdi

Medicinrådet vurderer, at niraparib til patienter med BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, æggelederne eller primær kræft i bughinden og respons på platinbaseret kemoterapi giver **ingen klinisk merværdi** sammenlignet med olaparib. Evidensens kvalitet er lav.

Medicinrådet vurderer, at niraparib til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, æggelederne eller primær kræft i bughinden og respons på platinbaseret kemoterapi giver en **ikkedokumenterbar klinisk merværdi** sammenlignet med bevacizumab. Evidensens kvalitet kan ikke vurderes.

Medicinrådet vurderer, at niraparib til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, æggelederne eller primær kræft i bughinden og respons på platinbaseret kemoterapi giver en **lille klinisk merværdi** sammenlignet med placebo. Evidensens kvalitet er lav.

6 Høring

Ansøger har den 19. december 2018 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

Omkostningerne ved behandling med niraparib sammenlignet med olaparib til patienter med BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, æggelederne eller primær kræft i bughinden og respons på platinbaseret kemoterapi er rimelige i forhold til den kliniske merværdi, lægemidlet tilbyder.

Omkostningerne ved behandling med niraparib sammenlignet med ingen behandling (placebo) til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, æggelederne eller primær kræft i bughinden og respons på platinbaseret kemoterapi er ikke rimelige i forhold til den kliniske merværdi, lægemidlet tilbyder. Ansøger har ikke har indsendt en analyse for niraparib sammenlignet med bevacizumab, og derfor har Amgros ikke vurderet de gennemsnitlige meromkostninger.

Meromkostningerne er i sammenligningen med både olaparib og ingen behandling (placebo) primært drevet af prisen på niraparib. Alle lægemiddelpriser i Amgros' afrapportering er på AIP-niveau. Amgros har indgået en aftale med Tesaro om indkøb af niraparib 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 Agla Fridriksdottir (projekt- og metodeansvarlig) Ditte Marie Irwin-Clugston (projektdeltager) Anne Sofie Gram (projektdeltager) Ilse Linde (fagudvalgskoordinator) Kirsten Holdt Henningsen (teamleder)

10 Versionslog

Version	Dato	Ændring
1.0	30.01.2019	Godkendt af Medicinrådet.

11 Bilag

Bilagsliste:

- Amgros' beslutningsgrundlag
- Amgros' sundhedsøkonomiske analyse
- Høringssvar fra ansøger
- Vurdering af niraparib til behandling af kræft i æggestokkene, æggelederne eller primær kræft i bughinden - vers. 1.0
- Ansøgers endelige ansøgning
- Protokol for vurdering af niraparib 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 niraparib (Zejula) som mulig standardbehandling til recidiverende high-grade serøst adenokarcinom (HGSC) i æggestokkene, herunder kræft i æggeledere og primær kræft i bughinden. Vurderingen er baseret på lægemidlets gennemsnitlige inkrementelle omkostninger (baseret på SAIP) sammenholdt med Medicinrådets vurdering af den kliniske merværdi.

Dato for Medicinrådsbeslutning	31-01-2019
Firma	Tesaro (ansøger)
Lægemiddel	Niraparib (Zejula)
Indikation	Monoterapi til vedligeholdelsesbehandling af voksne patienter med platinsensitiv, recidiverende high-grade serøst adenokarcinom (HGSC) i æggestokkene, herunder kræft i æggeledere og primær kræft i bughinden.

Amgros' vurdering

- Amgros vurderer at der **er** et rimeligt forhold mellem meromkostningerne og den kliniske merværdi for niraparib (Zejula) som mulig standardbehandling til voksne patienter med BRCA1/2-mutation og recidiverende HGSC i æggestokkene, herunder æggelederne eller primær kræft i bughinden (P1).

- Amgros **kan ikke vurdere** forholdet mellem meromkostninger og klinisk merværdi for niraparib (Zejula) som mulig standardbehandling til patienter med BRCA1/2-mutation og recidiverende HGSC i æggestokkene, herunder æggelederne eller primær kræft i bughinden, da Tesaro ikke har indsendt en analyse for denne population (P2).

- Amgros vurderer at der **ikke** er et rimeligt forhold mellem meromkostningerne og den kliniske merværdi for for niraparib (Zejula) som mulig standardbehandling til voksne patienter uden BRCA1/2-mutation og recidiverende HGSC i æggestokkene, herunder æggelederne eller primær kræft i bughinden (P3).

Overordnet konklusion

Medicinrådet har vurderet, at niraparib (Zejula) sammenlignet med de mulige komparatorer giver:

- **Ingen klinisk merværdi** til patientpopulationerne P1
- **Ikkedokumenterbar klinisk merværdi** til patientpopulation P2
- **Lille klinisk merværdi** til patientpopulationen P3

Behandling med niraparib (Zejula) er ikke forbundet med meromkostninger sammenlignet med olaparib ved behandling af P1. Amgros vurderer at forholdet mellem klinisk merværdi og omkostning **er** acceptabelt.

Behandling med niraparib (Zejula) sammenlignet med bevacizumab for P2 **kan ikke vurderes**, da Tesaro ikke har indsendt dokumentation for denne population.

Behandling med niraparib (Zejula) er forbundet med betydelige meromkostninger sammenlignet med SoC ved behandling af P3. Amgros vurderer at der for patientpopulationen, **ikke** er rimeligt forhold mellem den kliniske merværdi, som lægemidlet tilbyder sammenlignet med behandling med komparator. Meromkostninger drives af prisen på niraparib (Zejula).

Amgros har indgået en aftale med Tesaro om indkøb af niraparib (Zejula) til en SAIP, som er lavere end AIP. Konklusionen er baseret på SAIP for niraparib (Zejula).

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
P1: Patienter med BRCA1/2-mutation og recidiverende HGSC i æggestokkene, herunder æggelederne eller primær kræft i bughinden.	Olaparib	Ingen klinisk merværdi	Lav evidenskvalitet	Acceptabelt
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.	Bevacizumab	Ikkedokumenterbar klinisk merværdi	Vurderer ikke evidenskvalitet	Kan ikke vurderes
P3: Patienter uden BRCA1/2-mutation og med recidiverende HGSC i æggestokkene, herunder æggeleder eller primær kræft i bughinden.	Placebo (SoC)	Lille klinisk merværdi	Lav evidenskvalitet	Ikke acceptabelt

Supplerende informationer (resumé af resultaterne fra afrapporteringen)

Konklusion på omkostnings- og budgetkonsekvensanalyserne

Amgros' afrapportering af omkostnings- og budgetkonsekvensanalyser er baseret på AIP for niraparib (Zejula). Fortages analyserne på baggrund af SAIP og ikke på baggrund af AIP reduceres de inkrementelle omkostninger. 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 (AIP)

Behandling med niraparib (Zejula) er forbundet med meromkostninger af meget begrænset omfang sammenlignet med behandling med olaparib for P1.

- Patienter med BRCA1/2-mutation og recidiverende HGSC i æggestokkene, herunder æggelederne eller primær kræft i bughinden.

Behandling med niraparib (Zejula) er forbundet med meromkostninger sammenlignet med behandling med placebo (SoC) for patientgruppen P3.

- Patienter uden BRCA1/2-mutation og med recidiverende HGSC i æggestokkene, herunder æggeleder eller primær kræft i bughinden.

I tabel 2 og tabel 3 ses de inkrementelle omkostninger for niraparib (Zejula) og komparatorer for de to patientpopulationer.

Tabel 2: Gennemsnitlige behandlingsomkostninger for P1, DKK, AIP.

	Niraparib [DKK]	Olaparib [DKK]	Inkrementelle [DKK]
Lægemiddelomkostninger	927.758	817.513	110.244
Hospitalsomkostninger	925	139	786
Patientomkostninger	940	48	892
Totale omkostninger	**929.623**	**817.700**	**111.922**

Tabel 3: Gennemsnitlige behandlingsomkostninger for P3, DKK, AIP.

	Niraparib [DKK]	SoC [DKK]	Inkrementelle [DKK]
Lægemiddelomkostninger	688.355	0	688.354
Hospitalsomkostninger	925	46	879
Patientomkostninger	940	16	924
Totale omkostninger	**690.220**	**62**	**690.158**

Amgros' afrapportering – Budgetkonsekvenser (AIP)

Amgros vurderer at anbefaling af niraparib (Zejula) som mulig standardbehandling vil resultere i budgetkonsekvenser ca. 3 mio. DKK for P1 og >20 mio. DKK for P3 per år.

Kontrakt- og markedsforhold

Amgros har indgået en aftale med Tesaro, om køb af niraparib (Zejula). Aftalen er gældende indtil august 2020 og kan forlænges indtil fagudvalget har udarbejdet en terapivejledningen indenfor området æggestokkræft hvor lægemidlernes placering bliver beskrevet.

NIRAPARIB (ZEJULA)

KRÆFT I ÆGGESTOKKENE, ÆGGELEDERNE ELLER PRIMÆR KRÆFT I BUGHINDEN

AMGROS

AMGROS 14. december 2018

OPSUMMERING

Baggrund

Niraparib (Zejula) er som monoterapi indiceret til vedligeholdelsesbehandling af voksne patienter med platinsensitiv, recidiverende high-grade serøst adenokarcinom (HGSC) i æggestokkene, herunder kræft i æggeledere og primær kræft i bughinden. Omkring 250 nye patienter per år kandiderer årligt til behandling af den ansøgte indikation i Danmark. Amgros' vurdering tager udgangspunkt i dokumentation indsendt af Tesaro.

Analyse

I analysen estimeres de inkrementelle omkostninger forbundet med behandling med niraparib (Zejula) sammenlignet med olaparib (P1) og placebo (P3) som vedligeholdelsesbehandling af patienter der er hhv. BRCA1/2-muterede og ikke-muterede. Ansøger har valgt ikke at estimere de gennemsnitlige meromkostninger per patient ved brug af niraparib sammenlignet med bevacizumab (P2).

Inkrementelle omkostninger og budgetkonsekvenser

Amgros har vurderet de gennemsnitlige meromkostninger per patient ved brug af niraparib (Zejula) sammenlignet med komparator. De inkrementelle omkostninger er angivet i AIP.

I scenariet Amgros mener er mest sandsynligt, er de gennemsnitlige meromkostninger for niraparib (Zejula) følgende for hhv. P1, P2 og P3:

- P1: Ca. 110.000 DKK
- P2: Da ansøger ikke har indsendt en analyse for denne komparator, er det ikke muligt for Amgros at vurdere de gennemsnitlige meromkostninger
- P3: Ca. 690.000 DKK

Amgros vurderer at budgetkonsekvenserne for regionerne per år ved anbefaling af niraparib (Zejula) som standardbehandling vil være ca. 3 mio. DKK og 20-33 mio. DKK for hhv. P1 og P3.

Konklusion

Behandling med niraparib (Zejula) er forbundet med betydelige meromkostninger sammenlignet med behandling med placebo (SoC). Behandling med niraparib (Zejula) er sammenlignet med olaparib ligeledes forbundet med meromkostninger af betydelig størrelse. Meromkostningerne er næsten udelukkende drevet af lægemiddelomkostningerne for niraparib (Zejula), ved sammenligning med både SoC og olaparib.

Det er ikke muligt for Amgros at estimere meromkostningerne ved behandling med niraparib (Zejula) sammenlignet med bevacizumab, da ansøger ikke har indsendt dokumentation for dette.

Liste over forkortelser

AIP	Apotekernes indkøbspris
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
HGSC	High-Grade serøst adenokarcinom
SoC	Standard of Care
BRCA	Breast cancer
gBRCAmut	Patienter med BRCA-mutation
non-gBRCAmut	Patienter uden BRCA-mutation

INDHOLD

LOG

Ansøgning	
Lægemiddelfirma:	Tesaro
Handelsnavn:	Zejula
Generisk navn:	Niraparib
Indikation:	Monoterapi til vedligeholdelsesbehandling af voksne patienter med platinsensitiv, recidiverende high-grade serøst adenokarcinom (HGSC) i æggestokkene, herunder kræft i æggeledere og primær kræft i bughinden.
ATC-kode:	L01XX54

Proces	
Ansøgning modtaget hos Amgros:	19-09-2018
Endelig rapport færdig:	17-12-2018
Sagsbehandlingstid fra endelig ansøgning:	90 dage
Arbejdsgruppe:	**Pernille Winther Johansen** Lianna Christensen Line Brøns Jensen Louise Greve Dal Mark Friborg

Priser

Alle lægemiddelpriser i denne afrapportering er på AIP-niveau. Amgros har ofte aftaler om rabatter på de analyserede lægemidler. Derfor vil analyser på AIP-niveau ikke altid afspejle regionernes faktiske omkostninger til anskaffelse af lægemidlerne. Da rabatterne varierer betragteligt på tværs af lægemidler, vil prisforskellene i afrapporteringen, ikke altid afspejle de faktiske prisforskelle.

Anbefalingerne i Amgros' beslutningsgrundlag, som sendes sammen med denne afrapportering, bygger på regionernes faktiske anskaffelsespriser (SAIP).

1 BAGGRUND

Niraparib (Zejula) 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. Tesaro (herefter omtalt som ansøger) er markedsføringstilladelsesindehaver af niraparib (Zejula) og har den 19.09.2018 indsendt en ansøgning til Medicinrådet om anbefaling af niraparib (Zejula) som standardbehandling på danske sygehuse 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 inkrementelle omkostninger forbundet med behandling af voksne patienter med platinsensitiv, recidiverende HGSC i æggestokkene, herunder kræft i æggelederne og primær kræft i bughinden, i form af de gennemsnitlige inkrementelle omkostninger per patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af niraparib (Zejula) som standardbehandling på danske sygehuse af den nævnte indikation. I analyserne sammenlignes behandling med niraparib (Zejula) med behandling med olaparib og SoC (placebo).

1.2 Patientpopulation

HGSC i æggestokkene, herunder kræft i æggelederne og primær kræft i bughinden, opstår i langt de fleste tilfælde (> 90 %) 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 II, III eller IV på henholdsvis 68 %, 36 % og 25 % (tal fra 2005-2014) (2).

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 at være genetisk betinget, med breast cancer (BRCA) 1 eller 2 genmutationer (arvelige eller somatiske) som de mest kendte (2).

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.-linie 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). 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.-linie behandling en platinbaseret kombinationskemoterapi i form af enten carboplatin og paclitaxel eller carboplatin og pegyleret liposomal doxorubicin. Behandlingen afhænger endvidere af patienternes BRCA1/2 mutationstatus:

Patienter med BRCA 1/2-mutaion (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.-linie platinbaseret kombinationskemoterapi (4).

Patienter uden BRCA 1/2-mutation

Størstedelen af patienterne, der ikke fik bevacizumab i 1.-linie behandling, tilbydes bevacizumab i kombination med ovenstående platinbaserede kombinationskemoterapi i 2.-linie 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.-linie behandling, introduceres en ny linie platinbaseret kemoterapi. Hvis patienten ikke har fået bevacizumab tidligere, kan det tilbydes som beskrevet ovenfor. Nuværende behandlingsalgoritme efter 1.-linie behandling 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.-linje behandling.

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

*1.-linie 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 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 niraparib (Zejula)

Indikation

Niraparib 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.

Virkningsmekanisme

Niraparib er en selektiv hæmmer af PARP 1/2. PARP 1/2 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

Niraparib gives i kapselform, 100 mg, 3 kapsler dagligt, som vedligeholdelsesbehandling og administreres indtil tilbagefald af sygdommen eller intolerable bivirkninger måtte opstå.

1.3.1 Komparator

Medicinrådet har defineret hhv. olaparib, bevacizumab og placebo som komparatorer for P1-3, 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.	Olaparib
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.	Bevacizumab
P3: Patienter uden BRCA1/2-mutation og med recidiverende HGSC i æggestokkene, herunder æggeleder eller primær kræft i bughinden. 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 niraparib som vedligeholdelsesbehandling for følgende populationer:

- **P1:** Hvilken klinisk merværdi tilbyder vedligeholdelsesbehandling med niraparib sammenlignet med olaparib hos patienter med BRCA1/2-mutation og platinsensitiv, recidiverende HGSC og respons på platinbaseret kemoterapi
- **P2:** Hvilken klinisk merværdi tilbyder vedligeholdelsesbehandling med niraparib sammenlignet med bevacizumab hos patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC og respons på platinbaseret kemoterapi
- **P3:** Hvilken klinisk merværdi tilbyder niraparib vedligeholdelsesbehandling sammenlignet med placebo hos patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC og respons på platinbaseret kemoterapi

2 VURDERING AF INDSENDT ØKONOMISK ANALYSE

I analysen af gennemsnitlige behandlingsomkostninger per patient sammenlignes behandling med niraparib (Zejula) med behandling med olaparib og placebo (SoC). Ansøger har valgt ikke at inkludere en sammenligning af niraparib (Zejula) med bevacizumab. Dette begrundes med at der ikke er tilgængelige data for bevacizumab hvor der differentieres mellem patienter med BRCA-mutation (gBRCAmut) og patienter uden BRCA-mutation (non-gBRCAmut). Derudover argumenterer ansøger yderligere at bevacizumab ikke benyttes på samme måde som niraparib (Zejula), da bevacizumab indiceres i kombination med kemoterapi og efterfølgende fortsættes som vedligeholdelsesbehandling, mens niraparib (Zejula) først initieres når en patient har afsluttet kemoterapi med komplet eller delvis respons. Det gør at progressionsfri overlevelse i kliniske studier for bevacizumab måles fra kemoterapi initieres, hvilket ikke er tilfældet for niraparib (Zejula).

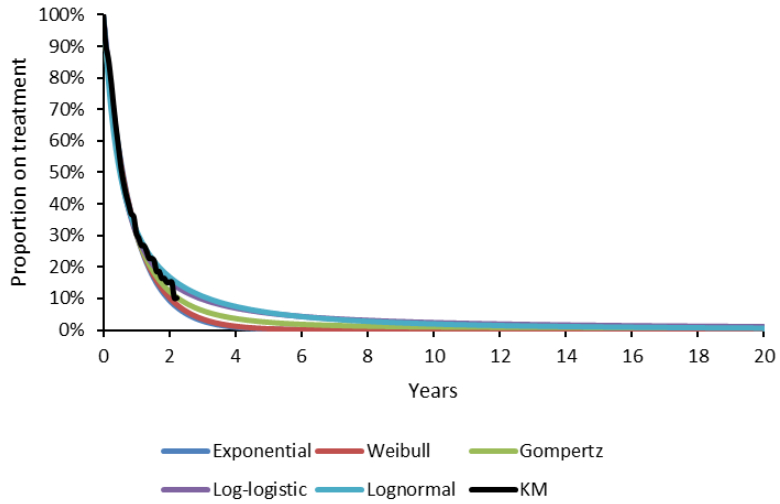
Amgros havde flere indvendinger mod den initiale model, som ansøger indsendte. Dette er den anden model, som ansøger har indsendt til Amgros i forbindelse med vurderingen. Det er kun den seneste indsendte model, som præsenteres herunder.

2.1 Model, metode og forudsætninger

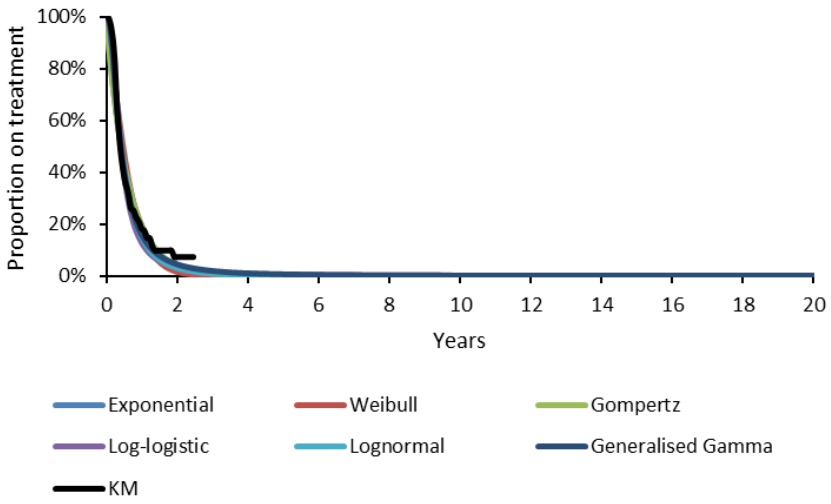
2.1.1 Modelbeskrivelse

Ansøger har indsendt en pationed suvival model for behandling af patienter i de nævnte populationer.
I analysen estimeres de gennemsnitlige omkostninger per patient der behandles med niraparib (Zejula) sammenlignet med placebo (SoC) for non-gBRCAmut patienter og med olaparib for gBRCAmut patienter. Analysen medtager omkostninger til lægemidler, bivirkninger, patientomkostninger og blodmonitorering for en periode på fem år.

Ansøger har ekstrapoleret individuelle patientdata fra ENGOT-OV16/NOVA studiet for at estimere den gennemsnitlige behandlingslænge for niraparib (Zejula), eftersom alle patienter i ENGOT-OV16/NOVA studiet endnu ikke havde afsluttet deres behandling ved seneste opfølgningsdato. Den gennemsnitlige behandlingslængde blev estimeret for niraparib (Zejula) og for SoC ved at ekstrapolere tid til behandlingsafbrydelse (TTD) for både non-gBRCAmut og gBRCAmut kohorter. Parametriske kurver blev fittet til Kaplan-Meier (KM) kurverne for TTD. De følgende seks parametriske distributioner blev undersøgt i forhold til bedste fit til KM kurverne; eksponential, weibull, log-logistisk, lognormal og generaliseret gamma.
Figur 1 og figur 2 viser KM kurven for TTD og de parametriske destributioner for populationen med non-gBRCAmut for hhv. niraparib (Zejula) og SoC.

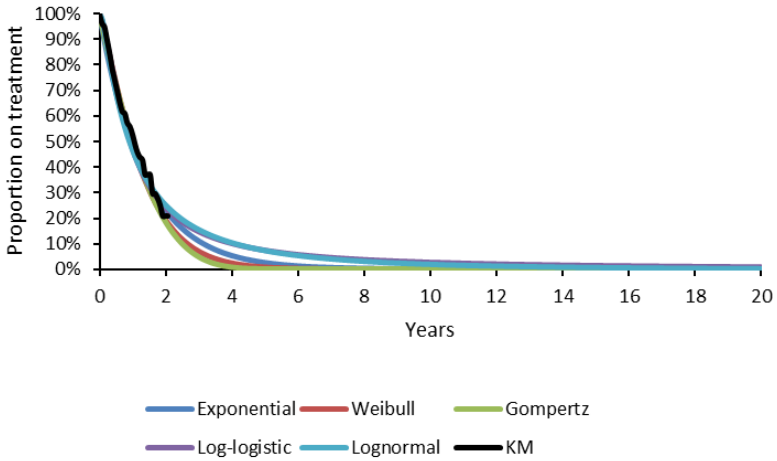


Figur 1: Niraparib TTD KM og parametriske distributioner for tid til behandlingsophør for non-gBRCAmut.

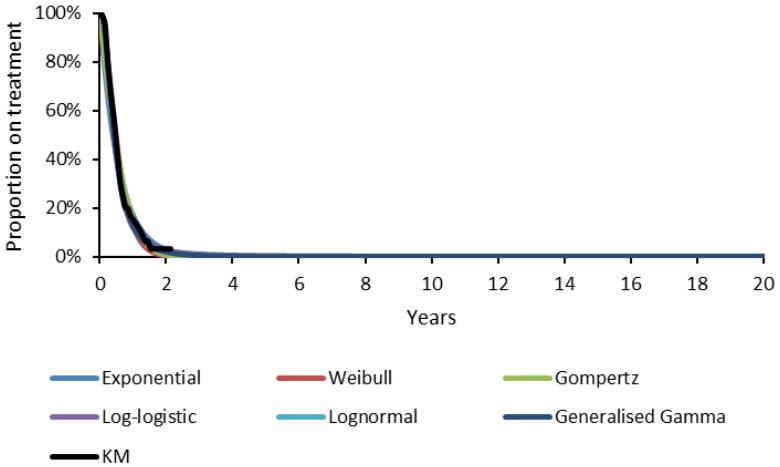


Figur 2: SoC TTD KM parametrisk distributioner for tid til behandlingsophør for non-gBRCAmut.

Figur 3 og Figur 4 viser KM kurven for TTD og de parametriske distributioner for populationen med gBRCAmut for hhv. niraparib (Zejula) og SoC.

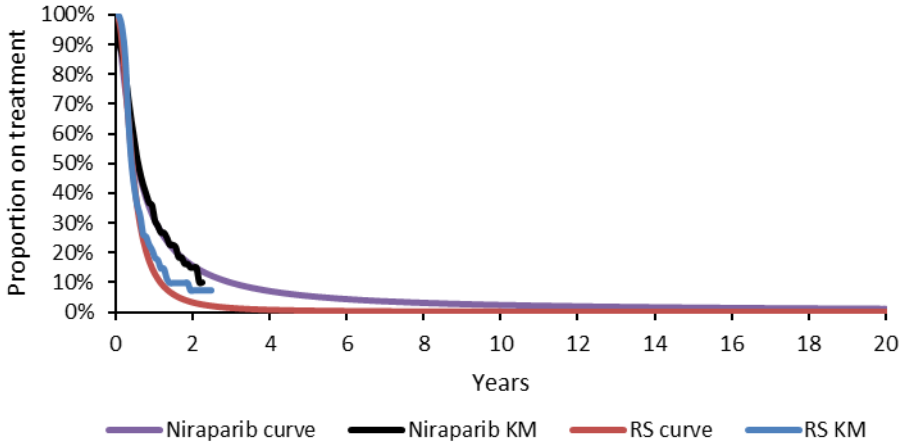


Figur 3: Niraparib TTD KM og parametriske distributioner for tid til behandlingsophør for gBRCAmut.

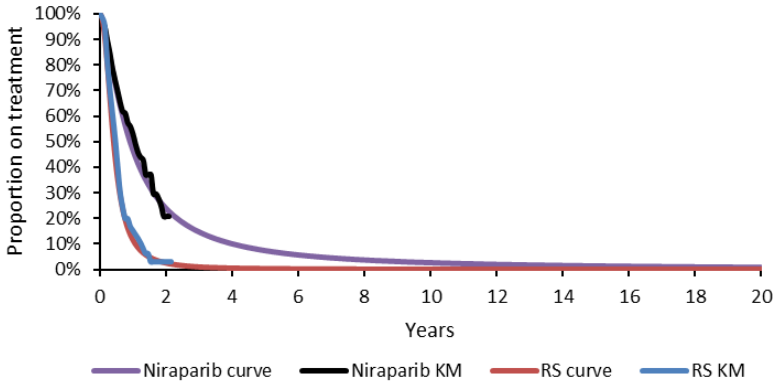


Figur 4: SoC TTD KM og parametriske distributioner for tid til behandlingsophør for gBRCAmut.

Ansøgers har valgt distributioner på basis af en række statistiske test af fit (Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC]) og visuel inspektion. For non-gBRCAmut populationen vurderede ansøger at bedste fit for både niraparib og SoC var den log-logistiske distribution. Se figur 5. For gBRCAmut populationen vurderede ansøger ligeledes, at bedste fit var den log-logistiske distribution. Se figur 6.



Figur 5: Niraparib (Zejula) og SoC TTD KM log-logistisk parametrisk distributioner for tid til behandlingsophør for non-gBRCAmut.



Figur 6: Niraparib og SoC TTD KM og log-logistisk parametrisk distributioner for tid til behandlingsophør for gBRCAmut.

Ansøger har valgt for begge populationer at afgrænse TTD kurverne til 20 år, på baggrund af en antagelse om, at det ikke er klinisk plausibelt at der er patienter i behandling i mere end 20 år. Dette har virksomheden fået valideret af en klinisk ekspert. Ansøger vælger dog kun at inkludere de lægemiddelomkostninger der ligger inden for en tidsperiode på de første fem år trods ekstrapolering af TTD kurver til 20 år.

Ansøger antager, at behandlingslængden for olaparib er identisk med behandlingslængden for niraparib (Zejula) for gBRCAmut populationen. Denne antagelse er lavet på baggrund af en sammenligning af progressionsfri overlevelse (PFS) mellem olaparib og niraparib (Zejula).

Amgros' vurdering

Ansøgers model er meget forsimplet i forhold til det pågældende sygdomsforløb.
At afgrænse omkostninger til lægemidler til kun at omfatte de første fem år, vurderes at føre til en underestimering, og Amgros mener at ansøgers valg om kun at inkludere omkostninger for de første fem år udelukkende, vil føre til en underestimering, når de estimerer at der vil være en lille andel af patienterne der er i behandling i 20 år.

Ansøger har ikke undersøgt den valgte parametriske funktions tilpasning til de observerede studiedata ved illustration af log kumulative hazard plots, hvilket er et krav i Amgros metodevejledning, når ansøger udfører ekstrapolering af kliniske forløbsdata.
Ansøgers antagelse om at olaparib og niraparib (Zejula) har behandlingslængder af samme varighed medfører usikkerhed, og den mindste variation i behandlingslængden mellem de to lægemidler vil have stor indflydelse på de inkrementelle omkostninger, da analysen hovedsaligt er drevet af lægemiddelomkostninger. Derfor findes en følsomhedsanalyse, hvor behandlingslængden mellem de to lægemidler varieres, relevant i forhold til at klarlægge betydningen af denne antagelse.

Amgros udarbejder egen hovedanalyse, hvor lægemiddelomkostninger inkluderes for 20 år, som er den periode, ansøger selv har estimeret, at nogle patienter vil være i behandling.

2.1.2 Analyseperspektiv

Ansøger har indsendt en omkostningsanalyse med et begrænset samfundsperspektiv. Analysen har en tidshorisont på 5 år, hvor omkostninger der ligger efter det første år, er diskonteret med en faktor på 4 %.

Amgros' vurdering

Analysens begrænsede samfundsperspektiv og diskonteringsrate er i tråd med Amgros' retningslinjer. Begrænsningen af tidshorisonten til fem år er ikke acceptabel, da der er lægemiddelomkostninger efter denne periode.

2.1.3 Omkostninger

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

Lægemiddelomkostninger

Ansøger har anvendt doser baseret på ENGOT-OV16/NOVA studiet for niraparib (Zejula) i analysen. Det betyder, at alle patienter modtager 300 mg dagligt i den første cyklus, og dosisjusteres de følgende cyklusser hvorefter de når et plateau i cyklus fem.
Ansøger har for olaparib anvendt en opstartsdosis på 600 mg dagligt for alle patienter som anbefales i SPC'et. Patienter i behandling med olaparib kan lige som patienter i behandling med niraparib (Zejula) blive dosisreduceret til en daglig dosis på 400 mg, men da virksomheden bag olaparib har valgt en flad prissætning for olaparib, argumenterer ansøger, at en dosisreduktion vil have indflydelse på lægemiddelomkostningerne for olaparib.

Ansøger har hentet lægemiddelpriser fra Medicinpriser.dk, se tabel 3.

Tabel 3: Anvendte lægemiddelpriser, AIP (august 2018)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Niraparib	100 mg kapsel	1 stk.	757,14	Medicinpriser.dk
Olaparib	100 mg tablet	1 stk.	351,03	Medicinpriser.dk
	150 mg tablet	1 stk.	351,03	Medicinpriser.dk

Amgros' vurdering

Ansøger har angivet at der er to styrker af olaparib, begge i tabletform. Udover de styrker ansøger har angivet, findes også en 50 mg olaparib kapsel hvor anbefalede daglige dosis er 800 mg. Behandling med 50 mg kapsler vil fører til en besparelse i forhold til tablet-behandlingen, da dosisreduktion her vil have indflydelse på lægemiddelomkostningerne, da det medfører en reduktion af det daglige antal olaparib-kapsler. Det er blevet Amgros bekendt, at 50 mg kapslerne vil blive taget af markedet inden for den nærmeste fremtid.

Amgros vurderer at ansøgers tilgang er acceptabel og er i tråd med lægemidlernes SPC.

Omkostninger til bivirkninger

Ansøger har valgt at inkludere omkostninger til bivirkninger, men argumenterer at de fleste bivirkningerne forbundet med de pågældende lægemidler er asymptomatiske, og meget sjældent fører til indlæggelse, men håndteres i form af dosisjustering. Derfor antager ansøger, at hver forekomst af bivirkning fører til ét besøg ved en læge. Enhedsomkostningen forbundet med lægebesøg estimeres af ansøger ved brug af en DRG-takst (DRG: BG50A – ambulant besøg, pat. Mindst 7 år).
Omkostningerne baseres på risikoen for grad 3 og 4 bivirkninger, mens ansøger antager at ingen økonomiske konsekvenser er forbundet med bivirkninger af grad 1-2. Bivirkninger rapporteret for ≥10 % af patienterne i en af behandlingsgrupperne i ENGOT-OV16/NOVA studiet, eller med mindst 1 % forskel mellem niraparib (Zejula) og SoC-gruppen blev inkluderet. Lignende incidents rater for olaparib har ansøger hentet fra NICE tekniske vurdering af olaparib (6).

Amgros' vurdering

Den valgte metode til at estimere bivirkninger, vurderes at være en meget forsimplet tilgang, og vil formentlig underestimere omkostningerne forbundet med at behandle med niraparib (Zejula), da frekvensen af bivirkninger for denne generelt er højere end for SoC og olaparib.
Valget om at inkludere bivirkninger med en frekvens på ≥10 % vurderes at være en høj grænse som ligeledes formentlig medfører en underestimering af de reelle omkostninger til bivirkninger for niraparib (Zejula).

Amgros accepterer den valgte tilgang til estimering af bivirkningsomkostninger trods stor usikkerhed forbundet med disse estimater.

Omkostninger til blodmonitorering

Ansøger antager at monitoreringen af patienter er ens for de forskellige lægemidler i analysen, og derfor ikke inkluderet i analysen, med undtagelse af tre komplette blodtællinger for niraparib (Zejula). Ansøger angiver at disse er inkluderet, da der i SPC for niraparib (Zejula) er anbefalet monitorering af komplet blodtælling i de første måneders behandling med niraparib (Zejula). Enhedsprisen har ansøger hentet fra Region Sjællands offentlige liste over priser på laboratorieydelser (7).

Amgros' vurdering

Amgros godtager ansøgers tilgang til estimering af disse omkostninger, da det vurderes at have begrænset indflydelse på resultaterne.

Patientomkostninger

Ansøger har inkluderet transportomkostninger og patienttid for ekstra blodprøver og ambulatoriebesøg i forbindelse med bivirkninger. Ansøger antager en 14 km rejsedistance hvilket giver en enhedsomkostning for hver kontakt på 100 DKK og patienttiden var antaget at være 30 minutters rejsetid samt 15 minutters ambulatorietid (jævnfør Amgros vejledning til værdisætning af enhedsomkostninger).

Amgros' vurdering

Estimering af transportomkostninger og patienttid er i tråd med Amgros' retningslinjer og godtages derfor.

2.2 Følsomhedsanalyser

Ansøger har udarbejdet en række følsomhedsanalyser hvor effekten af variation i forskellige parametre undersøges. Derudover er også en følsomhedsanalyse med inklusion af efterfølgende behandling udført.

- Inddragelse af efterfølgende behandlinger
- Variation af behandlingslængden med +/- 20%
- Variation af niraparib bivirkningsrater +/- 20%
- Variation af blodtælling for niraparib +/- 20%

Ansøgers følsomhedsanalyserne viser at variation af behandlingslængden har indflydelse på resultatet. Variation i andre undersøgte parametre har mindre betydning for resultatet.

Amgros' vurdering

Da analysen hovedsagelig er drevet af lægemiddelomkostninger, vurderes variation af behandlingslængden at være relevant.
Amgros vurderer at omfanget af følsomhedsanalyserne er meget begrænset og at andre parametre ville være mere relevante at undersøge betydningen af. Amgros udarbejdet egen følsomhedsanalyse der undersøger betydningen af eksklusion af dosisreduktion.

3 RESULTATER

3.1 Ansøgers hovedanalyse

Ansøgers hovedanalyse resulterer i gennemsnitlige meromkostninger per patient for P3 niraparib (Zejula) sammenlignet med SoC på ca. 585.000 DKK for non-gBRCAmut patienter.
Resultaterne fra ansøgers hovedanalyse præsenteres i tabel 4 og tabel 5 for hhv. non-gBRCAmut og gBRCAmut patienter.

Tabel 4:: Resultatet af ansøgers hovedanalyse for non-gBRCAmut patienter, DKK

	Niraparib	SoC	Inkrementelle omkostninger
Lægemiddelomkostninger	580.796	0	580.796
Hospitalsomkostninger	925	46	879
Patientomkostninger	940	16	924
Totale omkostninger	**582.661**	**62**	**582.598**

For gBRCAmut patienter estimerer ansøger i hovedanalysen de gennemsnitlige meromkostninger per patient for P1 niraparib (Zejula) sammenlignet med olaparib til at være ca. 100.000 DKK.

Tabel 5: Resultatet af ansøgers hovedanalyse for gBRCAmut patienter, DKK.

	Niraparib	Olaparib	Inkrementelle omkostninger
Lægemiddelomkostninger	786.054	686.116	99.938
Hospitalsomkostninger	925	139	786
Patientomkostninger	940	48	892
Totale omkostninger	**787.919**	**686.303**	**101.616**

3.2 Amgros' hovedanalyse

3.2.1 Antagelser i Amgros hovedanalyse

Baseret på Amgros' kritiske vurdering af den tilsendte model, har Amgros udarbejdet sin egen hovedanalyse. Forudsætningerne er som i ansøgers analyse bortset fra følgende:

- Lægemiddelomkostninger for alle 20 år, som ansøger har estimeret at patienter vil være i behandling, bliver inkluderet

3.2.2 Resultat af Amgros hovedanalyse

Resultaterne fra Amgros' hovedanalyse præsenteres i tabel 6 og tabel 7.
Amgros' hovedanalyse resulterer i gennemsnitlige meromkostninger per patient for P3 niraparib (Zejula) sammenlignet med SoC på ca. 690.000 DKK for non-gBRCAmut patienter.

Tabel 6: Resultatet af Amgros' hovedanalyse for non-gBRCAmut patienter, DKK.

	Niraparib	SoC	Inkrementelle omkostninger
Lægemiddelomkostninger	688.355	0	688.354
Hospitalsomkostninger	925	46	879
Patientomkostninger	940	16	924
Totale omkostninger	**690.220**	**62**	**690.158**

For gBRCAmut patienter resulterer Amgros' hovedanalyse i gennemsnitlige meromkostninger per patient for P1 niraparib (Zejula) sammenlignet med olaparib på ca. 110.000 DKK.
For begge populationer skyldes meromkostningerne primært prisen på niraparib (Zejula).

Tabel 7: Resultatet af Amgros' hovedanalyse for gBRCAmut patienter, DKK.

	Niraparib	Olaparib	Inkrementelle omkostninger
Lægemiddelomkostninger	927.758	817.513	110.244
Hospitalsomkostninger	925	139	786
Patientomkostninger	940	48	892
Totale omkostninger	**929.623**	**817.700**	**111.922**

3.2.3 Amgros' følsomhedsanalyser

Amgros har udarbejdet en analyse, hvor patienterne i behandling niraparib (Zejula) og olaparib ikke dosisjusteres, for at undersøge hvad konsekvenser der er ved at dosisjusteringen varierer fra estimatet i denne analyse.
Resultaterne fra Amgros' følsomhedsanalyse præsenteres i **Fejl! Henvisningskilde ikke fundet.** og tabel 7.
Amgros' følsomhedsanalyse resulterer i gennemsnitlige meromkostninger per patient for niraparib (Zejula) sammenlignet med SoC på ca. 960.000 DKK for non-gBRCAmut patienter.

Tabel 8: Resultatet af Amgros' følsomhedsanalyse af gennemsnitlig omkostning per patient uden dosisreduktion for non-gBRCAmut patienter, DKK.

	Niraparib	SoC	Inkrementelle omkostninger
Lægemiddelomkostninger	960.247	0	960.247
Hospitalsomkostninger	925	46	879
Patientomkostninger	940	16	924
Totale omkostninger	**962.112**	**62**	**962.050**

For gBRCAmut patienter resulterer Amgros' følsomhedsanalyse hvor patienterne ikke dosisjusteres i gennemsnitlige meromkostninger per patient for niraparib (Zejula) sammenlignet med olaparib på ca. 505.000 DKK.

Tabel 9: Resultatet af Amgros' følsomhedsanalyse af gennemsnitlig omkostning per patient uden dosisreduktion for gBRCAmut patienter, DKK.

	Niraparib	Olaparib	Inkrementelle omkostninger
Lægemiddelomkostninger	1.322.484	817.513	504.970
Hospitalsomkostninger	925	139	786
Patientomkostninger	940	48	892
Totale omkostninger	**1.324.349**	**817.700**	**506.648**

4 BUDGETKONSEKVENSER

4.1 Ansøgers estimater

4.1.1 Patientpopulation og markedsandel

På baggrund af tal fra Nordcan (3), der viser at der er 500 til 600 patienter i Danmark der diagnosticeres med ovariecancer om året estimerer ansøger, at cirka 117 patienter om året vil være kandidater til at modtage niraparib (Zejula) behandling i Danmark. Ud af disse antages det på baggrund af et studie fra 2012 (8), at ca. 38% af patienterne vil have BRCA mutation og at niraparib (Zejula) vil erstatte olaparib behandlingen for disse patienter ved en anbefaling. For de resterende 62% af patienterne er niraparib (Zejula) et alternativ til SoC og vil dermed ikke erstatte en egentlig behandling.
Ansøger antager at de vil have et markedsoptag på 40% det første år ved en evt. godkendelse og 50% de følgende fire år for både non-gBRCAmut og gBRCAmut populationerne. Derudover antages det, at 10 patienter med gBRCA årligt vil modtage SoC. Tabel 10 og tabel 11 viser ansøgers estimat af antal patienter årligt for hhv. non-gBRCAmut populationen og gBRCAmut populationen.

Tabel 10: Ansøgers estimat af antal nye patienter per år for non-gBRCAmut.

	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
Niraparib	29	36	36	36	36	0	0	0	0	0
SoC	44	36	36	36	36	73	73	73	73	73

Tabel 11: Ansøgers estimat af antal nye patienter per år for gBRCAmut.

	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
Niraparib	18	22	22	22	22	0	0	0	0	0
Olaparib	17	12	12	12	12	35	35	35	35	35
SoC	10	10	10	10	10	10	10	10	10	10

Amgros' vurdering af estimeret antal patienter

Ansøger har antaget at 10 gBRCAmut patienter årligt vil modtage SoC behandling. Til denne population er olaparib angivet som komparator i Medicinrådets protokol. På baggrund af dette vurderer Amgros at det er mere retvisende at alle patienter i den omtalte population modtager enten niraparib (Zejula) eller olaparib. I Medicinrådets protokol estimeres det årlige antal patienter der vil være egent til behandling med niraparib (Zejula), at være 250, hvoraf de 30% vil have gBRCAmut. Derfor anses antallet af patienter årligt i budgetkonsekvens analysen ikke at være retvisende.
Ansøgers estimater af markedsoptag vurderer Amgros at være lavt sat, især for non-gBRCAmut populationen, hvor komparator er placebo og niraparib (Zejula) erstatter derved ikke en egentlig behandling ved godkendelse. Amgros vælger derfor at undersøge budgetkonsekvenserne ved markedsoptag på 75% og 100%.

4.1.2 Estimat af budgetkonsekvenser

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som der er inkluderet i omkostningsanalysen dog uden patientomkostninger og diskontering af omkostninger efter første år.
Med de indlagte antagelser estimerer ansøger, at anvendelse af niraparib (Zejula) vil resultere i budgetkonsekvenser på 11-22 mio. DKK per år for non-gBRCAmut populationen og 1-2 mio. DKK per år for gBRCAmut populationen.
Ansøgers estimat af budgetkonsekvenserne fremgår af tabel 12 og tabel 13.

Tabel 12: Ansøgers hovedanalyse for totale budgetkonsekvenser for non-gBRCAmut, mio. DKK, ikke-diskonterede tal.

	År 1	År 2	År 3	År 4	År 5
Anbefales	11	16	19	20	22
Anbefales ikke	0	0	0	0	0
Totale budgetkonsekvenser	**11**	**16**	**19**	**20**	**22**

Tabel 13: Ansøgers hovedanalyse for totale budgetkonsekvenser for gBRCAmut, mio. DKK, ikke diskonterede tal.

	År 1	År 2	År 3	År 4	År 5
Anbefales	14	20	23	25	27
Anbefales ikke	13	18	21	23	25
Totale budgetkonsekvenser	**1**	**2**	**2**	**2**	**2**

Amgros' vurdering

Ansøgers estimater er i overensstemmelse med Amgros' metodevejledning og kan på baggrund heraf accepteres. Amgros udarbejder egen budgetkonsekvensanalyse, med ændring i markedsoptag. Budgetkonsekvensanalysen er baseret på ansøgers hovedanalyse hvor omkostningerne er begrænset til de første fem år.

4.2 Amgros' estimater af budgetkonsekvenser

Amgros har korrigeret følgende estimater i forhold til ansøgers analyse:

- Incidensen for gBRCAmut vil være 75 patienter om året
- Incidensen for non-BRCAmut vil være 125 patienter om året
- For populationen med gBRCAmut vil alle patienter enten modtage olaparib eller niraparib (Zejula)
- Markedsoptag ved godkendelse på 75%

Med de indlagte antagelser estimerer Amgros, at anvendelse af niraparib (Zejula) vil resultere i budgetkonsekvenser på 34-56 mio. DKK per år for non-gBRCAmut populationen og 6-9 mio. DKK per år for gBRCAmut populationen, se hhv. tabel 14 og tabel 15.

Tabel 14: Amgros' hovedanalyse for totale budgetkonsekvenser for non-gBRCAmut, mio. DKK, ikke-diskonterede tal.

	År 1	År 2	År 3	År 4	År 5
Anbefales	34	44	50	53	56
Anbefales ikke	0	0	0	0	0
Totale budgetkonsekvenser	**34**	**44**	**50**	**53**	**56**

Tabel 15: Amgros' hovedanalyse for totale budgetkonsekvenser for gBRCAmut, mio. DKK, ikke diskonterede tal.

	År 1	År 2	År 3	År 4	År 5
Anbefales	31	43	50	55	58
Anbefales ikke	25	36	42	46	48
Totale budgetkonsekvenser	**6**	**8**	**8**	**9**	**9**

4.2.1 Følsomhedsanalyse af budgetkonsekvenser

Amgros har estimeret de maksimale budgetkonsekvenserne ved et markedsoptag på 100%.
Med de indlagte antagelser estimerer Amgros, at anvendelse af niraparib (Zejula) vil resultere i budgetkonsekvenser på ca. 45-75 mio. DKK per år for non-gBRCAmut populationen, og ca. 8-13 mio. DKK per år for gBRCAmut populationen.
Estimat af budgetkonsekvenserne fremgår af tabel 16 og tabel 17.

Tabel 16: Amgros' estimat af maksimale budgetkonsekvenser for non-gBRCAmut, mio. DKK, ikke-diskonterede tal.

	År 1	År 2	År 3	År 4	År 5
Anbefales	45	58	66	71	75
Anbefales ikke	0	0	0	0	0
Totale budgetkonsekvenser	**45**	**58**	**66**	**71**	**75**

Tabel 17: Amgros' estimat af maksimale budgetkonsekvenser for gBRCAmut, mio. DKK, ikke diskonterede tal.

	År 1	År 2	År 3	År 4	År 5
Anbefales	33	46	53	58	61
Anbefales ikke	25	36	42	46	48
Totale budgetkonsekvenser	**8**	**10**	**11**	**12**	**13**

5 DISKUSSION

Behandling med niraparib (Zejula) er forbundet med betydelige meromkostninger sammenlignet med behandling med placebo (SoC). Behandling med niraparib (Zejula) er sammenlignet med olaparib ligeledes forbundet med meromkostninger af betydelig størrelse. Meromkostningerne er næsten udelukkende drevet af lægemiddelomkostningerne for niraparib (Zejula) ved både sammenligning med SoC og olaparib. Hospitalsomkostninger har overordnet lille betydning for resultatet.

Ansøgers antagelse om at niraparib (Zejula) og olaparib har samme behandlingslængde er forbundet med usikkerheder og da meromkostningerne i analysen hovedsaligt er drevet af lægemiddelomkostninger, vil variation i behandlingslængden mellem de to lægemidler have stor indflydelse på analysens resultat.

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on 19-12-2018 17:42

CJ

Cathy Jarrold <cjarrold@tesarobio.com>

RE: [EXTERNAL] niraparib assessment report - final version

Til Agla Jael Fridriksdottir

Cc Helene Plank; Ditte Marie Irwin-Clugston; Anne Sofie Gram; Mats Persson

Dear Agla,

Many thanks for the opportunity to comment on the DMC assessment report. At this stage we have no further comment on the document. We have found small discrepancies in some of the data in the submission but these probably reflect using different data sources for the same data points, rather than a mis-representation of the data.

Given that platinum sensitive recurrent ovarian cancer is incurable with very poor overall survival and that there is currently an inequality of access to PARP inhibitors for women dependent on their BRCA status in Denmark, we hope to be able to achieve access for eligible women as soon as possible.

Kind regards

Cathy

Medicinrådet

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

Medicinrådets konklusion vedrørende klinisk merværdi

Medicinrådet vurderer, at niraparib til patienter med BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, æggelederne eller primær kræft i bughinden, og respons på platinbaseret kemoterapi giver **ingen klinisk merværdi** sammenlignet med olaparib. Evidensens kvalitet vurderes at være lav.

Medicinrådet vurderer, at niraparib til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, æggelederne eller primær kræft i bughinden, og respons på platinbaseret kemoterapi giver **ikkedokumenterbar klinisk merværdi** sammenlignet med bevacizumab. Evidensens kvalitet vurderes ikke.

Medicinrådet vurderer, at niraparib til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, æggelederne eller primær kræft i bughinden, og respons på platinbaseret kemoterapi giver en **lille klinisk merværdi** sammenlignet med placebo. Evidensens kvalitet vurderes at være lav.

Handelsnavn	Zejula®
Generisk navn	Niraparib
Firma	Tesaro
ATC-kode	L01XX54
Virkningsmekanisme	Niraparib er en selektiv hæmmer af enzymerne poly (adenosin diphosphat [ADP]-ribose) polymerase (PARP) 1/2, der deltager i DNA reparation. Blokering af PARP 1/2 i tumorceller, som i forvejen har mange genomiske skader, inducerer celledød.
Administration/dosis	Peroral kapsel, 100 mg, 3 kapsler dagligt
EMA-indikation	Zejula is indicated as monotherapy for the maintenance treatment of adult patients with platinum sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum based chemotherapy.
Godkendelsesdato Offentliggørelsesdato Dokumentnummer Versionsnummer	12. december 2018 12. december 2018 33775 1.0

Definition af klinisk merværdi:

Medicinrådet kategoriserer lægemidlets 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.

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.

Forkortelser

AML:	Akut myeloid leukæmi
AR:	Bivirkning (*adverse reaction)*
BRCA1/2:	*BReast CAncer1/2* (tumor suppressorgen)
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*
FACT-O*:*	*Functional Assessment of Cancer Therapy-Ovary*
FOSI:	*FACT Ovarian Symptom Index*
HGSC:	High-grade serøst adenokarcinom (*high-grade serous carcinoma*)
HR:	*Hazard ratio*
HRD:	Defekt homolog rekombination (*homologous recombination deficiency*)
ITT:	*Intention-to-treat*
MDS:	Myelodysplastisk syndrom
NA:	Ikke tilgængeligt (*not available*)
OS:	Samlet overlevelse (*overall survival*)
PS:	Performance status
PFS:	Progressionsfri overlevelse (*progression free survival*)
RECIST:	*Response Evaluation Criteria In Solid Tumors*
RR:	Relativ risiko
TFST:	Tid til første efterfølgende behandling (*time to first subsequent treatment*)
TSST:	Tid til efterfølgende behandling nummer 2 (*time to second subsequent treatment*)

Indhold

1 Formål

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

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

2 Baggrund

HGSC i æggestokkene, herunder kræft i æggelederne og primær kræft i bughinden, opstår i langt de fleste tilfælde (> 90 %) 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 4.600 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 at være genetisk betinget med breast cancer (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]. En del patienter bedømmes primært inoperable og tilbydes neoadjuverende kemoterapi og ny vurdering med henblik på mulighed for operation efter 3 serier carboplatin + paclitaxel. Næsten alle patienter, der opereres makroskopisk radikalt (hvad enten det er *upfront kirurgi* eller som *interval debulking*), tilbydes efterfølgende adjuverende platinbaseret kombinationskemoterapi i form af carboplatin og paclitaxel. 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]. Nogle patienter, der primært blev makroskopisk radikalt opereret, vil 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-mutationstatus.

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

Patienter uden BRCA1/2-mutation
Største delen af patienterne, der ikke fik 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 aktuelt kun én 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
Niraparib er en selektiv hæmmer af PARP 1/2. PARP 1/2 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].

Niraparib gives i kapselform, 100 mg, 3 kapsler én gang dagligt som vedligeholdelsesbehandling. Ved bivirkninger kan dosis reduceres fra 300 mg til 200 mg og evt. 100 mg dagligt. Niraparib administreres indtil tilbagefald af sygdommen, eller intolerable bivirkninger måtte opstå trods dosisreduktion.

Niraparib blev godkendt af det Europæiske Lægemiddelagentur (*European Medicines Agency* (EMA)) i 2017 som vedligeholdelsesbehandling til platinsensitiv, recidiverende HGSC i æggestokkene, herunder æggelederne og primær kræft i bughinden, som responderer på platinbaseret kombinationskemoterapi (komplet eller partiel respons). Platinsensitivitet vurderes at være forbundet med PARP-hæmmer sensitivitet pga. høj prævalens af forandringer/mutationer i DNA-reparation mekanismer i platinsensitiv, recidiverende HGSC i æggestokkene. Fagudvalget vurderer, at der i Danmark diagnosticeres omkring 250 patienter pr. år, der vil være egnet til behandling. Omkring 30 % af patienterne bærer en BRCA1/2-mutation. I tabel 1 er placering af niraparib i den nuværende behandlingsalgoritme indikeret med rødt.

Fagudvalget vil gerne fremhæve, at indplacering af niraparib 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. Niraparibs placering i behandlingsalgoritmen er indikeret med rødt.

	Patienter med BRCA1/2-mutation	Patienter uden BRCA1/2 mutation	
2. linjebehandling*	Platinbaseret kombinationskemoterapi efterfulgt af olaparib eller niraparib vedligeholdelsesbehandling	Platinbaseret kombinationskemoterapi i kombination med bevacizumab efterfulgt af bevacizumab vedligeholdelsesbehandling eller niraparib vedligeholdelsesbehandling	Platinbaseret kombinationsterapi efterfulgt af niraparib 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 gives aktuelt kun én gang i patientens behandlingsforløb.

3 Metode

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

Ansøger har i overensstemmelse med protokollen [6] indsendt en endelig ansøgning den 19. september 2018, herunder også en omkostningsanalyse. Ansøgningen indeholder en narrativ sammenligning af niraparib og olaparib, en narrativ sammenligning af niraparib og bevacizumab og en direkte sammenligning af niraparib og placebo.

Ansøger har anvendt og fulgt den præspecificerede metode, jf. protokol som blev godkendt i Medicinrådet den 18. maj 2018.

4 Litteratursøgning

Ansøger har foretaget en systematisk litteratursøgning efter kliniske studier på niraparib og relevante komparatorer. Søgningen blev foretaget i flere databaser end specificeret i protokollen og inkluderede også registre for kliniske studier (Clinicaltrials.gov og WHO ICTRP) og konferenceabstrakts. Ansøgers PRISMA-diagram og litteraturgennemgang fremgår af ansøgningen. Søgningen resulterede i identifikation af syv publikationer fra fem randomiserede dobbeltblindede kliniske studier (RCT), som opfyldte Medicinrådets præspecificerede kriterier. Disse er oplistet nedenfor:

***Niraparib*:**

- **ENGOT-OV16/NOVA-studiet (NOVA-studiet)**: Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med 2016. 375: 2154–2164 [7].

***Olaparib*:**

- **Studie 19**: 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 [8].
- **Planlagt retrospektiv analyse baseret på BRCA-mutationsstatus fra Studie 19:** 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 [9].
- **Opdaterede overlevelsesdata fra Studie 19:** 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 [10].
- **ENGOT-OV21/SOLO2-studiet (SOLO2-studiet)**: Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomized, placebo-controlled, phase 3 trial. Lancet Oncol 2017. 18: 1274–1284 [11].

***Bevacizumab*:**

- **OCEANS-studiet**: 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 [12].
- **GOG0213-studiet**: Coleman RL, Brady MF, Herzog TJ, 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: 779–791 [13].

Ved gennemgang af ansøgers litteratursøgning og udvælgelse af publikationer har Medicinrådets sekretariat opdateret listen med inkluderede studier ved at tilføje følgende publikationer:

***Niraparib*:**

- **Opdaterede livskvalitetsdata fra NOVA-studiet:** Oza AM, Matulonis UA, Malander S 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 [14].
- **Supplerende data vedrørende safety og dosismodifikation:** Berek JS, Matulonis UA, Peen U et al. Safety and dose modification for patients receiving niraparib. Ann Oncol 2018;29:1784-92 [15].

***Olaparib*:**

- **Opdaterede livskvalitetsdata fra SOLO2-studiet:** Friedlander M, Gebski V, Gibbs E, 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 [16].

***Bevacizumab*:**

- **Opdaterede overlevelsesdata fra OCEANS-studiet:** 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 [17].

De overnævnte primærstudier samt European Product Assessment Report (EPAR) og produktresumé for niraparib [18,19], olaparib [20,21] og bevacizumab [22–24] udgør dermed datagrundlaget for de kvantitative og narrative analyser, der benyttes til besvarelsen af de tre kliniske spørgsmål.

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.

5 Databehandling

Klinisk spørgsmål 1
Til besvarelse af klinisk spørgsmål 1, hvor niraparib sammenlignet med olaparib vurderes til patienter med BRCA1/2-mutation, har ansøger af flere årsager valgt at foretage en naiv sammenligning fremfor at gennemføre en formel indirekte sammenligning baseret på niraparibdata fra NOVA-studiet og olaparibdata fra Studie 19 og SOLO2-studiet. Fagudvalget og Medicinrådets sekretariat er enige i ansøgers valg, hovedsagelig på grund af følgende:

- Ansøger har udført en test for at vurdere, om PFS-analysen i de tre studier overholder antagelsen om proportionelle 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 [25].
- Patienterne i Studie 19 havde modtaget gennemsnitlig flere linjer kemoterapi sammenlignet med patienterne fra NOVA- og SOLO2-studierne. Dette kan potentielt resultere i en forskel i størrelsesordenen på effektestimaterne mellem Studie 19 og de to andre studier til fordel for NOVA- og SOLO2-studierne.

På baggrund af ovenstående har fagudvalget valgt at foretage en narrativ sammenligning af de tre studier. I den narrative sammenligning er resultaterne fra studierne sammenholdt overfor hinanden ved at inddrage de identificerede forskelle mellem studierne i vurderingen af den kliniske merværdi.

Derudover har fagudvalget og Medicinrådets sekretariat konstateret at:

- Ansøger har ikke indsendt data på median samlet overlevelse (OS) for niraparib fra NOVA-studiet samt olaparib fra SOLO2-studiet, da disse data endnu ikke er modne. Der foreligger derfor kun data på median OS for olaparib fra Studie 19.
- Ansøger har indsendt bivirkningsdata for både niraparib og olaparib i form af uønskede hændelser (adverse events (AE)), som dækker over både de protokoldefinerede bivirkninger (adverse reactions (AR)) og øvrige hændelser opstået under behandlingen. Fagudvalget vurderer, at dette ikke vil påvirke vurderingen af effektestimatet.
- AE bliver opgjort for hele studiepopulationen fra NOVA-studiet (data for patienter med og uden BRCA1/2-mutation poolet sammen), men kun på patienter med BRCA1/2-mutation i Studie 19 og SOLO2-studiet. Fagudvalget forventer ikke, at det vil ændre vurderingen, hvis bivirkninger ville have været opgjort på patienter opdelt efter BRCA-mutationsstatus.
- De publicerede data fra SOLO2-studiet er ikke opgjort på den måde, som fagudvalget har defineret i protokollen. Data fra NOVA-studiet og Studie 19 ligger til grund for den narrative vurdering.
- I Studie 19 modtog patienterne olaparib som kapsler i modsætning til tabletter i SOLO2-studiet. De to doseringer er ikke bioækvivalente, men EMA har vurderet, at de har sammenlignelig klinisk effekt ved de godkendte doser [20].
- Ansøger har indsendt data på PFS2, tid til første efterfølgende behandling (TFST) og det kemoterapifrie interval (CFI). Alle effektmål blev vurderet som mindre vigtige i protokollen. Disse data inddrages derfor ikke i kategoriseringen af den kliniske merværdi.

Klinisk spørgsmål 2
Til besvarelse af klinisk spørgsmål 2, hvor niraparib sammenlignet med bevacizumab vurderes til patienter uden BRCA1/2-mutation, har ansøger argumenteret for, at en statistisk sammenligning baseret på niraparib-data fra NOVA-studiet og bevacizumab-data fra OCEANS og GOG0213-studierne ikke er mulig på grund af følgende væsentlige forskelle mellem studierne:

- BRCA1/2-mutationstatus blev ikke analyseret i OCEANS- og GOG0213-studierne, 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-mutationstatus. Dette afviger fra NOVA-studiet, som indeholder to kohorter: patienter med BRCA1/2-mutation og patienter uden BRCA1/2-mutation. Ansøger har vurderet, at disse forskelle i patientsammensætningen i de omtalte studier ikke tillader en sammenligning af studiedata, hverken indirekte eller narrativt.
- Behandling med bevacizumab gives *samtidigt* med kemoterapi, efterfulgt af bevacizumab vedligeholdelsesbehandling. Til gengæld gives niraparib som vedligeholdelsesbehandling *efter* endt kemoterapi. Dette vil medføre en forskel i opgørelsen af effektmålet PFS, som bliver målt over forskellige tidsintervaller i NOVA-studiet (fra afslutning af kemoterapi) og bevacizumabstudierne (fra opstart af kemoterapi). En statistisk sammenligning er dermed ikke meningsfuld.

Fagudvalget og Medicinrådets sekretariat er enige i ansøgers argumentation for, at statistisk sammenligning mellem niraparib og bevacizumab ikke kan gennemføres meningsfuldt pga. af de ovennævnte forskelle i studierne. Derfor vurderer fagudvalget, at der ikke foreligger noget grundlag for en formel indirekte eller narrativ sammenligning af studierne.

Klinisk spørgsmål 3
Til besvarelse af klinisk spørgsmål 3, hvor niraparib sammenlignet med placebo vurderes til patienter uden BRCA1/2-mutation, har ansøger indsendt data fra den direkte sammenligning, der foreligger fra NOVA-studiet [7]. Medicinrådet har ikke fundet anledning til at foretage yderligere 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 på median samlet overlevelse (OS) for niraparib fra NOVA-studiet, da disse endnu ikke er modne.
- Ansøger har indsendt bivirkningsdata i form af uønskede hændelser (adverse events (AE's)), som dækker over både de protokoldefinerede bivirkninger (adverse reactions (AR's)) og øvrige hændelser opstået under behandlingen. Fagudvalget vurderer, at dette ikke vil påvirke vurderingen af effektestimatet.
- AE er opgjort for hele studiepopulationen i NOVA-studiet (data for patienter med og uden BRCA1/2-mutation poolet sammen). Fagudvalget forventer ikke, at det vil ændre vurderingen, i forhold til hvis bivirkninger var opgjort på patienter opdelt efter BRCA-mutationsstatus.
- Ca. 13 % af patienterne i NOVA-studiet i kohorten uden arvelig BRCA1/2-mutation havde en somatisk BRCA1/2-mutation. Det er fagudvalgets opfattelse, at dette kan medføre en risiko for overestimering af effekten af PFS for hele kohorten, da patienter med somatisk BRCA1/2-mutation har en sammenlignelig effekt af behandling med PARP-hæmmere som patienter med arvelig BRCA1/2-mutation. Risikoen kan ikke kvantificeres.
- Ifølge den endelige ansøgning er den relative risiko for PFS for patienter med BRCA1/2-mutation ikke konstant over tid i NOVA-studiet (se ovenfor). Fagudvalget vurderer, at samme vil gøre sig gældende for patienter uden BRCA1/2-mutation i NOVA-studiet. Antagelsen om proportionelle hazarder holder dermed ikke for PFS.
- Ansøger har indsendt data på PFS2, tid til første efterfølgende behandling (TFST) og det kemoterapifrie interval (CFI) som blev vurderet som et mindre vigtigt effektmål i protokollen. Disse data inddrages derfor ikke i kategoriseringen af den kliniske merværdi.

6 Klinisk merværdi

6.1 Konklusion klinisk spørgsmål 1

Hvilken klinisk merværdi tilbyder vedligeholdelsesbehandling med niraparib sammenlignet med olaparib hos patienter med BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC og respons på platinbaseret kemoterapi?

Fagudvalget vurderer, at niraparib til patienter med BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, æggelederne eller primær kræft i bughinden, og respons på platinbaseret kemoterapi giver **ingen klinisk merværdi** (lav evidenskvalitet) sammenlignet med olaparib.

6.1.1 Gennemgang af studier

Karakteristika

I sammenligningen af niraparib med olaparib indgår data fra de tre identificerede studier: NOVA-studiet [7,14], Studie 19 [8–10] og SOLO 2-studiet [11,16].

NOVA-studiet [7,15,18]

Dette studie er et randomiseret, dobbeltblindet, placebokontrolleret fase 3-studie. Det var et multicenterstudie (107 onkologiske centre) hvor patienter blev inkluderet i to uafhængige kohorter: patienter med arvelig BRCA1/2-mutation (gBRCAmut kohorte) og patienter uden arvelig BRCA1/2-mutation (non-gBRCAmut kohorte). I alt blev 553 patienter (372 i niraparibarmen og181 i placeboarmen) randomiseret (senest 8 uger efter endt platinbaseret kemoterapi) i en 2:1 ratio til at modtage niraparib (300 mg dagligt) eller placebo indtil sygdomsprogression, forekomst af uacceptabel toksicitet, dødsfald, tilbagekaldelse af samtykke eller manglende opfølgning. Den første patient blev randomiseret den 26. august 2013, og data præsenteret i denne rapport stammer fra database-lock den 20. juni 2016. Patienter i hver kohorte blev stratificeret efter tid til progression efter deres næstsidste platinbaserede kemoterapi (6-12 måneder vs. ≥ 12 måneder), bevacizumab anvendelse i kombination med deres næstsidste eller sidste platinbaserede kemoterapi og respons (komplet eller partiel) ved deres sidste platinbaserede kemoterapi. Patienterne i studiet havde platinsensitiv HGSC i æggestokkene, æggelederne eller primær kræft i bughinden og havde minimum modtaget 2 linjer platinbaseret kemoterapi tidligere. Studiets primære endepunkt var PFS, defineret som progression (målt radiologisk via RECIST v1.1) eller død, vurderet af en uafhængig bedømmer. Isoleret CA 125 stigning var ikke defineret progression. Patienter blev skannet hver 8. uge. Sekundære endepunkter var TFST, CFI, PFS2, tid til anden efterfølgende kemoterapi (time to second subsequent chemotherapy, TSST), OS, sikkerhed samt livskvalitet (FACT Ovarian Symptom Index (FOSI) og EQ-5D). Ved database-lock modtog 93 patienter i niraparibarmen og 16 patienter i placeboarmen stadigvæk behandling. Median opfølgningstid i ITT-populationen ved data-cutoff (30. maj 2016) var 16,9 måneder (16, 4 måneder i gBRCAmut kohorten og 17,5 måneder i non-gBRCAmut kohorten). Effektanalyser blev udført på ITT-populationen. Sikkerhedsanalyser blev udført på alle patienter, der som minimum modtog en dosis studiemedicin (safety population).

Studie 19 [8–10,20]

Dette studie er et randomiseret, dobbeltblindet, placebokontrolleret fase 2-studie. Det var et multicenterstudie (82 onkologiske centre), hvor i alt 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. Patienter blev randomiseret fra den 28. august 2008 til den 9. februar 2010 med data-cutoff for den første primæranalyse af PFS den 30. juni 2010 [8], efterfulgt af en planlagt retrospektiv analyse af data baseret på BRCA-mutationsstatus, som også inkluderede OS-data (data-cutoff den 26. november 2012) [9] samt opdateret opgørelse på OS-data fra den 30. september 2015 [10]. 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 patienter i placeboarmen ved studiestart. Øvrige patienter blev analyseret for deres BRCA-mutationsstatus retrospektivt. Patienterne i studiet havde platinsensitiv HGSC i æggestokkene, æggelederne eller primær kræft i bughinden og havde minimum modtaget 2 linjer platinbaseret kemoterapi tidligere. Studiets primære endepunkt var PFS, defineret som progression (målt radiologisk via RECIST retningslinjer) eller død, vurderet af investigator. Patienter blev skannet hver 12. uge. Sekundære endepunkter var tid til progression (i henhold til RECIST retningslinjer eller CA-125 niveau), objektiv responsrate, sygdomskontrolrate (i henhold til RECIST retningslinjer, 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). Ved sidste data-cutoff (den 9. maj 2016) modtog 14 patienter i olaparibarmen og 1 patient i placeboarmen stadigvæk behandling. Median opfølgningstid i ITT-populationen ved data-cutoff for PFS primæranalysen (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 en dosis studiemedicin (safety population).

SOLO2 [11,20]
Dette studie er et randomiseret, dobbeltblindet, placebokontrolleret fase 3-studie. Det var et multicenterstudie (119 onkologiske centre), hvor i alt 295 patienter (196 i olaparibarmen og 99 i placeboarmen) blev randomiseret (senest 8 uger efter endt platinbaseret kemoterapi) 2:1 til at modtage olaparib (600 mg dagligt som tabletter) eller placebo indtil sygdomsprogression, eller indtil investigator vurderede, at patienten ikke længere havde gavn af behandlingen. Patienter blev randomiseret fra den 3. september 2013 til den 21. november 2014 med data-cutoff den 19.september 2016 [11,20]. Patienter blev stratificeret efter tid til progression efter deres næstsidste platinbaserede kemoterapi (6-12 måneder vs. ≥ 12 måneder) og respons (komplet eller partiel) ved deres sidste platinbaserede kemoterapi. Patienterne i studiet havde en BRCA1/2-mutation og platinsensitiv HGSC i æggestokkene, æggelederne eller primær kræft i bughinden eller high-grade endometrioid kræft og havde tidligere modtaget minimum 2 linjer platinbaseret kemoterapi. Studiets primære endepunkt var PFS, defineret som progression (målt radiologisk via RECIST v1.1) eller død, vurderet af investigator. Patienter blev skannet hver 12. uge. Sekundære endepunkter var TFST, TSST, PFS2, tid til studieophør eller dødsfald, OS, sikkerhed samt livskvalitet (ændring fra baseline i FACT-Os TOI score). Ved data-cutoff (den 19. september 2016) modtog 83 patienter i olaparibarmen og 13 patienter i placeboarmen stadigvæk behandling. Median opfølgningstid i ITT-populationen ved data-cutoff (19. september 2016) var 22,1 måneder i olaparibarmen og 22,2 måneder i placeboarmen. Effektanalyser blev udført på ITT-populationen. Sikkerhedsanalyser blev udført på alle patienter, der som minimum modtog en dosis studiemedicin (safety population).

Overordnet vurderer fagudvalget, at:

- det forhold at det primære effektmål PFS blev bedømt af en uafhængig bedømmer i NOVA-studiet, men af investigator i Studie 19 og SOLO2-studiet ikke påvirker vurderingen eller tiltroen til effektestimatet.
- det forhold, at patienter blev skannet på forskellige tidspunkter i henholdsvis NOVA-studiet (hver 8.uge), Studie 19 og SOLO2-studiet (hver 12. uge), eventuelt kan have påvirket censureringstidspunktet af patienter. Fagudvalget bemærker, at denne forskel kan bidrage både til en risiko for underestimering og overestimering af PFS. På grund af det kortere interval mellem skanningerne i NOVA-studiet vil der teoretisk være en risiko for en lille undervurdering af PFS sammenlignet med studie 19 og SOLO2. Den potentielle forskel anses dog for at være så lille, at fagudvalget vurderer, at den ikke påvirker vurderingen eller tiltroen til effektestimatet.
- det at patienternes BRCA-mutationsstatus blev undersøgt før deltagelse i NOVA- og SOLO2-studierne, men blev analyseret i en planlagt post hoc-analyse i Studie 19, ikke påvirker vurderingen af effektestimatet, men påvirker tiltroen til effektestimatet.

Population
Der var ikke nogen relevante forskelle i baselinekarakteristika mellem placebo- og interventionsarmen i de tre studier. Derfor rapporteres kun de relevante baselinekarakteristika for patienter med BRCA1/2-mutation i interventionsarmen fra de tre studier i tabel 2.

Tabel 2. Baselinekarakteristika for patienter med BRCA1/2-mutation i interventionsarmen i NOVA, Studie 19 og SOLO2-studierne

	NOVA-studiet (n = 138)	**Studie 19 (n = 74)**	**SOLO2-studiet (n = 196)**
Median alder, år	57,0 (36-83)	57,5 (38-89)	56,0 (51-63)
Race, n (%)			
Kaukasiske	123 (89,1)	70 (94,6)	173 (88,3)
Afrikanske	1 (0,7)	2 (2,7)	1 (0,5)
Asiatiske	2 (1,4)	1 (1,4)	22 (11,2)
Andet	1 (0,7)	1 (1,4)	0
Ukendt	11 (8,0)	0	0
ECOG PS, n (%)			
0	91 (65,9)	62 (83,8)	162 (82,7)
1	47 (34,1)	11 (14,9)	32 (16,3)
2	0	0	0
Ukendt	0	1 (1,4)	2 (1,0)
Tumortype, n (%)			
Æggestokke	122 (88,4)	65 (87,8)	162 (82,7)
Bughinden	7 (5,1)	8 (10,8)	18 (9,2)
Æggeleder	9 (6,5)	1 (1,4)	13 (6,6)
Andet/ukendt	0	0	3 (1,5)
Histologisk subtype, n (%)			
Serøs	117 (88,6)	NA	183 (93,4)
Endometrioid	8 (6,1)	NA	9 (4,6)
Mucinøs	0	NA	0
Andet	13 (9,8)	NA	3 (1,5)
Ukendt		NA	1 (0,5)
Kræftstadie ved diagnose, n (%)			
I eller II	23 (16,7)	NA	NA
III	95 (68,8)	NA	NA
IV	20 (14,5)	NA	NA
Tid til progression efter næstsidste platinbaserede kemoterapi, n (%)			
6 til < 12 måneder	54 (39,1)	28 (37,8)	79 (40,3)
≥ 12 måneder	84 (60,9)	46 (62,2)	117 (59,7)
Respons på sidste platinbaserede kemoterapi, n (%)			
Komplet	71 (51,4)	36 (48,6)	91 (46,4)
Partiel	67 (48,6)	38 (51,4)	105 (53,6)
Tidligere anvendelse af bevacizumab, n (%)			
Ja	33 (23,9)	NA	33 (16,8)
Antal linjer kemoterapi (%)			
> 3	49	65	31
> 4	NA	27	9
> 5	NA	15	4

Fagudvalget finder, at baselinekarakteristika fra NOVA- og SOLO2-studierne er sammenlignelige, dog er der flere asiatiske patienter i SOLO2-studiet. Data skønnes at kunne overføres på en tilsvarende dansk patientpopulation. Patienterne i Studie 19 har modtaget flere linjer kemoterapi sammenlignet med patienterne i de to andre studier. Dette kan påvirke effekten af olaparib i negativ retning. Patienterne i alle tre studier har high-grade serøst karcinom i æggestokkene (i SOLO2 og NOVA indgik endvidere også få patienter med high grade endometrioidt karcinom), som svarer til den population, der blev defineret i det kliniske spørgsmål i protokollen.

Fagudvalget bemærker, at der er flere patienter i performancestatus 1 i NOVA-studiet sammenlignet med de to andre studier. Desuden har flere patienter modtaget bevacizumab tidligere i deres behandlingsforløb i NOVA-studiet sammenlignet med SOLO2-studiet. Denne information er ukendt for Studie 19. De ovennævnte afvigelser skønnes ikke at påvirke vurderingen af effektestimaterne fra studierne samt sammenligneligheden af disse til den danske patientpopulation.

6.1.2 Resultater og vurdering

Resultater og vurdering af de effektmål, som fagudvalget har præspecificeret som henholdsvis kritiske og vigtige, følger nedenfor. Sammenligningen af niraparib med olaparib er narrativt. Årsagen hertil er, at der ikke findes *head-to-head*-studier på patienter med BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, æggelederne eller primær kræft i bughinden, og respons på platinbaseret kemoterapi, som muliggør en direkte sammenligning, og at det ikke er muligt at lave en indirekte sammenligning mellem NOVA-, Studie 19- og SOLO2-studierne pga. studieforskelle (jf. afsnit 5). Den samlede kliniske merværdi af niraparib baseres på længst mulig opfølgningstid.

Samlet overlevelse (OS) (kritisk)

OS ønskes opgjort som median OS. Median OS er ikke opnået i NOVA- eller SOLO2-studierne efter median opfølgningstid på henholdsvis 16,4 [18] og 22,1 måneder [20]. OS-data fra Studie 19 har en median opfølgningstid på 71 måneder [10].

Tabel 3. Vurdering af klinisk merværdi: median OS

	NOVA (niraparib vs. placebo)	**Studie 19 (olaparib vs. placebo)**	**SOLO2 (olaparib vs. placebo)**
Absolut effektestimat for den aktive arm sammenlignet med placebo	NA	4,7 måneder	NA
Relativt effektestimat for den aktive arm sammenlignet med placebo	HR = 0,91 [0,36; 2,28] p = 0.83*	HR = 0,62 [0,41; 0,94] p = 0,025	HR = 0,80 [0,50; 1,31] p = 0.43*
Evidensens kvalitet	Vurderes ikke		

*Præliminære data

Fagudvalget understreger, at OS-data for NOVA og SOLO2 ikke er modne, og at de opgjorte HR derfor er præliminære. I NOVA-studiet var median OS ikke opnået for patienter med BRCA1/2-mutation efter median opfølgningstid på 16,4 måneder. 16 ud af 138 patienter (12 %) døde i niraparibarmen sammenlignet med 8 ud af 65 (12 %) i placeboarmen. Det giver en foreløbig HR på 0,91 [0,36; 2,28] (p = 0,83) [18]. SOLO2-studiet havde en foreløbig HR på 0,80 [0,50; 1,31] (p = 0,43) efter en median opfølgningstid på 22,1 måneder [20]. 45 ud af 196 patienter (23 %) døde i olaparibarmen sammenlignet med 27 ud af 99 (27 %) i placeboarmen. Median OS for patienter med BRCA1/2-mutation var 34,9 måneder i olaparibarmen

sammenlignet med 30,2 måneder i placeboarmen i Studie 19 [10], hvilket giver en absolut effektforskel på 4,7 måneder til fordel for olaparib. HR var 0,62 [0,41;0,94] (p = 0,025) [10].
Fagudvalget bemærker desuden, at OS ikke var den primære effektparameter i Studie 19, der således ikke var dimensioneret til at detektere en forskel i OS.

På baggrund af ovenstående vurderer fagudvalget, at niraparib har **ikkedokumenterbar klinisk merværdi** på nuværende tidspunkt sammenlignet med olaparib til patienter med BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, hvad angår median OS.

Progressionsfri overlevelse (PFS) (kritisk)
PFS ønskes opgjort som median PFS. I sammenligningen anvendes der data for niraparib fra NOVA-studiet samt data for olaparib fra Studie 19 og SOLO2-studiet.

Tabel 4. Vurdering af klinisk merværdi: median PFS

	NOVA (niraparib vs. placebo)	Studie 19 (olaparib vs. placebo)	SOLO2 (olaparib vs. placebo)
Absolut effektestimat for den aktive arm sammenlignet med placebo	15,5 måneder	6,9 måneder	13,6 måneder
Evidensens kvalitet	Lav		

Da de relative værdier for PFS ikke er konstante over tid (jf. afsnit 5, klinisk spørgsmål 1), har fagudvalget lagt vægt på de absolutte effektestimater ved den narrative sammenligning. Mindske klinisk relevante forskel blev defineret som 6 måneder i protokollen [6]. Den absolutte effektforskel på PFS for patienter med BRCA1/2-mutation i NOVA-studiet var 15,5 måneder til fordel for niraparib. Tilsvarende lå den på 6,9 måneder og 13,6 måneder til fordel for olaparib fra henholdsvis Studie 19 og SOLO2-studierne. Fagudvalget bemærker, at forskellen i PFS er af samme størrelsesorden i NOVA- og SOLO2-studierne, mens den er kortere i Studie 19, hvilket formentlig skyldes, at patienterne har fået flere linjer kemoterapi (jf. tabel 2). Fagudvalget bemærker, at i såvel NOVA-studiet som Studie 19 og SOLO2-studiet forekom hyppige forlængelser af dosisintervallet og hyppige dosisreduktioner i starten af undersøgelserne (se bivirkninger for de nøjagtige tal). Det er ikke muligt med sikkerhed at vurdere, om dette har resulteret i nedsat effekt (om effekten hos patienter, der forblev på startdosis, var bedre end hos de, der blev reduceret i dosis). Med hensyn til NOVA-studiet blev størstedelen af patienterne (73 %) reduceret i dosis til 200 mg dagligt (og nogle senere til 100 mg dagligt), hvorfor det ikke er sandsynligt, at de effektforskelle, der fandtes i NOVA-studiet (sammenlignet med placebo), udelukkende kan tilskrives effekt hos patienter, der forblev på startdosis (300 mg dagligt).

Samlet vurderer fagudvalget, at niraparib har **ingen klinisk merværdi** sammenlignet med olaparib til patienter med BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, hvad angår median PFS med lav evidenskvalitet. Vurderingen er primært baseret på studiernes opgjorte absolutte effektestimater, som ved en narrativ sammenligning viste, at der ikke var tale om en absolut effektforskel af klinisk betydning. De forskelle, der er mellem studierne, jf. afsnit 6.1.1, forventes ikke at afspejle klinisk betydelige forskelle i effektestimaterne.

Bivirkninger (kritisk)
Udover en kvalitativ vurdering af bivirkninger ønskes bivirkninger opgjort som: andel af patienter der ophører behandling pga. bivirkninger samt andel patienter, som oplever en eller flere grad 3-4 bivirkninger. 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.

Andel af patienter der ophører behandling pga. bivirkninger

I sammenligningen anvendes der data for niraparib fra NOVA-studiet samt data for olaparib fra Studie 19 og SOLO2-studiet. Resultater fra NOVA-studiet stammer fra hele studiepopulationen og ikke fra patienter med BRCA1/2-mutation. Resultater fra olaparib-studierne stammer fra patienter med BRCA1/2-mutation.

Tabel 5. Vurdering af klinisk merværdi: Andel af patienter der ophører behandling pga. bivirkninger

	NOVA (niraparib vs. placebo)	Studie 19 (olaparib vs. placebo)	SOLO2 (olaparib vs. placebo)
Absolut effektestimat for den aktive arm sammenlignet med placebo	12,5 %-point	6,8 %-point	8,7 %-point
Relativt effektestimat for den aktive arm sammenlignet med placebo	RR = 6,58 [2,42; 17,89]	RR = 9,24 [0,52; 163,89]*	RR = 5,33 [1,28; 22,8]
Evidensens kvalitet	Moderat		

*Kontinuitet rettelse fra NICE DSU Teknisk support dokument 2 [26].

Mindste klinisk relevante forskel blev defineret som 5 %-point i protokollen [6]. Den absolutte effektforskel i NOVA-studiet var 12,5 %-point til fordel for placebo. Tilsvarende var den 6,8 og 8,7 %-point til fordel for placebo fra henholdsvis Studie 19 og SOLO2-studierne.

Ved den narrative sammenligning bemærker fagudvalget, at resultaterne er forventelige for kliniske studier med placeboarm, samt at konfidensintervallerne er brede, især for Studie 19. Studie 19 adskiller sig fra NOVA- og SOLO2-studierne, da patienterne er tungere behandlet.

Samlet vurderer fagudvalget, at niraparib har **ingen klinisk merværdi** sammenlignet med olaparib til patienter med BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, hvad angår andel af patienter, der ophører behandling pga. bivirkninger med moderat evidenskvalitet.

Andel af patienter, som oplever en eller flere grad 3-4 bivirkninger

I sammenligningen anvendes der data for niraparib fra NOVA-studiet samt data for olaparib fra Studie 19 og SOLO2-studiet. Effektmålet blev opgjort som grad 3-4 uønskede hændelser (adverse events (AE's)). Resultater fra NOVA-studiet stammer fra hele studiepopulationen og ikke fra patienter med BRCA1/2-mutation. Resultater fra olaparib-studierne stammer fra patienter med BRCA1/2-mutation.

Tabel 6. Vurdering af klinisk merværdi: Andel af patienter, som oplever en eller flere grad 3-4 bivirkninger

	NOVA (niraparib vs. placebo)	Studie 19 (olaparib vs. placebo)	SOLO2 (olaparib vs. placebo)
Absolut effektestimat for den aktive arm sammenlignet med placebo	51,2 %	21,4 %	18,2 %
Relativt effektestimat for den aktive arm sammenlignet med placebo	RR = 3,24 [2,46; 4,26]	RR = 2,21 [1,20; 4,05]	RR = 2,00 [1,27; 3,16]
Evidensens kvalitet	Moderat		

Mindste klinisk relevante forskel blev defineret som 10 %-point i protokollen [6]. Den absolutte effektforskel i NOVA-studiet var 51,2 %-point til fordel for placebo. Tilsvarende var den 21,4 og 18,2 %-point til fordel for placebo fra henholdsvis Studie 19 og SOLO2-studierne.

Ved den narrative sammenligning bemærker fagudvalget, at behandling med niraparib er forbundet med flere grad 3-4 bivirkninger sammenlignet med olaparib. Da de fleste grad 3-4 bivirkninger med niraparib og olaparib var hæmatologiske, kan det have haft betydning, at den ældste patient blot var 63 år i SOLO2-studiet, mens den ældste i NOVA-studiet var 83 år. Til trods for stort set ens medianaldre i de to studier (57 versus 56 år i henholdsvis NOVA-studiet og SOLO2-studiet) udgøres den del af patientpopulationen, der er ældre end medianalderen i NOVA-studiet af 58-83-årige og i SOLO2-studiet af 57-63-årige. Dette kan have haft betydning, da knoglemarvsfunktionen aftager med alderen (knoglemarvstoksiciteten stiger).

Samlet vurderer fagudvalget, at niraparib har en **negativ klinisk merværdi** sammenlignet med olaparib til patienter med BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, hvad angår andel af patienter, som oplever en eller flere grad 3-4 bivirkninger med moderat evidenskvalitet.

Kvalitativ gennemgang af bivirkninger

Bivirkningsprofilen for niraparib blev vurderet kvalitativt sammenlignet med olaparib som supplement til de ovenstående kvantitative vurderinger af bivirkninger. Den kvalitative gennemgang stammer fra studiernes safety population.

Behandlingslængde og dosisjusteringer

NOVA-studiet

80 % af patienterne som fik niraparib i NOVA-studiet havde en dosisafbrydelse (alle årsager). 73% af patienterne i undersøgelsen blev dosisreduceret til 200 mg dagligt, der var den mest almindeligt anvendte dosis til niraparibbehandlede patienter i NOVA-studiet [15,19]. Nogle af disse patienter blev efterfølgende reduceret til 100 mg dagligt. Forlængelse af dosisintervallet og/eller dosisreduktionerne skete helt overvejende i den første måned efter behandlingsstart og næsten udelukkende indenfor de første 3 måneder. De hyppigste årsager til forlængelse af dosisintervallet og/eller dosisreduktion var hæmatologiske bivirkninger, heraf specielt trombopeni. 14,7% af patienterne ophørte med niraparib.

Studie 19

Forekomsten af dosisafbrydelser, -reduktioner og -seponeringer på grund af en bivirkning var 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 [21].

SOLO2-studiet

Forekomsten af dosisafbrydelser, -reduktioner og -seponeringer på grund af en bivirkning var henholdsvis 45,1 %, 25,1 % og 10,8 %. Dosisafbrydelserne forekom hyppigst i de første 3 måneder og dosisreduktionerne i de første 3-6 måneder af behandlingen [21]. De hyppigste bivirkninger, som førte til dosisafbrydelse eller dosisreduktion, var anæmi, kvalme og opkastning [21].

Bivirkningstyper

I NOVA-studiet var de hyppigste ikkehæmatologiske uønskede hændelser kvalme (73,6 % vs. 35,2 % i placebo), træthed (59,4 % vs. 41,3 % i placebo), forstoppelse (39,8 % vs. 20,1 % i placebo) og opkastning (34,3 % vs. 20,1 % i placebo). De fleste hændelser var milde til moderate og blev behandlet med dosisjusteringer. 74,1 % af patienterne oplevede en eller flere grad 3-4 uønskede hændelser i niraparibarmen sammenlignet med 22,9 % af patienterne i placeboarmen. De fleste af disse var hæmatologiske hændelser. Frekvensen faldt markant ved dosisreduktion til 200 mg, især for trombocytopeni (fra 33,8 % til 5,1 %) og neutropeni (fra 9,5 % til 5,9 %) med undtagelse for anæmi og hypertension, hvor frekvensen først faldt ved

100 mg dosis (se tabel 41 i niraparib´s EPAR [18]). 1,4 % af patienterne som modtog niraparib udviklede myelodysplastisk syndrom (MDS) eller akut myeloid leukæmi (AML) sammenlignet med 1,1 % af patienterne i placeboarmen. De fleste patienter havde tidligere modtaget adskillige platinbaserede behandlinger. Da opfølgningstiden i NOVA-studiet er relativt kort, kan det på nuværende tidspunkt ikke udelukkes, at der er risiko for at udvikle MDS/AML ved behandling med niraparib. Risk-management-planen for niraparib kræver, at risikoen for udviklingen af MDS/AML karakteriseres yderligere. Tabel 9 giver oversigt over frekvensen af de hyppigste ≥ grad 3-hændelser i NOVA-studiet.

I Studie 19 var de hyppigste ikkehæmatologiske uønskede hændelser kvalme (73 % vs. 32 % i placebo), træthed (54 % vs. 37 % i placebo), opkastning (36 % vs. 8 % i placebo) og diarré (30 % vs. 29 % i placebo). De fleste var af CTCAE grad 1-2. 39,2 % af patienterne oplevede en eller flere grad 3-4 uønskede hændelser i olaparibarmen sammenlignet med 17,7 % af patienterne i placeboarmen. Tabel 9 giver oversigt over frekvensen af de hyppigste ≥ grad 3 hændelser i Studie 19. I SOLO2-studiet var de hyppigste ikkehæmatologiske uønskede hændelser kvalme (73 % vs. 33 % i placebo), træthed (62 % vs. 37 % i placebo), opkastning (35 % vs. 18 % i placebo), mavesmerter (22 % vs. 28 % i placebo) og diarré (30 % vs. 29 % i placebo). De fleste var af CTCAE grad 1-2. 36 % af patienterne oplevede en eller flere grad 3-4 uønskede hændelser i interventionsarmen sammenlignet med 18 % af patienterne i placeboarmen. Tabletadministration giver flere hæmatologiske bivirkninger, især anæmi (se tabel 9), sammenlignet med kapseladministration. Trombocytopeni- og neutropenihændelser ved olaparib var sjældne sammenlignet med niraparib. Ud af de 6.558 patienter, der har modtaget olaparib, har 32 (0,49 %) udviklet MDS/AML. Frekvensen ligger indenfor den rapporterede frekvens (0,15 % til 1,8 %) for udviklingen af sekundær MDS/AML i patienter med kræft i æggestokkene [20]. Ligesom for niraparib har alle olaparibbehandlede patienter, der har udviklet MDS/AML, tidligere modtaget en række platinbaserede behandlinger. Kausaliteten mellem udviklingen af MDS/AML og olaparibbehandling er stadigvæk ukendt. Tabel 9 giver oversigt over frekvensen af de hyppigste ≥ grad 3-hændelser i SOLO2-studiet.

Tabel 7. Hyppigste hændelser ≥ grad 3 samt frekvensen af MDS og AML i NOVA-, Studie 19- og SOLO2-studierne

	NOVA-studiet	**Studie 19**	**SOLO2-studiet**
	Niraparib (n = 367)	Olaparib (n = 136)	Olaparib (n = 195)
Trombocytopeni, n (%)	124 (33,8)	1 (0,7)	0 (0)
Anæmi, n (%)	93 (25,3)	8 (5,9)	38 (19,5)
Leukopeni, n (%)	79 (21,5)	3 (2,2)	3 (1,5)
Neutropeni, n (%)	72 (19,6)	5 (3,7)	5 (2,6)
Hypertension	30 (8,2)	-	-
Træthed	30 (8,2)	11 (8,1)	2 (1)
Mavesmerter	4 (1,1)	3 (2,2)	5 (2,6)
Kvalme	11 (3)	3 (2,2)	5 (2,6)
Opkastning	7 (1,9)	3 (2,2)	5 (2,6)
MDS	5 (1,4)	NA	1 (0,5)
AML	0 (0)	NA	2 (1)

Tabel 8. Samlet vurdering af effektmålet bivirkninger

Effektmål	Vigtighed	Merværdi	Evidenskvalitet
Ophør pga. bivirkninger	Kritisk	Ingen	Moderat
AE's grad 3-4	Kritisk	Negativ	Moderat
Samlet vurdering		**Ingen**	**Moderat**

Antallet af patienter, der udgår af NOVA- og SOLO2- studierne (hvor populationerne ligner hinanden mest), er sammenlignelige (14,9 % versus 10,8 %). Fagudvalget anerkender dog, at niraparib adskiller sig fra olaparib, hvad angår hæmatologiske bivirkninger, som er hyppigere ved en startdosis på 300 mg niraparib end ved en startdosis på 800 mg olaparib (kapsler) eller 600 mg olaparib (tabletter). I NOVA-studiet (og i klinisk praksis) blev/bliver niraparib oftest justeret ned i dosis (se kvalitativ gennemgang af bivirkninger på side 18-19). Det bemærkes ligeledes, at grad 3-4 bivirkninger er sjældent forekomne efter dosisjustering af niraparib.

Fagudvalget bemærker, at på nuværende tidspunkt kan man ikke vurdere, om der er forskel, hvad angår risikoen for udviklingen af MDS/AML mellem niraparib og olaparib.

Generelt vurderer fagudvalget, at bivirkningerne ved niraparib og olaparib er sammenlignelige, acceptable og håndterbare i klinisk praksis, hvis der tages højde for de hyppige dosisjusteringer ved niraparibbehandling. Samlet vurderer fagudvalget, at for det samlede effektmål bivirkninger, har niraparib **ingen klinisk merværdi** sammenlignet med olaparib til patienter med BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, hvad angår bivirkninger med moderat evidenskvalitet.

Livskvalitet (vigtig)

Livskvalitet ønskes opgjort som andel patienter, der ikke viser statistisk signifikant forværring i livskvalitet. I sammenligningen anvendes der data for niraparib fra NOVA-studiet samt data for olaparib fra Studie 19 og SOLO2-studiet. Der foreligger kun data på det ønskede effektmål fra NOVA-studiet og Studie 19.

Tabel 9. Vurdering af klinisk merværdi: Livskvalitet

	NOVA	Studie 19 (olaparib vs. placebo)	SOLO2 (olaparib vs. placebo)
Absolut effektestimat for den aktive arm sammenlignet med placebo	5,6 %-point	2,2 %-point	NA
Evidensens kvalitet	Moderat		

NOVA-studiet

I NOVA-studiet blev livskvalitet vurderet ved brug af FOSI (måleinstrument taget fra FACT-O omhandlende sygdomsrelaterede symptomer), EQ-5D-5-levels (generisk spørgeskema som anvendes til vurdering af helbredsrelateret livskvalitet) og EQ-5D-5L-VAS (EQ-5D-5L visuel analog skala hvor patienterne selvrapporterer deres helbred). Alle instrumenter viste, at der ikke sås en statistisk forværring i livskvalitet i hverken niraparib- eller placeboarmen [14]. Den kumulative frekvens af patienter, der ikke viser statistisk signifikant forværring i livskvalitet målt med FOSI lå på 52,9 % i niraparibarmen og 58,5 % i placeboarmen, som giver en absolut effektforskel på 5,6 %-point.

Studie 19

I Studie 19 blev livskvalitet vurderet ved brug af FACT-O (sygdomsspecifikt spørgeskema, som anvendes til vurdering af helbredsrelateret livskvalitet hos patienter med kræft i æggestokkene), FOSI og trial outcome index (TOI). Alle instrumenter viste, at der ikke sås en statistisk forværring i livskvalitet i hverken olaparib- eller placeboarmen [27]. Andel patienter, der ikke viser statistisk signifikant forværring i livskvalitet målt

med FACT-O, lå på 78,9 % i olaparibarmen og 81,1 % i placeboarmen, som giver en absolut effektforskel på 2,2 %-point.

SOLO2-studiet
I SOLO2-studiet blev livskvalitet vurderet ved brug af FACT-O og TOI. Begge instrumenter viste, at der ikke sås en statistisk forværring i livskvalitet i hverken olaparib- eller placeboarmen [11,16]. Det har ikke været muligt at få opgjort andel patienter, der ikke viser statistisk signifikant forværring i livskvalitet. Supplerende livskvalitetsdata fra SOLO2-studiet forventes at blive publiceret på et senere tidspunkt.

Mindste klinisk relevante forskel blev defineret som 10 %-point i protokollen [6]. Samlet vurderer fagudvalget, at niraparib har en **ingen klinisk merværdi** sammenlignet med olaparib til patienter med BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, hvad angår livskvalitet med moderat evidenskvalitet. Ved vurderingen har fagudvalget lagt vægt på, at to studier viser, at der ikke ses en statistisk signifikant forværring i livskvalitet.

6.1.3 Evidensens kvalitet

Evidensens kvalitet for den kliniske merværdi, som niraparib tilbyder sammenlignet med olaparib til patienter med BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, æggelederne eller primær kræft i bughinden, og respons på platinbaseret kemoterapi er samlet set vurderet som værende **lav**. Overvejelser vedrørende evidensens kvalitet kan ses i bilag 2.

Der er udarbejdet én GRADE-profil for det kliniske spørgsmål. Hvor evidensen er nedgraderet, er dette foretaget på baggrund af indirekte evidens (der er ikke grundlag for en indirekte formel sammenligning) og unøjagtighed (median OS ikke opnået fra NOVA- og SOLO2-studierne og antagelsen om proportionelle hazarder holder ikke (PFS)).

6.1.4 Konklusion for klinisk spørgsmål 1

Fagudvalget vurderer, at niraparib til patienter med BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, æggelederne eller primær kræft i bughinden, og respons på platinbaseret kemoterapi giver en **ingen klinisk merværdi** sammenlignet med olaparib (meget lav evidenskvalitet).

Nedenstående tabel viser en oversigt med konklusioner vedrørende klinisk merværdi af niraparib pr. effektmål til patienter med BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC 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	Ikkedokumenterbar	Vurderes ikke
PFS	Kritisk	Ingen	Lav
Bivirkninger: - Ophør pga. bivirkninger - AE's grad 3-4	Kritisk	Ingen	Moderat
Livskvalitet	Vigtig	Ingen	Moderat
Samlet vurdering		**Ingen**	**Lav**

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

- to ud af de tre kritiske effektmål er blevet vurderet som havende ingen klinisk merværdi.
- det ikke på nuværende tidspunkt vides, om den dokumenterede PFS-gevinst for niraparib/olaparib vs. placebo fra studierne vil resultere i forskellige OS-gevinster mellem niraparib og olaparib.
- de dokumenterede bivirkninger forbundet med niraparibbehandling ikke afspejler den kliniske virkelighed, hvor dosisjustering er hyppig. Når der tages højde for dosisjustering, anser fagudvalget niraparib og olaparib som sammenlignelige hvad angår sværhedsgraden og håndterbarheden af bivirkninger.

6.2 Konklusion klinisk spørgsmål 2

Hvilken klinisk merværdi tilbyder vedligeholdelsesbehandling med niraparib sammenlignet med bevacizumab hos patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC og respons på platinbaseret kemoterapi?

På baggrund af de forskelle fremhævet i afsnit 5 vurderer fagudvalget, at hverken en formel indirekte eller narrativ sammenligning er mulig.

Samlet vurderer fagudvalget, at niraparib til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, æggelederne eller primær kræft i bughinden, og respons på platinbaseret kemoterapi giver en **ikkedokumenterbar klinisk merværdi** (evidenskvalitet vurderes ikke) sammenlignet med bevacizumab.

6.3 Konklusion klinisk spørgsmål 3

Hvilken klinisk merværdi tilbyder vedligeholdelsesbehandling med niraparib sammenlignet med placebo hos patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC og respons på platinbaseret kemoterapi?

Fagudvalget vurderer, at niraparib til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, æggelederne eller primær kræft i bughinden, og respons på platinbaseret kemoterapi giver en **lille klinisk merværdi** (lav evidenskvalitet) sammenlignet med placebo.

6.3.1 Gennemgang af studier

Karakteristika

I sammenligningen af niraparib med placebo indgår kohortedata for patienter uden BRCA1/2-mutation fra det identificerede studie, NOVA-studiet [7,14].

NOVA [7,18]

Jævnfør tilsvarende beskrivelse for klinisk spørgsmål 1 (afsnit 6.1.1).

Population

Relevante baselinekarakteristika for patienter uden BRCA1/2-mutation i interventions- og placeboarmen fra NOVA-studiet fremgår i tabel 11.

Tabel 11. Baselinekarakteristika for patienter uden BRCA1/2-mutation i interventions- og placeboarmen i NOVA-studiet.

	Niraparib (n = 234)	**Placebo (n = 116)**
Median alder, år (range)	63 (33-84)	61 (34-82)
Race, n (%)		
Kaukasiske	201 (85,9)	101 (87,1)
Afrikanske	4 (1,7)	1 (0,9)
Asiatiske	10 (4,3)	4 (3,4)
Andet	0 (0,0)	0 (0)
Ukendt	19 (8,1)	10 (8,6)
ECOG PS, n (%)		
0	160 (68,4)	78 (67,2)
1	74 (31,6)	38 (32,8)
Tumortype, n (%)		
Æggestokke	192 (82,1)	96 (82,8)
Bughinden	24 (10,3)	8 (6,9)
Æggeleder	18 (7,7)	11 (9,5)
Andet/ukendt	0 (0)	
Histologisk subtype, n (%)		
Serøs	215 (96,4)	110 (99,1)
Endometrioid	1 (0,4)	1 (0,9)
Mucinøs	0 (0)	0 (0)
Andet	11 (4,9)	3 (2,7)
Ukendt	0 (0)	
Kræftstadie ved diagnose, n (%)		
I eller II	22 (9,4)	5 (4,3)
III	173 (73,9)	86 (74,1)
IV	38 (16,2)	24 (20,7)
Tid til progression efter næstsidste platinbaserede kemoterapi, n (%)		
6 til < 12 måneder	90 (38,5)	44 (37,9)
≥ 12 måneder	144 (61,5)	72 (62,1)
Respons på sidste platinbaserede kemoterapi, n (%)		
Komplet	117 (50,0)	60 (51,7)
Partiel	117 (50,0)	56 (48,3)
Tidligere anvendelse af bevacizumab, n (%)		
Ja	62 (26,5)	30 (25,9)
Antal linjer platinbaseret kemoterapi, n (%)		
1	0 (0)	0
2	174 (74,4)	87 (75,0)
> 2	62 (25,6)	28 (24,1)
Ukendt	0 (0)	1 (0,9)

Der var ikke nogen relevante forskelle i baselinekarakteristika mellem placebo- og interventionsarmen for patienter uden BRCA1/2-mutation. Data skønnes at kunne overføres på en tilsvarende dansk patientpopulation. Stort set alle patienterne i studiet har high-grade serøst karcinom i æggestokkene, som svarer til den population, der blev defineret i det kliniske spørgsmål i protokollen. Jf. afsnit 5 så har ca. 13 % af patienterne i kohorten en somatisk BRCA1/2-mutation. Fagudvalget bemærker, at det i princippet kan medføre en risiko for overestimering af effekten af PFS for hele kohorten, da patienter med somatisk BRCA1/2-mutation har en sammenlignelig effekt af behandling med PARP-hæmmere som patienter med arvelig BRCA1/2-mutation.

6.3.2 Resultater og vurdering

Resultater og vurdering af de effektmål, som fagudvalget har præspecificeret som henholdsvis kritiske og vigtige, følger nedenfor. Sammenligningen af niraparib med placebo baseres på en direkte sammenligning fra NOVA-studiet. Den samlede kliniske merværdi af niraparib baseres på længst mulig opfølgningstid.

Samlet overlevelse (OS) (kritisk)

OS ønskes opgjort som median OS. I analysen anvendes der kohortedata for patienter uden BRCA1/2-mutation fra NOVA-studiet. Median OS er ikke opnået i NOVA-studiet efter median opfølgningstid på 17,5 måneder [18].

Forskel i absolutte værdier kan ikke opgøres og dermed ikke sammenlignes med den mindste klinisk relevante forskel. 44 ud af 234 patienter (19 %) døde i niraparibarmen sammenlignet med 27 ud af 116 (23 %) i placeboarmen. Det giver en foreløbig HR på 0,74 [0,45;1,20] (p = 0,22) [18]. De relative effektestimater indikerer, at på nuværende tidspunkt har niraparib ingen klinisk merværdi sammenlignet med placebo, hvad angår effektmålet median OS, da konfidensintervallets øvre grænse er > 1,0. Fagudvalget understreger dog, at OS-data stadig ikke er modne på nuværende tidspunkt, så den opgjorte HR afspejler præliminære data.

Samlet vurderer fagudvalget, at niraparib har **ikkedokumenterbar klinisk merværdi** på nuværende tidspunkt sammenlignet med placebo til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, hvad angår median OS.

Progressionsfri overlevelse (PFS) (kritisk)

PFS ønskes opgjort som median PFS. I analysen anvendes der kohortedata for patienter uden BRCA1/2-mutation fra NOVA-studiet.

Tabel 12. Vurdering af klinisk merværdi: median PFS

	Forhåndsdefineret grundlag for vurdering	Resultater
Absolutte forskelle	3 måneder	5,4 måneder
Evidensens kvalitet	Lav	

Da de relative værdier for PFS ikke er konstante over tid (jf. afsnit 5, klinisk spørgsmål 3), har fagudvalget lagt vægt på de absolutte effektestimater ved vurderingen af den kliniske merværdi. Median PFS for niraparib er 9,3 måneder [7,2;11,2] sammenlignet med 3,9 måneder [3,7;5,5] for placebo. Forskellen på 5,4 måneder til fordel for niraparib overstiger dermed den prædefinerede mindste klinisk relevante forskel på 3 måneder.

Samlet vurderer fagudvalget, at niraparib har en **vigtig klinisk merværdi** sammenlignet med placebo til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, hvad angår median PFS med lav evidenskvalitet. I vurderingen har fagudvalget vægtet studiets opgjorte absolutte effektestimat, der er knap to gange større end den mindste klinisk relevante forskel.

Bivirkninger (kritisk)
Udover en kvalitativ vurdering af bivirkninger ønskes bivirkninger opgjort som: andel af patienter der ophører behandling pga. bivirkninger samt andel patienter, som oplever en eller flere grad 3-4 bivirkninger. 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.

Andel af patienter der ophører behandling pga. bivirkninger
I analysen anvendes der data for niraparib fra NOVA-studiet. Resultaterne stammer fra hele studiepopulationen og ikke fra patienter uden BRCA1/2-mutation.

Tabel 13. Vurdering af klinisk merværdi: Andel af patienter der ophører behandling pga. bivirkninger

	Forhåndsdefineret grundlag for vurdering		Resultater
Absolutte forskelle	5 %-point		12,5 %-point
Relative forskelle	Stor merværdi		
	Vigtig merværdi		
	Lille merværdi		
	Ingen merværdi		
	Negativ merværdi	Nedre konfidensgrænse > 1,00	RR = 6,58 [2,42; 17,89]
Evidensens kvalitet	Lav		

14,7 % af patienter, som modtog niraparib, ophørte behandlingen pga. bivirkninger sammenlignet med 2,2 % af patienterne i placeboarmen. Forskellen på 12,5 %-point overstiger dermed den mindste klinisk relevante forskel, men til fordel for placebo. Fagudvalget bemærker, at dette er forventeligt i sammenligningen af en aktiv behandling med placebo. Den relative forskel på 6,58 [2,42;17,89] kategoriseres som negativ klinisk merværdi, da både den øvre samt nedre grænse på konfidensintervallet ligger over 1.

Samlet vurderer fagudvalget, at niraparib har en **negativ klinisk merværdi** sammenlignet med placebo til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, hvad angår andel af patienter, der ophører behandling pga. bivirkninger med lav evidenskvalitet.

Andel af patienter, som oplever en eller flere grad 3-4 bivirkninger
I analysen anvendes der data for niraparib fra NOVA-studiet. Resultaterne stammer fra hele studiepopulationen og ikke fra patienter uden BRCA1/2-mutation.

Tabel 14. Vurdering af klinisk merværdi: Andel af patienter, som oplever en eller flere grad 3-4 bivirkninger

	Forhåndsdefineret grundlag for vurdering		Resultater
Absolutte forskelle	10 %-point		51,2 %-point
Relative forskelle	Stor merværdi		
	Vigtig merværdi		
	Lille merværdi		
	Ingen merværdi		
	Negativ merværdi	Nedre konfidensgrænse > 1,00	RR = 3,24 [2,46; 4,26]
Evidensens kvalitet	Lav		

74,1 % af patienter, som modtog niraparib, oplevede grad 3-4 bivirkninger sammenlignet med 22,9 % af patienterne i placeboarmen. Forskellen på 51,2 %-point overstiger dermed den mindste klinisk relevante forskel, men til fordel for placebo. Fagudvalget bemærker, at dette er forventeligt i sammenligningen af en

aktiv behandling med placebo. Den relative forskel på 3,24 [2,46; 4,26] kategoriseres som negativ klinisk merværdi, da både den øvre samt nedre grænse på konfidensintervallet ligger over 1.

Samlet vurderer fagudvalget, at niraparib har en **negativ klinisk merværdi** sammenlignet med placebo til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, hvad angår andel af patienter, som oplever en eller flere grad 3-4 bivirkninger med lav evidenskvalitet.

Kvalitativ gennemgang af bivirkninger
Der henvises til afsnit 6.1.2.

Tabel 15. Samlet vurdering af effektmålet bivirkninger

Effektmål	**Vigtighed**	**Merværdi**	**Evidenskvalitet**
Ophør pga. bivirkninger	Kritisk	Negativ	Lav
AE's grad 3-4	Kritisk	Negativ	Lav
Samlet vurdering		**Negativ**	**Lav**

Fagudvalget konstaterer, at niraparib giver mange hæmatologiske hændelser ved 300 mg dosis. I NOVA-studiet (og i klinisk praksis) blev/bliver niraparib oftest justeret ned i dosis (se kvalitativ gennemgang af bivirkninger på side 18-19). Det bemærkes ligeledes, at grad 3-4 bivirkninger er sjældent forekomne efter dosisjustering af niraparib.

Hvad angår risikoen for udviklingen af MDS/AML er der aktuelt ikke signifikant øget risiko for udvikling af disse bivirkninger sammenlignet med placebo, men udviklingen bør følges fremover.

Generelt vurderer fagudvalget, at bivirkningerne ved niraparib er acceptable og håndterbare i klinisk praksis. Samlet vurderer fagudvalget, at for det samlede effektmål bivirkninger har niraparib **negativ klinisk merværdi** sammenlignet med placebo til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, med lav evidenskvalitet.

Fagudvalget fremhæver, at niraparib udskyder tiden til næste kemoterapi i forhold til placebo med 4,6 måneder (median 11,8 versus 7,2 måneder, HR, 0,55; 95% CI, 0,41-0,72; p < 0,001). Det betyder for det samlede effektmål bivirkninger, at niraparib har negativ klinisk merværdi sammenlignet med placebo så længe patienterne i placeboarmen ikke har behov for yderligere kemoterapi, men har værdi sammenlignet med placebo i de (mediant) ekstra 4,6 måneder som niraparibbehandlede patienter undgår bivirkninger fra kemoterapi. Endvidere vil flere i niraparibarmen være platinsensitive på tidspunktet for progression, hvilket har betydning for chancen for respons på efterfølgende kemoterapi (chancen for respons er størst hos platinsensitive patienter). Det understreges, at der er uenighed i fagudvalget hvad angår denne bemærkning men at den ikke har påvirket den samlede vurdering af det kliniske spørgsmål.

Livskvalitet (vigtig)
Livskvalitet ønskes opgjort som andel patienter, der ikke viser statistisk signifikant forværring i livskvalitet. I analysen anvendes der livskvalitetsdata fra FOSI-instrumentet fra NOVA-studiet.

Tabel 16. Vurdering af klinisk merværdi: livskvalitet

	Forhåndsdefineret grundlag for vurdering	Resultater
Absolutte forskelle	10 %-point	3,0 %-point
Evidensens kvalitet	Lav	

Den kumulative frekvens af patienter, der ikke viser statistisk signifikant forværring i livskvalitet målt med FOSI lå på 50,4 % i niraparibarmen sammenlignet med 53,4 % i placeboarmen. Den absolutte effektforskel

på 3,0 %-point til fordel for placebo ligger dermed under den mindste klinisk relevante forskel på 10 %-point.

Samlet vurderer fagudvalget, at niraparib har **ingen klinisk merværdi** sammenlignet med placebo til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, hvad angår livskvalitet med lav evidenskvalitet.

6.3.3 Evidensens kvalitet

Evidensens kvalitet for den kliniske merværdi, som niraparib tilbyder sammenlignet med placebo til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, æggelederne eller primær kræft i bughinden, og respons på platinbaseret kemoterapi, er samlet set vurderet som værende **lav**. Overvejelser vedrørende evidensens kvalitet kan ses i bilag 1.

Der er udarbejdet én GRADE-profil for det kliniske spørgsmål. Hvor evidensen er nedgraderet, er dette foretaget på baggrund af inkonsistens (der foreligger kun ét studie) og unøjagtighed (median OS ikke opnået og bredt konfidensinterval på HR (OS), brede konfidensintervaller (bivirkninger), antagelsen om proportionelle hazarder holder ikke (PFS) og manglende konfidensinterval (livskvalitet)).

6.3.4 Konklusion for klinisk spørgsmål 3

Fagudvalget vurderer, at niraparib til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, æggelederne eller primær kræft i bughinden, og respons på platinbaseret kemoterapi giver en **lille klinisk merværdi** sammenlignet med placebo (lav evidenskvalitet).

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

Tabel 17. Oversigt over merværdi og evidenskvalitet for kritiske og vigtige effektmål

Effektmål	**Vigtighed**	**Merværdi**	**Evidenskvalitet**
OS	Kritisk	Ikkedokumenterbar	Vurderes ikke
PFS	Kritisk	Vigtig	Lav
Bivirkninger: - Ophør pga. bivirkninger - AE's grad 3-4	Kritisk	Negativ	Lav
Livskvalitet	Vigtig	Ingen	Lav
Samlet vurdering		**Lille**	**Lav**

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

- det kritiske effektmål PFS kategoriseres som havende vigtig klinisk merværdi.
- det ikke på nuværende tidspunkt vides, om den dokumenterede PFS-gevinst fra studiet vil resultere i OS-gevinst.
- niraparibbehandling er forbundet med bivirkninger sammenlignet med placebo, som trækker den samlede kliniske merværdi ned. Fagudvalget understreger, at de dokumenterede bivirkninger ikke afspejler den kliniske virkelighed, hvor dosisjustering er hyppig. Bivirkningerne er derfor håndterbare.

7 Andre overvejelser

Fagudvalget er overbevist om, at den doseringsvejledning, som p.t. behandles af EMA og tager hensyn til patientens legemsvægt og startværdi for trombocyttal, vil reducere antallet og sværhedsgraden af bivirkninger. Den nye doseringsvejledning er i tråd med tilgængelige data vurderet af fagudvalget og anvendes allerede i dag i de senest initierede undersøgelser. Fagudvalget opfordrer alligevel Medicinrådet til at følge overlevelsesdata for den nye dosering (der formentlig vedtages af EMA i 2. kvartal af 2019).

8 Fagudvalgets vurdering af samlet klinisk merværdi og samlet evidensniveau

Fagudvalget vurderer, at niraparib til patienter med BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, æggelederne eller primær kræft i bughinden, og respons på platinbaseret kemoterapi giver:

- **ingen klinisk merværdi** sammenlignet med olaparib. Evidensens kvalitet vurderes at være lav.

Fagudvalget vurderer, at niraparib til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, æggelederne eller primær kræft i bughinden, og respons på platinbaseret kemoterapi giver:

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

Fagudvalget vurderer, at niraparib til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, æggelederne eller primær kræft i bughinden, og respons på platinbaseret kemoterapi giver:

- **lille klinisk merværdi** sammenlignet med placebo. Evidensens kvalitet vurderes at være lav.

9 Rådets vurdering af samlet klinisk merværdi og samlet evidensniveau

Rådet vurderer, at niraparib til patienter med BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, æggelederne eller primær kræft i bughinden, og respons på platinbaseret kemoterapi giver:

- **ingen klinisk merværdi** sammenlignet med olaparib. Evidensens kvalitet vurderes at være lav.

Rådet vurderer, at niraparib til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, æggelederne eller primær kræft i bughinden, og respons på platinbaseret kemoterapi giver:

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

Rådet vurderer, at niraparib til patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC i æggestokkene, æggelederne eller primær kræft i bughinden, og respons på platinbaseret kemoterapi giver:

- **lille klinisk merværdi** sammenlignet med placebo. Evidensens kvalitet vurderes at være lav.

10 Relation til eksisterende behandlingsvejledning

Der findes ingen RADS-behandlingsvejledning på området.

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12 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
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Birthe Lemley Patient/patientrepræsentant	Danske Patienter
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13 Bilag 1: GRADE-evidensprofiler

13.1 Cochrane Risk of Bias

Risk of bias – NOVA-studiet	Vurdering	Begrundelse
Random sequence generation (selection bias)	• Lav risiko for bias	Randomisering var udført via et interaktivt web-baseret system. Patienter blev randomiseret indenfor to uafhængige kohorter og stratificeret efter: • tid til progression efter deres næstsidste platinbaseret kemoterapi • bevacizumab anvendelse i kombination med deres næstsidste eller sidste platinbaserede kemoterapi • respons ved deres sidste platinbaserede kemoterapi. Patienter blev randomiseret 2:1 til niraparib eller placebo indenfor hver kohorte. Ingen cross-over var tilladt.
Allocation concealment (selection bias)	• Lav risiko for bias	
Blinding of participants and personnel (performance bias)	• Lav risiko for bias	Både patienter og personale var blindede.
Blinding of outcome assessment (detection bias)	• Lav risiko for bias	Study management team og uafhængige bedømmere af PFS var blindede.
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	• Lav risiko for bias	

Risk of bias – Studie 19	Vurdering	Begrundelse
Random sequence generation (selection bias)	• Lav risiko for bias	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 BRCA-mutationsstatus blev udført post-hoc.
Allocation concealment (selection bias)	• Lav risiko for bias	

Blinding of participants and personnel (performance bias)	• Lav risiko for bias	Både patienter og personale var blindede.
Blinding of outcome assessment (detection bias)	• Lav risiko for bias	Behandlinger blev maskeret for de, der vurderede effektmål (site investigator) og udførte analyser ved brug af unikke identifiers genereret ved randomisering.
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	• Lav risiko for bias	Opgørelse af data efter BRCA-mutationsstatus er en prædiktive og prognostisk faktor. Derfor nedgraderes der ikke for risk of bias på trods af, at denne analyse blev lavet post hoc.

Risk of bias – SOLO2-studiet	**Vurdering**	**Begrundelse**
Random sequence generation (selection bias)	• Lav risiko for bias	Randomisering var udført via et interaktivt voice webbaseret responssystem med et computergenereret randomiseringsskema. Patienter blev stratificeret efter: • tid til progression efter deres næstsidste platinbaserede kemoterapi • respons ved deres sidste platinbaserede kemoterapi. Patienter blev randomiseret 2:1 til olaparib- eller placeboarmen. Ingen cross-over var tilladt.
Allocation concealment (selection bias)	• Lav risiko for bias	
Blinding of participants and personnel (performance bias)	• Lav risiko for bias	Både patienter og personale var blindede.
Blinding of outcome assessment (detection bias)	• Lav risiko for bias	Behandlinger blev maskeret for de, der vurderede effektmål (site investigator) og udførte analyser ved brug af unikke behandlingskoder genereret ved randomisering.
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	• Lav risiko for bias	

13.2 GRADE-evaluering af evidenskvaliteten til vurdering af den kliniske merværdi af niraparib

Hvilken klinisk merværdi tilbyder vedligeholdelsesbehandling med niraparib sammenlignet med olaparib hos patienter med BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC og respons på platinbaseret kemoterapi?

Certainty assessment							Impact	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Median samlet overlevelse (OS) - not reported									
-	-	-	-	-	-	-	Narrativ sammenligning	-	CRITICAL
Median progressionsfri overlevelse (PFS)									
3	randomised trials	not serious	not serious	serious [a]	serious [b]	none	Narrativ sammenligning	⊕⊕◯◯ LOW	CRITICAL
Ophør pga. bivirkninger									
3	randomised trials	not serious	not serious	serious [a]	not serious	none	Narrativ sammenligning	⊕⊕⊕◯ MODERATE	CRITICAL
Bivirkninger grad 3-4									
3	randomised trials	not serious	not serious	serious [a]	not serious	none	Narrativ sammenligning	⊕⊕⊕◯ MODERATE	CRITICAL
Livskvalitet									

Certainty assessment							Impact	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
3	randomised trials	not serious	not serious	serious [a]	not serious	none	Narrativ sammenligning	⨁⨁⨁◯ MODERATE	IMPORTANT

CI: konfidensinterval; **HR:** Hazard ratio; **RR:** Risk ratio

Forklaringer

a. Der nedgraderes for indirekte evidens da der ikke er grundlag for at lave en formel indirekte sammenligning.
b. Antagelsen om proportionelle hazarder holder ikke.

Hvilken klinisk merværdi tilbyder vedligeholdelsesbehandling med niraparib sammenlignet med placebo hos patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC og respons på platinbaseret kemoterapi?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**niraparib**	**placebo**	**Relative (95 % CI)**	**Absolute (95 % CI)**		
Median samlet overlevelse (OS) - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Median progressionsfri overlevelse (PFS)												
1	randomised trials	not serious	serious [a]	not serious	serious [b]	none	9,3	3,9	-	forskel **5,4 måneder higher** (0 to 0)	⊕⊕◯◯ LOW	CRITICAL
Ophør pga. bivirkninger												
1	randomised trials	not serious	serious [a]	not serious	serious [c]	none	54/367 (14,7 %)	4/179 (2,2 %)	**RR 6,58** (2,42 to 17,89)	**125 more per 1.000** (from 32 more to 377 more)	⊕⊕◯◯ LOW	CRITICAL
Bivirkninger grad 3-4												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**niraparib**	**placebo**	**Relative (95 % CI)**	**Absolute (95 % CI)**		
1	randomised trials	not serious	serious [a]	not serious	serious [c]	none	272/367 (74,1 %)	41/179 (22,9 %)	**RR 3,24** (2,46 to 4,26)	**513 more per 1.000** (from 334 more to 747 more)	⨁⨁◯◯ LOW	CRITICAL
Livskvalitet												
1	randomised trials	not serious	serious [a]	not serious	serious [d]	none	50,4	53,4	-	forskel **3 higher** (0 to 0)	⨁⨁◯◯ LOW	IMPORTANT

CI: konfidensinterval; **HR:** Hazard ratio; **RR:** Risk ratio

Forklaringer

a. Data kommer fra ét studie.
b. Antagelsen om proportionelle hazarder holder ikke.
c. Bredt konfidensinterval.
d. Intet konfidensinterval,

Application for the assessment of clinically added value of Zejula for cancer of the ovaries fallopian tubes or primary peritoneal cancer

Contents

General information

This is a template of the application form to be submitted to the Danish Medicines Council (*Medicinrådet*) for the assessment of the clinically added value of new medicines and new indications. The purpose of the form is to provide an overview of the basic information, literature search, study, and analysis results that will serve as the basis for the assessment. It indicates the minimum required information needed for the assessment.

The assessment of the pharmaceutical will be based on the outcomes defined in the protocol. Results for all critical and important outcomes (*kritiske og vigtige effektmål*) must be addressed in the application. The results of less important outcomes (*mindre vigtige effektmål*) do not need to be addressed. For all the data provided, a reference is mandatory.

During the completion of this form, elements should not be removed from the document. All sections should be filled in (if a section is not applicable, state "not applicable" and explain why). Table examples are provided in the form. Layout may deviate from the template to accommodate data; however, all requested information must be stated. We accept submission of appendices. Audits of data analyses and literature searches will occur.

In order to minimize any translation errors between the application and the assessment report, submission in the Danish language is preferred.

If confidential data are submitted, highlight the data in yellow and write the expected publication date in a comment. If confidential data are submitted in an appendix, the document must in addition be watermarked as "confidential."

The application will be published simultaneously with the final assessment and recommendation report on the Danish Medicines Council's web page (www.medicinraadet.dk). Any data that will be considered in the assessment report will be published with the final application.

Checklist before submitting the application form:

- Are all relevant fields in the application form filled in?
- Is the application explicit and self-explanatory?
- Does the application meet the general requirements defined in the *Process and Methods Guide* of the Danish Medicines Council for new medicines and new indications?
- Does the application meet the specific requirements in the protocol?
- Are deviation(s) from the protocol (if any) described?
- Are deviation(s) from the protocol (if any) justified?

1 Basic information

Table 1 Contact information

Name	Cathy Jarrold
Title	Market Access Director UK, Ireland and Nordics
Area of responsibility	Market Access Director UK, Ireland and Nordics
Phone	+44 7435 262 271
E-mail	cjarrold@tesarobio.com

Table 2 Overview of the pharmaceutical

Proprietary name	Zejula
Generic name	Niraparib
Marketing authorization holder in Denmark	Tesaro UK Limited
ATC code	L01XX54
Pharmacotherapeutic group	PARP 1/2 inhibitor, other antineoplastic agents
Active substance(s)	Niraparib
Pharmaceutical form(s)	Hard capsules
Mechanism of action	Niraparib is a potent and selective PARP-1 and -2 inhibitor, which selectively kills tumour cells in vitro and in mouse xenograft models. PARP-1 and -2 are zinc-finger DNA-binding enzymes that play a crucial role in DNA repair by the process of base excision repair (BER). PARP detects single strand DNA damage and converts it into intracellular signals that activate the BER pathway. Inhibiting PARP enzymes and BER can cause an accumulation of DNA damage, which requires repair by other processes.[1,2] DNA damage repair deficiencies are common in patients with platinum-sensitive OC, and therefore, these patients are more sensitive to the effects of PARP inhibition. There is a similarity of effect between platinum-based chemotherapy agents and PARP inhibitors, whereby DNA damage is induced beyond the capacity of the tumour cells to recover and survive.[3] Clinical studies have shown that PARP inhibitors have antitumour activity in patients with certain types of cancer, including, but not limited to those with loss of function *BRCA* mutations.[4–7] Niraparib selectively inhibits PARP-1 and -2 enzymes, with minimal off-target activity.[8] In pre-clinical studies, niraparib concentrates in the tumour, delivering selective, greater than 90% durable PARP inhibition, and a persistent anti-tumour effect.[9,10] Niraparib concentrates in the tumour relative to plasma due to moderate binding to plasma proteins and high permeability.[9] Drug resistance to some anti-cancer treatments can be caused by increased expression of membrane drug transporters

	(including p-glycoprotein, or P-gp) and evidence suggests that this is particularly influential in OC when treated with paclitaxel and PARP inhibitors.[11] The potential effect of P-gp on niraparib, as a substrate, is anticipated to be limited, due in part to the high biomembrane permeability of the compound.[10]
Dosage regimen	Niraparib is taken as monotherapy. The dose of niraparib is three 100 mg capsules taken orally once daily, equivalent to a total daily dose of 300 mg. With treatment continued until disease progression. For patients less than 58kg a starting dose of 200mg once daily can be considered. The most frequently used dose in the phase III ENGOT-OVA16/NOVA study was 200mg once daily.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Zejula is indicated for maintenance treatment of adult patients with platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response [CR] or partial response [PR]) to platinum-based chemotherapy.
Other approved therapeutic indications	No
Will dispensing be restricted to hospitals?	Yes, Zejula is an oral treatment, but is expected to be dispensed in hospitals.
Combination therapy and/or co-medication	No
Packaging – types, sizes/number of units, and concentrations	Niraparib is formulated as a 100 mg immediate-release hard gelatin capsule, with two available package sizes containing 56 or 84 capsules.
Orphan drug designation	Yes

2 Abbreviations

Table 3 Abbreviations list

AE	Adverse event
AML	Acute myeloid leukaemia
BMI	Body mass index
BRCA	Breast cancer susceptibility gene
BV	Bevacizumab
CENTRAL	Cochrane Central Register of Controlled Trials
CFI	Chemotherapy-free interval
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
DOR	Duration of response
ECG	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
FACT-O	Functional Assessment of Cancer Therapy-Ovarian Cancer
FOSI	Functional Assessment of Cancer Therapy–Ovarian Symptom Index
g*BRCA*mut	Germline breast cancer susceptibility gene mutation
GC	Gemcitabine and carboplatin
GI	Gastro intestinal
HGSC	High grade serous carcinoma
HR	Hazard ratio
HRQoL	Health-related quality-of-life
HRD	Homologous recombination DNA repair deficiency
HTA	Health Technology Assessment
IRC	Independent review committee
ITC	Indirect treatment comparison
ITT	Intention to treat
IQR	Inter-quartile range
KM	Kaplan Meier
MDS	Myelodysplastic syndrome
NE	Not estimated
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NNH	Number needed to harm
NNT	Number needed to treat
NR	Not reported

OCEANS	Ovarian Cancer Study Comparing Efficacy and Safety of Chemotherapy and Anti-Angiogenic Therapy in Platinum-Sensitive Recurrent Disease
ORR	Overall response rate
OS	Overall survival
PARP	Poly-ADP ribose polymerase
PD	Progressed disease
PFS	Time to objective disease progression/progression-free survival
PFS2	Time to second objective disease progression
PL	Placebo
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RR	Relative risk
SD	Standard deviation
SLR	Systematic literature review
TOI	Trial outcome index
ULN	Upper limit of normal
TFST	Time to first subsequent treatment
TSST	Time to second subsequent treatment
TWiST	Time without symptoms and toxicity
WHO ICTRP	World Health Organisation International Clinical Trials Registry Platform

3 Summary

The purpose of this application is to answer the clinical questions posed by the DMC for the assessment of niraparib as a potential standard maintenance treatment indicated for adult patients with platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response [CR] or partial response [PR]) to platinum-based chemotherapy compared to Danish standard therapy.

A systematic literature review (SLR) identified five randomized controlled trials (RCTs) (ENGOT-OV16/NOVA, GOG-0213, OCEANS, Study 19, and SOLO2/ENGOT-OV16) that were considered relevant to the clinical questions posed. Niraparib, olaparib and placebo are compared in the clinical question responses herein. A comparison with bevacizumab was not possible due to: 1) a lack of *BRCA*-stratification in the bevacizumab trials; 2) bevacizumab's positioning in the treatment pathway differs; its use is initiated in combination with chemotherapy and then continued as a maintenance therapy (as opposed to purely maintenance therapy); and 3) differences in the time period for which progression-free (PFS) was collected; PFS was measured at the start of chemotherapy for bevacizumab as opposed to after chemotherapy in the ENGOT-OV16/NOVA study.

This assessment summarises the outcome objectives outlined in the DMC protocol and, where appropriate, comparative analyses between studies. Overall survival (OS) data were immature for ENGOT-OV16/NOVA and SOLO-2, so could not be compared. In ENGOT-OV16/NOVA, niraparib prolonged PFS compared to placebo in both patient cohorts, with statistical significance in the germline breast cancer susceptibility gene mutation (g*BRCA*mut) cohort with a median PFS of 21.0 months for niraparib versus 5.5 months for placebo (HR, 0.27; 95% CI, 0.17-0.41; p<0.001) and in the non-g*BRCA*mut cohort with a median of 9.3 months for niraparib versus 3.9 months for placebo (HR, 0.45; 95% CI, 0.34-0.61; p<0.001). A naïve side by side comparison of PFS in the g*BRCA*mut cohort demonstrates that niraparib extends PFS by 15.5 months versus placebo, in comparison to 6.9 months or 13.6 months for olaparib versus placebo, from Study 19 and SOLO-2, respectively. This naïve side-by-side comparison is the most appropriate approach due to the study design of Study 19, SOLO-2 and ENGOT-OV16/NOVA such that there are several issues in conducting an indirect treatment comparison (ITC).

ENGOT-OV16/NOVA demonstrated that niraparib is well-tolerated, with a low discontinuation rate due to adverse events (AEs) (14.7% vs. 2.2% for placebo), due to the effective management of most AEs by dose reductions or treatment interruptions. The most common grade 3/4 AEs included thrombocytopenia (33.8% niraparib vs. 0.6% placebo) and anaemia (25.3% niraparib vs. 0% placebo). However, most events occurred in the first three treatment cycles (12 weeks), and the frequency of these events dropped significantly over time following dose modifications. An AE ITC is not presented since this analysis is not relevant to the anticipated label change of a lower starting dose for niraparib. This dose modification has been shown to avoid significant haematological toxicity and is expected to significantly lower discontinuation.

HRQoL measured by EQ-5D-5L and FOSI, was similar for both niraparib and placebo and pre-treatment levels were maintained throughout the treatment period in ENGOT-OV16/NOVA.

In conclusion, niraparib is a novel poly-ADP ribose polymerase (PARP) inhibitor that provides significant clinical benefit to a patient group in great need of additional treatment options. Survival and quality of life is poor in patients with recurrent platinum sensitive ovarian cancer and there is an important desire to find new effective maintenance treatment options that can increase PFS, prolong the interval between rounds of chemotherapy and thereby enable them to live longer while maintaining good quality of life.

4 Literature search

Databases and search strategy

An SLR was designed to identify RCTs and observational evidence published to November 2016. It was conducted in accordance with the requirements of the National Institute for Health and Care Excellence (NICE),[12,13] Centre for Reviews and Dissemination (CRD) guidance,[14] as well as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15]

The research questions addressed by the clinical SLR are:

1. What is the efficacy of maintenance therapy in the treatment of recurrent ovarian cancer?

2. What is the safety of maintenance therapy in the treatment of recurrent ovarian cancer?

Bibliographic databases were searched using predefined search strategies (Table 20 and Table 21 see Appendix A) that were developed for the purposes of this SLR. Searches were conducted in EMBASE, MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), and the CRD Health Technology Assessment (HTA) Database using Ovid®. In addition to bibliographic databases, unpublished data were identified from two clinical trial registries (ClinicalTrials.gov and WHO ICTRP) and from conference abstracts. No date restrictions were placed on the search strategies except for conference abstracts which were searched in EMBASE from 2014–present. A separate systematic search was conducted to identify SLRs to facilitate a manual search.

An update of the clinical SLR was conducted in June 2017. The original clinical search strategy was replicated and conducted from the date of the original search (November 16, 2016) to June 28, 2017.

A second update of the clinical SLR was conducted in June 2018. This update included relevant literature only from MEDLINE (accessed through Ovid®) and CENTRAL (via Cochrane Library). The original clinical search strategy was replicated and conducted from the date of the first SLR update to June 11, 2018.

Full details of the search strategy implemented are provided in Appendix A (Table 20 and Table 21). Selection of studies for inclusion was determined using the PICOS criteria in

Table 4. Prior to screening, duplicates were removed. Two investigators independently reviewed all titles and abstracts in the literature search; for the second update, only one researcher examined the titles and abstracts for relevance. Titles and abstracts were compared against eligibility criteria and advanced to full-text screening if deemed eligible. The same two investigators (one investigator for the second update) independently reviewed the relevant full-text articles. Articles deemed eligible at this stage were included in the SLR. Discrepancies between reviewers during study selection were addressed by discussion or in cases where agreement could not be reached, a third party adjudicate was used.

PICOS criteria describing the relevant population, interventions, comparators, outcomes, and study design were used to determine the relevance of each article (

Table 4).

Table 4 PICOS criteria for clinical evidence

Criteria	Definition
Population	• Females 18 years or older • Undergoing treatment for ovarian cancer, fallopian tube cancer, and primary peritoneal cancer • At least one recurrence of disease • Platinum sensitive • In response (complete or partial) to chemotherapy with a platinum-based agent • Either a *BRCA* mutation (germline and/or somatic) or a high grade serous histology
Interventions	Maintenance therapy with any of the following: • PARP Inhibitors (Niraparib, Olaparib, Rucaparib, Veliparib, Talazoparib) • Pazopanib • Bevacizumab
Comparators	• Any comparator • Placebo
Outcomes	• PFS • PFS2 • CFI • OS • Functional assessments of cancer therapy • NNT • NNH • Treatment discontinuation rates • AEs
Study design	• Randomized controlled trials, single-arm trials, and observational studies (retrospective and prospective)

Abbreviations: AE – Adverse event; CFI – Chemotherapy-free interval; NNH – Number needed to harm; NNT – Number needed to treat; OS – Overall survival; PARP – Poly-ADP ribose polymerase; PFS – Time to objective disease progression; PFS2 – Time to second objective disease progression

Data were extracted by one researcher using a comprehensive data extraction form in Microsoft Excel and validated independently by a second researcher. For the second update, data were extracted by one researcher, with spot checks of validity conducted by a second researcher. Quality assessment of all studies included in the data extraction form was conducted independently by two researchers. Disagreements were addressed via discussion, with involvement of a third researcher as necessary.

4.1 Relevant studies

A PRISMA diagram of the references identified in the literature search is presented in Appendix A (Figure 17). After screening the 2,860 records identified during the searches using the PICOS criteria outlined in

Table 4, a total of 270 articles were included. One additional reference was manually added. The process of study selection is presented in detail in Appendix A (Figure 17).

A total of 22 reports were included in the clinical SLR. Of these reports, 11 were in seven main RCTs and ten were associated publications (e.g., long-term follow-up data, subgroup analyses). All primary publications and associated publications were included for data extraction. One observational study was also included.

The reasons for exclusion of the remaining 249 references is provided in Appendix B (Table 22).

There were 19 reports associated with five RCTs (ENGOT-OV16/NOVA, GOG-0213, OCEANS, Study 19, and SOLO2/ENGOT-OV16), of these, 7 primary publications were extracted and included in this assessment (Table 5). The remaining 12 reports (presented in Table 23, Appendix B) were not extracted for inclusion in this assessment as they were either secondary publications or conference abstracts. There were a further three reports not relevant to this assessment and are provided in Appendix B (Table 23).

Table 5 Relevant studies included in the assessment

Reference (title, author, journal, year)	**Trial name**	**NCT number**	**Dates of study (start and expected completion date)**	**Relevant for clinical question 1, 2 or 3?**	**Appropriate for comparison?**
Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer, Mirza M.R. et al., New England Journal of Medicine, 2016	ENGOT-OV16/NOVA	NCT01847274	June 2013 – June 2016	1, 2, 3	1,3: Yes 2: No
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, Coleman R.L. et al., Lancet Oncology, 2017	GOG0213	NCT00565851	December 2007 – March 2019	2	No
OCEANS: A Randomized, Double-Blind, Placebo-Controlled Phase III Trial of Chemotherapy with or without Bevacizumabin Patients with Platinum-Sensitive Recurrent Epithelial Ovarian, Primary Peritoneal, or Fallopean Tube Cancer, Aghajanian C., et al., Journal of Clinical Oncology, 2012	OCEANS	NCT00434642	April 2007 – July 2013	2	No
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, Ledermann J.A. et al., Lancet Oncology, 2016	Study 19	NCT00753545	August 2008 – December 2018	1	Yes
Olaparib Maintenance Therapy in Patients with Platinum-Sensitive					

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question 1, 2 or 3?	Appropriate for comparison?
Relapsed Serous Ovarian Cancer: A Preplanned Retrospective Analysis of Outcomes by *BRCA* status in a Randomized Phase 2 Trial, Ledermann J. et al., New England Journal of Medicine, 2014					
Olaparib Maintenance Therapy in Platinum-Sensitive Relapsed Ovarian Cancer, Ledermann J. et al., New England Journal of Medicine, 2012					
Olaparib Tablets as Maintenance Therapy in Patients with Platinum-Sensitive, Relapsed Ovarian Cancer and a *BRCA*1/2 Mutation (SOLO2/ENGOT-OV21): A Double-Blind, Randomised, Placebo-Controlled, Phase 3 Trial, Pujade-Lauraine E. et al., The Lancet Oncology, 2017	SOLO2/ENGOT-OV21	NCT01874353	September 2013 – May 2021	1	Yes

4.2 Main characteristics of included studies

Table 6 to Table 10 present the main characteristics of the five RCTs (ENGOT-OV16/NOVA, GOG-0213, OCEANS, Study 19, and SOLO2/ENGOT-OV16) relevant to this clinical assessment.

Table 6 ENGOT-OV16/NOVA trial (Mirza et al. 2016)[8]

Trial name	ENGOT-OV16/NOVA
NCT number	NCT01847274
Objective	To evaluate the efficacy of niraparib versus placebo as maintenance treatment for patients with platinum–sensitive, recurrent ovarian cancer
Publications – title, author, journal, year	Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med 2016. 375: 2154–2164 [8]

Study type and design	A randomised, placebo-controlled, phase 3 trial. Two independent cohorts on the basis of the presence or absence of a germline *BRCA* mutation were enrolled. 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.
Method of randomisation and blinding	Patients in each cohort (g*BRCA*mut or non-g*BRCA*mut) were independently randomised 2:1 to niraparib or placebo, respectively. Randomisation within each cohort was stratified according to: • Time to progression after completion of the penultimate platinum regimen (6–12 months vs. ≥12 months) • Use of bevacizumab in combination with the penultimate or last platinum regimen • Best response (CR or PR) during the last platinum regimen Randomisation was performed via an interactive web response system. Study patients, investigators, study coordinators, and TESARO's study team and its representatives were blinded to the identity of the assigned treatment from the time of randomisation until final database lock. Patients who were ongoing in the study at the time of database lock remained blinded to their treatment assignments, as did the site investigators. Treatment identity was concealed by the use of appearance-matched placebo and identical packaging, labelling, and schedule of administration.
Follow-up time	The median duration of follow-up at the time of data cut-off was 16.9 months for all the patients in the intention-to-treat population, a duration that was similar in the g*BRCA* cohort and in the non-g*BRCA* cohort (16.4 months and 17.5 months, respectively). The longest follow-up at the time of the database lock was 24 months.
Population (inclusion and exclusion criteria)	Inclusion Criteria: • 18 years of age or older, female, any race • Histologically diagnosed ovarian cancer, fallopian tube cancer or primary peritoneal cancer • High grade (or grade 3) serous histology or known to have g*BRCA*mut • Has received at least 2 previous courses of platinum-containing therapy, and has disease that was considered platinum sensitive following the penultimate (next to last) platinum course (more than 6 month period between penultimate platinum regimen and progression of disease) • Has responded to last the platinum regimen, remains in response and is enrolled on study within 8 weeks of completion of the last platinum regimen • ECOG 0-1 • Adequate bone marrow, kidney and liver function 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

<table>
<tr><td>Intervention (n=372)</td><td>Niraparib
372 patients in intervention group were randomised to niraparib 300 mg once daily in 28-day cycles (with no treatment breaks) until disease progression. At the time of the database lock, 93 patients in the niraparib group were receiving ongoing treatment. Treatment could be interrupted for up to 28 days because of hematologic toxicity; after the resolution of such toxicity, treatment could be restarted at a reduced dose of 200 mg according to protocol-specified criteria to manage adverse events (AEs) and minimize drug discontinuation. Dose reductions were mandated for thrombocytopenia (recurrence of grade 1 or occurrence of grade 2 or above), and additional reductions of up to 100 mg were permitted.</td></tr>
<tr><td>Comparator (n=181)</td><td>Placebo
181 patients were randomised to the placebo group. At the time of the database lock, 16 patients in the placebo group were receiving ongoing treatment</td></tr>
<tr><td>Baseline characteristics</td><td>Baseline characteristics
<table>
<tr><th rowspan="2">Characteristic</th><th colspan="2">gBRCAmut</th><th colspan="2">Non-gBRCAmut</th></tr>
<tr><th>Niraparib (n=138)</th><th>Placebo (n=65)</th><th>Niraparib (n=234)</th><th>Placebo (n=116)</th></tr>
<tr><td>Median age, years (range)</td><td>57 (36–83)</td><td>58 (38–73)</td><td>63 (33–84)</td><td>61 (34–82)</td></tr>
<tr><td colspan="5">Age (years), n (%)</td></tr>
<tr><td>18–64</td><td>110 (79.7)</td><td>49 (75.4)</td><td>130 (55.6)</td><td>69 (59.5)</td></tr>
<tr><td>65–74</td><td>24 (17.4)</td><td>16 (24.6)</td><td>85 (36.3)</td><td>39 (33.6)</td></tr>
<tr><td>≥65</td><td>28 (20.3)</td><td>16 (24.6)</td><td>104 (44.4)</td><td>47 (40.5)</td></tr>
<tr><td>≥75</td><td>4 (2.9)</td><td>0</td><td>19 (8.1)</td><td>8 (6.9)</td></tr>
<tr><td colspan="5">Race, n (%)</td></tr>
<tr><td>White</td><td>123 (89.1)</td><td>55 (84.6)</td><td>201 (85.9)</td><td>101 (87.1)</td></tr>
<tr><td>Black</td><td>1 (0.7)</td><td>1 (1.5)</td><td>4 (1.7)</td><td>1 (0.9)</td></tr>
<tr><td>Asian</td><td>2 (1.4)</td><td>3 (4.6)</td><td>10 (4.3)</td><td>4 (3.4)</td></tr>
<tr><td>American Indian/Alaska Native</td><td>1 (0.7)</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Native Hawaiian/Pacific Islander</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Unknown</td><td>11 (8.0)</td><td>6 (9.2)</td><td>19 (8.1)</td><td>10 (8.6)</td></tr>
<tr><td>BMI (kg/m^2), n</td><td>138</td><td>64</td><td>229</td><td>114</td></tr>
<tr><td>Mean (SD)</td><td>26.06 (5.749)</td><td>26.78 (6.003)</td><td>26.29 (5.606)</td><td>26.31 (4.859)</td></tr>
<tr><td>Median</td><td>24.70</td><td>25.50</td><td>25.48</td><td>25.71</td></tr>
<tr><td>Min, Max</td><td>14.0, 44.6</td><td>19.0, 50.4</td><td>16.8, 45.6</td><td>18.1, 45.7</td></tr>
<tr><td colspan="5">ECOG performance status, n (%)</td></tr>
<tr><td>0</td><td>91 (65.9)</td><td>48.0 (73.8)</td><td>160 (68.4)</td><td>78 (67.2)</td></tr>
<tr><td>1</td><td>47 (34.1)</td><td>17 (26.2)</td><td>74 (31.6)</td><td>38 (32.8)</td></tr>
</table></td></tr>
</table>

Primary tumour site, n (%) [†]				
Ovary	122 (88.4)	53 (81.5)	192 (82.1)	96 (82.8)
Primary peritoneum	7 (5.1)	6 (9.2)	24 (10.3)	8 (6.9)
Fallopian tube	9 (6.5)	6 (9.2)	18 (7.7)	11 (9.5)
Histologic subtype[‡]				
Serous	117 (88.6)	59 (90.8)	215 (96.4)	110 (99.1)
Endometrioid	8 (6.1)	3 (4.6)	1 (0.4)	1 (0.9)
Mucinous	0	0	0	0
Others	13 (9.8)	3 (4.6)	11 (4.9)	3 (2.7)
Geographic region, n (%)				
US and Canada	53 (38.4)	28 (43.1)	96 (41.0)	44 (37.9)
Europe and Israel	85 (61.6)	37 (56.9)	138 (59.0)	72 (62.1)
Cancer stage at time of diagnosis, n (%) [§]				
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, n (%)				
6 to <12 months	54 (39.1)	26 (40.0)	90 (38.5)	44 (37.9)
≥12 months	84 (60.9)	39 (60.0)	144 (61.5)	72 (62.1)
Best response to most recent platinum therapy, n (%)				
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, n (%)				
Yes	33 (23.9)	17 (26.2)	62 (26.5)	30 (25.9)
Germline BRCA mutation, n (%) [¶]				
BRCA1	85 (61.6)	43 (66.2)	N/A	N/A
BRCA2	51 (37.0)	18 (27.7)	N/A	N/A
BRCA1, BRCA2 rearrangement, or both	9 (6.5)	4 (6.2)	N/A	N/A
Duration since diagnosis (years), n				
Mean (SD)	4.37 (2.564)	4.07 (2.999)	3.33 (2.210)	3.59 (1.991)
Median	3.66	3.02	2.69	2.99
Min, Max	0.3, 13.6	1.8, 19.5	0.1, 19.2	0.1, 9.3
Previous lines of therapy, n (%) [††]				
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)

<table>
<tr><td></td><td>
<table>
<tr><td colspan="5">Number of lines of platinum therapy, n (%)</td></tr>
<tr><td>1</td><td>1 (0.7)</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>2</td><td>79 (57.2)</td><td>37 (56.9)</td><td>174 (74.4)</td><td>87 (75.0)</td></tr>
<tr><td>>2</td><td>58 (42.0)</td><td>28 (43.1)</td><td>60 (25.6)</td><td>28 (24.1)</td></tr>
<tr><td>Missing</td><td>0</td><td>0</td><td>0</td><td>1 (0.9)</td></tr>
<tr><td colspan="5">Number of metastatic sites, n (%)</td></tr>
<tr><td><3</td><td>89 (64.5)</td><td>40 (61.5)</td><td>157 (67.1)</td><td>79 (68.1)</td></tr>
<tr><td>≥3</td><td>49 (35.5)</td><td>25 (38.5)</td><td>77 (32.9)</td><td>36 (31.0)</td></tr>
</table>
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>
Primary endpoint
PFS – defined as the time from the date of treatment randomisation to the date of first documentation of progression (by independent blinded central review) or death by any cause in the absence of documented progression, whichever occurred first.
Tumour assessments were based on:
• Computed tomography or magnetic resonance imaging, according to RECIST v1.1 performed in a blinded fashion at baseline, every 8 weeks through cycle 14 and then every 12 weeks until treatment discontinuation
• CA-125 was assessed per GCIG criteria, and conducted at screening and day 1 of each cycle

Secondary/tertiary outcomes included:
• TFST – defined as the time from the date of randomisation to the start date of the first subsequent anti-cancer therapy or death
• CFI – defined as the time from the last platinum therapy prior to randomisation to the initiation of the next anti-cancer therapy after maintenance treatment
• PFS2 – defined as the time from treatment randomisation to the earlier of the date of disease progression on the next anti-cancer therapy following study treatment or death due to any cause
• TSST – defined as the time from the date of randomisation to the start date of the second subsequent anti-cancer therapy
• OS – defined as time from study randomization to the date of death due to any cause
</td></tr>
<tr><td>Method of analysis</td><td>Efficacy data were analysed in the intention-to-treat population. For each primary efficacy population, a two-sided log-rank test was performed using randomisation stratification factors to analyse progression-free survival, which was summarised with the use of Kaplan–Meier methods. Hazard ratios with two-sided 95% confidence intervals were estimated using a stratified Cox proportional- hazards model, with the stratification factors used in randomisation.</td></tr>
<tr><td>Subgroup analyses</td><td>Progression-free survival was assessed independently in the gBRCA cohort and in the non-gBRCA cohort. A hierarchical- testing procedure was predefined for the non-gBRCA cohort in which statistical analysis was first performed in patients with HRD-positive tumours, and if the results were significant, a test of the overall non-gBRCA cohort was performed. An exploratory analysis of progression-free survival was performed for patients in the various biomarker populations within the three subgroups without a germline BRCA mutation</td></tr>
</table>

	(HRD-positive plus somatic *BRCA* mutation, HRD-positive plus wild-type *BRCA*, and HRD-negative). Subgroup analyses were performed to determine the relevance of certain baseline and demographic factors that might have influenced the primary end point. Potential heterogeneity of treatment effect between subgroups was examined with statistical interaction tests and forest plots.

Abbreviations: BRCA – Breast cancer susceptibility gene; CFI – Chemotherapy-free interval; CR – Complete response; ECOG – Eastern Cooperative Oncology Group; HRD – Homologous recombination DNA repair deficiency; OS – Overall survival; PARP – Poly-ADP ribose polymerase; PFS – Progression-free survival; PFS2 – Time to second objective disease; PR – Partial response; TFST – Time to first subsequent therapy; TSST – Time to second subsequent therapy.
†Data with respect to primary tumour site were not available for one patient in the placebo group in the non-g*BRCA*mut cohort;
‡Some patients had only cytology results available for confirmation of histologic subtype. Staging was performed according to the FIGO system. Among the patients with non-g*BRCA*mut, data with respect to staging was 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.
Based on centralised (Myriad) laboratory test; patients can report *BRCA*1/2 rearrangement and *BRCA*1 and *BRCA*2.
††Among the patients with non-g*BRCA*mut, data with respect to previous line of therapy was not available for one patient in the placebo group.

Table 7 Study 19 trial (Ledermann 2012, 2014 and 2016)[16–18]

Trial name	Study 19
NCT number	NCT00753545
Objective	To assess the effect of maintenance treatment with olaparib in patients with platinum-sensitive recurrent serous ovarian cancer including those with a *BRCA*1 and *BRCA*2 mutation
Publications – title, author, journal, year	Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med. 2012;366(15):1382-1392 Ledermann J, Harter P, Gourley C et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by *BRCA* status in a randomised phase 2 trial. Lancet Oncol. 2014 Jul;15(8):852-61 Ledermann, J. A., Harter, P., Gourley, C., Friedlander, M., Vergote, I., Rustin, G., ... & Matei, D. (2016). 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, 17(11), 1579-1589.
Study type and design	Double-blind, randomised, placebo-controlled, multicentre, phase 2 international study. Patients were randomly assigned in a 1:1 ratio to receive olaparib capsules, at dose of 400 mg twice daily, or matching placebo within 8 weeks after completion of the last dose of platinum-based chemotherapy
Method of randomisation and blinding	Patients were randomly assigned (1:1) to receive olaparib or placebo within 8 weeks following completion of their most recent platinum-based regimen. An interactive voice response system assigned patients to their treatment using a randomisation scheme generated by a computer program (AstraZeneca randomisation and unblinding system).

<table>
<tr><td></td><td>The investigator who enrolled patients contacted an interactive voice response system centralised randomisation office by telephone for allocation of randomized treatment.
Randomisation was stratified by ancestry (Jewish vs non-Jewish), time to progression from completion of penultimate platinum-based regimen (6-12 months vs > 12 months), and response to most recent platinum-based regimen (complete vs partial response). Randomisation was stratified by ancestry to avoid imbalance caused by the substantially higher frequency of BRCAm in Jewish population than in the general population.
Treatment assignment was masked from patients and from anyone administering interventions, assessing outcomes, or analyzing data, by the use of unique identifiers generated during randomization. Olaparib and placebo capsules were identical in appearance and packaging.</td></tr>
<tr><td>Follow-up time</td><td>Patients were followed until progression of disease. At the time of the data cut-off point, the median duration of exposure to the treatment was 206.5 days (3-469) for olaparib and 141 days (34-413) for placebo. At the data cut-off for the primary PFS analysis (30th June 2010), the median follow-up was 5.6 months</td></tr>
<tr><td>Population (inclusion and exclusion criteria)</td><td>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 weeks of completion of their final dose of the platinum containing regimen.
Exclusion Criteria:
Previous treatment with PARP inhibitors including AZD2281
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).</td></tr>
<tr><td>Intervention (n=136)</td><td>Olaparib
136 patients were randomly assigned to receive olaparib, at a dose of 400 mg twice daily. At the data cut-off point (30th June 2010), 68 patients (50%) in the olaparib group were still receiving the study treatment.</td></tr>
<tr><td>Comparator (n=129)</td><td>Placebo
129 patients were randomly assigned to receive placebo. At the data cut-off point (30th June 2010), 21 (16%) in the placebo group were still receiving the study treatment.</td></tr>
<tr><td>Baseline characteristics</td><td>Study 19 baseline characteristics
<table>
<tr><th>Characteristic</th><th>Olaparib (N=136)</th><th>Placebo (N=129)</th></tr>
<tr><td>Median Age (Range)</td><td>58.0 (21-89)</td><td>59.0 (33-84)</td></tr>
<tr><td>Non-Jewish, n (%)</td><td>116 (85.3)</td><td>112 (86.8)</td></tr>
<tr><td>Jewish , n (%)</td><td>20 (14.7)</td><td>17 (13.2)</td></tr>
</table></td></tr>
</table>

	Jewish; Ashkenzai, n (%)	16 (11.8)	12 (9.3)
	Jewish; Sephardi or Mizrahi, n (%)	3 (2.2)	2 (1.6)
	Jewish; Other or unknown, n (%)	1 (0.7)	3 (2.3)
	ECOG performance status, n (%)		
	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 tumour location, n (%)		
	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, n (%)		
	>6-12 months	53 (39.0)	54 (41.9)
	>12 months	83 (61.0)	75 (58.1)
	Objective response to most recent platinum-based regimen, n (%)		
	Complete	57 (41.9)	63 (48.8)
	Partial	79 (58.1)	66 (51.2)
	***BRCA*-germline-mutation status, n (%)**		
	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	0 (0)	1 (0.8)
	Negative	18 (3.2)	20 (15.5)
	Unknown	87 (64.0)	81 (62.8)
	Previous chemotherapy regimens, n		
	Median	3	3
	Range	0-11	2-8
	Previous platinum-based chemotherapy regimens, n		
	Median	2	2
	Range	0-7	2-8
Primary endpoints	The primary end point was PFS, as assessed by the site investigator and defined as the time from randomization (on completion of chemotherapy) until objective assessment of disease progression according to RECIST guidelines, or death.		
Secondary endpoints	Secondary efficacy end points were time to progression, according to RECIST guidelines or CA-125 level, whichever showed earlier progression; objective response rate, as determined according to RECIST guidelines or a combination of RECIST guidelines and CA-125 level; disease-control rate, according to RECIST guidelines; percentage change from baseline in the size of the target tumour lesion at weeks 12 and 24; and OS.		
Method of analysis	Analyses of efficacy and patient-reported outcomes included all patients who were randomly assigned to a study group, and safety analyses included all patients who received at least one dose of the assigned study medication. Time-to-event variables (i.e., PFS, OS, and time to worsening of disease related symptoms and health-related quality of life) were		

	analysed with the use of a Cox proportional-hazards model that included covariates that were used as stratification factors at randomisation.
Subgroup analyses	Predictive and prognostic factors for progression-free survival were explored with the use of pre-planned subgroup analyses, including status with respect to *BRCA*1/2 germline mutation, age, Jewish or non-Jewish ancestry, response status at baseline, and time to progression from the start of the penultimate platinum-based regimen.

Abbreviations: *BRCA*, Breast cancer susceptibility gene; ECOG, Eastern Cooperative Oncology Group; OS – Overall Survival; PARP – Poly-ADP ribose polymerase; PFS – Progression-free survival

Table 8 SOLO-2 trial (Pujade-Lauraine 2017)[19]

Trial name	SOLO-2
NCT number	NCT01874353
Objective	To confirm the findings of Study 19, where olaparib had previously shown efficacy as a maintenance treatment in patients with platinum-sensitive, relapsed high-grade serous ovarian cancer with a *BRCA*1 or *BRCA*2 mutation, using a new tablet formulation of olaparib.
Publications – title, author, journal, year	Pujade-Lauraine, E., Ledermann, J. A., Selle, F., Gebski, V., Penson, R. T., Oza, A. M., et al. (2017). Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA*1/2 mutation (SOLO-2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. The Lancet Oncology, 18(9), 1274-1284.
Study type and design	International, multicentre, double-blind, randomised placebo-controlled, phase 3 study. Patients were randomly assigned in a 2:1 ratio to receive olaparib tablet maintenance monotherapy, or matching placebo within 8 weeks after completion of the last dose of platinum-based chemotherapy
Method of randomisation and blinding	Eligible patients were randomised (2:1) to receive olaparib tablet maintenance monotherapy or placebo. The randomisation scheme was produced by a computer software program that generates random numbers (Global Randomisation System) and was loaded into an interactive voice and web response system database. Investigators (or nominated assistants) contacted the interactive voice and web response system centralised randomisation centre for allocation of randomised therapy. Randomisation was completed within 8 weeks of the patients' last dose of chemotherapy, and was stratified by response to previous chemotherapy (complete vs partial) and length of platinum-free interval (6-12 months vs 12 months). Treatment masking was achieved using individual treatment codes assigned by the interactive voice and web response system. Treatment assignment was masked for patients, those giviing the interventions, data collectors, and data analysers. Olaparib and placebo tablets were manufactured by AstraZeneca (Macclesfield, UK), looked identical, and were presented in the same packaging. Unmasking was only permitted in medical emergencies where appropriate management of the patient required knowledge of the treatment randomisation.
Follow-up time	Patients were followed until disease progression. After disease progression, patients were followed every 12 weeks for second progression and survival. At data cut-off (19th September 2016) the median follow-up for progression-free survival was 22.1 months (21.9-27.4) in the olaparib group and 22.2 months (8.3-27.5) for placebo.

Population (inclusion and exclusion criteria)	Inclusion: • Provision of informed consent prior to any study specific procedures • Patients must be ≥ 18 years of age • Female patients with histologically diagnoses relapse high grade serous ovarian cancer (including primary peritoneal and/or fallopian tube cancer) or high grade endometrioid cancer • Document mutation *BRCA*1 or *BRCA*2 that is predicted to be deleterious or suspected deleterious (known as 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 • Pre-treatment CA-125 measurements must meet criterion specified below: o If the first value is within upper limit of normal (ULN) the patient is eligible to be randomised and a second sample is not required o If the first value is greater than ULN a second assessment must be performed at least 7 days after the first. If the second assessment is ≥ 15% more than the first the patient is not eligible • Patients must have normal organ and bone marrow function measured within 28 days of randomisation • ECOG performance status 0-1 • Patients must have a life expectancy of ≥ 16 weeks • Postmenopausal or evidence of non-childbearing status for women of childbearing potential • Patient is willing to comply with the protocol for the duration of the study including undergoing treatment and schedule visits and examinations • Formalin fixed, paraffin embedded tumour sample from the primary or recurrent cancer must be available for central testing 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 *BRCA*2 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 • Previous randomisation in the present study • Participation in another clinical study with an investigational product during the chemotherapy course immediately prior to randomisation • Any previous treatment with a PARP inhibitor, including olaparib • Patients with a known hypersensitivity to olaparib or any of the excipients of the product • Other malignancy within the last 5 years except: adequately treated non-melanoma skin cancer, curatively treated in situ cancer of the cervix, ductal carcinoma *in situ*, Stage 1, grade 1 endometrial carcinoma, or other solid tumours including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for ≥5 years. Patients with history of primary breast cancer may be eligible provided they completed their definitive anticancer treatment

	more than 3 years ago and they remain breast cancer disease free prior to start of study treatment. • Resting ECG with QTc > 470 msec on 2 or more time points within a 24 hour period or family history of long QT syndrome • Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treatment (or a longer period depending on the defined characteristics of the agents used). • Concomitant use of known potent CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfinavir • Persistent toxicities (Common Terminology Criteria for AE grade 2) caused by previous cancer therapy, excluding alopecia • Patients with myelodysplastic syndrome/acute myeloid leukaemia • Patients with symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases is not required. The patient can receive a stable dose of corticosteroids before and during the study as long as these were started at least 4 weeks prior to treatment. Patients with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days • Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery • Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, superior vena cava syndrome, extensive interstitial bilateral lung disease on high resolution computed tomography (HRCT) scan or any psychiatric disorder that prohibits obtaining informed consent • Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication • Breast feeding women • Immunocompromised patients, e.g., patients who are known to be serologically positive for human immunodeficiency virus • Patients with known active hepatitis (i.e., Hepatitis B or C) due to risk of transmitting the infection through blood or other body fluids • Previous allogeneic bone marrow transplant • Whole blood transfusions in the last 120 days prior to entry to the study (packed red blood cells and platelet transfusions are acceptable, for timing refer to inclusion criteria no.7)
Intervention (n=196)	**Olaparib** 196 patients were randomly assigned to receive olaparib, at a dose of 300 mg twice daily. At the data cut-off point (19th September 2016), 195 patients (>99%) in the olaparib group had received the study treatment, and 83 (43%) were in still receiving the study treatment.
Comparator (n=99)	**Placebo**

<table>
<tr><td></td><td>99 patients were randomly assigned to receive placebo. At the data cut-off point (19th September 2016), 13 patients (11%) in the placebo group were still receiving placebo.</td></tr>
<tr><td>Baseline characteristics</td><td>SOLO-2 baseline characteristics
<table>
<tr><th>Characteristic</th><th>Olaparib (N=196)</th><th>Placebo (N=99)</th></tr>
<tr><td>Median Age (Range)</td><td>56.0 (51-63)</td><td>59.0 (49-63)</td></tr>
<tr><td colspan="3">ECOG performance status, n (%)</td></tr>
<tr><td>0</td><td>162 (83)</td><td>77 (78)</td></tr>
<tr><td>1</td><td>31 (16)</td><td>22 (22)</td></tr>
<tr><td>Missing</td><td>2 (1)</td><td>0 (0)</td></tr>
<tr><td colspan="3">Primary tumour location, n (%)</td></tr>
<tr><td>Ovary</td><td>164 (84)</td><td>86 (87)</td></tr>
<tr><td>Fallopian tubes or primary peritoneal</td><td>31 (16)</td><td>13 (13)</td></tr>
<tr><td>Missing</td><td>1 (1)</td><td>0 (0)</td></tr>
<tr><td colspan="3">Histology type, n (%)</td></tr>
<tr><td>Serous</td><td>183 (93)</td><td>86 (87)</td></tr>
<tr><td>Endometrioid</td><td>9 (5)</td><td>8 (8)</td></tr>
<tr><td>Mixed</td><td>3 (2)</td><td>5 (5)</td></tr>
<tr><td>Missing</td><td>1 (1)</td><td>0 (0)</td></tr>
<tr><td>Patients with > 2cm target lesion at baseline</td><td>30 (15)</td><td>18 (18)</td></tr>
<tr><td colspan="3">Confirmed germline BRCA mutation, n (%)</td></tr>
<tr><td>BRCA1</td><td>132 (67)</td><td>61 (62)</td></tr>
<tr><td>BRCA2</td><td>58 (30)</td><td>35 (35)</td></tr>
<tr><td>Both</td><td>0 (0)</td><td>0 (0)</td></tr>
<tr><td>Missing</td><td>6 (3)</td><td>3 (3)</td></tr>
<tr><td colspan="3">Response to previous platinum-based regimen, n (%)</td></tr>
<tr><td>Complete</td><td>91 (46)</td><td>47 (47)</td></tr>
<tr><td>Partial</td><td>105 (54)</td><td>52 (53)</td></tr>
<tr><td colspan="3">Number of previous platinum-base regimens, n (%)</td></tr>
<tr><td>Two</td><td>110 (56)</td><td>62 (63)</td></tr>
<tr><td>Three</td><td>60 (31)</td><td>20 (20)</td></tr>
<tr><td>Four</td><td>18 (9)</td><td>12 (12)</td></tr>
<tr><td>Five or more</td><td>7 (4)</td><td>5 (5)</td></tr>
<tr><td colspan="3">Platinum-free interval, n (%)</td></tr>
<tr><td>> 6-12 months</td><td>79 (40)</td><td>40 (40)</td></tr>
<tr><td>> 12 months</td><td>117 (60)</td><td>59 (60)</td></tr>
</table></td></tr>
<tr><td>Primary endpoints</td><td>The primary endpoint was investigator assessment of progression-free survival, defined as the time from randomization until objective radiological disease progression of death using modified RECIST version 1.1.</td></tr>
<tr><td>Secondary endpoints</td><td>Secondary endpoints were time to first subsequent therapy or death; time to second subsequent therapy or death; time to study treatment discontinuation or death; time to second progression (determined by RECIST, serum CA-125 levels or symptomatic progression); time to earliest progression (by RECIST or CA-125 levels) or death; investigator assessment of overall survival; safety and tolerability; and health-related quality of life (change from baseline in TOI score of FACT-O). In addition, secondary</td></tr>
</table>

	endpoints also included efficacy of olaparib according to *BRCA*1/2 gene variants and exposure to olaparib in the patients in the olaparib group.
Method of analysis	Analyses of efficacy and patient-reported outcomes included all patients who were in the intention-to-treat population, which included all randomised patients. 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	Preplanned subgroup analyses for progression-free survival were used to evaluate the consistency of the treatment effect across several prognostic factors including previous administration of bevacizumab and present of a Myriad Genetics-confirmed *BRCA*1/2 mutation of part of trial.

Abbreviations: *BRCA* – Breast cancer susceptibility gene; ECOG – Eastern Cooperative Oncology Group; ULN – Upper limit of normal; PARP – Poly-ADP ribose polymerase; ECG – Echocardiogram; TOI – Trial outcome index; FACT-O – Functional Assessment of Cancer Therapy-Ovarian Cancer

Table 9 OCEANS trial (Aghajanian 2012)[20]

Trial name	Ovarian Cancer Study Comparing Efficacy and Safety of Chemotherapy and Anti-Angiogenic Therapy in Platinum-Sensitive Recurrent Disease (OCEANS)
NCT number	NCT00434642
Objective	To determine the efficacy and safety of bevacizumab with gemcitabine and carboplatin (GC) compared to GC in platinum-sensitive recurrent ovarian, primary peritoneal, of fallopian tube cancer.
Publications – title, author, journal, year	Aghajanian, C., Blank, S. V., Goff, B. A., Judson, P. L., Teneriello, M. G., Husain, A., ... & Nycum, L. R. (2012). OCEANS: a randomised, 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. Journal of clinical oncology, 30(17), 2039.
Study type and design	Double-blind, randomised, placebo-controlled, multicentre, phase 3. Patients were randomly assigned in a 1:1 ratio to receive CG plus bevacizumab or GC plus placebo only. Randomization was stratified by time from last platinum treatment to recurrence (6 to 12 vs. > 12 months) and cytoreductive surgery for recurrent ovarian cancer. The trial was initiated as a phase 2 study, with extensive safety reviews focused on gastro-intestinal (GI) toxicity. After approximately 20 patients were accrued in each arm, and no GI perforations were reported after more than 10 weeks of follow-up, the trial was converted to a phase 3 trial.
Method of randomisation and blinding	Eligible patients were randomly assigned to the BV or PL arm using an interactive voice response system in a one-to-one ratio; randomisation was stratified by the time from last platinum treatment to recurrence (6 to 12 vs > 12 months) and cytoreductive surgery for ROC (yes vs no).

	The study sponsor (Genentech, South San Francisco, CA), contract research organization, investigators, and patients were blinded to treatment assignment. At the time of documented progressive disease (PD), patients could be unblinded to treatment assignment at the request of the investigator.
Follow-up time	At time of final PFS analysis (338) events, the median follow-up time was 24 months.
Population (inclusion and exclusion criteria)	Inclusion criteria: • Patients ≥ 18 years old • Histologically confirmed recurrent ovarian cancer and disease progression ≥ 6 months after completion of front-line platinum-based chemotherapy • No prior chemotherapy in the recurrent setting • Measurable disease according to the RECIST version 1.0 • ECOG performance status of 0 or 1 • Life expectancy of less than 12 weeks • Adequate bone marrow, coagulation, renal and hepatic function • Signed and approved informed consent in accordance to federal state and local requirements, as well as authorisation permitting the release of personal health information Exclusion criteria: • Prior treatment with bevacizumab or other vascular endothelia growth factor pathway-targeted therapy • Other malignancies within 5 years (unless low risk of occurrence) • History of abdominal fistula, GI perforation, intra-abdominal abscess, clinical signs or symptoms of GI obstruction and/or requirement for parenteral nutrition • Non healing wound, ulcer or bone fraction • Bleeding diathesis or significant coagulopathy • Central nervous system neuron disease • Clinically significant cardiovascular disease • Major surgical procedure with 28 days of enrolment or anticipated to occur while participating in study
Intervention (n=242)	**Bevacizumab** 242 patients in intervention group were randomised to GC plus bevacizumab. Of these patients 1 did not receive study treatment; 213 patients were known to have discontinued bevacizumab; 104 due to disease progression, 55 due to an adverse event and 54 due to patient/physician decision.
Comparator (n=242)	**Placebo** 242 patients in intervention group were randomised to GC plus placebo. Of these patients 4 did not receive study treatment; 222 patients were known to have discontinued placebo; 160 due to disease progression, 12 due to an adverse event and 50 due to patient/physician decision.

Baseline characteristics	**Baseline characteristics**		
		GC + placebo (n=242), n (%)	**GC + Bevacizumab (n=242), n (%)**
	Age, years		
	Mean	61.6	60.5
	SD	10.2	9.8
	Median	61.0	60.0
	25th percentile	55.0	53.0
	75th percentile	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)	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)	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)
	Endometriod	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 (0.9)	30 (12.4)
	No	218 (90.1)	212 (87.6)
	Time to recurrence since for recurrent disease		
	6-12	102 (42.1)	100 (41.3)
	> 12	140 (57.9)	142 (58.7)
Primary and secondary endpoints	Primary endpoint • The primary outcome measure was PFS, as determined by investigators. PFS was defined as the time from random assignment to progressed-disease (PD) or death as a result of any case. For patients alive without assignment to PD at the time of the analysis, PFS was censorted at the time of the last tumour assessment Secondary endpoints • Secondary outcomes measures were objective response rate (ORR), OS and duration of response • 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, patient without baseline assessment were considered to be non-responders.		
Method of analysis	Efficacy analyses were performed in the ITT population. The safety population consisted of all randomly assigned patients who have received at least one partial dose of any component of protocol treatment. For PFS a two-side long-rank test at the 0.05 level of significance with 80% power as assumed. Two interim OS analyses were planned: one at time of final PFS analysis and the other at approximately 214 deaths. Kaplan-Meier methodology was applied to estimate the median PFS and DOR for each treatment group. Brookmeyer-Crowly methodology was used to construct 95% CI for median values. The stratified HR was estimated using a Cox regression model. ORRs were compared by the Cochran-Mantel-Haenszel test		
Subgroup analyses	Subgroup analyses examined age, baseline ECOG performance status, platinum-free interval and cytoreductive surgery for recurrent disease		

Abbreviations: BV – Bevacizumab; CI – Confidence interval; DOR – Duration of response; ECOG – Eastern Cooperative Oncology Group; GC – Gemcitabine and carboplatin; GI – Gastro intestinal; HR – Hazard ratio; ITT – Intention-to-treat; OCEANS – Ovarian Cancer Study Comparing Efficacy and Safety of Chemotherapy and Anti-Angiogenic Therapy in Platinum-Sensitive Recurrent Disease; ORR – Overall response rate; OS – Overall survival; PD – Progressed disease; PFS – Progression-free survival; PL – Placebo; SD – Standard deviation

Table 10 GOG-0213 trial (Coleman 2017)[21]

Trial name	NRG Oncology/ Gynecologic Oncology Group study (GOG)-0213

NCT number	NCT00565851
Objective	To explore the roles of secondary surgical cytoreductive and bevacizumab in recurrent, platinum-sensitive ovarian cancer
Publications – title, author, journal, year	Coleman, R. L., Brady, M. F., Herzog, T. J., Sabbatini, P., Armstrong, D. K., Walker, J. L., ... & Davidson, S. A. (2017). 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. The Lancet Oncology, 18(6), 779-791.
Study type and design	A multicenter, open-label, randomised phase 3 trial conducted in 67 predominately academic centres across the United States of America (65), Japan (1) and South Korea (1). Patients were randomly assigned (1:1) to standard chemotherapy (six 3-weekly cycles of paclitaxel [175 mg/m² of body surface area] and carboplatin [area under the curve]) or the same chemotherapy regimen plus bevacizumab (15 mg/kg of bodyweight) every 3 weeks and continued as maintenance every 3 weeks until disease progression or unacceptable toxicity. Individuals who participated in both the bevacizumab objective and surgical objective were randomly assigned (1:1:1:1) to receive either of these two chemotherapy regimens with or without prior secondary cytoreductive surgery. Randomisation for the bevacizumab objective was stratified by treatment-free interval and participation in the surgical objective
Method and randomisation	Individuals who participated only in the bevacizumab objective were randomly assigned (1:1) to receive paclitaxel and carboplatin chemotherapy or paclitaxel and carboplatin chemotherapy with bevacizumab followed by bevacizumab maintenance therapy until disease progression or unacceptable toxicity, whichever occurred first. Individuals who participated in both the bevacizumab and surgical objectives were randomly assigned (1:1:1:1) to receive either of these two drug regimens with or without prior secondary cytoreductive surgery. Study treatments were allocated sequentially from lists composed of random permuted blocks of random sizes of the study treatments. The list of treatments was prepared by the GOG Statistical and Data Center Buffalo, NY, USA) and remained concealed during conduct of the study. For the bevacizumab objective, the treatment allocation procedure was stratified by previous treatment-free interval (6-12 months vs > 12 months from last platinum infusioin) and by participation in the surgical objective (yes vs no). An automated electronic web-based procedure was used to enrol patients and randomly assign them to treatments. Each individual's treatment assignment remained concealed until after she was successfully enrolled. This trial was open label: patients and study physicians were aware of treatment assignment.
Follow-up time	At data cut-off (5th November 2014), median follow-up time was 49.6 months in each treatment group, with a range of 41.5-62.2 and 40.8-59.3 in the chemotherapy plus bevacizumab and chemotherapy only treatment arms, respectively.
Population (inclusion and exclusion criteria)	Inclusion • Women ≥ 18 years old • Recurrent clinically evident (measurable according to RECIST version 1.0 criteria) epithelial ovarian, primary peritoneal, or fallopian tube cancer • Clinical response at last cycles of primary platinum-based chemotherapy as determined by negative clinical examination and a normal CA-125 level as well as disease free for at least 6 months following the last infused cycle of platinum • If performed as an assessment of response, abdominopelvic computerised tomography or magnetic resonance imaging had to be negative for disease, and if

<table>
<tr><td></td><td>assessment was made by second-look surgery, all surgical specimens had to be pathologically negative
• ECOG performance status 0-2
• Adequate bone marrow, renal and hepatic function
• Platelet count of at least 100,000/µl
Exclusion
• Receiving concurrent immunotherapy or radiotherapy
• Previous radiotherapy to any portion of the abdominal cavity or pelvis
• More than one previous chemotherapy regimen (maintenance therapy is allowed if administered after a complete clinical or pathological response, but must have been discontinued ≥ 6 months before documentation of recurrent disease)
• Previous chemotherapy for any abdominal or pelvic tumour
• Uncontrolled infection
• Active bleeding or conditions associated with a high risk of bleeding
• History of CNS</td></tr>
<tr><td>Intervention (n=337)</td><td>Chemotherapy plus Bevacizumab
337 patients were randomised to receive chemotherapy plus bevacizumab. Of these patients, 7 did not start treatment, 6 refused treatment and 1 died before treatment initiation.</td></tr>
<tr><td>Comparator (n=337)</td><td>Chemotherapy plus placebo
337 patients were randomised to receive chemotherapy only. Of these patients, 10 did not start treatment, 8 refused treatment, 1 patient was ineligible and 1 died before treatment initiation.</td></tr>
<tr><td>Baseline characteristics</td><td>Baseline characteristics
<table>
<tr><th>Characteristic</th><th>Standard chemotherapy (n=337)</th><th>Standard chemotherapy plus bevacizumab (n=337)</th></tr>
<tr><td>Median age, years (IQR)</td><td>60.6 (53.6-67.7)</td><td>59.5 (53.6-66.4)</td></tr>
<tr><td>Range</td><td>23-85</td><td>26-84</td></tr>
<tr><td colspan="3">Race</td></tr>
<tr><td>American Indian</td><td>1 (<1)</td><td>4 (1)</td></tr>
<tr><td>Asian</td><td>44 (13)</td><td>48 (14)</td></tr>
<tr><td>African American</td><td>15 (4)</td><td>15 (4)</td></tr>
<tr><td>Native Hawaiian/ Pacific Islander</td><td>0</td><td>1 (<1)</td></tr>
<tr><td>White</td><td>271 (80)</td><td>266 (79)</td></tr>
<tr><td>Missing/ Unknown</td><td>6 (2)</td><td>3 (1)</td></tr>
<tr><td colspan="3">Stage</td></tr>
<tr><td>I</td><td>17 (5)</td><td>22 (7)</td></tr>
<tr><td>II</td><td>36 (11)</td><td>18 (5)</td></tr>
<tr><td>III</td><td>246 (73)</td><td>261 (77)</td></tr>
<tr><td>IV</td><td>38 (11)</td><td>36 (11)</td></tr>
</table></td></tr>
</table>

Histology		
Serous*	272 (81)	273 (81)
Endometrioid	23 (7)	20 (6)
Clear cell	14 (4)	10 (3)
Muscinous	2 (1)	2 (1)
Other ¥	26 (8)	32 (9)
Grade of differentiation		
Well	17 (5)	20 (6)
Moderate	44 (13)	53 (16)
High	253 (75)	249 (74)
Not available	22 (7)	15 (4)
Cytoreductive surgery$^{\alpha}$		
Randomised, no surgery	27 (8)	27 (8)
Randomised, surgery	27 (8)	26 (8)
Not randomised	283 (84)	284 (84)
Previous treatment-free interval$^{\beta}$		
6-12 months	105 (31)	105 (31)
>12 months	232 (69)	232 (69)
Previous platinum-free interval$^{\Omega}$		
6-12 months	84 (25)	91 (27)
>12 months	253 (75)	232 (69)
Measurable disease		
No	50 (15)	36 (19)
Yes	287 (85)	274 (81)
Previous therapies		
Systemic chemotherapy		
Yes	337 (100)	337(100)
No	0 (0)	0 (0)
Intraperitoneal chemotherapy		
Yes	66 (20)	55 (16)
No	271 (80)	282 (84)
Hormone chemotherapy		
Yes	10 (3)	11 (3)
No	327 (97)	326 (97)
Anti-VEGF chemotherapy		
Yes	33 (10)	34 (10)
No	303 (97)	303 (90)

<table>
<tr><td></td><td>
<table>
<tr><td>Not specified</td><td>1 (<1)</td><td>0 (0)</td></tr>
<tr><td colspan="3">First-line maintenance therapies</td></tr>
<tr><td colspan="3">Taxane</td></tr>
<tr><td>Yes</td><td>27 (8)</td><td>20 (6)</td></tr>
<tr><td>No</td><td>310 (92)</td><td>317 (94)</td></tr>
<tr><td colspan="3">Bevacizumab</td></tr>
<tr><td>Yes</td><td>22 (7)</td><td>14 (4)</td></tr>
<tr><td>No</td><td>315 (93)</td><td>323 (96)</td></tr>
<tr><td colspan="3">Other</td></tr>
<tr><td>Yes</td><td>2 (1)</td><td>4 (1)</td></tr>
<tr><td>No</td><td>335 (99)</td><td>333 (99)</td></tr>
</table>
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>Primary endpoint
The primary endpoint was OS, measured from randomisation to death from any cause
Secondary endpoint
Investigator assessed PFS, defined as the time from randomisation to disease progression or death due to any cause
The incidence of carboplatin and paclitaxel hypersensivity
The effect of treatment on patient-reported outcomes and quality of life</td></tr>
<tr><td>Method of analysis</td><td>The primary analysis of OS was done by intention-to-treat. Safety analyses included only those patients who had started therapy. PFS and OS were calculated from the date of randomisation. The primary analysis used log-rank test stratified by treatment-free interval and participation in the surgical objective to compare OS or PFS between treatment groups. The proportional hazards model was used to estimate treatment HRs with their corresponding confidence intervals. SAS version 9.4 was using in all analyses.</td></tr>
<tr><td>Subgroup analyses</td><td>Prior treatment interval, participation in surgical randomisation and previous use of bevacizumab were all pre-planned analytical subgroups.</td></tr>
</table>

Abbreviations: CNS – Central nervous system; ECOG – Eastern Cooperative Oncology Group; HR – Hazard ratio; IQR – Interquartile range; RECIST – Response Evaluation Criteria in Solid Tumours; OS – Overall survival; PFS – Progression-free survival; VEGF – Vascular endothelial growth factor. * Low-grade serous cancer was not excluded but was not specifically defined in this trial. ¥ Others include adenocarcinoma, not otherwise specified. α Stratification variable. β Treatment-free interval reported here are data submitted immediately before randomisation and not data recorded in the electronic case-report forms. Ω variable as reported on the electronic case-report forms

5 Clinical questions

5.1 Clinical question 1: What sort of increased clinical value does maintenance therapy with niraparib offered compared to olaparib in patients with a BRCA1/2 mutation and platinum-sensitive, relapse HGSC and response to platinum-base chemotherapy

5.1.1 Presentation of relevant studies

One relevant Phase 3 RCT (ENGOT-OV16/NOVA trial) was identified for niraparib for the maintenance therapy in patients with platinum-sensitive, relapse high grade serous carcinoma (HGSC) and response to platinum-based chemotherapy. A summary of the trial is provided in Table 6 (section 4.2).[8]

Two relevant RCTs were identified for olaparib for the maintenance therapy in patients with platinum-sensitive, relapse HGSC and response to platinum-based chemotherapy; Study 19 (Phase 2) and SOLO-2 (Phase 3). A summary of the Phase 2 study, Study 19 and Phase 3 study, SOLO-2 trials are provided in Table 7 and Table 8 (section 4.2), respectively.[16,17,19] It should be noted that Study 19 was the Phase 2 study for the original license for olaparib and the current reimbursement of olaparib in Denmark in the *BRCA*mut population. The Phase 3 study, SOLO-2, was published recently and is in the g*BRCA*mut population only, which is more reflective of the g*BRCA* cohort in the ENGOT-OVA16/NOVA study. It was however not part of the original reimbursement decision for olaparib.

5.1.1.1 Patient characteristics

Clinically relevant differences between the patient cohorts of ENGOT-OV16/NOVA, Study 19 and SOLO-2 have been identified. Predominantly ENGOT-OV16/NOVA has a greater number of patients with only two lines of chemotherapy in the treatment arm than those in Study 19 in g*BRCA*mut patients (50.7% vs. 35.0%, respectively). It might be expected that patients who have had two prior lines of therapy would have longer PFS on maintenance therapy than patients who have had three prior lines, and therefore the patient groups cannot be viewed as similar. The number of patients who have received two prior lines of platinum-based chemotherapy in SOLO-2 is 56%, which is closer to the value recorded in the ENGOT-OV16/NOVA trial.[8, 16,19]

The ENGOT-OV16/NOVA trial also included significantly fewer g*BRCA*mut patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 in the treatment group than in Study 19 (*BRCA*mut) or SOLO-2 (g*BRCA*mut) (65.9% vs. 84% vs. 83%, respectively). The ECOG performance status assesses how a patient's disease is progressing; a higher score correlates to a decrease in ability to care for themselves, daily activity, and physical ability.[22] Therefore, the difference in ECOG scores indicates that the population in Study 19 (*BRCA*mut) and SOLO2 (g*BRCA*mut) are healthier than the g*BRCA*mut ENGOT-OV16/NOVA population.

In addition, the ENGOT-OV16/NOVA and SOLO-2 trials were prospectively characterised for patients with g*BRCA*mut and non-g*BRCA*mut, and g*BRCA*mut patients, respectively, whereas only a minority of patients were sufficiently characterised prospectively with respect to the mutation status in Study 19. For example, in Study 19, only 59 patients were identified with a *BRCA1* or *BRCA2* mutation compared with 203 patients with a g*BRCA*mut in the ENGOT-OV16/NOVA study and 286 patients with a g*BRCA*mut in the SOLO-2 study.[8, 16,19]

Study Characteristics

The primary endpoint of PFS was not consistent across the three studies. The ENGOT-OV16/NOVA PFS primary endpoint assessed by an independent review committee (IRC) included all radiological and clinical progression events and deaths, while Study 19 and SOLO-2 PFS primary endpoints by investigator assessment included only radiological events and death (Table 11).[8, 16,19]

Secondly, in Study 19, stratification and analysis by *BRCA* mutation status was not part of the initial study design and was only included as a post-hoc analysis. In addition SOLO-2 was limited to g*BRCA*mut patients only. Finally, the scanning interval was different in ENGOT-OV16/NOVA to Study 19 and SOLO-2 with scans being performed every 8 weeks in ENGOT-OV16/NOVA and every 12 weeks in Study 19 and SOLO-2. This shorted scanning interval in NOVA may potentially lead to shorter median PFS than in Study 19 and SOLO-2.[8, 16,19]

Table 11 Comparison of Study Endpoints

	Investigator Led PFS				Independent Central Review PFS			
	Primary endpoint	Radiologic PD	Clinical PD	Death	Primary Endpoint	Radiologic PD	Clinical PD	Death
ENGOT-OV16/NOVA	×	✓	✓	✓	✓	✓	✓	✓
Study 19	✓	✓	×	✓	×	✓	×	×
SOLO-2	✓	✓	×	✓	×	✓	×	×

Abbreviations: PFS – Progression-free survival; PD – Progressed disease

5.1.2 Results per study

5.1.2.1 ENGOT-OV16/NOVA

A summary of results for the intention-to-treat (ITT) and safety g*BRCA*mut cohort from the ENGOT-OV16/NOVA trial is provided in Table 12. The ITT population was considered to be the primary set for all efficacy analyses. The three predefined primary efficacy populations were the g*BRCA*mut cohort, the homologous recombination DNA repair deficiency (HRD)-positive subgroup of the non-g*BRCA*mut cohort (non-g*BRCA*mut HRD-positive) and the overall non-g*BRCA*mut cohort. Safety data were analysed in the safety population, which included all the patients who had received at least one dose of niraparib or placebo.[8]

Table 12 ENGOT-OV16/NOVA gBRCAmut results (Mirza 2016)[8,23]

Trial name:	ENGOT-OV16/NOVA									
NCT number:	NCT01847274									
Outcome	Study arm	N	Result	Estimated absolute difference in effect			Estimated relative difference in effect			Description used for e
				Difference	95% CI	P value	Hazard/Odds/ Risk ratio	95% CI	P value	
Median overall survival months (Immature, median not reached)	Niraparib	138	NE	NE	NE	NE	HR: 0.91	(0.360, 2.282)	p=0.8346	A two-sided test using ra stratification used to analy which was su with the use methods. Th estimated us side 95% con intervals usir stratified Cox proportional model, with stratification used in rand
	Placebo	65	NE							
Median progression-free survival (Assessed by IRC)	Niraparib	138	21.0 (12.9, NE) months	15.5	NE	NE	HR: 0.27	(0.173, 0.410)	p<0.0001	A two-sided test using ra stratification used to analy which was su

	Placebo	65	5.5 (3.8, 7.2) months							with the use methods. Th estimated us side 95% cor intervals usir stratified Cox proportional model, with stratification used in rand
Adverse reactions: Number and percentage of patients that stops therapy due to adverse reactions	Niraparib	367	54 (14.7%)	12.5%	NR	NR	RR: 6.58	(2.42, 17.89)	NE	Adverse ever serious adve were collecte time of signi informed cor through trea discontinuat serious adve (including de collected for after treatme discontinuat
	Placebo	179	4 (2.2%)							
Adverse reactions: Number and percentage of patients that experiences one or more grade 3-4 adverse reactions	Niraparib	367	272 (74.1%)	51.2%	NR	NR	RR: 3.24	(2.46, 4.26)	NE	Adverse ever serious adve were collecte time of signi informed cor through trea discontinuat serious adve (including de
	Placebo	179	41 (22.9%)							

										collected for after treatme discontinuati
Adverse reactions: Number and percentage of myelodysplastic syndrome	Niraparib	138	3 (2%)	0.8%	NR	NR	RR: 3.32*	(0.17, 63.42)*	NE	Adverse even serious adve were collecte time of signi informed con through trea discontinuati serious adve (including de collected for after treatme discontinuati
	Placebo	65	0 (0%)							
Adverse reactions: Number and percentage of acute myeloid leukaemia	Niraparib	138	0 (0%)	-0.6%	NR	NR	RR: 0.16*	RR: (0.01, 3.83)*	NE	Adverse even serious adve were collecte time of signi informed con through trea discontinuati serious adve (including de collected for after treatme discontinuati
	Placebo	65	1 (2%)							

Quality of life	See section 5.1.2.1.4 on Health-related Quality-of-life below								
PFS2 months (Assessed by IRC; immature, median not reached)	Niraparib	138	25.8 (20.3, NE)	6.3	NE	NE	HR: 0.48	(0.280, 0.821)	0.006	A two-sided lo using random stratification f used to analys which was sur with the use o methods. The estimated use side 95% conf intervals using Cox proportio model, with s factors used i randomisation
	Placebo	65	19.5 (13.3, NE)							
Median time to first subsequent therapy months	Niraparib	138	21.0 (17.5, NE)	12.6	NE	NE	HR: 0.31	(0.205, 0.481)	<0.0001	A two-sided lo using random stratification f used to analys which was sur with the use o methods. The estimated use side 95% conf intervals using Cox proportio model, with s
	Placebo	65	8.4 (6.6, 10.6)							

										factors used i randomisatio
Median time to second subsequent therapy months (Immature, median not reached)	Niraparib	138	25.8 (22.4, NE)	5.3	NE	NE	HR: 0.48	(0.280, 0.821)	0.0062	A two-sided l using random stratification used to analy which was su with the use methods. The estimated use side 95% conf intervals using Cox proportio model, with s factors used i randomisatio
	Placebo	65	20.5 (16.0, NE)							
Median Chemotherapy-free interval months	Niraparib	138	22.8 (17.9, NE)	13.4	NE	NE	HR: 0.26	(0.166,0.409)	<0.0001	A two-sided l using random stratification analyse CFI, w summarised of the KM me HR was estim two-side 95% intervals using Cox proportio model, with s factors used i randomisatio
	Placebo	65	9.4 (7.9, 10.6)							

Abbreviations: CI – Confidence interval; CFI – Chemotherapy-free interval; HR – Hazard ratio; IRC – Independent review committee; KM – Kaplan Meier; NE – Not estimated; NR – Not reported; N/A – Not applicable; OS – Overall survival; PFS – Progression-free survival; PFS2 – Progression-free survival 2; RR – Relative risk; TFST – Time to first subsequent therapy; TSST – Time to second subsequent therapy

*Continuity correction DSU TSD2[24]

5.1.2.1.1 Overall survival

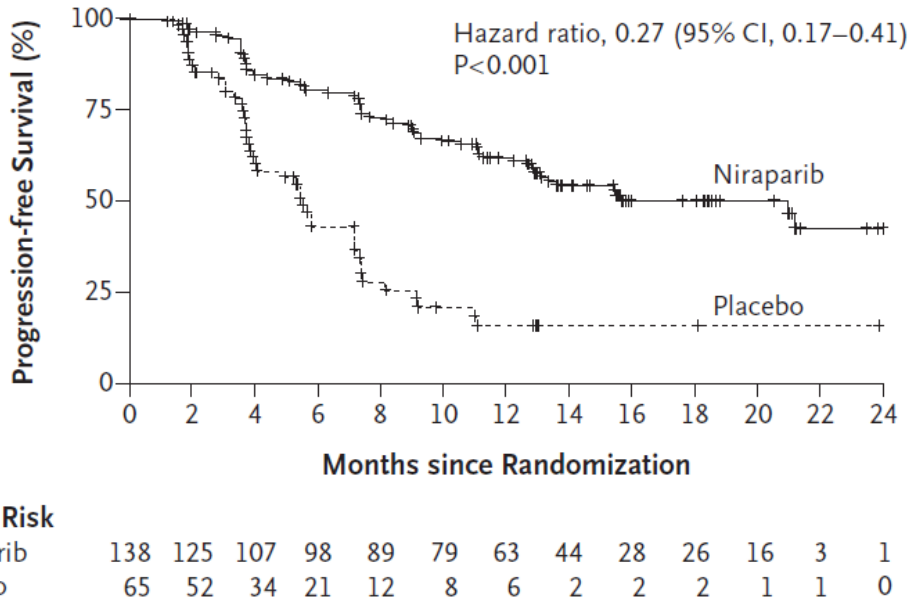
Overall survival (OS) was defined as the time from study randomisation to the date of death due to any cause. Patients known to be alive were censored at the last known survival follow-up date. OS data are currently immature; at the time of database lock for PFS analysis a total of 24 patients had died in the gBRCAmut cohort, including 16 (12%) of all 138 patients randomised to niraparib and 8 (12%) of all 65 patients randomised to placebo.[23]

5.1.2.1.2 Progression-free survival

PFS was defined as the time from date of treatment randomisation to the date of first documentation of progression or death by any cause in the absence of documented progression, whichever occurred first. The duration of PFS in the primary efficacy analysis was to be based on the determination of progression made by an IRC. In the ENGOT-OV16/NOVA trial, niraparib met the primary endpoint of prolonging PFS versus placebo in all three prospectively defined primary patient populations. In the g*BRCA*mut cohort, the treatment effect was statistically significant with niraparib achieving a median PFS of 21.0 months versus 5.5 months for patients in the placebo group, a difference of 15.5 months (HR, 0.27; 95% CI, 0.17-0.41; p<0.001). Niraparib reduced the risk of disease progression or death by 73% in these patients. Thus, patients in the placebo group were 3.7 times more likely to have progression of disease or die at any time compared with patients in the niraparib group. [23] As evident from the Kaplan-Meier (KM) plot, the PFS benefit achieved with niraparib was observed approximately 2 months from randomisation and was maintained throughout the trial (Figure 1). Consistent with this, there was a substantially greater proportion of patients in the niraparib group who were progression-free (or who had not died) at each 6-month interval.

In addition, by extending time to progression after platinum-based chemotherapy, niraparib treatment will in turn increase the number of patients who are considered for retreatment with platinum-based chemotherapy in the next treatment line. This is a key aspect of treatment, as once patients become platinum-resistant, treatment options are limited and prognosis is poor. By increasing PFS and the likelihood of consideration for retreatment with platinum-based therapies in the next treatment line, niraparib maintenance therapy can extend OS to greater extent than that already gained through PFS. Furthermore, by prolonging time to progression, niraparib extends the time until the next line of platinum-based chemotherapy, which is associated with burdensome AEs for patients. Hence niraparib patients have the potential to remain progression and toxicity free for longer than patients receiving placebo.

Figure 1 Kaplan–Meier estimates of progression-free survival for niraparib and placebo gBRCAmut cohort



Abbreviations: CI – Confidence interval; g*BRCA*mut – Germline breast cancer susceptibility gene mutation; HR – Hazard ratio. Mirza et al., 2016[8]

5.1.2.1.3 Adverse events

Results from the Phase 3 ENGOT-OV16/NOVA trial provide a robust assessment of the safety profile of niraparib maintenance therapy in women with platinum-sensitive recurrent ovarian cancer. The tolerability of niraparib is demonstrated by the relatively low total discontinuation rate (14.7% vs. 2.2% for placebo) due to AEs, owing predominantly to the effective management of most AEs by dose reductions or treatment interruptions.[8]

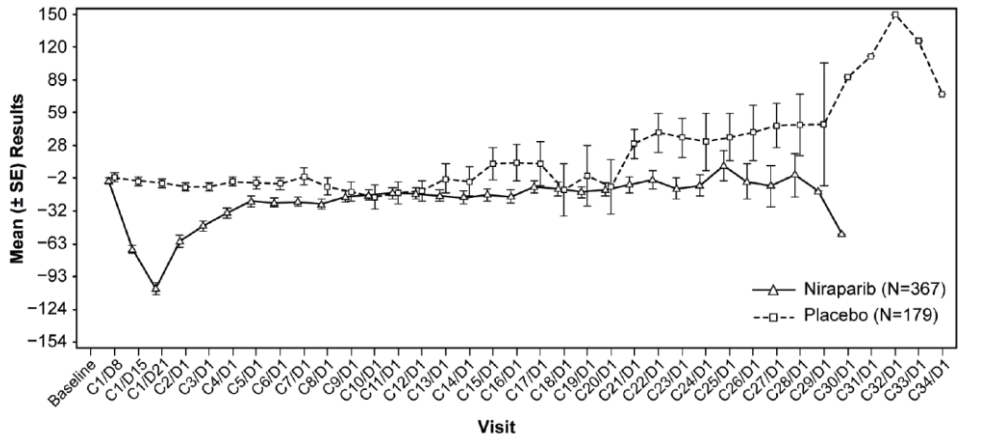
Niraparib therapy was received by 367 patients in whom it was generally well tolerated, with the AEs observed in the trial consistent with the known safety profile of niraparib and other PARP inhibitors. The most common non-haematological AEs of any grade observed in the niraparib group were nausea (73.6% vs. 35.2% for placebo), fatigue events (includes fatigue, asthenia, malaise, and lethargy) (59.4% vs. 41.3%), constipation (39.8% vs. 20.1%), and vomiting (34.3% vs. 16.2%).[8] Most of these events were mild-to-moderate in severity, and managed by dose reductions.

The incidence of any grade 3/4 AEs was 74.1% in the niraparib group compared with 22.9% in the placebo group.[8] In line with previously published results for PARP inhibitors, haematological events such as thrombocytopenia events (grade 3/4: 33.8% niraparib vs. 0.6% placebo) and anaemia events (grade 3/4: 25.3% niraparib vs. 0% placebo) were amongst the most commonly reported AEs.[8,25] Most events, however, occurred in the first three treatment cycles, and the frequency of these events dropped significantly over time following dose modifications.[8,26]

The majority of thrombocytopenia laboratory abnormalities occurred in the first three cycles. After dose adjustment on the basis of individual AE profile, the incidence of grade 3/4 thrombocytopenia events was infrequent beyond cycle 3.[8,26] Platelet levels in the niraparib group increased from a nadir during cycle 1,

returning to baseline levels by the third cycle, and thereafter remaining stable during the course of the study (Figure 2).

Figure 2 Platelet levels over time during therapy with niraparib or placebo in the ENGOT-OV16/NOVA trial: Data are presented for all patients in the safety population (N=546)



Abbreviations: C – Cycle; D – Day; SE – Standard error. NEJM Appendices, 2016[8]

There were no on-treatment deaths reported during the study in either treatment arm.[8]

A recent publication analysed the ENGOT-OV16/NOVA data further.[27] The analysis identified that patients with a low body weight (<77 kg) or low baseline platelet count (<150,000/µL platelets) in the ENGOT-OV16/NOVA study experienced a greater incidence of grade ≥ 3 thrombocytopenia during the first month of niraparib treatment. It was observed that 35% of patients below the cut-offs compared to 12% of patients above these cut-off criteria for both baseline characteristics experienced grade ≥ 3 adverse events. Hence, this publication recommended an additional modification to the dosing regimen: the publication recommended a starting-dose of 200 mg niraparib for patients with baseline weight of <77 kg and/or baseline platelets of <150,000/µL to avoid significant haematologic toxicity, especially thrombocytopenia.[27]

The frequency of myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) was low in both g*BRCA*mut treatment arms; 2% and 0% of niraparib, and 0% and 2% of placebo patients experienced MDS and AML, respectively.[23]

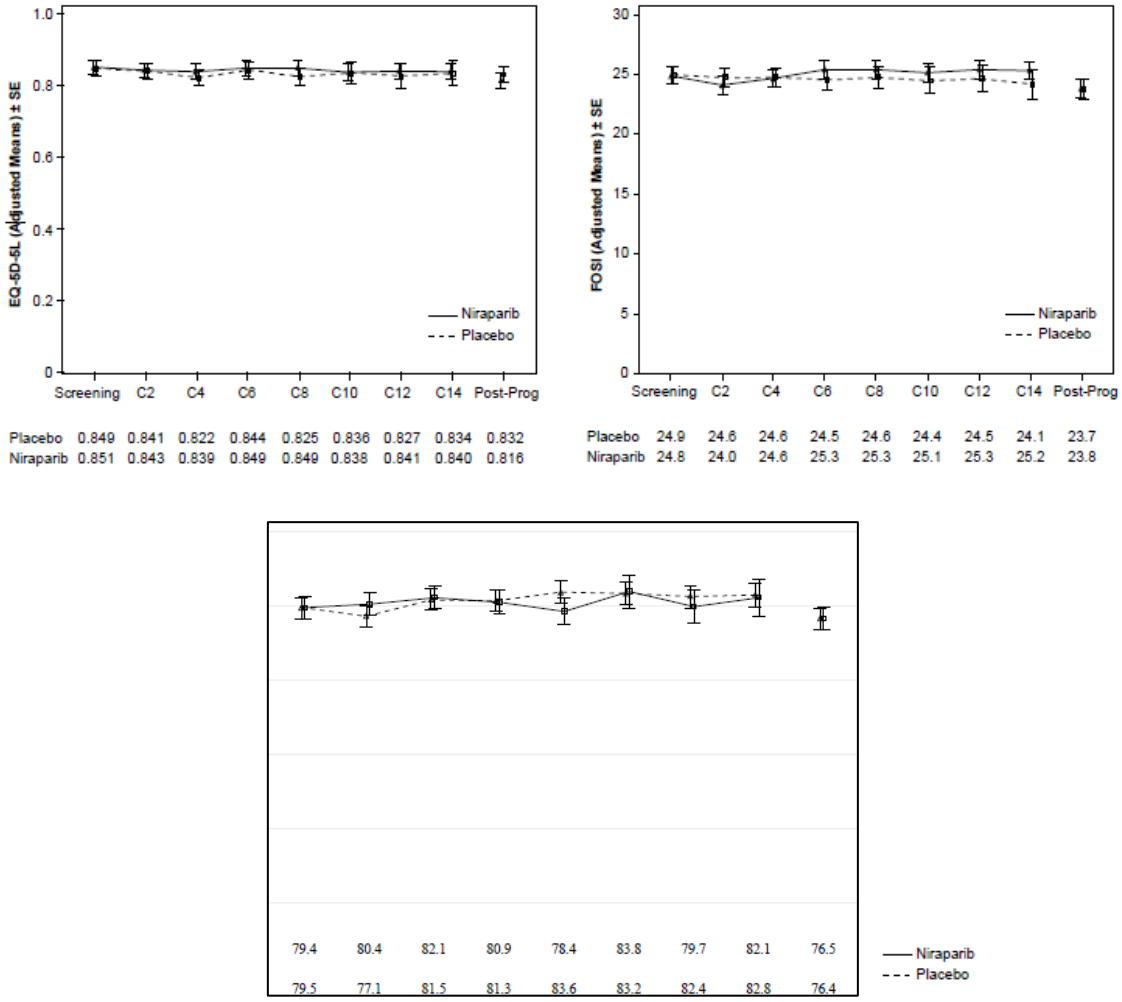
In conclusion, niraparib maintenance therapy was well tolerated as treatment for patients with platinum-sensitive OC, with the incidence of most AEs reducing significantly in later treatment cycles due to individualised dose modification.

5.1.2.1.4 Health-related Quality-of-life

Health-related quality of life (HRQoL) was assessed using the Functional Assessment of Cancer Therapy–Ovarian Symptom Index (FOSI) (based on a subset of questions from the Function assessment of Cancer Therapy Ovarian [FACT-O] questionnaire) and EuroQol-5-dimension-5-levels (EQ-5D-5L) and EQ-5D-5L-VAS, after every two cycles through to cycle 14, and then after every three cycles, whereby a cycle was defined as 4 weeks. If the patient discontinued study treatment, an assessment was performed at that time and a further single assessment was performed 8 weeks (+/- 2 weeks) later regardless of subsequent treatment.

According to all measures, HRQoL was similar in both treatment groups and pre-treatment levels were maintained throughout the treatment period. KM plots of EQ-5D-5L, EQ-5D-5L-VAS, and FOSI time to symptom worsening also showed no statistically significant difference between niraparib and placebo (Figure 3).

Figure 3 Patient-reported outcomes for EQ-5D-5L and FOSI by study visit (Top left – EQ-5D-5L, Top right – FOSI, Bottom – EQ-5D-5L-VAS)



Abbreviations: EQ-5D-5L, EuroQol 5-dimension 5-level; EQ-5D-5L-VAS, EuroQol 5-dimension 5-level visual analogue scale;FOSI, Functional Assessment of Cancer Therapy – Ovarian Symptom Index; g*BRCA*mut, germline breast cancer susceptibility gene mutation; NEJM, New England Journal of Medicine

NEJM Appendices, 2016

FOSI

The FOSI score remained stable throughout the study and was maintained at baseline levels. In the g*BRCA*mut cohort, at screening, the mean FOSI score for niraparib patients was 24.8 compared with 24.9 for placebo. Scores for cycle 14 were 25.2 (niraparib) and 24.1 (placebo). There were no statistical differences in the two treatment groups for the g*BRCA*mut cohort (p>0.05). The KM curve for FOSI time to symptom worsening also found no statistically significant difference between niraparib and placebo (log rank p=0.405).

Pain and fatigue symptoms on the FOSI were examined separately. Overall, the percentage of patients reporting pain tended to be lower in the niraparib group versus the placebo group at each assessment point. Additionally, patients receiving niraparib tended to have lower rates of fatigue versus placebo.

Time to symptom worsening on the overall FOSI score was defined as the time from randomization to the first FOSI assessment with a worse score compared to the baseline score. If a patient reported a 2-point decrease from baseline, the patient was considered to have "worsened". A change from baseline within ±2 points was considered "stable". For the g*BRCA*mut cohort, analyses demonstrated that patients did not show a statistically significant change in FOSI score from baseline ($p > 0.05$). During the maintenance period, 53.5%, 55.0%, and 50.5% in the niraparib cohort, and 56.4%, 58.1%, and 52.8% in the placebo cohort, were reported as "stable" for Cycles 2, 4, and 6, respectively. No statistically significant differences were observed between the cohorts who reported as "worsened" (28.9%, 23.9%, and 21.1% in the niraparib cohort, 23.6%, 23.3%, and 30.6% in the placebo cohort for Cycles 2, 4, and 6, respectively; $p > 0.05$).[23]

Cumulatively, the percentage of patients who were reported as "worsened" was higher in the niraparib cohort for all 3 cycle time points (23.9% at Cycle 2 to 38.4% at Cycle 6 in the niraparib cohort; 20.0% to 32.3% in the placebo cohort), although no statistically significant differences were observed ($p > 0.05$). During the post-progression assessment, the overall cumulative "worsened" percent of patients increased to 47.1% in the niraparib group and 41.5% in the placebo group, although similarly no statistically significant differences were observed ($p > 0.05$). The cumulative percentage of patients that does not show significant worsening in quality of life can then be calculated as 52.9% in the niraparib group and 58.5% in the placebo group. This is a difference of 5.6 percentage points, and hence is not considered clinically relevant as defined by the DMC.[23]

Haematological AEs were found to have no significant negative effect on QoL assessed by FOSI within the ENGOT-OV16/NOVA. In the g*BRCA*mut cohort, at baseline, the mean FOSI score was similar for niraparib patients compared with for placebo (25.1, 25.6). These QoL scores remained stable during the treatment and preprogression period in the niraparib group and no significant differences were observed between the niraparib and placebo group.[28]

EQ-5D-5L

EQ-5D-5L was assessed using health utility index (HUI) and visual analogue scale (VAS). In the g*BRCA*mut cohort, mean baseline HUI was 0.851 (niraparib) and 0.849 (placebo). Scores for cycle 14 were 0.840 (niraparib) and 0.834 (placebo). The corresponding mean baseline VAS scores were 74.6 (niraparib) and 75.2 (placebo).

Haematological AEs were found to have no significant negative effect on QoL assessed by EQ-5D-5L and EQ-5D-5L-VAS within the ENGOT-OV16/NOVA. In the g*BRCA*mut cohort, at baseline, the mean HUI score was similar for niraparib patients compared with for placebo (0.850, 0.847). These QoL scores remained stable during pre-progression and post-progression. Mean HUI scores pre-progression were 0.838 and 0.834 for niraparib and placebo, respectively. Mean HUI scores post-progression were 0.801 and 0.794 for niraparib and placebo, respectively.[28]

Time without symptoms and toxicity (TWiST)

Niraparib maintenance treatment has been shown to provide greater time with out symptoms or toxicity compared to placebo, in patients with recurrent ovarian cancer. A TWiST analysis was conducted based upon the ENGOT-OV16/NOVA trial.

TWiST is a methodology that partitions PFS into two health states; time with toxicity (TOX) and time without symptoms or toxicity. The method evaluates the trade-off between treatment toxicity and time to progression. It provides an estimate of time when a patient is progression and toxicity-free, and hence should be expected to maintain a good HRQoL.

The primary TWiST analysis was performed on the ITT population of the ENGOT-OV16/NOVA g*BRCA*mut and non-g*BRCA*mut cohorts, who had received at least two platinum-based chemotherapy regimens. Patient characteristics were well balanced in the two cohorts at baseline.

Mean PFS was estimated for niraparib and RS by fitting parametric survival curves to Kaplan Meier (KM) data for 553 patients enrolled in the ENGOT-OV16/NOVA trial. Mean TOX was estimated based on area under the KM for symptomatic AEs including grade ≥2 fatigue, nausea, and vomiting. Haematological AEs were not considered for the TWiST analysis was they were found to have no significant negative effect on QoL assessed by FOSI, EQ-5D-5L and EQ-VAS within the ENGOT-OV16/NOVA.[28]

TOX time was calculated as the number of days a patient experienced an AE after randomization and prior to disease progression. TWiST was then estimated as the difference between mean PFS and mean TOX between niraparib and RS.

Treatment with niraparib resulted in a mean PFS benefit of 3.23 years and a mean TOX of 0.28 years compared with placebo in the g*BRCA*mut cohort. Hence, treatment with niraparib resulted in a mean TWiST benefit of 2.95 years compared with placebo in the gBRCAmut. Thus, patients treated with niraparib in the ENGOT-OV16/NOVA trial experienced more time without symptoms or toxicities compared with placebo.[29]

5.1.2.1.5 Other endpoints

Time to first subsequent therapy

Time to first subsequent chemotherapy (TFST) was defined as the time from randomisation to date of the first subsequent anti-cancer therapy. Patients who did not receive subsequent anti-cancer therapy were censored at their last contact date. In the g*BRCA*mut cohort, maintenance treatment with niraparib significantly prolonged TFST by 12.6 months compared with placebo. The median TFST was 21.0 months in the niraparib group compared with 8.4 months in the placebo group (HR, 0.31; 95% CI, 0.21-0.48; p<0.001). Patients in the placebo group were therefore 3.2 times more likely to require subsequent anti-cancer therapy or to have died at any time compared with patients in the niraparib group.

PFS2 and TSST

Progression-free survival on next line of therapy (PFS2) and time to second subsequent therapy (TSST) data from the ENGOT-OV16/NOVA trial is currently immature. TSST was defined as the time from randomisation to the data of the second subsequent anti-cancer therapy. PFS2 was defined as the time from the date of randomisation in the current study to the date of assessment of progression during the receipt of the next

anti-cancer therapy after the study treatment or until death by any cause. If progression could not be determined the start date of subsequent anti-cancer therapy was used as a surrogate date of disease progression. If the date of progression, date of death, and start date of the second line subsequent anti-cancer therapy were unknown, then PFS2 was censored at the stop date of the first line of subsequent anti-cancer therapy. If the stop date was unknown, PFS2 was censored on the last contact date.

Interim results show that the duration of PFS2 and TSST were significantly prolonged in the niraparib group in the g*BRCA*mut cohort (HR, 0.48; 95% CI, 0.28-0.82; p=0.006 and HR, 0.48; 95% CI, 0.280-0.821; p=0.0062 respectively).[23]

Chemotherapy free interval

The chemotherapy-free interval (CFI) was defined as the time from the end of treatment with the last platinum therapy until initiation of the next anti-cancer therapy (excluding maintenance therapy). If no subsequent anti-cancer therapy (excluding maintenance therapy) was initiated, CFI was to be censored on the last date of treatment on the current study. In the g*BRCA*mut cohort, maintenance treatment with niraparib significantly prolonged CFI by 13.4 months compared with placebo; median CFI was 22.8 months in the niraparib group compared with 9.4 months in the placebo group (HR, 0.26; 95% CI, 0.166-0.409; p<0.0001). Patients receiving niraparib treatment thus remained free of chemotherapy for a longer duration, hence delaying the deleterious effects of chemotherapy. Results for TFST were consistent with those for CFI.[23]

5.1.2.2 Study 19

A summary of results for the *BRCA*mut subgroup from Study 19 is provided in Table 13. Efficacy analyses and patient-reported outcomes included all patients who were randomly assigned to a study group, and safety analyses included all patients who received at least one dose of the assigned study medication. A pre-planned analysis of retrospectively identified *BRCA*mut patients was performed.[16,18]

Table 13 Study 19 BRCAmut results (Ledermann 2014, Ledermann 2016, olaparib CHMP report (original and updated), NICE TA381)[17,18,30–32]

Trial name:	Study 19									
NCT number:	NCT00753545									
Outcome	Study arm	N	Result	Estimated absolute difference in effect			Estimated relative difference in effect			Description of method used for estimation
				Difference	95% CI	P value	Hazard/Odds/ Risk ratio	95% CI	P value	
Median overall survival (months)	Olaparib	74	34.9 (29.2-54.6)	4.7	NR	NR	HR: 0.62	(0.41-0.94)	0.025	Overall survival was analysed with the use of a Cox proportional hazards model that included covariates tha was used as stratification factors at randomization.
	Placebo	62	30.2 (23.1-40.7)							
Median progression-free survival months (Investigator assessed)	Olaparib	74	11.2 (8.3-NE)	6.9	NE	NE	HR: 0.18	(0.10-0.31)	0.0001	Progression-free survival was analysed with the use of a Cox proportional hazards model that included covariates that was used as stratification factors at randomization.
	Placebo	62	4.3 (3.0-5.4)							

Adverse reactions: Number and percentage of patients that stops therapy due to adverse reactions	Olaparib	74	5 (6.8%)	6.8%	NR	NR	RR: 9.24*	(0.52, 163.89)*	NE	Safety analyses included all patients who received at least one dose of the assigned study medication. Safety was assessed throughout the study by monitorin for adverse events, biochemical laboratory tests, assessment of vital signs and physical examination
	Placebo	62	0 (0%)							
Adverse reactions: Number and percentage of patients that experiences one or more grade ≥3 adverse reactions	Olaparib	74	29 (39.2%)	21.4%	NR	NR	RR: 2.21	(1.20, 4.05)	NE	Safety analyses included all patients who received at least one dose of the assigned study medication. Safety was assessed throughout the study by monitorin for adverse events, biochemical laboratory tests, assessment of vital signs and physical examination
	Placebo	62	11 (17.7%)							
Adverse reactions: Number and percentage of	Olaparib	NR	NR	NR	NR	NR	NR	NR	NR	NR

myelodysplastic syndrome	Placebo	NR	NR							
Adverse reactions: Number and percentage of acute myeloid leukaemia	Olaparib	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo	NR	NR							
Quality of life	See section 5.1.2.2.4 on Health-related Quality-of-life below									
PFS2 months	Olaparib	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo	NR	NR							
Median time to first subsequent	Olaparib	74	15.6 (12.3-28.2)	9.4	NR	NR	HR: 0.33	(0.22-0.50)	<0.0001	TFST was analysed wit the use of a Cox proportional hazards model that included covariates that was

treatment months	Placebo	62	6.2 (5.3-9.2)							used as stratification factors at randomization.
Median time to second subsequent treatment months	Olaparib	74	23.8 (17.7 – NE)	8.6	NR	NR	HR: 0.44	(0.29-0.67)	0.00013	TSST was analysed with the use of a Cox proportional hazards model that included covariates that was used as stratification factors at randomization.
	Placebo	62	15.2 (13.9- 18.7)							
Median Chemotherapy-free interval months	Olaparib	74	NR	9	NR	NR	NR	NR	NR	NR
	Placebo	62	NR							

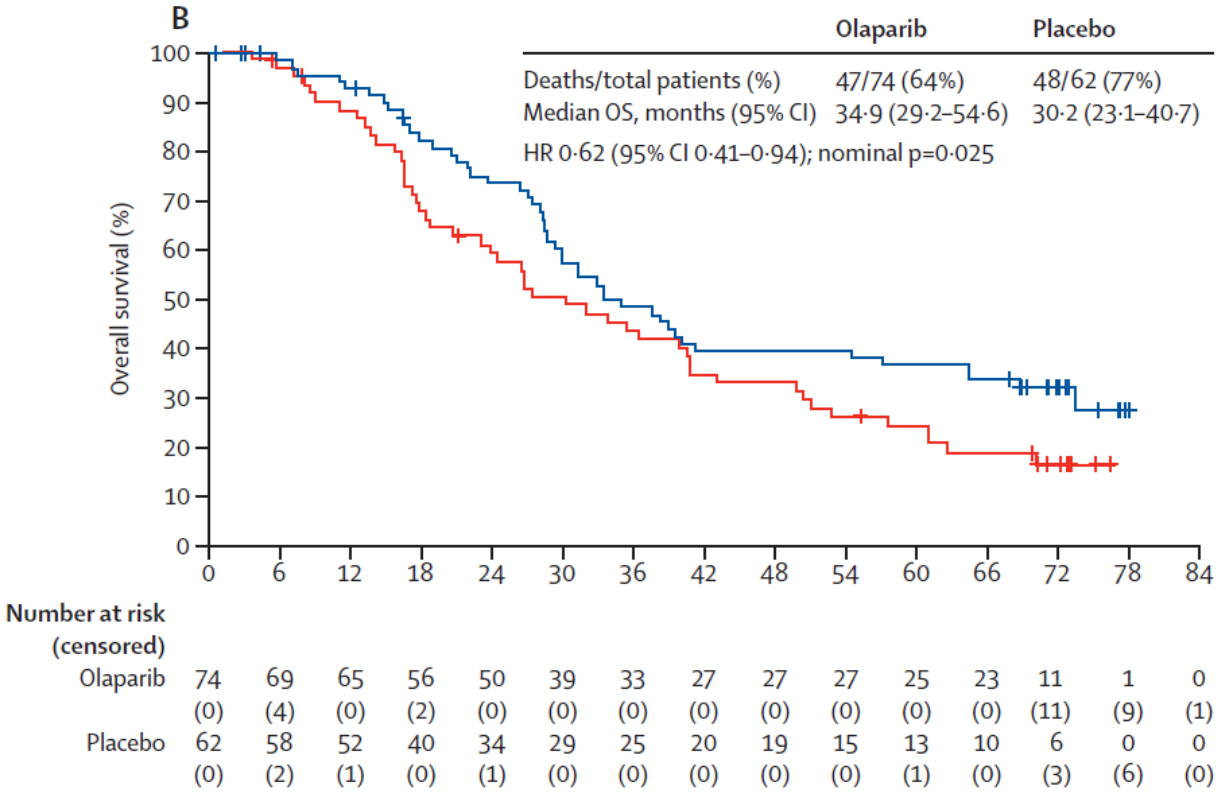
Abbreviations: CI – Confidence interval; CFI – Chemotherapy-free interval; CHMP – Committee for Medicinal Products for Human Use; HR – Hazard ratio; NE – Not estimated; NR – Not reported; N/A – Not applicable; PFS – Progression-free survival; PFS2 – Progression-free survival 2; RR – relative risk; TA – Technology appraisal; TFST – Time to first subsequent therapy; TSST – Time to second subsequent therapy

*Continuity correction DSU TSD2[24]

5.1.2.2.1 Overall survival

OS was defined as the time from date of randomisation to the date of death from any cause.[30] At point of data cut-off (30th September 2015), the median OS was 34.9 and 30.2 months for olaparib and placebo in the *BRCA*mut population, respectively (HR 0.62 [95% CI 0.41-0.94], nominal p=0.025). Figure 4 presents KM OS data for olaparib and placebo *BRCA*mut. Crossover was not allowed in Study 19; however at data cut-off 17 (13%) of 129 patients from the placebo arm had received post-discontinuation PARP inhibitor treatment, of whom 14 (23%) of 62 patients had *BRCA*mut, via other clinical studies. These additional treatments were deemed to have had a potential to confound the OS data. An exploratory analysis was conducted for the *BRCA*mut subgroup where all patients were excluded from sites where a least one patient from the placebo group received post-discontinuation PARP inhibitor treatment. Results of this analysis showed a greater treatment effect.[18,33]

Figure 4 Overall survival Kaplan-Meier for olaparib and placebo *BRCA*mut (Ledermann 2016)[18]



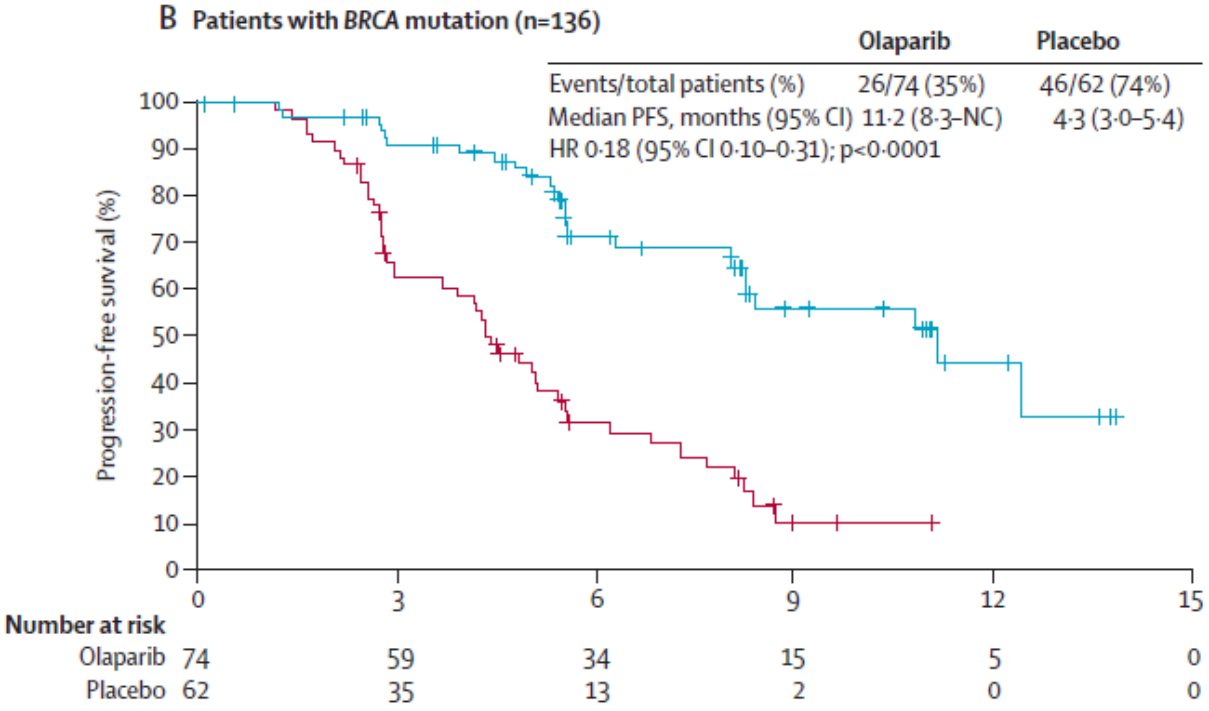
Abbreviations: *BRCA* – Breast cancer susceptibility gene; CI – Confidence interval; HR – Hazard ratio; OS – Overall survival

5.1.2.2.2 Progression-free survival

PFS was defined as the time from the date of randomisation on completion of chemotherapy until the date of objective assessment (by the site investigator) of disease progression according to the RECIST guidelines or death (by any cause in the absence of progression).[30] At point of data cut-off (30th June 2010), the median progression-free survival (PFS) was 11.2 and 4.3 months for olaparib and placebo in the *BRCA*mut

population, respectively (HR 0.18 [95% CI 0.10-0.31], p<0.0001). Figure 5 presents KM PFS data for olaparib and placebo *BRCA*mut.[17]

Figure 5 Progression-free survival Kaplan-Meier for olaparib and placebo BRCAmut (Ledermann 2014)[17]



Abbreviations: *BRCA* – Breast cancer susceptibility gene; CI – Confidence interval; HR – Hazard ratio; PFS – Progression-free survival; NC – Not calculated; OS – Overall survival

5.1.2.2.3 Adverse events

Results from the Study 19 trial were consistent with a large pooled dataset of patients receiving olaparib 400 mg capsules as a monotherapy, and demonstrated that the most frequently occurring AEs are generally intermittent and low grade (National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) grade 1 or 2).[30]

The most common non-haematological AEs of any grade observed for olaparib and placebo were nausea (73% vs. 32% for placebo), fatigue (54% vs. 37%), vomiting (36% vs. 8%) and diarrhea (30% vs. 29%).[30]

A numerically higher percentage of all patients in the olaparib group reported AEs of CTCAE grade ≥ 3 or higher (39.2% vs. 17.7%). Haematological AEs accounted for 15.8% of CTCAE grade ≥ 3 AEs, and included anaemia (5.4%1 vs. 1.6%), Leukopenia (2.7% vs. 0%) and neutropenia (4.1% vs. 1.6%).[31]

Side effects of the treatment were managed through dose interruptions (32.1% vs. 7.0%) and dose reductions (18.9% vs. 4.7%) in the g*BRCA*mut subgroup for olaparib and placebo, respectively.[31] Discontinuation due to AEs was infrequent, with 6.8% of *BRCA*mut patients discontinuing in the olaparib group and 0% of *BRCA*mut patients discontinuing in the placebo group.[30]

MDS and AML were reported in a small number of patients who received olaparib alone or in combination with other anticancer drugs. The majority of these cases have been fatal. The duration of therapy with

olaparib in patients who developed MDS or AML varied from less than 6 months to more than 2 years. However, the exact proportion of patients who experienced a MDS and AML in Study 19 is not reported.[30]

There were no additional reports of AEs resulting in death at the 2015 data cutoff compared with the 2012 data cutoff, at which one patient had died solely from AEs (haemorrhagic stroke and thrombocytopenia, deemed to be treatment related).[18]

5.1.2.2.4 Health-related Quality-of-life

HRQoL was assessed for patients while on study treatment, using the FACT-O questionnaire, FOSI and the trial outcomes index (TOI). Patient reported outcomes were not measured post-progression, therefore Study 19 was not able to determine the impact on HRQoL and symptoms post-progression. According to all three measures, the active treatment of olaparib in a maintenance setting demonstrated no detriment to HRQoL scores and maintained QoL for patients receiving olaparib compared to placebo pre-progression.[30]

FACT-O

FACT-O was administered at randomisation (baseline) and every 4 weeks until progression. Olaparib demonstrated no difference to placebo in terms of symptom control and in maintaining patient's HRQoL.[30]

The percentage of patients who reported an improvement in symptoms was based on considering a patient to have improved if they had two visit responses of "improved" with a minimum of 21 days apart without an intervening visit response of "worsened". "Improved" was defined as an increase from baseline of ≥9.[34]

The percentage of patients that showed improvement throughout the study duration was 21.1% in the olaparib 400 mg BID cohort compared with 18.9% in the placebo cohort.[34] The percentage of patients that does not show significant worsening in quality of life was hence 78.9% in the niraparib group and 81.1% in the placebo group.

The odds ratio was 1.16, indicating a greater chance of improvement with olaparib than placebo, although these results were not statistically significant (p=0.656). The time to worsening of disease-related symptoms (2.8 months olaparib, 4.6 months placebo) was shorter with olaparib than with placebo; however, the difference was not significant.[34]

FOSI

Patient experience of important symptoms, as measured by FOSI, remained consistent over the treatment period and similar for olaparib and placebo patients. No significant changes from baseline were observed.[30]

TOI

Patients had high baseline scores in both treatment arms which would be expected as all patients were in response to their most recent chemotherapy and in remission. The primary endpoint of HRQoL, as measured by TOI, remained consistent over time and similar for olaparib and placebo. The greatest decrease was observed for month 1 for olaparib and month 4 for placebo.[30]

5.1.2.2.5 Other endpoints

Time to first subsequent therapy

TFST was defined as the time from randomisation to the start of the first cancer therapy received following discontinuation of randomised treatment or death. In the *BRCA*mut cohort, maintenance treatment with olaparib extended TFST by 9.4 months compared with placebo. The median TFST was 15.6 months in the olaparib arm compared with 6.2 months in the placebo arm (HR, 0.33; 95% CI, 0.22-0.50; p≤0.0001).[30]

Time to second subsequent therapy

TSST was defined as the time from randomisation to the start of the second cancer therapy subsequent to discontinuation of randomised treatment or death. In the *BRCA*mut cohort, maintenance treatment with olaparib extended TSST by 8.6 months compared with placebo. The median TSST was 23.8 months in the olaparib arm compared with 15.2 months in the placebo arm (HR, 0.44; 95% CI, 0.29-0.67; p=0.00013).[30]

PFS2

Follow-up of PFS2 was not recorded in Study 19, therefore TSST was used as a proxy measure for PFS2.[30]

Chemotherapy free interval

A difference in the CFI of 9 months was observed in Study 19.[30]

5.1.2.3 SOLO-2

SOLO-2 patients were required to have a predicted deleterious or suspected deleterious *BRCA*1/2 mutation, and all patients had to consent to provide two blood samples for confirmatory germline *BRCA1*/2 testing. Efficacy and patient reported outcomes were analysed in the ITT population, which included all patients randomised. Safety was analysed in all patients from the ITT population who received at least one dose of study treatment. A summary of results from SOLO-2 is provided in Table 14.[19] It should be noted that the SOLO-2 data was not used in the current reimbursement decision for olaparib in Denmark.

Table 14 SOLO-2 gBRCAmut results (Pujade-Lauraine 2017)[19]

Trial name:	SOLO-2								
NCT number:	NCT00753545								
Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effec		
				Difference	95% CI	P value	Hazard/Odds/ Risk ratio	95% CI	P va
Median overall survival months (immature)	Olaparib	196	NE	NE	NE	NE	HR: 0.80	(0.50-1.31)	p=0.
	Placebo	99	NE						
Median progression-free survival months (Investigator assessed)	Olaparib	196	19.1 (16.3-25.7)	13.6	NR	NR	HR: 0.30	(0.22-0.41)	p<0.0
	Placebo	99	5.5 (5.2-5.8)						

Adverse reactions: Number and percentage of patients that stops therapy due to adverse reactions	Olaparib	195	21 (10.8%)	8.7%	NR	NR	RR: 5.33	(1.28, 22.8)	NI
	Placebo	99	2 (2.0%)						
Adverse reactions: Number and percentage of patients that experiences one or more grade 3-4 adverse reactions	Olaparib	195	71 (36%)	18.2%	NR	NR	RR: 2.00	(1.27, 3.16)	NI
	Placebo	99	18 (18%)						
Adverse reactions: Number and percentage of myelodysplastic syndrome	Olaparib	195	1 (1%)	-2.5%	NR	NR	RR: 0.17	(0.02, 1.61)	NI
	Placebo	99	3 (3%)						

Adverse reactions: percentage of acute myeloid leukaemia	Olaparib	195	2 (1%)	0%	NR	NR	RR: 1.02	(0.09, 11.06)	NI
	Placebo	99	1 (1%)						
Quality of life	See section 5.1.2.3.4 on Health-related Quality of Life below								
Time to second progression	Olaparib	196	NE (24.1, NE)	NE	NE	NE	HR: 0.50	(0.34-0.72)	p<0.0
	Placebo	99	18.4 (15.4-22.8)						
Median time to first subsequent	Olaparib	196	27.9 (22.6-NE)	20.8	NE	NE	HR: 0.28	(0.21-0.38)	p<0.0

treatment months	Placebo	99	7.1 (6.3-8.3)						
Median time to second subsequent treatment months	Olaparib	196	NE	NE	NE	NE	HR: 0.37	(0.26-0.53)	p<0.0
	Placebo	99	18.2 (15.0-20.5)						
Median Chemotherapy-free interval months	Olaparib	196	NR	NR	NR	NR	NR	NR	NI
	Placebo	99	NR						

Abbreviations: CI – Confidence interval; HR – Hazard ratio; NE – Not estimated; NR – Not reported; N/A – Not applicable; RR – Relative risk

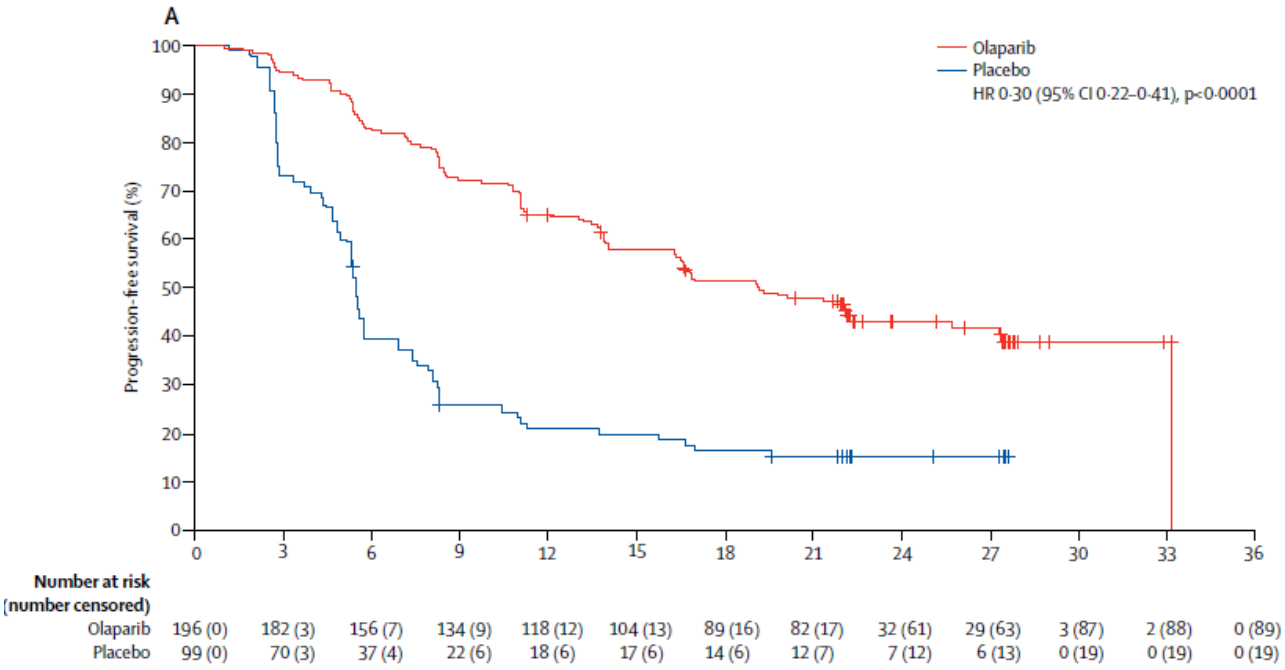
5.1.2.3.1 Overall survival

OS was defined as the time from the date of randomization until death due to any cause. OS data are currently immature, at point of data cut-off (19th September 2016), the OS data was at 23% (45 events) and 27% (27 events) maturity in the olaparib and placebo treatment arms of SOLO-2, respectively.[19]

5.1.2.3.2 Progression-free survival

PFS was defined as the time from randomisation until objective radiological disease progression or death using modified RECIST version 1.1 by investigator assessment. At point of data cut-off (19th September 2016), the median PFS was 19.1 and 5.5 months for olaparib and placebo treatment arms of SOLO-2, respectively (HR 0.30 [95% CI 0.22-0.41], p<0.0001). Figure 6 presents KM OS data for olaparib and placebo.[19]

Figure 6 Progression-free survival Kaplan-Meier for olaparib and placebo (Pujade-Lauraine 2017)[19]



Abbreviations: CI, confidence interval; HR, hazard ratio

5.1.2.3.3 Adverse events

The most common AEs of grade 1-2 in both treatment arms were non-haematological; nausea (73% vs. 33%), fatigue or asthenia (62% vs. 37%), vomiting (35% vs. 18%), abdominal pain (22% vs. 28%), and diarrhea (32% vs. 20%).[19]

The overall incidence of grade 3/4 AEs was low in both treatment groups (olaparib vs. placebo; 36% vs. 18%). Anaemia was the most common grade 3/4 AE in the olaparib arm (19%), whilst neutropenia was the most common grade 3/4 AE in the placebo arm (4%).[19]

The frequency of AEs leading to dose interruptions and reductions was higher in the olaparib group than in the placebo group: 45% vs. 18%, and 25% vs. 3%, respectively. AEs resulting in treatment discontinuation occurred in 10.8% and 2.0% of olaparib and placebo patients, respectively. Any toxicity observed during the study treatment phase was managed by interruption of the dose of study treatment if deemed appropriate by an investigator.[19]

The frequency of MDS and AML was low in both treatment arms; 1% and 1% of olaparib, and 3% and 1% of placebo patients experienced MDS and AML, respectively.[19]

One death in the olaparib group had a fatal treatment-related adverse event (AML). No other deaths were considered to be related to study treatment by the investigator.[19]

5.1.2.3.4 Health-related Quality-of-life

Patient reported outcomes were assessed in the ITT population, with HRQoL assessed in patients only if, they had both an evaluable score at baseline and at least one evaluable follow-up form. An evaluable form was defined as having at least on subscale that could be measured, or a form that was not completed because the patient was deemed too heavily affected by the symptoms of disease. Patient-reported outcomes showed no appreciable difference in quality-of-life for patients receiving olaparib compared with those receiving placebo.

The primary analysis measure, mean change from baseline in TOI of the FACT-O (assessed in 185 [94%] of 196 patients in the olaparib group and 94 [95%] of 99 in the placebo group), was similar in both groups over the first 12 months (adjusted mean −2·90 points [95% CI −4·13 to −1·67] vs −2·87 points [−4·64 to −1·10]; estimated difference −0·03 points [–2·19 to 2·13]; p=0·98). Non-compliance with the FACT-O questionnaire resulted in the exclusion of 11 (6%) of 196 patients in the olaparib group and five (5%) of 99 patients in the placebo group from the analysis.

Although FACT-O data was recorded during the SOLO-2 study, the percentage of patients that does not show statistically significant worsening in quality of life was not presented, nor was data reported that would enable calculation of these results.[19] Therefore, this parameter cannot be presented for this study.

In addition to the data available from the SOLO-2 primary publication, an additional study published in 2018, evaluated HRQoL and patient reported outcomes with olaparib maintenance after chemotherapy in patients with platinum-sensitive, relapsed OC from SOLO-2. HRQoL was evaluated by change from baseline in the FACT-O TOI score during the first 12 months of the study. Patient-centred outcomes of quality-adjusted PFS and TWiST were analysed as secondary endpoints of the study.[35]

The results indicated that olaparib did not negatively affect mean TOI score over the first 12 months of the study. The average adjusted mean change from baseline over the first 12 months in TOI was -2.90 (-4.13, -1.67) with olaparib (n=185) and -2.87 (-4.64, -1.10) with placebo (n=94), with an estimated mean difference of -0.03 (-2.19, 2.13, p=0.98). Mean total FACT-O and FACT-O HRQoL scores also remained stable over the course of treatment in patients receiving olaparib.[35]

Olaparib was associated with patient-centred benefits based on quality-adjusted PFS and TWiST, despite the toxicity experienced by patients receiving olaparib versus placebo. Mean quality-adjusted PFS was longer with olaparib than with placebo (13.96 [SD 10.96] vs. 7.28 [SD 5.22] months; difference 6.68 95% CI 4.98, 8.54; p<0.0001). The mean duration of TWiST was also longer for patients receiving olaparib than for

those receiving placebo (15.03 [SD 12.79] vs. 7.70 [SD 6.42] months; difference 7.33, 95% CI 4.70, 8.96; p<0.0001).[35]

5.1.2.3.5 Other endpoints

Time to first subsequent therapy

TFST was defined as the time from the date of randomisation to the earlier of the date of therapy start date following study treatment discontinuation or death. Any patient not known to have died at the time of the analysis and not known to have had a further intervention was censored at last known time to have not received subsequent therapy. At data cut-off (19th September 2016, 58% maturity) median time to TFST was recorded as 27.9 months (95% CI 22.6 to not calculable) and 7.1 months (95% CI 6.3-8.3) for olaparib and placebo, respectively (HR 0.28 [95% CI 0.21-0.38], p<0.0001).[19]

Time to second subsequent therapy

TFST was defined as the time from the date of randomisation to the earlier of the date of second subsequent therapy start date following study treatment discontinuation or death. Any patient not known to have died at the time of the analysis and not known to have had a further intervention was censored at last known time to have not received a second subsequent therapy. At data cut-off (19th September 2016, 43% maturity) median time to TSST had not been reached in the olaparib group (95% CIs not calculable) and was recorded as 18.2 (95% CI 15.0-20.5) months in the placebo group (HR 0.37 [95% CI 0.26-0.53], p<0.0001).[19]

PFS2

PFS2 was defined as the time from the date of randomisation to the earliest of the progression even subsequent to that used for the primary variable PFS or death. At data cut-off (19th September 2016, 40% maturity) median time to second progression had not been reached in the olaparib group (95% CI 24.1 to not calculable) and was recorded as 18.4 (95% CI 15.4-22.8) months in the placebo group (HR 0.50 [95% CI 0.34-0.72], p<0.0002).[19]

5.1.3 Comparative analyses

A comparison of the results for the g*BRCA*mut cohort from the ENGOT-OV16/NOVA trial, *BRCA*mut subgroup from Study 19 and the g*BRCA*mut cohort from SOLO-2 is provided in Table 15.

Table 15 Comparison of results from gBRCAmut ENGOT-OV16/NOVA, BRCAmut Study 19 and gBRCAmut SOLO-2[8, 17–19, 23,30–32]

Results per outcome	Studies included in the analysis	Estimated absolute difference in effect			Estimated relative difference in effect			Methods used for quantitative synthesis
		Difference	CI	P value	Hazard/Odds/Risk ratio	CI	P value	
Median overall survival (months)	ENGOT-OV16/NOVA (Immature, median not reached)	NE	NE	NE	HR: 0.91	(0.360, 2.282)	p=0.8346	A two-sided log-rank test using randomised stratification factors was used to analyse OS, which was summarised with the use of the KM methods. The HR was estimated used a two-side 95% confidence intervals using a stratified Cox proportional hazards model, with stratification factors used in randomization.
	Study 19	4.7	NR	NR	HR: 0.62	(0.41-0.94)	0.025	Overall survival was analysed with the use of a Cox proportional hazards model that included covariates that was used as stratification factors at randomization.
	SOLO-2 (Immature)	NE	NE	NE	HR: 0.80	(0.50-1.31)	p=0.43	Overall survival as analysed at the same time of progression-free survival using a two-side significance level of 5% and analyses it with a log-rank test, using the randomisation stratification factors
Median progression-free survival	ENGOT-OV16/NOVA (Assessed by IRC)	15.5	NE	NE	HR: 0.27	(0.173,0.410)	p<0.0001	A two-sided log-rank test using randomised stratification factors was used to analyse PFS, which was summarised with the use of the KM methods. The HR was estimated used a two-side 95% confidence intervals using a stratified Cox proportional hazards model, with stratification factors used in randomization.

	Study 19 (Investigator assessed)	6.9	NE	NE	HR: 0.18	(0.10-0.31)	0.0001	Progression-free survival was analysed with the use of a Cox proportional hazards model that included covariates that was used as stratification factors at randomization.
	SOLO-2 (Investigator assessed)	13.6	NR	NR	HR: 0.30	(0.22-0.41)	p<0.0001	Progression-free survival at a two-side significance level of 5% and analyses it with a log-rank test, using the randomisation stratification factors
Adverse reactions: Percentage of patients that stop therapy due to adverse reactions	ENGOT-OV16/NOVA	12.5%	NR	NR	RR: 6.58	(2.42, 17.89)	NE	Adverse events and serious adverse events were collected from the time of signing the main informed consent form through treatment discontinuation. New serious adverse events (including deaths) were collected for 30 days after treatment discontinuation.
	Study 19	6.8%	NR	NR	RR: 9.24*	(0.52, 163.89)*	NE	Safety analyses included all patients who received at least one dose of the assigned study medication. Safety was assessed throughout the study by monitoring for adverse events, biochemical laboratory tests, assessment of vital signs and physical examination
	SOLO-2	8.7%	NR	NR	RR: 5.33	(1.28, 22.8)	NE	Safety was analysed in all patients from the intention-to-treat population who received at least one dose of study treatment (safety analysis set).
Adverse reactions: Percentage of patients that experience one or more grade 3-4 adverse reactions	ENGOT-OV16/NOVA (grade 3-4)	51.2%	NR	NR	RR: 3.24	(2.46, 4.26)	NE	Adverse events and serious adverse events were collected from the time of signing the main informed consent form through treatment discontinuation. New serious adverse events (including deaths) were collected for 30 days after treatment discontinuation.

	Study 19 (grade ≥3)	21.4%	NR	NR	RR: 2.21	(1.20, 4.05)	NE	Safety analyses included all patients who received at least one dose of the assigned study medication. Safety was assessed throughout the study by monitoring for adverse events, biochemical laboratory tests, assessment of vital signs and physical examination
	SOLO-2 (grade 3-4)	18.2%	NR	NR	RR: 2.00	(1.27, 3.16)	NE	Safety was analysed in all patients from the intention-to-treat population who received at least one dose of study treatment (safety analysis set).
Adverse reactions: percentage of myelodysplastic syndrome	ENGOT-OV16/NOVA	0.8%	NR	NR	RR: 3.32*	(0.17, 63.42)*	NE	Adverse events and serious adverse events were collected from the time of signing the main informed consent form through treatment discontinuation. New serious adverse events (including deaths) were collected for 30 days after treatment discontinuation.
	Study 19	NR	NR	NR	NR	NR	NR	NR
	SOLO-2	-2.5%	NR	NR	RR: 0.17	(0.02, 1.61)	NE	Safety was analysed in all patients from the intention-to-treat population who received at least one dose of study treatment (safety analysis set).
Adverse reactions: percentage of acute myeloid leukaemia	ENGOT-OV16/NOVA	-0.6%	NR	NR	RR: 0.16*	RR: (0.01, 3.83)*	NE	Adverse events and serious adverse events were collected from the time of signing the main informed consent form through treatment discontinuation. New serious adverse events (including deaths) were collected for 30 days after treatment discontinuation.
	Study 19	NR	NR	NR	NR	NR	NR	NR
	SOLO-2	0%	NR	NR	RR: 1.02	(0.09, 11.06)	NE	Safety was analysed in all patients from the intention-to-treat population who received at least one dose of study treatment (safety analysis set).

Quality of life	See section 5.1.3.4 on Health-related Quality-of-life below

Abbreviations: CI – Confidence interval; HR – Hazard ratio; KM – Kaplan Meier; NE – Not estimated; NR – Not reported; OS – Overall survival; PFS – Progression-free survival

*Continuity correction DSU TSD2[24]

5.1.3.1 Overall Survival

As no mature OS data are available from ENGOT-OV16/NOVA and SOLO-2, a comparative analysis of OS benefit between niraparib and olaparib cannot be conducted.

5.1.3.2 Progression-free Survival

A naïve side by side comparision of PFS benefit observed in the g*BRCA*mut populations of ENGOT-OV16/NOVA and SOLO-2, and the *BRCA*mut population of Study 19 indicates that treatment with niraparib leads to increased PFS benefit compared to olaparib. Results from ENGOT-OV16/NOVA demonstrate that niraparib extends PFS by 15.5 months compared to placebo. This is in comparison to 6.9 months and 13.6 months PFS benefit compared to placebo for olaparib treatment in Study 19 and SOLO-2, respectively. Therefore, niraparib PFS benefit is 2.2 and 1.1 times larger than that recorded for olaparib in Study 19 and SOLO-2, respectively.

In addition, the fact that a higher proportion of patients in ENGOT-OV16/NOVA had received two or more prior chemotherapy lines and a lower proportion of patients had an ECOG performance status of 0 than in Study 19 or SOLO-2, which suggests that patients are potentially less healthy, further demonstrates the clinical benefit of niraparib in prolonging time to progression. Furthermore, the difference between niraparib and Study 19 olaparib PFS is greater than the clinically relevant threshold (6 months) as defined by the DMC: niraparib, 21.0 months; olaparib (Study 19) 11.2 months; median difference, 9.8 months. However, despite the fact that niraparib median PFS is greater than SOLO-2 olaparib PFS the median difference is not greater than the DMC's clinically relevant threshold: niraparib, 21.0 months; olaparib (SOLO-2) 19.0 months, median difference 2 months.

The prognostic impact of baseline characteristics in oncology has been evaluated across published literature. Prognostic factors include; tumour site, stage and grade, histology, weight, age, performance status, previous chemotherapy and age.[36–41] In particular, the ECOG performance status has been identified as a survival predictor in oncology patients, specifically in patients with stage III epithelial OC. The population relevant to this submission.

Marco *et al.* 2005 assessed prognostic factors in advanced cancer patients by conducting a systematic literature search. It was concluded that a patient's performance status was one of the most significant clinical signs and symptoms associated with the prognosis of advanced cancer patients. In addition, Marco *et al.* 2005 reported that at low performance status is considered a reliable prognostic factor to predict short-term survival. [38]

Furthermore, Grajales-Alvarez *et al.* 2017 evaluated the impact of a range of baseline characteristics on the prognosis of patients with carcinoma of unknown primary site. It was concluded that the ECOG performance status was an important predictor of response to chemotherapy, and the ECOG performance status was observed as a significant independent predictor of progression ($p<0.0001$) and mortality ($p<0.0001$).[42]

A paper by Erdogan *et al.*, in 2013 also concluded that performance status was an important prognostic factor in second line treatment of pancreaticobiliary adenocarcinoma, with disease control rate statistically higher in patients with a good performance status ($p=0.03$).[37]

Finally, Ezzati *et al.* 2014 evaluated the prognostic factors of epithelial ovarian carcinoma, the population relevant to this submission. It was concluded that a better performance status confers a greater tolerance

to various therapeutic modalities, from surgery to chemotherapy. Ezzati *et al.* 2014 also suggested that a better performance status leads to the adoption of more aggressive treatment plan by clinicians, which in turn may lead to better survival prognosis for patients. [36]

From the evidence discussed above it is clear that the ECOG performance status has a significant impact on the prognosis of oncology patients, as such will be expected to impact a patient's PFS. Therefore, it can be anticipated that the variation of baseline ECOG score in patients from ENGOT-OV16/NOVA, Study 19 and SOLO-2 would lead to significant differences in the PFS benefit of niraparib and olaparib.

In addition to ECOG performance status, Lin-Chau Chang *et al.* 2018 identified that histology, taxane-based adjuvant chemotherapy, stage and age of diagnosis have a significant impact on OS for advanced epithelial OC patients, with all p-values less than 0.05.[40] Therefore, it is clear that baseline characteristics have a significant impact on a patient's prognosis in OC. As there are clinically meaningfully differences in the baseline characteristics of ENGOT-OV16/NOVA, Study 19 and SOLO-2 it would be anticipated that PFS benefit for niraparib and olaparib would be affected as a result of this.

Due to the relevant prognostic factors discussed above and the study design of Study 19, SOLO-2 and ENGOT-OV16/NOVA (see section 5.1.1), there are several issues in conducting an indirect comparison between olaparib and niraparib.

Firstly, the primary endpoint of PFS was not the same across the studies. The ENGOT-OV16/NOVA PFS primary endpoint by an IRC included all radiological and clinical progression events, determined by RECIST v1.1 and clinical criteria i.e. increase in CA-125 with confirmed reponse by other test e.g. ultrasound or clinical symtpoms, and deaths, while the Study 19 and SOLO-2 PFS primary endpoints by investigator assessment included only radiologic events and death (Table 16). Secondly, in Study 19, stratification and analysis by *BRCA* mutation status was not part of the initial study design and was only included as a post-hoc analysis. Finally, the scanning interval was different in ENGOT-OV16/NOVA to Study 19 and SOLO-2 with scans being performed every 8 weeks through week 52 then every 12 weeks until treatment discontinuation in ENGOT-OV16/NOVA. Whilst scans were performed every 12 weeks through week 60 in Study 19 and week 72 in SOLO-2 followed by every 24 weeks until progression or withdrawal of patient consent, posing a challenge in performing indirect comparisons. Even if the studies had used the same definition of PFS, the shorter scan interval in NOVA may potentially result in a shorter median PFS than in Study 19 or SOLO-2.

Table 16 Comparisons of primary endpoints

	Investigator Led PFS				Independent Central Review PFS			
	Primary endpoint	Radiologic PD	Clinical PD	Death	Primary Endpoint	Radiologic PD	Clinical PD	Death
ENGOT-OV16/NOVA	×	✓	✓	✓	✓	✓	✓	✓
Study 19	✓	✓	×	✓	×	✓	×	×
SOLO-2	✓	✓	×	✓	×	✓	×	×

Abbreviations: PFS – Progression-free survival; PD – Progressed disease

In addition to the differences in study design, a test was conducted to assess the proportional hazards assumption between treatment arms in the ENGOT-OV16/NOVA trial, Study 19 and the SOLO-2 trial. This test was undertaken, as the proportional hazards assumption must hold between all treatment arms in all studies under consideration for an indirect treatment comparison to be appropriate.

To assess the validity of the proportional hazards assumption, log-cumulative plots were generated for PFS g*BRCA*mut Kaplan-Meier (KM) data for niraparib and RS from the ENGOT-OV16/NOVA trial, and for *BRCA*mut and g*BRCA*mut 2L+ for olaparib and RS from Study 19 and SOLO-2, respectively. Olaparib and RS PFS KM were digititized using GetData Graph Digitizer from Ledermann 2014 and Pujade-Lauraine 2018 for *BRCA*mut and g*BRCA*mut 2L+, respectively.[17,19] The PFS KM data is presented in Figure 7, Figure 8 and Figure 9 for the ENGOT-OV16/NOVA, Study 19 and SOLO-2, respectively.

For ENGOT-OV16/NOVA g*BRCA*mut 2L+ the log-cumulative hazard plot presented in Figure 10 characterised by non-monotonic lines, which converge before diverging away. This implies that the hazards are changing over time and as such the proportional hazards assumption does not hold between niraparib and RS.

For Study 19 *BRCA*mut 2L+ the log-cumulative hazards plot presented in Figure 11 is characterised by non-monotonic lines, which converge before diverging. This implies that the hazards are changing over time and as such the proportional hazards assumption does not hold between olaparib and RS.

For SOLO2 g*BRCA*mut 2L+ the log-cumulative hazards plot presented in Figure 12 is characterised by non-monotonic lines, which converge and diverge over the observational period. This implies that the hazards are changing over time and as such the proportional hazards assumption does not hold between olaparib and RS.

As a result of the above analysis, it is clear that the proportional hazards assumption does not hold between niraparib and RS PFS for g*BRCA*mut 2L+ ENGOT-OV16/NOVA, and between olaparib and RS PFS for *BRCA*mut 2L+ and g*BRCA*mut 2L+ from Study 19 and SOLO-2.[8,17] In addition, it was shown that the proportional hazards assumption does not hold between olaparib and RS OS for *BRCA*mut 2L+ from Study 19 as part of NICE TA381.[43] As the proportional hazards assumption does not hold between niraparib and RS, and olaparib and RS, it can be concluded that the proportional hazards assumption will not hold between niraparib and olaparib. Therefore, any hazard ratio estimated from an indirect treatment comparision could not be used to estimate relative treatment effect between niraparib and olaparib. Therefore, an indirect treatment comparison to estimate the comparative efficacy of PFS between niraparib and olaparib in the g*BRCA*mut 2L+ population would not be appropriate.

Given that the proportional hazards assumption does not hold between any treatment arms across all three studies, the differences between study design and baseline characteristics, it is believed that a naïve side-by-side comparison is the most appropriate approach.

Figure 7. PFS KM data for niraparib and RS gBRCAmut 2L+

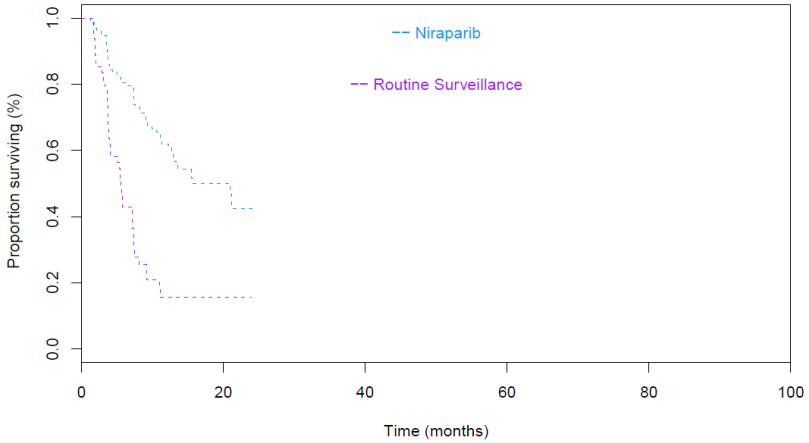


Figure 8. PFS KM data for olaparib and RS Study 19 BRCAmut 2L+

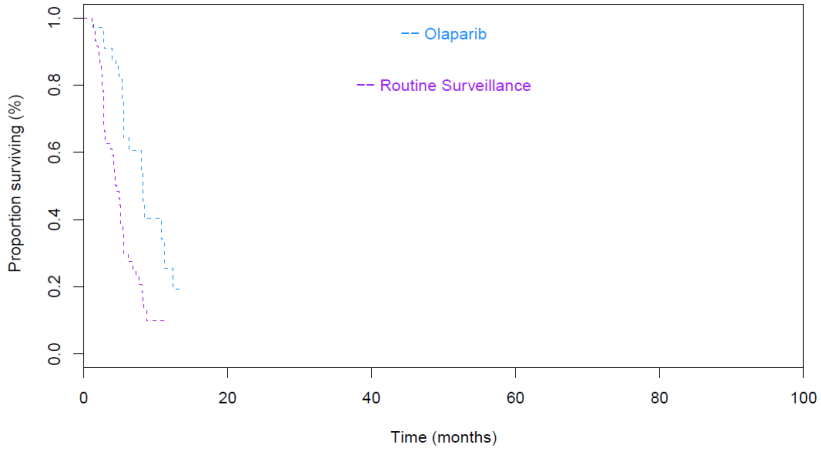


Figure 9. PFS KM data for olaparib and RS SOLO-2 gBRCAmut 2L+

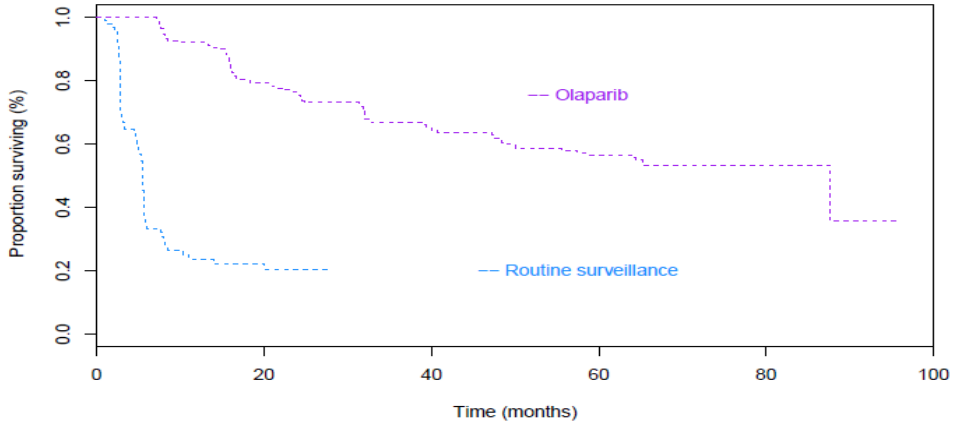


Figure 10. Log cumulative hazard for niraparib and RS ENGOT-OV16/NOVA gBRCAmut 2L+

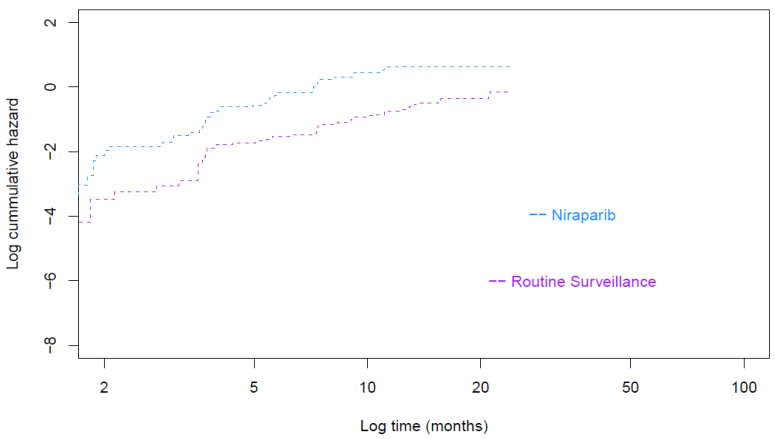


Figure 11. Log cumulative hazard for olaparib and routine surveillance Study 19 BRCAmut 2L+

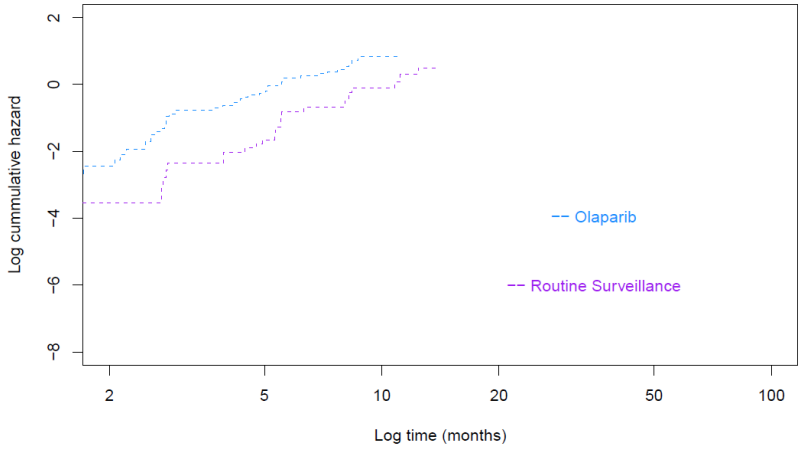
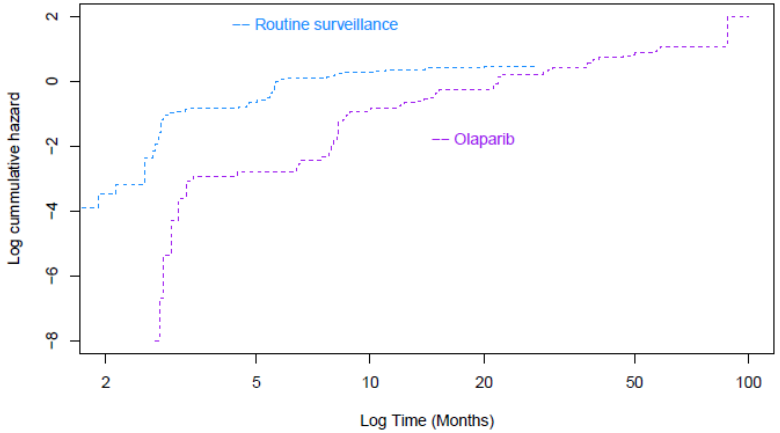


Figure 12. Log cumulative hazard for olaparib and routine surveillance SOLO2 gBRCAmut 2L+



5.1.3.3 Adverse Events

A greater proportion of patients on the niraparib treatment arm of ENGOT-OV16/NOVA discontinued treatment due to AEs, compared to olaparib patients in Study 19 and SOLO-2 (14.7% vs. 6.8% vs. 10.8%, respectively. However, the difference between SOLO-2 g*BRCA*mut olaparib patients and ENGOT-OV16/NOVA g*BRCA*mut niraparib patients is less than the DMC's least clinically relevant threshold of 5%. The frequency of MDS and AML was low in both g*BRCA*mut treatment arms of ENGOT-OV16/NOVA and SOLO-2, with 2% or less of niraparib and olaparib, and 3% or less of placebo patients experiencing either event.[19,23] The exact incidence of MDS and AML was not reported in Study 19.[30] A greater proportion of patients on the niraparib treatment arm of the ENGOT-OV16/NOVA suffered grade 3 or 4 adverse events, compared to olaparib patients in Study 19 (grade ≥3 reported) and SOLO-2 (grade 3 or 4 reported) (74.1% vs. 35.3% vs. 36%), respectively. This difference is greater than the DMC's clinically relevant threshold of 10% for niraparib compared to olaparib in both Study 19 and SOLO-2. However, since Study 19 did not report on grade 3/4 adverse events, but grade 3/4/5 adverse events, formal comparison between Study 19 and the other trials is inhibited.

A further analysis of the ENGOT-OV16/NOVA data, lead to a recent publication to recommend a dose modification to a starting dose of 200 mg for niraparib patients with baseline weight of <77 kg and/or baseline platelets of <150,000/µL to avoid significant haematological toxicity, especially thrombocytopenia.[44] A type II variation to the current license has been submitted to the EMA, forpatients with a baseline weight of <77 kg and/or thrombocytes < 150,000/µL to receive a starting dose of 200 mg and patients ≥ 77kg and thrombocytes ≥ 150,000/µL to start on 300 mg (anticipated approval date: March 2019). For the 200mg starting dose , SwissMedic also approved niraparib with a starting dose of 200 mg in this patient group (August 8th, 2018) This anticipated reduction in haematological AEs had been demonstrated in TOPACIO/Keynote-12, where the occurrence of grade ≥ 3 thrombocytopenia and decreased platelet counts is lower than that observed for only grade 3 or 4 AEs in ENGOT-OV16/NOVA (thrombocytopenia, 9% vs. 28.3%; decreased platelet count, 6% vs. 7.4%), with a niraparib dose reduction to 200 mg.[23, 32,45]

A post-hoc analysis of ENGOT-OV16/NOVA investigating this starting dose change shows that the incidence of grade 3 or grade 4 thrombocytopenia events is 5.9% among patients receiving a starting dose of 200 mg compared to 33.2% for patients initiating with 300 mg niraparib.[46] In addition, the majority of patients (40%, 21/54 patients) who discontinued in the ENGOT-OV16/NOVA trial due to AEs had baseline weight <58 kg.[23] This is lower than the type II label variation cutoff weight of 77 kg. Hence, it is expected that a lower starting dose under the type II variation of the license will lead to significantly lower discontinuation rates than reported in the above trials.

An indirect treatment comparison is not presented for discontinuation due to AEs or for the proportion of patients experiencing a grade 3 or 4 adverse event due to several challenges that inhibit feasibility. Firstly, with this anticipated label change, it is expected that a reduction in haematological toxicity will be observed in patients receiving niraparib, hence these data will no longer be relevant once the type II variation of the license is in place. Furthermore, the label change is expected to change clinical practice for niraparib dosing, such that real world practice will not reflect these trial dosing regimens or discontinuation rates observed in the trials. In addition, although ENGOT-OV16/NOVA and SOLO-2 present the proportion of patients who experienced grade 3 or grade 4 adverse events, Study 19 does not report grade 3 and grade 4 AEs separately from grade 5 AEs, inhibiting comparison with this study.

Future studies investigating nirparib treatment have dosing regimens in line with the type II license variation, with a starting dose of 200 mg niraparib (e.g. NCT02655016). Hence it is anticipated that an ITC conducted between these studies would be more appropriate, when results are available.

5.1.3.4 Health-related Quality-of-Life

Both maintenance therapy with niraparib in ENGOT-OV16/NOVA and olaparib Study 19 compared to placebo show no appreciable difference in HRQoL for patients pre-progression. In addition, this is supported by a recent published HRQoL study, which demonstrated that HRQoL for patients as measured by the FOSI, EQ-5D-5L and EQ-VAS PRO remained stable during the treatment and pre-progression period in the niraparib group; with no significant differences observed between the niraparib and placebo group.[28]HRQoL was also maintained between niraparib and placebo patients post-progression in ENGOT-OV16/NOVA trial (Figure 3). However, as patient reported outcomes were not were recorded post-progression in Study 19 it is not possible to compare Study 19 and ENGOT-OV16/NOVA post-progression results. HRQoL analysis available for SOLO-2 was conducted within the first 12 months of treatment with olaparib, therefore it is not clear what proportion of patients were pre or post-progression. Despite this, treatment with olaparib within the first 12 months of SOLO-2 did not negatively affect mean TOI score.

HRQoL was measured using FOSI scores in ENGOT-OV16/NOVA, in contrast to Study 19 and SOLO-2, which used FACT-O scores. This causes problems with direct HRQoL result comparison; however, assuming that the overall results are comparable, for the g*BRCA*mut cohort, the cumulative percentage of patients who worsened during the maintenance period of ENGOT-OV16/NOVA was 38.4% at Cycle 6 and 47.1% for the post progression period for the niraparib cohort.[47] Study 19 reported that 21.1% of patients in the olaparib cohort improved.[34] However, the percentage of patients who worsened was not reported. The percentage of patients worsening was not recorded during SOLO-2.[19] Hence worsening data from these trials cannot be compared.

In line with patient-reported outcome data indicated no appreciable differences for olaparib-treated patients compared to placebo in SOLO-2; assessed by the change from baseline in the TOI of the FACT-O. However, it is unclear what proportion of these patients were pre or post-progression.

A TWiST analysis demonstrated that treatment with niraparib resulted in a mean TWiST benefit of 2.95 years compared to placebo for g*BRCA*mut patients.[29] A recent publication which evaluated the TWiST difference between olaparib and RS in SOLO-2 demonstrated that the olaparib mean TWiST benefit using restricted mean PFS was 0.61 years.[35] As the ENGOT-OV16/NOVA analysis extrapolated PFS to evaluate TWiST difference, the niraparib and olaparib TWiST benefit are not comparable. However, the mean TOX time for niraparib and olaparib is similar between analyses (0.31 years vs. 0.21 years).[29,35]

5.2 Clinical Question 2: What sort of increased clinical value does maintenance therapy with niraparib offer compared to bevacizumab in patients without BRCA1/2 mutation, but with platinum-sensitive, relapsed HGSC and response to platinum-based chemotherapy

5.2.1 Presentation of relevant studies

One relevant Phase 3 RCT (ENGOT-OV16/NOVA trial) was identified for niraparib for the maintenance therapy in patients with platinum-sensitive, relapse HGSC and response to platinum-based chemotherapy. A summary of the trial is provided in Table 6 (section 4.2).[8]

Two relevant RCTs were identified for bevacizumab for the maintenance therapy in patients with platinum-sensitive, relapse HGSC and response to platinum-based chemotherapy; OCEANS (Phase 3 trial) and GOG-0213 (Phase 3 trial).[20,21] A summary of OCEANS and GOG-0213 trials are provided in Table 9 and Table 10 (section 4.2), respectively.

However it should be noted that a comparison between niraparib and bevacizumab is not appropriate for the following reasons (please refer to section 5.2.3.2 for more information):

1. The available data for bevacizumab does not differentiate between patients with or without a g*BRCA* mutation, therefore this is not an appropriate population in either bevacizumab study to make the comparison.
2. Bevacizumab is not used in the same way as niraparib. Bevacizumab is initiated in combination with chemotherapy and then continued as maintenance therapy, whereas niraparib is initiated only once a patient has completed chemotherapy and had complete or partial response.
    a. In the clinical trials for bevacizumab PFS is therefore measured from the start of chemotherapy as opposed to following chemotherapy at the point of randomisation in the ENGOT-OVA16/NOVA study. Therefore the PFS from the studies can not be compared.

The data from the studies are presented but no comparison has been made due to these two challenges.

Patient characteristics

Clinically relevant differences between the patient cohorts of ENGOT-OV16/NOVA, OCEANS and GOG-0213 have been identified. Primarily, the OCEANS and GOG-0213 trials limited their eligibility criteria to include patients who had only received one previous line of chemotherapy. This is in contrast to all niraparib patients in the non-g*BRCA*mut ENGOT-OV16/NOVA trial who had received 2 or more previous lines of chemotherapy. As with the Study 19 and SOLO-2 comparison, it might be expected that patients who have had one or none prior lines of chemotherapy would have longer PFS maintenance therapy than patients who have had two prior lines. In addition, a lower proportion of niraparib patients in ENGOT-OV16/NOVA had an ECOG score of 0 compared to bevacizumab patients in OCEANS (68.4% [non-g*BRCA*mut] vs. 75.2%). As discussed above in Section 5.1.1, a higher proportion of patients with an ECOG score of 0 could indicate that OCEANS patients are healthier than ENGOT-OV16/NOVA patients. Therefore, the patient groups cannot be viewed as similar.[8,20,21]

Study Characteristics

The primary endpoint was not consistent across the three studies. ENGOT-OV16/NOVA and OCEANS both had a primary endpoint of PFS. However, ENGOT-OV16/NOVA PFS was assessed by an IRC, whilst OCEANS PFS was investigator assessed. In addition, the primary endpoint of GOG-0213 was OS, and investigator assessed PFS was recorded as a secondary endpoint.[8,20,21]

Despite the fact that the three trials record PFS, the definition and measurement between the trials is not the same. OCEANS and GOG-0213 trials both assess the efficacy of chemotherapy in combination with bevacizumab or placebo; therefore patients initiate a course of chemotherapy before beginning their study treatment. PFS is recorded from the time of randomisation, therefore includes the chemotherapy interval. Patients in the ENGOT-OV16/NOVA trial begin their study treatment immediately; therefore any prior chemotherapy time is not captured in their PFS.[8,20,21]

Each study differed in terms of design, GOG-0213 is an open label, unblinded study, whilst ENGOT-OV16/NOVA and OCEANS are double blind, placebo-controlled studies.[8,20,21]

In addition, OCEANS and GOG-0213 trial did not stratify by *BRCA* mutation status, whilst the ENGOT-OV16/NOVA trial had two independent cohorts enrolled on the basis of the presence or absence of the germline *BRCA* mutation.[8,20,21]

5.2.2 Results per study

5.2.2.1 ENGOT-OV16/NOVA

A summary of results for the ITT non-g*BRCA*mut cohort from the ENGOT-OV16/NOVA trial is provided in Table 17. The ITT population was considered to be the primary set for all efficacy analyses. The three predefined primary efficacy populations were the g*BRCA*mut cohort, the HRD-positive subgroup of the non-g*BRCA*mut cohort (non-g*BRCA*mut HRD-positive) and the overall non-g*BRCA*mut cohort.

Table 17 ENGOT-OV16/NOVA non-gBRCAmut (ITT population) results (Mirza 2016, niraparib CSR)[8,23]

Trial name:	ENGOT-OV16/NOVA									
NCT number:	NCT01847274									
Outcome	Study arm	N	Result	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
				Difference	95% CI	P value	Hazard/Odds/ Risk ratio	95% CI	P value	
Median overall survival months (Immature, median not reached)	Niraparib	234	NE	NE	NE	NE	HR: 0.74	(0.452, 1.200)	p=0.2181	A two-sided log rank test using randomised stratification factors was use to analyse OS, which was summarised with the use of the KM methods. The HR was estimated used two-side 95% confidence intervals using stratified Cox proportional hazards model, with stratification factors used in randomization.
	Placebo	116	NE							

Median progression-free survival (Assessed by IRC) (Months)	Niraparib	234	9.3 (7.2, 11.2)	5.4	NR	NR	HR: 0.45	(0.338-0.607)	p<0.0001	A two-sided log rank test using randomised stratification factors was use to analyse PFS, which was summarised with the use of the KM methods. The HR was estimated used two-side 95% confidence intervals using a stratified Cox proportional hazards model, with stratification factors used in randomization.
	Placebo	116	3.9 (3.7, 5.5)							
Adverse reactions: Number and percentage of patients that stops therapy due to adverse reactions	Niraparib	367	54 (14.7%)	12.5%	NR	NR	RR: 6.58	(2.42, 17.89)	NE	Adverse events and serious adverse events were collected from the time o signing the mai informed consent form
	Placebo	179	4 (2.2%)							

										through treatment discontinuation New serious adverse events (including deaths) were collected for 30 days after treatment discontinuation
Adverse reactions: Number and percentage of patients that experiences one or more grade 3-4 adverse reactions	Niraparib	367	272 (74.1%)	51.2%	NR	NR	RR: 3.24	(2.46, 4.26)	NE	Adverse events and serious adverse events were collected from the time o signing the mai informed consent form through treatment discontinuation New serious adverse events (including deaths) were collected for 30 days after treatment discontinuation
	Placebo	179	41 (22.9%)							

Adverse reactions: Number and percentage of myelodysplastic syndrome	Niraparib	234	2 (0.9%)	-0.1%	NR	NR	RR: 0.99	(0.09, 10.82)	NE	Adverse events and serious adverse events were collected from the time c signing the mai informed consent form through treatment discontinuation New serious adverse events (including deaths) were collected for 30 days after treatment discontinuation
	Placebo	116	1 (0.9%)							
Adverse reactions: Number and percentage of acute myeloid leukaemia	Niraparib	234	0 (0%)	0%	NR	NR	RR: 0.50*	(0.01, 4.94)*	NE	Adverse events and serious adverse events were collected from the time c signing the mai informed consent form through treatment discontinuation New serious
	Placebo	116	0 (0%)							

										adverse events (including deaths) were collected for 30 days after treatment discontinuation
Quality of life		See section 5.2.2.1.4 on Health-related Quality-of-life below								
PFS2 months (Immature)	Niraparib	234	18.6 (16.2, 21.7)	3.0	NR	NR	HR: 0.69	(0.494, 0.964)	p=0.0293	A two-sided log rank test using randomised stratification factors was use to analyse PFS2 which was summarised with the use of the KM methods. The HR was estimated used two-side 95% confidence intervals using stratified Cox proportional hazards model, with
	Placebo	116	15.6 (13.2, 20.9)							

										stratification factors used in randomisation
Median time to first subsequent treatment months	Niraparib	234	11.8 (9.7, 13.1)	4.6	NR	NR	HR: 0.55	(0.412, 0.721)	p<0.0001	A two-sided log rank test using randomised stratification factors was sue to analyse TFST which was summarised with the use of the KM methods. The HR was estimated used two-side 95% confidence intervals using a stratified Cox proportional hazards model, with stratification factors used in randomisation
	Placebo	116	7.2 (5.7, 8.5)							
Median time to second subsequent	Niraparib	234	21.1 (18.5. NE)	0.8	NE	NE	HR: 0.74	(0.519 , 1.066)	p=0.1063	A two-sided log rank test using randomised stratification

treatment months	Placebo	116	20.3 (15.1, NE)							factors was use to analyse TSST which was summarised with the use of the KM methods. The HR was estimated used two-side 95% confidence intervals using stratified Cox proportional hazards model, with stratification factors used in randomisation
Median Chemotherapy-free interval months	Niraparib	234	12.7 (11.0, 14.7)	3.1	NR	NR	HR: 0.50	(0.370, 0.666)	p<0.0001	A two-sided log rank test using randomised stratification factors to analyse CFI, which was summarised

	Placebo	116	8.6 (6.9, 10.0)							with the use of the KM methods. The HR was estimated used two-side 95% confidence intervals using a stratified Cox proportional hazards model, with stratification factors used in randomisation

Abbreviations: *BRCA* – Breast cancer susceptibility gene; CFI – Chemotherapy-free interval; CI – Confidence interval; HR – Hazard ratio; ITT – Intention-to-treat; IRC – Independent review committee; KM – Kaplan-Meier; NE – Not estimated; NICE – National Institute of Health and Care Excellence; NR – Not reported; N/A – Not applicable; OS – Overall survival; PFS – Progression-free survival; PFS2 – Progression-free survival 2; RR – Relative risk; TFST – Time to first subsequent treatment; TSST – Time to second subsequent treatment.

*Continuity correction DSU TSD2[24]

5.2.2.1.1 Overall survival

OS was defined as the time from study randomisation to the date of death due to any cause. Patients known to be alive were censored at the last known survival follow-up date. OS data are currently immature, at the time of database lock for PFS analysis a total of 71 patients in the non-gBRCA cohort had died, including 44 (19%) of all 234 patients randomised to niraparib and 27 (23%) of all 116 patients.[23]

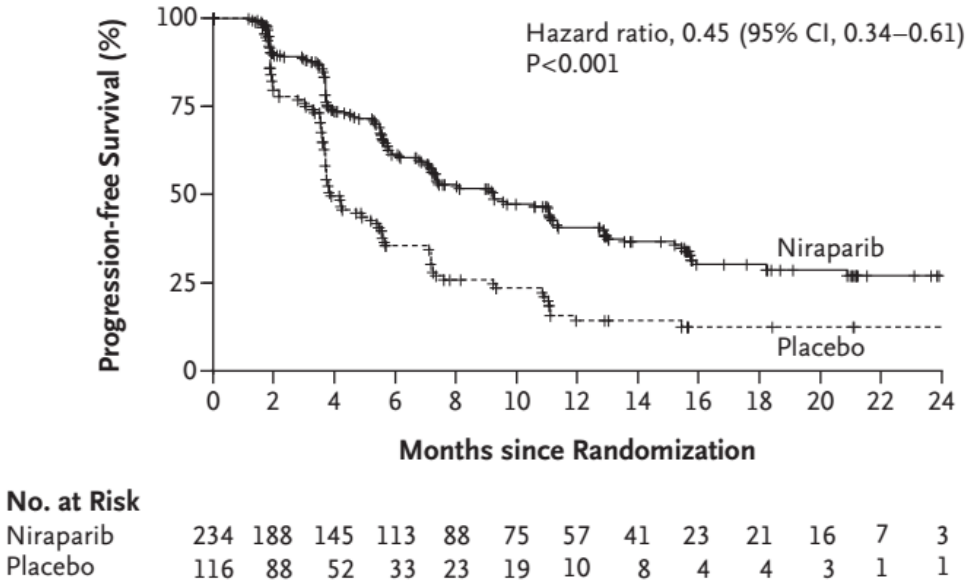
5.2.2.1.2 Progression-free survival

PFS was defined as the time from date of treatment randomisation to the date of first documentation of progression or death by any cause in the absence of documented progression, whichever occurred first. The duration of PFS in the primary efficacy analysis was to be based on the determination of progression made by IRC. In the ENGOT-OV16/NOVA trial, niraparib met the primary endpoint of prolonging PFS versus placebo in all three prospectively defined primary patient populations. In the non-g*BRCA*mut cohort the treatment effect was statistically significant with niraparib achieving a median PFS of 9.3 months versus 3.9 months for patients in the placebo group, a difference of 5.4 months (HR, 0.45; 95% CI, 0.34-0.61; p<0.001). Niraparib reduced the risk of disease progression or death by 55% in these patients. Patients in the placebo group are thus 2.2 times more likely to experience disease progression or die at any time at any time compared with the placebo group.[8]

Divergence between treatment groups in the Kaplan–Meier plot was evident early and was sustained throughout the rest of the follow-up period (Figure 13).

In addition, as discussed in Section 5.1.2.1.2, by extending PFS after platinum-based chemotherapy, treatment with niraparib will increase the proportion of patients who are considered platinum-sensitive. This increases in the number of treatment options available to patients, as once patients become platinum-resistant limited treatment is available and prognosis is poor. By increasing time to progression, and the likelihood of consideration for retreatment with platinum-based therapies, niraparib maintenance can extend OS to a greater extent that that already gained through PFS. On top of this, subsequent platinum-based chemotherapy is associated with increased AEs for patients. Therefore, niraparib patients may remain progression and toxicity free for longer than patients receiving placebo.

Figure 13 Kaplan–Meier estimates of progression-free survival for niraparib and placebo non-gBRCAmut cohort[8]



Abbreviations: *BRCA*, breast cancer susceptibility gene; CI, confidence interval; HR, hazard ratio; No., number

5.2.2.1.3 Adverse events

A summary of ENGOT-OV16/NOVA trial adverse event profile for niraparib and placebo is presented above in Section 5.1.2.1.3.

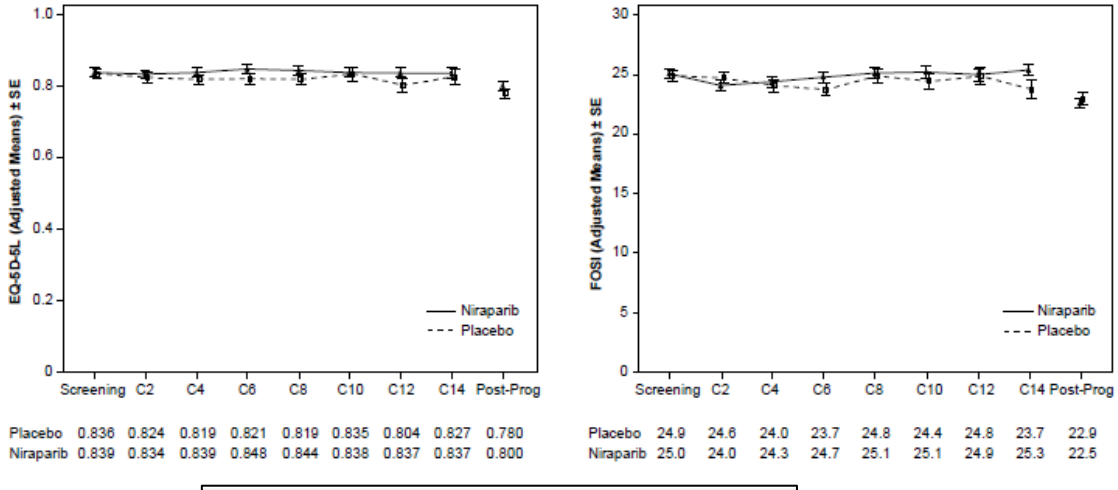
The frequency of MDS was low in both non-g*BRCA*mut treatment arms; with 2 (0.9%) and 1 (0.9%) niraparib and placebo patients experiencing an event, respectively. No patients experienced an AML in either treatment arm.[23]

5.2.2.1.4 Health-related Quality-of-life

HRQoL was assessed using FOSI (based on a subset of questions from the FACT-O questionnaire), EQ-5D-5L and EQ-5D-5L-VAS, after every two cycles through to cycle 14, and then after every three cycles, whereby a cycle was defined as 4 weeks. If the patient discontinued study treatment, an assessment was performed at that time and a further single assessment was performed 8 weeks (+/- 2 weeks) later regardless of subsequent treatment.

According to all measures, HRQoL was similar in both treatment groups and pre-treatment levels were maintained throughout the treatment period. KM plots of EQ-5D-5L, EQ-5D-5L-VAS, and FOSI time to symptom worsening also showed no statistically significant difference between niraparib and placebo Figure 14.

Figure 14 Patient-reported outcomes for EQ-5D-5L and FOSI by study visit (Top left – EQ-5D-5L, Top right – FOSI, Bottom – EQ-5D-5L-VAS)



Abbreviations: EQ-5D-5L – EuroQol 5-dimension 5-level; FOSI – Functional Assessment of Cancer Therapy – Ovarian Symptom Index; g*BRCA*mut – Germline breast cancer susceptibility gene mutation; NEJM – New England Journal of Medicine
NEJM Appendices, 2016

FOSI

The FOSI score remained stable throughout the study and was maintained at baseline levels. In the non-g*BRCA*mut cohort, at screening, the mean FOSI score for niraparib patients was 25.0 compared with 24.9 for placebo.[28] Scores for cycle 14 were 25.3 (niraparib) and 23.7 (placebo). There were no statistical differences in the two treatment groups for the non-g*BRCA*mut cohort (p>0.05). The KM curve for FOSI time to symptom worsening also found no statistically significant difference between niraparib and placebo (log rank p=0.405).

Pain and fatigue symptoms on the FOSI were examined separately. Overall, the percentage of patients reporting pain tended to be lower in the niraparib group versus the placebo group at each assessment point. Additionally, patients receiving niraparib tended to have lower rates of fatigue versus placebo.

Time to symptom worsening on the overall FOSI score was defined as the time from randomization to the first FOSI assessment with a worse score compared to the baseline score. If a patient reported a 2-point

decrease from baseline, the patient was considered to have "worsened". A change from baseline within ±2 points was considered "stable". For the non-g*BRCA*mut cohort, a greater proportion of placebo-treated patients were reported as "stable" during the maintenance period (55.0%, 53.3%, and 55.6% in the niraparib cohort, and 69.1%, 49.4%, and 60.0% in the placebo cohort, for Cycles 2, 4, and 6, respectively). The percentage of patients reported as "worsened" was 31.7%, 28.7%, and 22.6% in the niraparib cohort, and 16.5%, 31.2%, and 24.0% in the placebo cohort for Cycles 2, 4, and 6, respectively.[23] A statistically significant higher percentage of niraparib-treated patients "worsened" compared to placebo-treated patients at Cycle 2 ($p = 0.006$) although no statistically significant differences were observed at Cycles 4 and 6 ($p > 0.05$).

Cumulatively, the percentage of patients who were reported as "worsened" was higher in the niraparib cohort for all 3 cycle time points (24.4% at Cycle 2 to 37.6% at Cycle 6 in the niraparib cohort; 13.8% to 32.8% in the placebo cohort), with statistical significance at Cycle 2 ($p = 0.025$) only and not at Cycles 4 and 6 ($p > 0.05$). During the post-progression assessment, the overall cumulative "worsened" percent of patients increased to 49.6% in the niraparib group and 46.6% in the placebo group, although no statistically significant differences were observed ($p > 0.05$). The cumulative percentage of patients that does not show significant worsening in quality of life can then be calculated as 50.4% in the niraparib group and 53.4% in the placebo group. This is a difference of 3.0 percentage points, and hence is not considered clinically relevant.[23]

Haematological AEs were found to have no significant negative effect on QoL assessed by FOSI within the ENGOT-OV16/NOVA. In the non-g*BRCA*mut cohort, at baseline, the mean FOSI score was similar for niraparib patients compared with for placebo (25.4, 25.0). These QoL scores remained stable during the treatment and preprogression period in the niraparib group and no significant differences were observed between the niraparib and placebo group.[28]

EQ-5D-5L

EQ-5D-5L was assessed using HUI and VAS. In the non-g*BRCA*mut cohort, mean baseline HUI was 0.839 (niraparib) and 0.836 (placebo).[28] Scores for cycle 14 were 0.837 (niraparib) and 0.827 (placebo). The corresponding mean baseline VAS scores were 75.8 (niraparib) and 75.9 (placebo).

Haematological AEs were found to have no significant negative effect on QoL assessed by EQ-5D-5L and EQ-5D-5L-VAS within the ENGOT-OV16/NOVA. In the non-g*BRCA*mut cohort, at baseline, the mean HUI score was similar for niraparib patients compared with for placebo (0.837, 0.824). These QoL scores remained stable during pre-progression and post-progression. Mean HUI scores pre-progression were 0.833 and 0.815 for niraparib and placebo, respectively. Mean HUI scores post-progression were 0.810 and 0.783 for niraparib and placebo, respectively.[28]

TWiST

Section 5.1.2.1.4 summarises the TWiST analysis methodology and results from the ENGOT-OV16/NOVA trial. Treatment with niraparib resulted in a mean PFS benefit of 1.44 years and a mean TOX of 0.10 years compared with placebo in the non-g*BRCA*mut cohort. Hence, treatment with niraparib resulted in a mean TWiST benefit of 1.34 years compared with placebo in the g*BRCA*mut cohort. In conclusion, patients treated with niraparib in the ENGOT-OV16/NOVA trial experienced more time without symptoms or toxicities compared with placebo.[29]

5.2.2.1.5 Other endpoints

Time to first subsequent therapy

TFST was defined as the time from randomisation to date of the first subsequent anti-cancer therapy. Patients who did not receive subsequent anti-cancer therapy were censored at their last contact date. In the non-g*BRCA*mut cohort, maintenance treatment with niraparib significantly prolonged TFST by 4.6 months compared with placebo. The median TFST was 11.8 months in the niraparib group compared with 7.2 months in the placebo group (HR, 0.55; 95% CI, 0.41-0.72; p<0.001). Patients in the placebo group were therefore 1.8 times more likely to require subsequent anti-cancer therapy or to have died at any time compared with patients in the niraparib group.[8]

PFS2 and TSST

PFS2 and TSST data from the ENGOT-OV16/NOVA trial are currently immature. TSST was defined as the time from randomisation to the date of the second subsequent anti-cancer therapy. PFS2 was defined as the time from the date of randomisation in the current study to the date of assessment of progression during the receipt of the next anti-cancer therapy after the study treatment or until death by any cause. If progression could not be determined the start date of subsequent anti-cancer therapy was used as a surrogate date of disease progression. If the date of progression, date of death, and start date of the second line subsequent anti-cancer therapy were unknown, then PFS2 was censored at the stop date of the first line of subsequent anti-cancer therapy. If the stop date was unknown, PFS2 was censored on the last contact date.[8]

Interim results show that the duration of PFS2 and TSST were prolonged in the niraparib group in the non-g*BRCA*mut cohort (HR, 0.69; 95% CI, 0.494-0.964; p=0.0293 and HR, 0.74; 95% CI, 0.519-1.066; p=0.1063, respectively).[8,23]

Chemotherapy free interval

The CFI was defined as the time from the end of treatment with the last platinum therapy until initiation of the next anti-cancer therapy (excluding maintenance therapy). If no subsequent anti-cancer therapy (excluding maintenance therapy) was initiated, CFI was censored on the last date of treatment on the current study. In the non-g*BRCA*mut cohort, maintenance treatment with niraparib significantly prolonged CFI by 4.1 months compared with placebo; median CFI was 12.7 months in the niraparib group compared with 8.6 months in the placebo group (HR, 0.50; 95% CI, 0.370-0.666; p<0.001). Patients receiving niraparib treatment thus remained free of chemotherapy for a longer duration, hence delaying the deleterious effects of chemotherapy. Results for TFST were consistent with those for CFI.[8]

5.2.2.2 OCEANS

A summary of results from the OCEANS trial is provided in Table 18. Efficacy analyses were performed in the ITT population, and the safety population consisted of all randomly assigned patients who received at least one partial dose of any component of protocol treatment.[20]

Table 18 OCEANS results (Aghajanian 2012)[20]

Trial name:	OCEANS								
NCT number:	NCT00434642								
Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect		
				Difference	95% CI	P value	Hazard/Odds/ Risk ratio	95% CI	P value
Median overall survival months	GC + BV	242	35.2 (29.9, 40.3)	1.9	NR	NR	HR: 1.027	(0.792, 1.331)	NR
	GC +Placebo	242	33.3 (29.8, 35.5)						
Median progression-free survival (Investigator assessed)	GC + BV	242	12.4 (11.4, 12.7)	4	NR	NR	HR: 0.484	(0.388, 0.605)	p<0.0001
	GC +Placebo	242	8.4 (8.3, 9.7)						

Adverse reactions: percentage of patients that stops therapy due to adverse reactions	GC + BV	247	19.8%	15.1%	NR	NR	RR: 4.20	(2.24, 7.88)	NE
	GC +Placebo	233	4.7%						
Adverse reactions: percentage of patients that experiences one or more grade 3-4	GC + BV	247	89.5%	7.1%	NR	NR	RR: 1.09	(1.01, 1.17)	NE
	GC +Placebo	233	82.4%						

adverse reactions									
Adverse reactions: percentage of myelodysplastic syndrome	GC + BV	247	NR	NR	NR	NR	NR	NR	NR
	GC +Placebo	233	NR						
Adverse reactions: percentage of acute myeloid leukaemia	GC + BV	247	NR	NR	NR	NR	NR	NR	NR
	GC +Placebo	233	NR						
Quality of life	See section 5.2.2.2.4 on Health-related Quality-of-life below								
PFS2 months (Investigator assessed)	GC + BV	NR	NR	NR	NR	NR	NR	NR	NR

	GC +Placebo	NR	NR						
Median time to first subsequent treatment months	GC + BV	NR	NR	NR	NR	NR	NR	NR	NR
	GC +Placebo	NR	NR						
Median time to second subsequent treatment months	GC + BV	NR	NR	NR	NR	NR	NR	NR	NR
	GC +Placebo	NR	NR						
Median Chemotherapy-free interval months	GC + BV	NR	NR	NR	NR	NR	NR	NR	NR
	GC +Placebo	NR	NR						

Abbreviations: BV – Bevacizumab; CI – Confidence interval; GC – Gemcitabine and carboplatin; HR – Hazard ratio; NR – Not reported; OS – Overall survival; PFS – Progression-free survival; PFS2 – Progression-free survival 2

5.2.2.2.1 Overall survival

OS was defined as the time from random assignment until death as a result of any cause. Patients alive at the time of the analysis were censored at the date of last contact. 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 will be conducted at 353 deaths. At the time of the final PFS analysis, the data were immature, with 141 deaths (29% of patients), and an additional analysis was conducted with a data cut-off date of 29th August 2011. Based on this analysis, 235 (48.6%) events had occurred. Median OS was 33.3 (95% CI 29.8, 35.5) and 35.2 (95% CI 29.9, 40.3) months for gemcitabine and carboplatin (GC) + bevacizumab and GC + placebo, respectively (HR 1.027; 95% CI, 0.792, 1.331).[20]

5.2.2.2.2 Progression-free survival

PFS was defined as the time from random assignment to progressed disease or death as a result of any cause. For patients alive without documented progressed disease at the time of analysis, PFS was censored at the time of the last tumour assessment. If no post-baseline assessment was performed, the date of random assignment plus one day was used as the censor date. The duration of PFS in the efficacy analysis was based on the investigator assessment. Median PFS was 12.4 (95% CI 11.4, 12.7) and 8.4 (95% CI 8.3, 9.7) months for GC + bevacizumab and GC + placebo, respectively (HR 0.484; 95% CI, 0.388, 0.605; log-rank p<0.0001).[20]

5.2.2.2.3 Adverse events

The most common AE of any grade in both treatment arms was neutropenia (GC + bevacizumab vs. GC + placebo; 20.6% vs. 21.9%). The overall incidence of grade ≥ 3 AE was high in both treatment groups (GC + bevacizumab vs. GC + placebo; 89.5% vs. 82.4%). The frequency of AEs leading to discontinuation was higher in the bevacizumab group than in the placebo group: 19.8% vs. 4.7%.[20]

Benign, malignant and unspecified neoplasms occurred in 2.0% and 0.9% of the GC + bevacizumab and GC + placebo treatment groups, respectively. Incidence of MDS and AML was not reported.[48]

5.2.2.2.4 Health-related Quality-of-life

The OCEANS trial did not include patient reported outcomes in the form HRQoL.[20]

5.2.2.3 GOG-0213

A summary of results from the GOG-0213 trial is provided in Table 19. Efficacy analyses were performed in the ITT population, and the safety population consisted of all randomly assigned patients who started study therapy.[21]

Table 19 GOG-0213 results (Coleman 2017)[21]

Trial name:	GOG-0213									
NCT number:	NCT00565851									
Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
				Difference	95% CI	P value	Hazard/Odds/ Risk ratio	95% CI	P value	
Median overall survival months	Chemotherapy + BV	337	42.2 (37.7, 46.2)	4.9	NR	NR	HR: 0.829	(0.683, 1.005)	p=0.056	The primary analysis of overall survival wa done by intention to treat. OS was calculated from the date of randomisation. The analysis used a log-rank test stratified by treatment-free interval (declared at enrolment) and participation in the surgical objective to compare overall survival. The proportion hazards model was used to estimate treatment HRs with their corresponding confidence intervals
	Chemotherapy + placebo	337	37.3 (32.6, 39.7)							

Median progression-free survival	Chemotherapy + BV	337	13.8 (13.0, 14.7)	3.4	NR	NR	HR: 0.628	(0.534, 0.739)	p<0.0001	The primary analysis of PFS was done by intention to treat. Th analysis used a log-rank test stratified by treatment-free interval (declared at enrolment) and participation in the surgical objective to compare overall survival. The proportion hazards model was used to estimate treatment HRs with their corresponding confidence intervals
	Chemotherapy + placebo	337	10.4 (9.7, 11.0)							
Adverse reactions: percentage of patients that stops therapy due to adverse reactions	Chemotherapy + BV	337	25%	NR	NR	NR	RR: 2.33	(1.63, 3.34)	NE	Safety analyses included only those patients who had started study therapy
	Chemotherapy + placebo	337	11%							
Adverse reactions: percentage of patients that	Chemotherapy + BV	325	96%	NR	NR	NR	RR: 1.15	(1.09, 1.21)	NE	Safety analyses included only those patients who had started study therapy

experiences one or more grade 3-4 adverse reactions	Chemotherapy + placebo	332	86%							Reported for Grade 3 or worse.
Adverse reactions: percentage of myelodysplastic syndrome	Chemotherapy + BV	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Chemotherapy + placebo	NR								
Adverse reactions: percentage of acute myeloid leukaemia	Chemotherapy + BV	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Chemotherapy + placebo	NR								
Quality of life	See section 5.2.2.3.4 on Health-related Quality-of-life below									
PFS2 months	Chemotherapy + BV	NR	NR	NR	NR	NR	NR	NR	NR	N/A

	Chemotherapy + placebo	NR	NR							
Median time to first subsequent treatment months	Chemotherapy + BV	NR	NR	NR	NR	NR	NR	NR	NR	N/A
	Chemotherapy + placebo	NR	NR							
Median time to second subsequent treatment months	Chemotherapy + BV	NR	NR	NR	NR	NR	NR	NR	NR	N/A
	Chemotherapy + placebo	NR	NR							
Median Chemotherapy-free interval months	Chemotherapy + BV	NR	NR	NR	NR	NR	NR	NR	NR	N/A
	Chemotherapy + placebo	NR	NR							

Abbreviations: BV – Bevacizumab; CI – Confidence interval; GOG – Gynecologic Oncology Group; HR – Hazard ratio; NR – Not reported; OS – Overall survival; PFS – Progression-free survival; PFS2 – Progression-free survival 2

5.2.2.3.1 Overall survival

OS was defined as the time from random assignment until death from any cause. At time of database lock, 415 deaths had occurred (214 in the chemotherapy group and 201 in the bevacizumab group). Median OS was 42.2 (95% CI 37.7, 46.2) and 37.3 (95% CI 32.6, 39.7) months for chemotherapy plus bevacizumab and chemotherapy plus placebo, respectively (HR 0.829; 95% CI 0.683, 1.005; p=0.056). A post-hoc sensitivity analysis was conducted using the actual platinum-free interval calculated from the electronic case-report forms. This analysis adjusted the HR for death slightly to 0·823 (95% CI 0·680–0·996; p=0·0447).[21]

5.2.2.3.2 Progression-free survival

PFS was defined as the time from randomisation to disease progression or death due to any cause. The duration of PFS in the efficacy analysis was to be based on investigator assessment. Median PFS was 13.8 (95% CI 13.0, 14.7) and 10.4 (95% CI 9.7, 11.0) months for chemotherapy plus bevacizumab and chemotherapy plus placebo, respectively (HR 0.628 [adjusted for surgery and treatment-free interval for progression or death]; 95% CI, 0.534, 0.739; p<0.0001).[21]

5.2.2.3.3 Adverse events

The AE profiles for treated patients in both groups were consistent with the known safety profile of the agents under study. The overall incidence of grade ≥ 3 AE was high in both treatment groups (chemotherapy plus bevacizumab vs. chemotherapy plus placebo; 96% vs. 86%). The most common AEs of grade ≥ 3 for chemotherapy plus bevacizumab versus chemotherapy alone were hypertension (12% vs. 1%), fatigue (8% vs. 2%) and proteinuria (8% vs. none).The frequency of AEs leading to withdrawal from any study drug was higher in the bevacizumab group than in the placebo group: 25% vs. 11%.[21]

The frequency of secondary malignancies were less than 1% for both treatment arms. MDS was associated with 1 treatment-related death for both study treatment groups.[21]

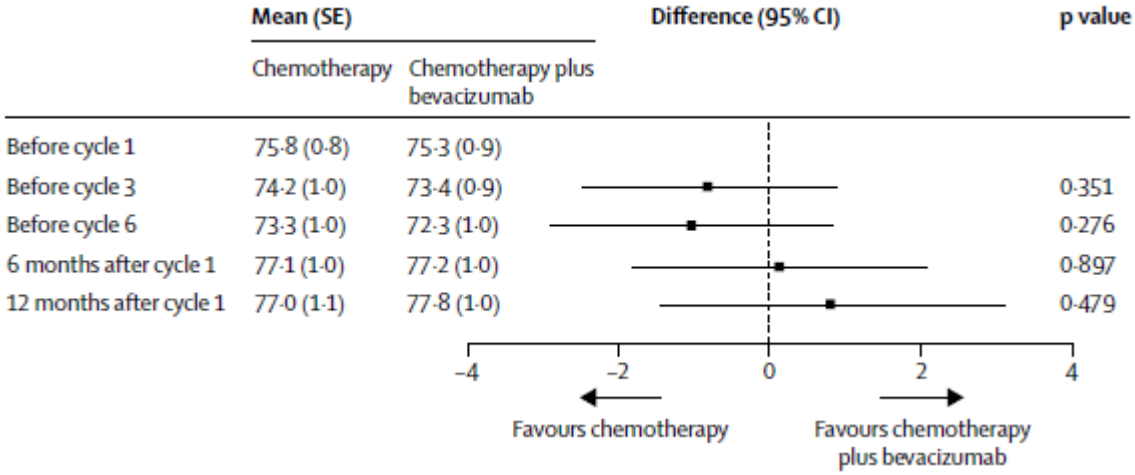
5.2.2.3.4 Health-related Quality-of-life

HRQoL among all cohorts was assessed by the FACT-O TOI, the FACT-O subscales Treatment Side Effects (TSE)-Bevacizumab (TSE-B) and TSE-Surgery (TSE-S; results of subscales not reported), and the physical functioning subscale of the RAND 36-item short form survey (SF-36). These assessments took place at six possible timepoints: before surgery (for those patients randomly allocated to cytoreductive surgery for the surgical objective), before initiation of chemotherapy, before cycle 3 (6 weeks after starting chemotherapy), before cycle 6 (15 weeks after starting chemotherapy), 6 months after starting chemotherapy, and 12 months after starting chemotherapy.

After adjustment for baseline score, age at enrolment, time since enrolment, participation in the surgical objective, and treatment-by-time interaction, the overall estimated difference in mean FACT-O TOI score (accounting for all datapoints) between the chemotherapy plus bevacizumab group and the chemotherapy group was −0·37 (95% CI −1·80 to 1·06; p=0·62). Both treatment groups were associated with a decrease in total FACT-O-TOI scores during therapy, but differences in scores between the groups were neither significant nor considered to be clinically meaningful at any time point. FACT-O-TOI scores returned to

above baseline 6 months after the first cycle in both treatment groups.[21] Figure 15 shows the mean FACT-O-TOI scores at each time point for both treatment groups.

Figure 15 Patient-reported outcomes with FACT-O TOI scores[21]



Means at baseline are raw means. Means at follow-ups are least-squared means estimated from the fitted linear mixed model. Treatment differences are estimated from the fitted linear mixed model. FACT-O TOI=Function Assessment of Cancer Therapy-Ovary trial outcome index.

Although FACT-O data was recorded during the GOG-0213 study, the percentage of patients that does not show statistically significant worsening in quality of life was not presented, nor was data reported that would enable calculation of these results.[21] Therefore, this parameter cannot be presented for this study.

5.2.3 Comparative analyses

No comparative analysis has been made due to the challenges detailed, further detail is provided in section 5.2.3.2.

5.2.3.1 Overall survival

No comparative analysis has been made due to the challenges detailed, further detail is provided in section 5.2.3.2.

5.2.3.2 Progression-free survival

There are three main reasons as to why a formal ITC to establish the comparative efficacy of PFS between niraparib and bevacizumab is not possible. Primarily, the patient population is inconsistent between ENGOT-OV16/NOVA, OCEANS and GOG-0213. ENGOT-OV16/NOVA predefined three primary efficacy populations; the g*BRCA*mut cohort, the HRD-positive subgroup of the non-g*BRCA*mut cohort and the overall non-g*BRCA*mut cohort. Efficacy was analysed per each predefined cohort. In comparison, OCEANS and GOG-0213 did not stratify by *BRCA* status, and therefore the proportion of g*BRCA*mut and non-g*BRCA*mut patients is unknown.

In addition, PFS was measured differently between niraparib and bevacizumab. PFS was assessed by IRC in ENGOT-OV16/NOVA, whilst investigator assessment determined progression in OCEANS and GOG-0213. In addition, PFS was not a primary endpoint in GOG-0213.

Finally, the ENGOT-OV16/NOVA trial defines PFS as the time from date of treatment randomisation to the date of first documentation of progression or death by any cause. Critically, this time span does not include any prior chemotherapy, and patients begin study treatment (niraparib or placebo) immediately. In comparison, both the OCEANS and GOG-0213 trials include an interval of prior chemotherapy before study treatment in PFS.[8,26,27]

5.2.3.3 Adverse event

No comparative analysis has been made due to the challenges detailed, further detail is provided in section 5.2.3.2.

5.2.3.4 Health-related quality of life

No comparative analysis has been made due to the challenges detailed, further detail is provided in section 5.2.3.2.

5.3 Clinical Question 3: What sort of increased clinical value does niraparib maintenance therapy offer compared to placebo in patients without BRCA1/2 mutation, but with platinum-sensitive, relapsed HGSC and response to platinum-based chemotherapy

5.3.1 Presentation of relevant studies

One relevant Phase 3 RCT (ENGOT-OV16/NOVA trial) was identified for niraparib compared to placebo for the maintenance therapy in patients with platinum-sensitive, relapse HGSC and response to platinum-based chemotherapy. A summary of the trial is provided in Table 6 (section 4.2).[8]

5.3.2 Results per study

5.3.2.1 ENGOT-OV16/NOVA

A summary of results for the ITT non-g*BRCA*mut cohort from the ENGOT-OV16/NOVA trial is provided in Section 5.2.2, Table 17.

5.3.2.1.1 Overall survival

OS was defined as the time from study randomisation to the date of death due to any cause. Patients known to be alive were censored at the last known survival follow-up date. OS data are currently

immature, at the time of database lock for PFS analysis a total of 71 patients in the non-gBRCA cohort had died, including 44 (19%) of all 234 patients randomised to niraparib and 27 (23%) of all 116 patients.[23]

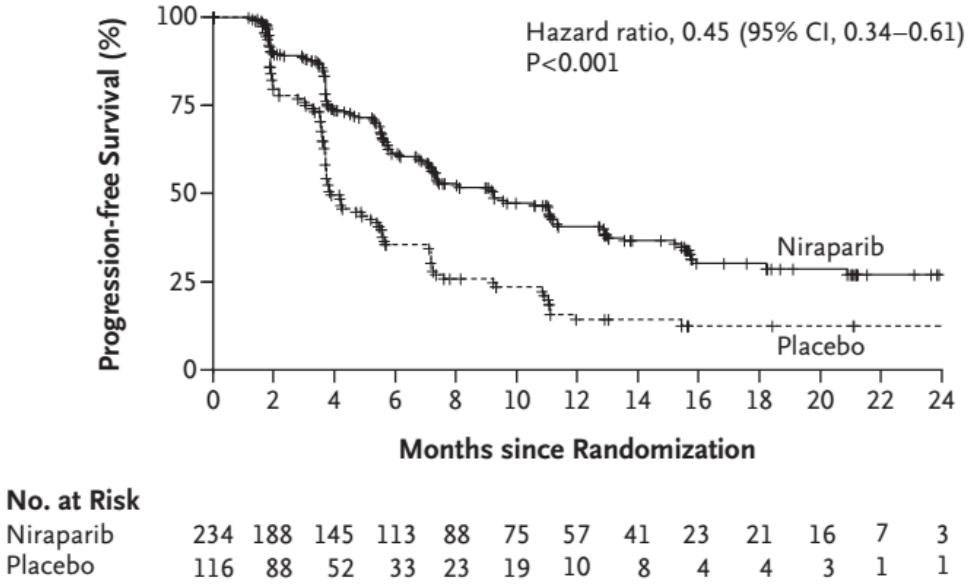
5.3.2.1.2 Progression-free survival

PFS was defined as the time from date of treatment randomisation to the date of first documentation of progression or death by any cause in the absence of documented progression, whichever occurred first. The duration of PFS in the primary efficacy analysis was to be based on the determination of progression made by IRC. In the ENGOT-OV16/NOVA trial, niraparib met the primary endpoint of prolonging PFS versus placebo in all three prospectively defined primary patient populations. In the non-g*BRCA*mut cohort the treatment effect was statistically significant with niraparib achieving a median PFS of 9.3 months versus 3.9 months for patients in the placebo group, a difference of 5.4 months (HR, 0.45; 95% CI, 0.34-0.61; p<0.001). Niraparib reduced the risk of disease progression or death by 55% in these patients. Patients in the placebo group are thus 2.2 times more likely to experience disease progression or die at any time at any time compared with the placebo group.[8]

Divergence between treatment groups in the Kaplan–Meier plot was evident early and was sustained throughout the rest of the follow-up period (Figure 16).

As discussed above in Section 5.2.2.1.2, by extending time to progression niraparib increased the options of subsequent chemotherapy regimens available to patients by increasing the number of patients eligible for platinum-based chemotherapy. This in turn, is associated with an increase in OS, to a greater extent than that observed in PFS. In addition, by delaying time to progression, there is a subsequent delay in further treatment lines, which are associated with troublesome AEs for patients. Therefore, by increasing time to progression niraparib patients may remain toxicity free for longer.

Figure 16 Kaplan–Meier estimates of progression-free survival for niraparib and placebo non-gBRCAmut cohort[8]



Abbreviations: *BRCA* – Breast cancer susceptibility gene; CI – Confidence interval; HR – Hazard ratio

5.3.2.1.3 Adverse events

A summary of the ENGOT-OV16/NOVA AE profile associated with niraparib and placebo treatment is provided in Section 5.2.2.1.3.

5.3.2.1.4 Health-related Quality-of-life

A summary of the ENGOT-OV16/NOVA HRQoL results for niraparib and placebo treatment is provided in Section 5.2.2.1.4.

5.3.2.1.5 Other endpoints

Time to first subsequent therapy

TFST was defined as the time from randomisation to date of the first subsequent anti-cancer therapy. Patients who did not receive subsequent anti-cancer therapy were censored at their last contact date. In the non-g*BRCA*mut cohort, maintenance treatment with niraparib significantly prolonged TFST by 4.6 months compared with placebo. The median TFST was 11.8 months in the niraparib group compared with 7.2 months in the placebo group (HR, 0.55; 95% CI, 0.41-0.72; p<0.001). Patients in the placebo group were therefore 1.8 times more likely to require subsequent anti-cancer therapy or to have died at any time compared with patients in the niraparib group.[8]

PFS2 and TSST

PFS2 and TSST data from the ENGOT-OV16/NOVA trial are currently immature. TSST was defined as the time from randomisation to the data of the second subsequent anti-cancer therapy. PFS2 was defined as the time from the date of randomisation in the current study to the date of assessment of progression during the receipt of the next anti-cancer therapy after the study treatment or until death by any cause. If progression could not be determined the start date of subsequent anti-cancer therapy was used as a surrogate date of disease progression. If the date of progression, date of death, and start date of the second line subsequent anti-cancer therapy were unknown, then PFS2 were censored at the stop date of the first line of subsequent anti-cancer therapy. If the stop date was unknown, PFS2 was censored on the last contact date.[8]

Interim results show that the duration of PFS2 was significantly prolonged in the niraparib group in the non-g*BRCA*mut cohort (HR, 0.69; 95% CI, 0.49-0.96; p=0.03). However, TSST was not shown to be significantly prolonged in the niraparib group in the interim results (HR, 0.74; 95% CI, 0.52-1.07; p=0.1063).[8,23]

Chemotherapy free interval

The CFI was defined as the time from the end of treatment with the last platinum therapy until initiation of the next anti-cancer therapy (excluding maintenance therapy). If no subsequent anti-cancer therapy (excluding maintenance therapy) was initiated, CFI was to be censored on the last date of treatment on the current study. In the non-g*BRCA*mut cohort, maintenance treatment with niraparib significantly prolonged CFI by 4.1 months compared with placebo; median CFI was 12.7 months in the niraparib group compared with 8.6 months in the placebo group (HR, 0.50; 95% CI, 0.37-0.67; p<0.001). Patients receiving niraparib treatment thus remained free of chemotherapy for a longer duration, hence delaying the deleterious effects of chemotherapy. Results for TFST were consistent with those for CFI.[8]

5.3.3 Comparative analyses

5.3.3.1 Overall Survival

As no mature OS data are available from the ENGOT-OV16/NOVA study (see section 5.2.2.1.1), a comparative analysis of OS benefit between niraparib and placebo cannot be conducted.

5.3.3.2 Progression-free Survival

Section 5.3.2.1.2 details the PFS results for niraparib versus placebo in the ENGOT-OV16/NOVA trial. Niraparib met the primary endpoint of prolonging PFS versus placebo in the non-g*BRCA*mut cohort, reducing the risk of disease progression or death with a statistically significant treatment effect ($p<0.001$). Niraparib reduced the risk of disease progression or death by 55%. The treatment effect was statistically significant with niraparib achieving a median PFS of 9.3 months versus 3.9 months for patients in the placebo group. Therefore, niraparib met the clinically relevant difference threshold (3 months) as defined by the DMC with a PFS benefit of 5.4 months. Consistent with this, the KM plot shows that PFS benefit was achieved with niraparib approximately two months from randomisation and was maintained throughout the trial (Figure 16).

5.3.3.3 Adverse Events

Section 5.2.2.1.3 summarises the AE results from the Phase 3 ENGOT-OV16/NOVA trial. The percentage of patients who discontinued due to adverse events was 14.7% in the niraparib arm and 2.2% in the placebo arm. This difference is clinically relevant; 12.5%. However, niraparib was generally well-tolerated with most AEs being mild-to-moderate in severity, and managed by dose reductions.[8]

Similarly, although Grade 3/4 AE percentage difference between niraparib and placebo was clinically relevant, with a 51.2% greater incidence rate for the niraparib group than the placebo group, the frequency of such events reduced significantly over time following individual dose management. These results indicated that AE symptoms can be sufficiently controlled by dose modifications on an individual basis.

In addition, as discussed in Section 5.1.3.4, a niraparib dose reduction has been associated with a lower in haematological toxicity, specifically thrombocytopenia and decrease platelet count.[44,45] This reduction further demonstrates niraparib has a manageable AE profile with appropriate individual patient dose management.

5.3.3.4 Health-related Quality-of-Life

Section 5.2.2.1.4 summarises the HRQoL results from the ENGOT-OV16/NOVA trial. Maintenance therapy with niraparib in ENGOT-OV16/NOVA compared to placebo show no appreciable difference in HRQoL for patients pre-progression.[8] In addition, this is supported by a recent published HRQoL study, which demonstrated that HRQoL for patients as measured by the FOSI, EQ-5D-5L and EQ-VAS PRO remained stable during the treatment and pre-progression period in the niraparib group; with no significant differences observed between the niraparib and placebo group.[28] Furthermore, treatment with niraparib

resulted in mean TWiST benefit compared to placebo, therefore niraparib within the ENGOT-OV16/NOVA trial spent more time without toxicities compared to control.[29]

HRQoL was also maintained between niraparib and placebo patients post-progression in ENGOT-OV16/NOVA trial (Figure 3).

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7 Appendices

7.1 Appendix A

Table 20 Search strategy for clinical SLR – Original search (Up to November 2016)

OVERVIEW – Original Search
Databases: • Ovid MEDLINE (Including Epub Ahead of Print & In Process) • OVID EMBASE • OVID EBM Reviews (Cochrane Library) including: ○ Cochrane Central Register of Controlled Trials (CENTRAL) • Clinical Trials.gov • WHO ICTRP Search syntax has been customized for each database. Date of Search: November 16, 2016 Study Types: Randomized Controlled Trials (RCTs) & Observational Studies Limits: none Note: †† "*", "# ", and "?" are truncation characters that retrieve all possible suffix variations of the root word e.g. surg* retrieves surgery, surgical, surgeon, etc.

Database	**Date Searched**	**Search Strategy**		
Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Pre sent	Nov. 16 2016 349 results	**#**	**Searches**	**Results**
		1	exp Ovarian Neoplasms/	79408
		2	Fallopian Tube Neoplasms/	2721
		3	Peritoneal Neoplasms/	13582
		4	((ovar* or fallopian or periton* or granulosa or krukenberg* or oviduct* or uterine tube*) adj5 (neoplas* or cancer* or tumour* or tumor* or carcino* or malignan* or adenocarcino* or metast* or mesothelioma)).mp.	125026
		5	dysgerminoma*.mp.	6242

		6	(ovar* adj2 seminoma*).mp.	59
		7	gynandroblastoma*.mp.	75
		8	or/1-7	131126
		9	"Poly(ADP-ribose) Polymerase Inhibitors"/	3078
		10	(inhibitor* adj2 (parp or poly adp ribose polymerase* or poly adp ribosylation)).mp.	4614
		11	(Niraparib or MK 4827 or MK4827).mp.	38
		12	(Olaparib or AZD 2281 or AZD2281 or "KU 0059436" or KU 59436 or KU0059436 or KU59436 or Lynparza).mp.	676
		13	(Rucaparib or "AG 014699" or AG014699 or "PF 01367338" or PF01367338 or PF 1367338 or AG 14447 or PF1367338 or AG14447 or AG 14699 or AG14699 or AG014699).mp.	108
		14	(Veliparib or ABT 888 or ABT888).mp.	314
		15	(Talazoparib or BMN 673 or BMN673 or BMN 673ts or BMN673ts).mp.	46
		16	(Pazopanib or Votrient or GW 786034 or GW786034 or GW 786034b or GW786034b or GW 786034x or GW786034x or SB 710468 or SB710468 or SB 710468a or SB710468a).mp.	1156
		17	Bevacizumab/	9574
		18	(Bevacizumab or Avastin or Altuzan or NSC 704865 or NSC704865).mp.	14729
		19	or/9-18	20273
		20	8 and 19	1394
		21	Randomized Controlled Trial.pt.	469734
		22	Pragmatic Clinical Trial.pt.	495
		23	exp Randomized Controlled Trials as Topic/	121406
		24	"Randomized Controlled Trial (topic)"/	0
		25	Randomized Controlled Trial/	469734
		26	Randomization/	95149
		27	Random Allocation/	95149
		28	Double-Blind Method/	147693
		29	Double Blind Procedure/	0
		30	Double-Blind Studies/	147693
		31	Single-Blind Method/	24537
		32	Single Blind Procedure/	0
		33	Single-Blind Studies/	24537

		34	Placebos/	35354
		35	Placebo/	0
		36	(random* or sham or placebo*).ti,ab,hw,kf,kw.	1302919
		37	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	215418
		38	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	619
		39	or/21-38	1327410
		40	20 and 39	210
		41	Epidemiologic studies/	7951
		42	exp case control studies/	876700
		43	exp cohort studies/	1713821
		44	Case control.tw.	110177
		45	(cohort adj (study or studies)).tw.	145369
		46	Cohort analy*.tw.	5892
		47	(Follow up adj (study or studies)).tw.	45440
		48	(observational adj (study or studies)).tw.	73181
		49	Longitudinal.tw.	205467
		50	Retrospective.tw.	389814
		51	Cross sectional.tw.	261647
		52	Cross-sectional studies/	254915
		53	or/41-52	2510072
		54	20 and 53	158
		55	40 or 54	349
Embase 1974 to 2016 Nov 15	Nov. 16, 2016 1362 results (non abstracts) 396 conference abstracts	**#**	**Searches**	**Results**
		1	ovary cancer/ or dysgerminoma/ or granulosa cell tumor/ or "hereditary breast and ovarian cancer syndrome"/ or ovary adenocarcinoma/ or ovary carcinoma/ or ovary metastasis/	96907
		2	uterine tube tumor/	1263
		3	uterine tube carcinoma/	1890
		4	peritoneum tumor/	4547
		5	peritoneum cancer/ or carcinomatous peritonitis/ or peritoneum mesothelioma/ or peritoneum metastasis/	12920
		6	((ovar* or fallopian or periton* or granulosa or krukenberg* or oviduct* or uterine tube*) adj5 (neoplas* or cancer* or tumour* or tumor* or	162442

			carcino* or malignan* or adenocarcino* or metast* or mesothelioma)).mp.	
		7	dysgerminoma*.mp.	3885
		8	(ovar* adj2 seminoma*).mp.	65
		9	gynandroblastoma*.mp.	80
		10	or/1-9	164559
		11	nicotinamide adenine dinucleotide adenosine diphosphate ribosyltransferase inhibitor/	4522
		12	(inhibitor* adj2 (parp or poly adp ribose polymerase* or poly adp ribosylation)).mp.	4718
		13	(Niraparib or MK 4827 or MK4827).mp.	327
		14	niraparib/	246
		15	(Olaparib or AZD 2281 or AZD2281 or "KU 0059436" or KU 59436 or KU0059436 or KU59436 or Lynparza).mp.	2178
		16	olaparib/	2087
		17	(Rucaparib or "AG 014699" or AG014699 or "PF 01367338" or PF01367338 or PF 1367338 or AG 14447 or PF1367338 or AG14447 or AG 14699 or AG14699 or AG014699).mp.	566
		18	rucaparib/	409
		19	(Veliparib or ABT 888 or ABT888).mp.	1340
		20	veliparib/	1076
		21	(Talazoparib or BMN 673 or BMN673 or BMN 673ts or BMN673ts).mp.	244
		22	talazoparib/	141
		23	(Pazopanib or Votrient or GW 786034 or GW786034 or GW 786034b or GW786034b or GW 786034x or GW786034x or SB 710468 or SB710468 or SB 710468a or SB710468a).mp.	5139
		24	pazopanib/	5085
		25	bevacizumab/	43536
		26	(Bevacizumab or Avastin or Altuzan or NSC 704865 or NSC704865).mp.	44198
		27	or/11-26	53285
		28	10 and 27	5154
		29	Randomized Controlled Trial.pt.	0
		30	Pragmatic Clinical Trial.pt.	0
		31	exp Randomized Controlled Trials as Topic/	124675
		32	"Randomized Controlled Trial (topic)"/	124675

		33	Randomized Controlled Trial/	462700
		34	Randomization/	83434
		35	Random Allocation/	79568
		36	Double-Blind Method/	114583
		37	Double Blind Procedure/	137980
		38	Double-Blind Studies/	97380
		39	Single-Blind Method/	25880
		40	Single Blind Procedure/	27330
		41	Single-Blind Studies/	27330
		42	Placebos/	267100
		43	Placebo/	326654
		44	(random* or sham or placebo*).ti,ab,hw,kf,kw.	1589653
		45	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	250571
		46	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	781
		47	or/29-46	1618713
		48	28 and 47	1217
		49	Clinical study/	253804
		50	Case control study/	122735
		51	Family study/	27982
		52	Longitudinal study/	105559
		53	Retrospective study/	514509
		54	Prospective study/	386473
		55	Randomized controlled trials/	124675
		56	54 not 55	381741
		57	Cohort analysis/	301152
		58	(Cohort adj (study or studies)).mp.	183940
		59	(Case control adj (study or studies)).tw.	100691
		60	(follow up adj (study or studies)).tw.	53574
		61	(observational adj (study or studies)).tw.	100972
		62	(epidemiologic$ adj (study or studies)).tw.	88968
		63	(cross sectional adj (study or studies)).tw.	131299
		64	or/49-53,56-63	1844198
		65	28 and 64	699
		66	48 or 65	1758

		67	limit 66 to (conference abstract or conference paper or conference proceeding or "conference review")	396
		68	66 not 67	1362
EBM Reviews - Cochrane Central Register of Controlled Trials October 2016	Nov.16, 2016 189 results	**#**	**Searches**	**Results**
		1	exp Ovarian Neoplasms/	1143
		2	Fallopian Tube Neoplasms/	37
		3	Peritoneal Neoplasms/	155
		4	dysgerminoma*.mp.	19
		5	(ovar* adj2 seminoma*).mp.	1
		6	gynandroblastoma*.mp.	0
		7	((ovar* or fallopian or periton* or granulosa or krukenberg* or oviduct* or uterine tube*) adj5 (neoplas* or cancer* or tumour* or tumor* or carcino* or malignan* or adenocarcino* or metast* or mesothelioma)).mp.	3905
		8	or/1-7	3935
		9	"Poly(ADP-ribose) Polymerase Inhibitors"/	12
		10	(inhibitor* adj2 (parp or poly adp ribose polymerase* or poly adp ribosylation)).mp.	90
		11	(Niraparib or MK 4827 or MK4827).mp.	6
		12	(Olaparib or AZD 2281 or AZD2281 or "KU 0059436" or KU 59436 or KU0059436 or KU59436 or Lynparza).mp.	55
		13	(Rucaparib or "AG 014699" or AG014699 or "PF 01367338" or PF01367338 or PF 1367338 or AG 14447 or PF1367338 or AG14447 or AG 14699 or AG14699 or AG014699).mp.	5
		14	(Veliparib or ABT 888 or ABT888).mp.	38
		15	(Talazoparib or BMN 673 or BMN673 or BMN 673ts or BMN673ts).mp.	3
		16	(Pazopanib or Votrient or GW 786034 or GW786034 or GW 786034b or GW786034b or GW 786034x or GW786034x or SB 710468 or SB710468 or SB 710468a or SB710468a).mp.	164
		17	Bevacizumab/	619
		18	(Bevacizumab or Avastin or Altuzan or NSC 704865 or NSC704865).mp.	1986
		19	or/9-18	2240
		20	8 and 19	189

Clinical Trials.gov	Nov. 16, 2016 227 results	1. 7 studies found for: Niraparib OR MK 4827 OR MK4827 | ovaries OR ovarian OR ovary OR fallopian OR peritoneal OR peritoneum OR granulosa OR krukenberg OR oviduct OR oviducts OR uterine tube OR uterine tubes 2. 42 studies found for: Olaparib OR AZD 2281 or AZD2281 OR KU 0059436 OR KU 59436 OR KU0059436 OR KU59436 OR Lynparza | ovaries OR ovarian OR ovary OR fallopian OR peritoneal OR peritoneum OR granulosa OR krukenberg OR oviduct OR oviducts OR uterine tube OR uterine tubes 3. 25 studies found for: Veliparib OR ABT 888 OR ABT888 | ovaries OR ovarian OR ovary OR fallopian OR peritoneal OR peritoneum OR granulosa OR krukenberg OR oviduct OR oviducts OR uterine tube OR uterine tubes 4. 8 studies found for: Talazoparib OR BMN 673 OR BMN673 OR BMN 673ts OR BMN673ts | ovaries OR ovarian OR ovary OR fallopian OR peritoneal OR peritoneum OR granulosa OR krukenberg* OR oviduct OR oviducts OR uterine tube OR uterine tubes 5. 18 studies found for: Pazopanib OR Votrient OR GW 786034 OR GW786034 OR GW 786034b OR GW786034b OR GW 786034x OR GW786034x OR SB 710468 OR SB710468 OR SB 710468a OR SB710468a | ovaries OR ovarian OR ovary OR fallopian OR peritoneal OR peritoneum OR granulosa OR krukenberg OR oviduct OR oviducts OR uterine tube OR uterine tubes 127 studies found for: Bevacizumab OR Avastin OR Altuzan OR NSC 704865 OR NSC704865 | ovaries or ovarian or ovary OR fallopian OR peritoneal OR peritoneum OR granulosa OR krukenberg OR oviduct OR oviducts OR uterine tube OR uterine tubes
WHO ICTRP	Nov. 16, 2016 87 results	Niraparib OR MK 4827 OR MK4827 OR Olaparib OR AZD 2281 or AZD2281 OR KU 0059436 OR KU 59436 OR KU0059436 OR KU59436 OR Lynparza ORVeliparib OR ABT 888 OR ABT888 OR Talazoparib OR BMN 673 OR BMN673 OR BMN 673ts OR BMN673ts OR Pazopanib OR Votrient OR GW 786034 OR GW786034 OR GW 786034b OR GW786034b OR GW 786034x OR GW786034x OR SB 710468 OR SB710468 OR SB 710468a OR SB710468a OR Bevacizumab OR Avastin OR Altuzan OR NSC 704865 OR NSC704865 AND ovaries OR ovarian OR ovary OR fallopian OR peritoneal OR peritoneum OR granulosa OR krukenberg OR oviduct OR oviducts OR uterine tube OR uterine tubes

Table 21: Search strategy for SLR update (up to June 2017)

OVERVIEW – Update
Databases: • Ovid MEDLINE (Including Epub Ahead of Print & In Process)

- OVID EMBASE
- OVID EBM Reviews (Cochrane Library) including:
    - Cochrane Central Register of Controlled Trials (CENTRAL)
- Clinical Trials.gov
- WHO ICTRP

Search syntax has been customized for each database.

Date of Search: June 28 2017

Study Types: Randomized Controlled Trials (RCTs) & Observational Studies

Limits: After November 16, 2016

Note:

†† "*", "# ", and "?" are truncation characters that retrieve all possible suffix variations of the root word e.g. surg* retrieves surgery, surgical, surgeon, etc.

Database	Date Searched	Search Strategy	
Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present	28 June 2017 36 results	1 exp Ovarian Neoplasms/	77197
		2 Fallopian Tube Neoplasms/	2690
		3 Peritoneal Neoplasms/	13542
		4 ((ovar* or fallopian or periton* or granulosa or krukenberg* or oviduct* or uterine tube*) adj5 (neoplas* or cancer* or tumour* or tumor* or carcino* or malignan* or adenocarcino* or metast* or mesothelioma)).mp.	122875
		5 dysgerminoma*.mp.	6214
		6 (ovar* adj2 seminoma*).mp.	56
		7 gynandroblastoma*.mp.	73
		8 or/1-7	129003
		9 "Poly(ADP-ribose) Polymerase Inhibitors"/	2850
		10 (inhibitor* adj2 (parp or poly adp ribose polymerase* or poly adp ribosylation)).mp.	4430
		11 (Niraparib or MK 4827 or MK4827).mp.	50

		12 (Olaparib or AZD 2281 or AZD2281 or "KU 0059436" or KU 59436 or KU0059436 or KU59436 or Lynparza).mp. 692 13 (Rucaparib or "AG 014699" or AG014699 or "PF 01367338" or PF01367338 or PF 1367338 or AG 14447 or PF1367338 or AG14447 or AG 14699 or AG14699 or AG014699).mp. 118 14 (Veliparib or ABT 888 or ABT888).mp. 287 15 (Talazoparib or BMN 673 or BMN673 or BMN 673ts or BMN673ts).mp. 59 16 (Pazopanib or Votrient or GW 786034 or GW786034 or GW 786034b or GW786034b or GW 786034x or GW786034x or SB 710468 or SB710468 or SB 710468a or SB710468a).mp. 1263 17 Bevacizumab/ 9656 18 (Bevacizumab or Avastin or Altuzan or NSC 704865 or NSC704865).mp. 15321 19 or/9-18 20793 20 8 and 19 1466 21 Randomized Controlled Trial.pt. 467292 22 Pragmatic Clinical Trial.pt. 599 23 exp Randomized Controlled Trials as Topic/ 116467 24 "Randomized Controlled Trial (topic)"/ 0 25 Randomized Controlled Trial/ 467292 26 Randomization/ 93332 27 Random Allocation/ 93332 28 Double-Blind Method/ 148180 29 Double Blind Procedure/ 0 30 Double-Blind Studies/ 148180 31 Single-Blind Method/ 24874

		32	Single Blind Procedure/	0
		33	Single-Blind Studies/	24874
		34	Placebos/	35035
		35	Placebo/	0
		36	(random* or sham or placebo*).ti,ab,hw,kf,kw.	1292038
		37	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	217225
		38	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	688
		39	or/21-38	1316414
		40	20 and 39	218
		41	Epidemiologic studies/	7662
		42	exp case control studies/	883799
		43	exp cohort studies/	1702977
		44	Case control.tw.	105298
		45	(cohort adj (study or studies)).tw.	143483
		46	Cohort analy*.tw.	5820
		47	(Follow up adj (study or studies)).tw.	44693
		48	(observational adj (study or studies)).tw.	75327
		49	Longitudinal.tw.	196651
		50	Retrospective.tw.	404039
		51	Cross sectional.tw.	260682
		52	Cross-sectional studies/	250002
		53	or/41-52	2496161
		54	20 and 53	162

		55 40 or 54 364 56 ("20161117" or "20161118" or "20161119" or 2016112* or 2016113* or 201612* or 2017*).dc. 752331 57 55 and 56 36
Embase 1996 to 2017 Week 26	June 28, 2017 158 results (non abstracts) 45 conference abstracts	1 ovary cancer/ or dysgerminoma/ or granulosa cell tumor/ or "hereditary breast and ovarian cancer syndrome"/ or ovary adenocarcinoma/ or ovary carcinoma/ or ovary metastasis/ 80296 2 uterine tube tumor/ 614 3 uterine tube carcinoma/ 1615 4 peritoneum tumor/ 2674 5 peritoneum cancer/ or carcinomatous peritonitis/ or peritoneum mesothelioma/ or peritoneum metastasis/ 12074 6 ((ovar* or fallopian or periton* or granulosa or krukenberg* or oviduct* or uterine tube*) adj5 (neoplas* or cancer* or tumour* or tumor* or carcino* or malignan* or adenocarcino* or metast* or mesothelioma)).mp. 131119 7 dysgerminoma*.mp. 1239 8 (ovar* adj2 seminoma*).mp. 22 9 gynandroblastoma*.mp. 53 10 or/1-9 131578 11 nicotinamide adenine dinucleotide adenosine diphosphate ribosyltransferase inhibitor/ 4251 12 (inhibitor* adj2 (parp or poly adp ribose polymerase* or poly adp ribosylation)).mp. 4979 13 (Niraparib or MK 4827 or MK4827).mp. 407 14 niraparib/ 325 15 (Olaparib or AZD 2281 or AZD2281 or "KU 0059436" or KU 59436 or KU0059436 or KU59436 or Lynparza).mp. 2544

		16 olaparib/ 2399 17 (Rucaparib or "AG 014699" or AG014699 or "PF 01367338" or PF01367338 or PF 1367338 or AG 14447 or PF1367338 or AG14447 or AG 14699 or AG14699 or AG014699).mp. 667 18 rucaparib/ 506 19 (Veliparib or ABT 888 or ABT888).mp. 1486 20 veliparib/ 1214 21 (Talazoparib or BMN 673 or BMN673 or BMN 673ts or BMN673ts).mp. 317 22 talazoparib/ 216 23 (Pazopanib or Votrient or GW 786034 or GW786034 or GW 786034b or GW786034b or GW 786034x or GW786034x or SB 710468 or SB710468 or SB 710468a or SB710468a).mp. 5590 24 pazopanib/ 5458 25 bevacizumab/ 45750 26 (Bevacizumab or Avastin or Altuzan or NSC 704865 or NSC704865).mp. 46964 27 or/11-26 56860 28 10 and 27 5645 29 Randomized Controlled Trial.pt. 0 30 Pragmatic Clinical Trial.pt. 0 31 exp Randomized Controlled Trials as Topic/ 129189 32 "Randomized Controlled Trial (topic)"/ 129189 33 Randomized Controlled Trial/ 410382 34 Randomization/ 66003 35 Random Allocation/ 62685 36 Double-Blind Method/ 90084

		37	Double Blind Procedure/	113460
		38	Double-Blind Studies/	97225
		39	Single-Blind Method/	25008
		40	Single Blind Procedure/	26540
		41	Single-Blind Studies/	26540
		42	Placebos/	193452
		43	Placebo/	249779
		44	(random* or sham or placebo*).ti,ab,hw,kf,kw.	1431410
		45	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	197380
		46	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	773
		47	or/29-46	1447080
		48	28 and 47	1328
		49	Clinical study/	99917
		50	Case control study/	110536
		51	Family study/	20622
		52	Longitudinal study/	94713
		53	Retrospective study/	519407
		54	Prospective study/	365355
		55	Randomized controlled trials/	129189
		56	54 not 55	361585
		57	Cohort analysis/	296454
		58	(Cohort adj (study or studies)).mp.	196323
		59	(Case control adj (study or studies)).tw.	97114

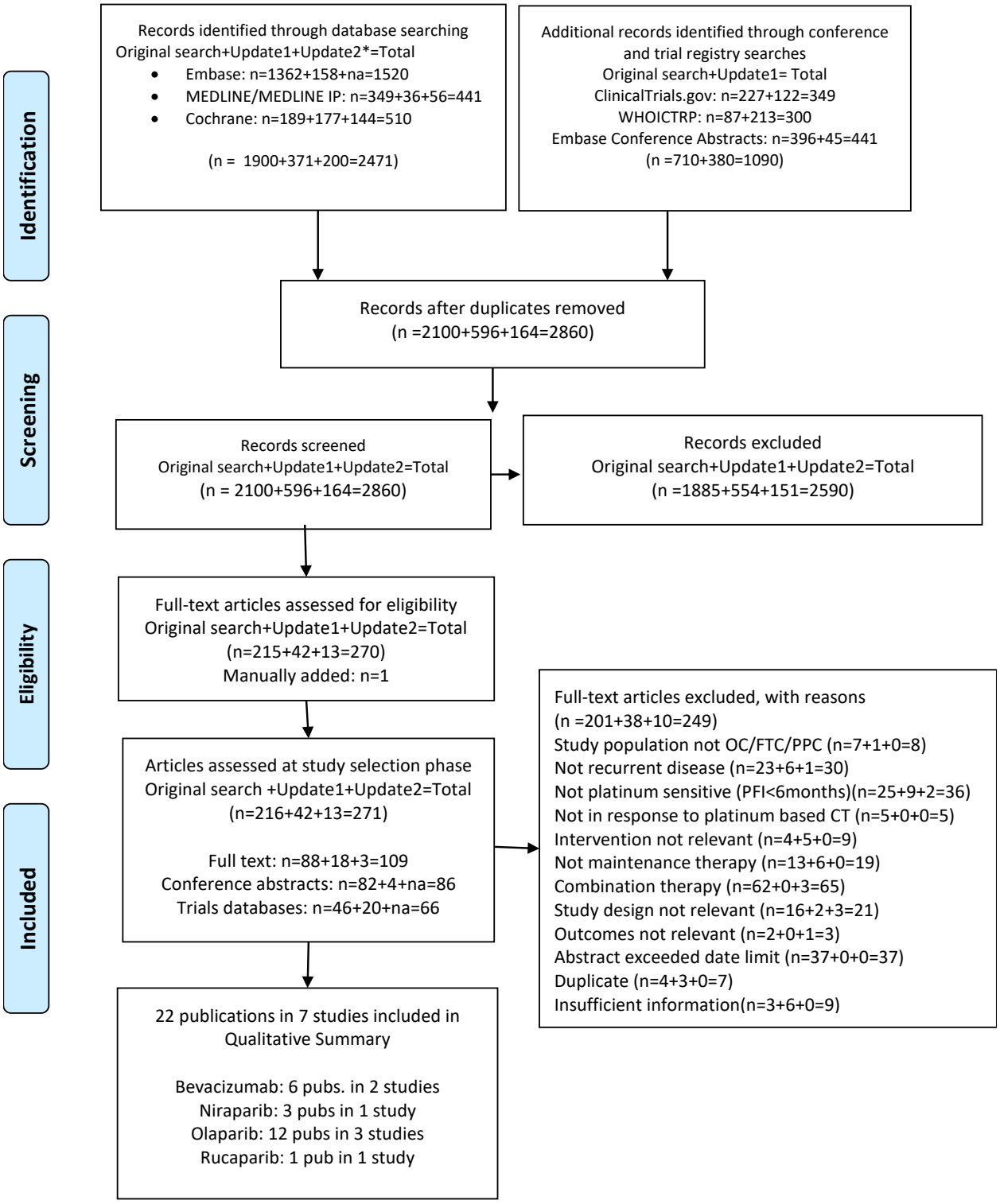
		60 (follow up adj (study or studies)).tw. 39770 61 (observational adj (study or studies)).tw. 109015 62 (epidemiologic$ adj (study or studies)).tw. 74188 63 (cross sectional adj (study or studies)).tw. 140117 64 or/49-53,56-63 1675627 65 28 and 64 551 66 48 or 65 1787 67 limit 66 to (conference abstract or conference paper or conference proceeding or "conference review") 452 68 66 not 67 1335 69 ("20161117" or "20161118" or "20161119" or 2016112* or 2016113* or 201612* or 2017*).dc,dd. 1139265 70 68 and 69 158 71 67 and 69 45
EBM Reviews - Cochrane Central Register of Controlled Trials May 2017	June 28, 2017 117 results	1 exp Ovarian Neoplasms/ 1161 2 Fallopian Tube Neoplasms/ 38 3 Peritoneal Neoplasms/ 165 4 dysgerminoma*.mp. 20 5 (ovar* adj2 seminoma*).mp. 1 6 gynandroblastoma*.mp. 0 7 ((ovar* or fallopian or periton* or granulosa or krukenberg* or oviduct* or uterine tube*) adj5 (neoplas* or cancer* or tumour* or tumor* or carcino* or malignan* or adenocarcino* or metast* or mesothelioma)).mp. 4510 8 or/1-7 4541 9 "Poly(ADP-ribose) Polymerase Inhibitors"/ 14

		10 (inhibitor* adj2 (parp or poly adp ribose polymerase* or poly adp ribosylation)).mp. 175 11 (Niraparib or MK 4827 or MK4827).mp. 19 12 (Olaparib or AZD 2281 or AZD2281 or "KU 0059436" or KU 59436 or KU0059436 or KU59436 or Lynparza).mp. 101 13 (Rucaparib or "AG 014699" or AG014699 or "PF 01367338" or PF01367338 or PF 1367338 or AG 14447 or PF1367338 or AG14447 or AG 14699 or AG14699 or AG014699).mp. 15 14 (Veliparib or ABT 888 or ABT888).mp. 66 15 (Talazoparib or BMN 673 or BMN673 or BMN 673ts or BMN673ts).mp. 13 16 (Pazopanib or Votrient or GW 786034 or GW786034 or GW 786034b or GW786034b or GW 786034x or GW786034x or SB 710468 or SB710468 or SB 710468a or SB710468a).mp. 234 17 Bevacizumab/ 685 18 (Bevacizumab or Avastin or Altuzan or NSC 704865 or NSC704865).mp. 2605 19 or/9-18 3009 20 8 and 19 300 21 ("201611" or "201612" or 2017*).up. 131851 22 20 and 21 117
Clinical Trials.gov	June 28, 2017 126 results	2. 7 studies found for: 1. Niraparib OR MK 4827 OR MK4827 | ovaries OR ovarian OR ovary OR fallopian OR peritoneal OR peritoneum OR granulosa OR krukenberg OR oviduct OR oviducts OR uterine tube OR uterine tubes |Studies received from 11/17/2016 to 06/28/2017 b) Niraparib OR MK 4827 OR MK4827 | ovaries OR ovarian OR ovary OR fallopian OR peritoneal OR peritoneum OR granulosa OR krukenberg OR oviduct OR oviducts OR uterine tube OR uterine tubes |Studies updated from 11/17/2016 to 06/28/2017 3. 41 studies found for: 1. Olaparib OR AZD 2281 or AZD2281 OR KU 0059436 OR KU 59436 OR KU0059436 OR KU59436 OR Lynparza | ovaries OR ovarian OR ovary OR fallopian OR peritoneal

		OR peritoneum OR granulosa OR krukenberg OR oviduct OR oviducts OR uterine tube OR uterine tubes |Studies received from 11/17/2016 to 06/28/2017 2. Olaparib OR AZD 2281 or AZD2281 OR KU 0059436 OR KU 59436 OR KU0059436 OR KU59436 OR Lynparza | Studies updated from 11/17/2016 to 06/28/2017 4. 13 studies found for: 1. Veliparib OR ABT 888 OR ABT888 | ovaries OR ovarian OR ovary OR fallopian OR peritoneal OR peritoneum OR granulosa OR krukenberg OR oviduct OR oviducts OR uterine tube OR uterine tubes |Studies received from 11/17/2016 to 06/28/2017 2. Veliparib OR ABT 888 OR ABT888 | ovaries OR ovarian OR ovary OR fallopian OR peritoneal OR peritoneum OR granulosa OR krukenberg OR oviduct OR oviducts OR uterine tube OR uterine tubes | Studies updated from 11/17/2016 to 06/28/2017 5. 6 studies found for: 1. Talazoparib OR BMN 673 OR BMN673 OR BMN 673ts OR BMN673ts | ovaries OR ovarian OR ovary OR fallopian OR peritoneal OR peritoneum OR granulosa OR krukenberg* OR oviduct OR oviducts OR uterine tube OR uterine tubes |Studies received from 11/17/2016 to 06/26/2017 2. Talazoparib OR BMN 673 OR BMN673 OR BMN 673ts OR BMN673ts | ovaries OR ovarian OR ovary OR fallopian OR peritoneal OR peritoneum OR granulosa OR krukenberg* OR oviduct OR oviducts OR uterine tube OR uterine tubes | Studies updated from 11/17/2016 to 06/28/2017 6. 6 studies found for: 1. Pazopanib OR Votrient OR GW 786034 OR GW786034 OR GW 786034b OR GW786034b OR GW 786034x OR GW786034x OR SB 710468 OR SB710468 OR SB 710468a OR SB710468a | ovaries OR ovarian OR ovary OR fallopian OR peritoneal OR peritoneum OR granulosa OR krukenberg OR oviduct OR oviducts OR uterine tube OR uterine tubes |Studies received from 11/17/2016 to 06/28/2017 2. Pazopanib OR Votrient OR GW 786034 OR GW786034 OR GW 786034b OR GW786034b OR GW 786034x OR GW786034x OR SB 710468 OR SB710468 OR SB 710468a OR SB710468a | ovaries OR ovarian OR ovary OR fallopian OR peritoneal OR peritoneum OR granulosa OR krukenberg OR oviduct OR oviducts OR uterine tube OR uterine tubes | Studies updated from 11/17/2016 to 06/28/2017 7. 53 studies found for: 1. Bevacizumab OR Avastin OR Altuzan OR NSC 704865 OR NSC704865 | ovaries or ovarian or ovary OR fallopian OR peritoneal OR peritoneum OR granulosa OR krukenberg OR oviduct OR oviducts OR uterine tube OR uterine tubes| Studies received from 11/17/2016 to 06/28/2017 2. Bevacizumab OR Avastin OR Altuzan OR NSC 704865 OR NSC704865 | ovaries or ovarian or ovary OR fallopian OR peritoneal OR peritoneum OR granulosa OR krukenberg OR oviduct OR oviducts OR uterine tube OR uterine tubes| Studies updated from 11/17/2016 to 06/28/2017

WHO ICTRP	June 28, 2017 213 results	Niraparib OR MK 4827 OR MK4827 OR Olaparib OR AZD 2281 or AZD2281 OR KU 0059436 OR KU 59436 OR KU0059436 OR KU59436 OR Lynparza OR Veliparib OR ABT 888 OR ABT888 OR Talazoparib OR BMN 673 OR BMN673 OR BMN 673ts OR BMN673ts OR Pazopanib OR Votrient OR GW 786034 OR GW786034 OR GW 786034b OR GW786034b OR GW 786034x OR GW786034x OR SB 710468 OR SB710468 OR SB 710468a OR SB710468a OR Bevacizumab OR Avastin OR Altuzan OR NSC 704865 OR NSC704865 in intervention AND ovaries OR ovarian OR ovary OR fallopian OR peritoneal OR peritoneum OR granulosa OR krukenberg OR oviduct OR oviducts OR uterine tube OR uterine tubes in condition

Figure 17 PRISMA diagram for clinical evidence



7.2 Appendix B

Table 22 Excluded studies from the clinical SLR with reason (n=249)

Study	Reason for exclusion
Gelmon, K. A.; Tischkowitz, M.; Mackay, H.; Swenerton, K.; Robidoux, A.; Tonkin, K.; Hirte, H.; Huntsman, D.; Clemons, M.; Gilks, B.; Yerushalmi, R.; Macpherson, E.; Carmichael, J.; Oza, A. "Olaparib in Patients with Recurrent High-Grade Serous or Poorly Differentiated Ovarian Carcinoma or Triple-Negative Breast Cancer: A Phase 2, Multicentre, Open-Label, Non-Randomised Study." *Lancet Oncology* 12, no. 9 (Sep 2011): 852-61.	**Study population not OC/FTC/PPC (n=8)**
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Liu, J. F.; Tolaney, S. M.; Birrer, M.; Fleming, G. F.; Buss, M. K.; Dahlberg, S. E.; et al.,. "A Phase 1 Trial of the Poly(Adp-Ribose) Polymerase Inhibitor Olaparib (Azd2281) in Combination with the Anti-Angiogenic Cediranib (Azd2171) in Recurrent Epithelial Ovarian or Triple-Negative Breast Cancer." *European Journal of Cancer* 49, no. 14 (2013).	
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Cambridge University Hospitals, N. H. S. Foundation Trust; University of, Cambridge; GlaxoSmithKline,. "Hypaz: Hypertension Induced by Pazopanib." 2014.	
Wilson, R. H., T. J. Evans, M. R. Middleton, L. R. Molife, J. Spicer, V. Dieras, P. Roxburgh*, et al.* "A Phase I Study of Intravenous and Oral Rucaparib in Combination with Chemotherapy in Patients with Advanced Solid Tumours." *British journal of cancer*, no. pagination (2017).	
ISRCTN91273375. "A Randomised, Two-Arm, Multicentre Gynaecologic Cancer Intergroup Trial of Adding Bevacizumab to Standard Chemotherapy (Carboplatin and Paclitaxel) in Patients with Epithelial Ovarian Cancer." 2006.	**Not recurrent disease (n=30)**
NCT01844986. "Olaparib Maintenance Monotherapy in Patients with Brca Mutated Ovarian Cancer Following First Line Platinum Based Chemotherapy.", 2013.	
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Table 23 Included studies from the clinical SLR not relevant to this clinical assessment (n=3)

Reference (title, author, journal, year)	**Reason for exclusion**
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Pr a Randomized, Double-Blind Phase 3 Trial of Maintenance Therapy with Niraparib Vs Placebo in Patients with Platinum-Sensitive Recurrent Ovarian Cancer (ENGOT-Ov16/NOVA Trial), Mirza M.R. et al., Annals of oncology. Conference: 41st European society for medical oncology congress, ESMO 27, 2016.	
Bevacizumab after Bevacizumab in Platinum-Sensitive Recurrent Ovarian Cancer: A Subgroup Analysis of GOG0213, Coleman R.L. et al., Journal of Clinical Oncology. Conference 34, 2016	
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 Platinum-Sensitive, Recurrent Ovarian, Peritoneal Primary and Fallopian Tube Cancer (Gynecologic Oncology Group 0213), Coleman R.L. et al., Gynecologic Oncology, 2015	
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, Aghajanian C. et al., Gynecologic Oncology, 2015	
Final Analysis of Overall Survival in OCEANS, a Randomized Phase III Trial of Gemcitabine, Carboplatin, and Bevacizumab Followed by Bevacizumab until Disease Progression in Patients with Platinum-Sensitive Recurrent Ovarian Cancer, Aghajanian C. et al., Gynecologic Oncology, 2014.	
Biological and Clinical Evidence for Somatic Mutations in *BRCA*1 and *BRCA*2 as Predictive Markers for Olaparib Response in High-Grade Serous Ovarian Cancers in the Maintenance Setting, Dougherty B.A. et al., Oncotarget, 2017	
Overall Survival (OS) in Patients (Pts) with Platinum-Sensitive Relapsed Serous Ovarian Cancer (Psr Soc) Receiving Olaparib Maintenance Monotherapy: An Interim Analysis, Ledermann J.A. et al., Journal of Clinical Oncology. Conference, 2016	
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, Matulonis U.A., et al., Cancer, 2016	
Frequency, Severity and Timing of Common Adverse Events (AEs) with Maintenance Olaparib in Patients (Pts) with Platinum-Sensitive Relapsed Serous Ovarian Cancer (Psr Soc), Matulonis U.A et al., Journal of Clinical Oncology. Conference, Suppl. 1, 2015	
Olaparib Maintenance Therapy in Patients with Platinum-Sensitive Relapsed Serous Ovarian Cancer and a *BRCA* Mutation: Overall Survival Adjusted for Post-Progression PARP Inhibitor Therapy, Matulonis U.A. et al., Gynecologic Oncology, 2015	
Assessment of Efficacy of AZD2281 in Platinum Sensitive Relapsed Serous Ovarian Cancer, AstraZeneca, ClinicalTrials.gov, 2010	
Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial. [Erratum appears in Lancet Oncol. 2015 Jan; 16(1):e6], [Erratum appears in Lancet Oncol. 2015 Feb; 16(2):e55] 16(1):87-97., Oza AMC, et al., Lancet Oncol. 2015	Olaparib in combination with chemotherapy
Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial, Coleman R.L. et al., Lancet (London, England). 2017	Rucaparib trial
Olaparib as maintenance therapy after platinum-sensitive relapsed ovarian cancer (PS-ROC). Latin American experience. Mendana A.L. et al., International Journal of gynecological cancer Conference: 16th biennial meeting of the international gynecologic cancer society Portugal, 2016	Observational study

Protokol for vurdering af den kliniske merværdi af niraparib til kræft i æggestokkene, æggelederne eller primær kræft i bughinden

Handelsnavn	Zejula®
Generisk navn	Niraparib
Firma	Tesaro
ATC-kode	L01XX54
Virkningsmekanisme	Niraparib er en selektiv hæmmer af enzymerne poly (adenosin disphosphat [ADP]-ribose) polymerase (PARP) 1/2, der deltager i DNA-reparation. Blokering af PARP 1/2 i tumorceller, som i forvejen har mange genomiske skader, inducerer celledød.
Administration/dosis	Per oral kapsel, 100 mg, 3 kapsler dagligt
EMA-indikation	Zejula is indicated as monotherapy for the maintenance treatment of adult patients with platinum sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum based chemotherapy.
Godkendelsesdato Offentliggørelsesdato Dokumentnummer Versionsnummer (Fagudvalgets sammensætning og sekretariatets arbejdsgruppe se bilag 1)	18.05.2018 18.05.2018 4412 1.0

Indhold

Forkortelser

AR:	Bivirkning (*Adverse reaction)*
ARR:	Absolut risikoreduktion
BRCA1/2:	*BReast CAncer1/2* (tumor suppressorgen)
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*)
SAR:	Alvorlig bivirkning (s*erious adverse reaction*)
SMD:	*Standardized mean difference*

1 Formål

Protokollen har til formål at definere de kliniske spørgsmål, der ønskes belyst i vurderingen af niraparib som mulig standardbehandling af patienter med platinsensitiv, recidiverende high-grade serøst adenokarcinom (HGSC) 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 niraparib modtaget den 19. september 2017.

Protokollen danner grundlaget for den endelige ansøgning for vurderingen af den kliniske merværdi af niraparib sammenlignet med dansk standardbehandling. Alle effektmål, der er opgivet i denne protokol skal besvares med en sammenlignende analyse mellem niraparib og komparator af både absolutte og relative værdier for de udspecificerede populationer i de angivne måleenheder (se tabel 2). Litteratursøgning og databehandling udføres som beskrevet i protokollen.

2 Baggrund

HGSC i æggestokkene, herunder kræft i æggelederne og primær kræft i bughinden, opstår i langt de fleste tilfælde (> 90 %) 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 II, III eller IV på henholdsvis 68 %, 36 % og 25 % (tal fra 2005-2014) [2].

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 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 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.-linie 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]. 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.-linie behandling en platinbaseret kombinationskemoterapi i form af enten carboplatin og paclitaxel eller carboplatin og pegyleret liposomal doxorubicin. Behandlingen afhænger endvidere af patienternes BRCA1/2 mutationstatus:

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.-linie platinbaseret kombinationskemoterapi [4].

Patienter uden BRCA1/2-mutation
Størstedelen af patienterne, der ikke fik bevacizumab i 1.-linie behandling, tilbydes bevacizumab i kombination med ovenstående platinbaserede kombinationskemoterapi i 2.-linie 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.-linie behandling, introduceres en ny linie platinbaseret kemoterapi. Hvis patienten ikke har fået bevacizumab tidligere, kan det tilbydes som beskrevet ovenfor. Nuværende behandlingsalgoritme efter 1.-linie behandling for patienter med platinsensitiv, recidiverende kræft i æggestokkene er opsummeret i tabel 1 nedenfor.

2.2 Niraparib

Niraparib er en selektiv hæmmer af PARP 1/2. PARP 1/2 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].

Niraparib gives i kapselform, 100 mg, 3 kapsler dagligt, som vedligeholdelsesbehandling og administreres indtil tilbagefald af sygdommen eller intolerable bivirkninger måtte opstå.

Niraparib blev godkendt af det Europæiske Lægemiddelagentur (*European Medicines Agency* (EMA)) i 2017 som vedligeholdelsesbehandling til platinsensitiv, recidiverende HGSC i æggestokkene, herunder æggelederne og primær kræft i bughinden, som responderer på platinbaseret kombinationskemoterapi (komplet eller partiel respons). Platinsensitivitet vurderes at være forbundet med PARP-hæmmer sensitivitet pga. høj prævalens af forandringer/mutationer i DNA-reparation mekanismer i platinsensitiv, recidiverende HGSC i æggestokkene. Fagudvalget vurderer, at der i Danmark diagnosticeres omkring 250

patienter pr. år, der vil være egnet til behandling. Omkring 30 % af patienterne bærer en BRCA1/2-mutation. I tabel 1 er placering af niraparib i den nuværende behandlingsalgoritme indikeret med rødt. Fagudvalget vil gerne fremhæve, at indplacering af niraparib i behandlingsalgoritmen afhænger af anvendelse af bevacizumab. Bevacizumab kan gives i 1.-linie, 2.-linie 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.-linie behandling. Niraparibs placering i behandlingsalgoritmen er indikeret med rødt.

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

*1.-linie 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 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.

3 Kliniske spørgsmål

De kliniske spørgsmål skal indeholde specifikation af patientgruppen, interventionen, alternativet/-erne til interventionen og effektmål. Ved definitionen af de kliniske spørgsmål har fagudvalget taget udgangspunkt i de forskellige standardbehandlinger til patienter med BRCA1/2-mutation og patienter uden BRCA1/2-mutation. 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 niraparib både med bevacizumab og placebo til denne patientpopulation.

3.1 Klinisk spørgsmål 1

Hvilken klinisk merværdi tilbyder vedligeholdelsesbehandling med niraparib sammenlignet med olaparib hos patienter med BRCA1/2-mutation og platinsensitiv, recidiverende HGSC og respons på platinbaseret kemoterapi

Population
Patienter med BRCA1/2-mutation og recidiverende HGSC i æggestokkene, herunder æggelederne eller primær kræft i bughinden. Patienterne skal være platinsensitive, dvs. responderet (komplet eller partiel respons) på platinbaseret kemoterapi.

Intervention
Niraparib

Komparator
Olaparib

Effektmål

Tabel 2 i afsnit 3.4 summerer de valgte effektmål, deres vigtighed, mindste klinisk relevante forskel og kategori.

3.2 Klinisk spørgsmål 2

Hvilken klinisk merværdi tilbyder vedligeholdelsesbehandling med niraparib sammenlignet med bevacizumab hos patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC og respons på platinbaseret kemoterapi

Population
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.

Intervention
Niraparib[1]

Komparator
Bevacizumab[2]

Effektmål
Tabel 2 i afsnit 3.4 summerer de valgte effektmål, deres vigtighed, mindste klinisk relevante forskel og kategori.

3.3 Klinisk spørgsmål 2

Hvilken klinisk merværdi tilbyder niraparib vedligeholdelsesbehandling sammenlignet med placebo hos patienter uden BRCA1/2-mutation og med platinsensitiv, recidiverende HGSC og respons på platinbaseret kemoterapi

Population
Patienter uden BRCA1/2-mutation og med recidiverende HGSC i æggestokkene, herunder æggeleder eller primær kræft i bughinden. Patienterne skal være platinsensitive, dvs. responderet (komplet eller partiel respons) på platinbaseret kemoterapi.

Intervention
Niraparib

Komparator
Placebo

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

Effektmål
Tabel 2 i afsnit 3.4 summerer de valgte effektmål, deres vigtighed, mindste klinisk relevante forskel og kategori.

3.4 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.

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 ikkealvorlige 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)**	
				Pt. med BRCA1/2-mutation	**Pt. uden BRCA1/2-mutation**
Overlevelse (OS)	Kritisk	Dødelighed	Median OS i antal måneder	En forskel på 3 måneder	En forskel på 3 måneder
Progressionsfri overlevelse (PFS)	Kritisk	Alvorlige symptomer og bivirkninger	Median PFS i antal måneder	En forskel på 6 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				
Tid til første efterfølgende behandling (TFST)	Mindre vigtig				
Det kemoterapifrie interval (CFI)	Mindre vigtig				

Tid til sekundær efterfølgende behandling (TSST)	Mindre vigtig			

* For alle effektmål ønskes data med længst mulig opfølgningstid.

Tidshorisont

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

3.4.1 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 niraparib og komparator for både patienter med og 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 niraparib vedligeholdelsesbehandling også afspejler, at der går længere tid til næste linie 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].

Fagudvalget finder, at en forskel på 6 og 3 måneder for hhv. patienter med BRCA1/2 og patienter uden BRCA1/2-mutation på median PFS mellem niraparib og komparator er klinisk relevant. Forskellen i valg af mindste klinisk relevante forskel for de to patientpopulationer afspejler den bedre prædiktion for effekt med PARP-hæmmere for patienter med BRCA1/2-mutation sammenlignet med patienter uden BRCA1/2-mutation.

Bivirkninger

Fagudvalget finder det relevant at definere bivirkninger (adverse reactions (AR)) som et effektmål, da det belyser, hvorvidt niraparib 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 niraparib og olaparib eller 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 niraparib 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.

3.4.2 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 niraparib 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, social velvære, følelsesmæssig velvære, funktionel 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 niraparib og komparator, er klinisk relevant.

3.4.3 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 randomisering 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.

[Niraparib, ZEJULA] *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***		
[Olaparib, LYNPARZA] *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.*		
[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.*		

Udover termer for det generiske navn skal handelsnavn, 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 kombinationsformuleringer. Det samme gælder for indikationen, inkl. alternative stavemåder.

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 på data fra publicerede fuldtekstartikler og data fra EMAs EPAR – Public assessment report. Data skal derudover stemme overens med protokollens beskrivelser. Upublicerede data og data fra f.eks. abstracts kan fremsendes og vil indgå i vurderingen, såfremt Medicinrådet finder, at de er nødvendige for at sikre en fair sammenligning. Data skal i så fald stamme fra de forsøg, hovedpublikationerne rapporterer fra, og ansøger skal acceptere, at Medicinrådet offentliggør dem i ansøgningsskemaet og i rapporten vedr. klinisk merværdi.

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.

Alt 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 ift. 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 risiko reduktion (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 har ikke yderligere overvejelser.

7 Referencer

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8 Bilag 1: sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende kræft i æggestokkene

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