Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende olaparib i kombination med bevacizumab til behandling af 1. linje vedligeholdelses-behandling af avanceret kræft i æggestokkene, æggelederne eller primær kræft i bughinden

Vers. 2.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. olaparib i kombination med bevacizumab
2. Forhandlingsnotat fra Amgros vedr. olaparib i kombination med bevacizumab
3. Ansøgers endelige ansøgning vedr. olaparib i kombination med bevacizumab

Medicinrådet
Dampfærgevej 21-23, 3. sal
2100 København Ø

22.03.2024

Vedr.: Udkast til Medicinrådets anbefaling vedr. olaparib + bevacizumab til 1. linje vedligeholdelses-behandling af avanceret kræft i æggestokkene

Vi takker for muligheden for at komme med bemærkninger til ovenstående udkast til anbefaling.

Klinisk effekt:
AstraZeneca er som udgangspunkt enig i Medicinrådets beskrivelse af PAOLA-1 og PRIMA studierne som værende placebo-kontrollerede multicenter fase III studier med udgangspunkt i avanceret kræft i æggestokkene. Samtidigt finder AstraZeneca det dog vigtigt at understrege, at de to studier fundamentalt adskiller sig i valg af komparator arm. Hvor PRIMA studiet vurderer effekten af tillæg af niraparib som eneste aktive vedligeholdelsesbehandling, undersøger PAOLA-1 studiet tillæg af olaparib til en allerede eksisterende aktiv vedligeholdelsesbehandling, nemlig bevacizumab.

I sin vurdering af PFS skriver Medicinrådet i vurderingsrapporten:

- *"Resultaterne indikerer at olaparib + bevacizumab som minimum har lige så god effekt på PFS som niraparib".*

- "*Baseret på tilgængeligt data og klinisk erfaring med olaparib og niraparib, vurderes det rimeligt at antage at olaparib + bevacizumab vs. niraparib er ligeværdige behandlinger".*

Medicinrådet har tidligere vurderet behandlingen med olaparib og niraparib af BRCA muterede patienter med avanceret kræft i æggestokkene som værende ligeværdige. Når Medicinrådet i denne ansøgning antager, at også olaparib+bevacizumab og niraparib er ligeværdige, rejser det spørgsmålet om Medicinrådet således ikke anser bevacizumab for at være en aktiv behandling?

AstraZeneca har i ansøgningen redegjort for den belyste effekt på overlevelse ved tillæg af bevacizumab til standard platinbaseret kemoterapi i både randomiserede kliniske afprøvninger, samt ved analyse af brugen af bevacizumab i klinisk praksis i en række europæiske lande. I begge tilfælde understreger overlevelsesdata betydningen af bevacizumab som en aktiv og effektiv komparator i PAOLA-1 studiet.

Netop effekten af en aktiv vedligeholdelsesbehandling med PARP-inhibitor på overlevelse kan nu vurderes på baggrund af modne overlevelses data fra PAOLA-1 studiet. Den statistiske analyse plan for PAOLA-1 studiet specificerer, at Final OS Analysis var planlagt ved data maturity på ~60% eller 3 år efter PFS1 analyse, alt efter hvad der indtraf først. Derfor er AstraZeneca heller ikke enige i Medicinrådets vurdering af, at der er begrænsede OS-data tilgængelige fra PAOLA-1 studiet. Data præsenteret i ansøgningen repræsenterer den endelige OS-analyse, men selvsagt bidrager subgrupper med forskellige prognostisk og prædiktive faktorer relativt forskelligt til OS analysen for ITT-population.

Disse modne overlevelsesdata fra PAOLA-1 studiet blev præsenteret på ESMO 2022, 4,5 år efter Last Subject In (LSI). Dette står i kontrast til at First Subject In i PRIMA-studiet fandt sted 3. august 2016, og at man forventede final OS analysis 70 måneder senere, dvs. juni 2022. Til trods for at man i studiet ekskluderede lav-risiko patienter med en favorable prognose, er overlevelsesdata her næsten 6 år efter LSI endnu ikke blevet præsenteret. AstraZeneca kan selvsagt ikke vurdere hvorfor, men uanset hvad baggrunden måtte være, syntes Medicinrådets bemærkning om, at der for begge behandlinger er begrænsede OS-data således ikke at være rimelig.

Opsummerende anser AstraZeneza på baggrund af MAIC analysens resultater og de modne OS data, kombinationen *olaparib + bevacizumab* som en særskilt behandlingsmulighed, der for HRD+ BRCAwt forbedrer behandlingseffekten.

Patientantal hvis kombinationen anbefales:
Medicinrådets foreslåede behandlingsalgoritme (figur 1 i vurderingsrapporten) tager udgangspunkt i ~520 patienter i stadie 3-4 og med god performance status. Afledt heraf er 155 (30%) patienter BRCAm og 105 (20%) patienter HRD+/BRCAwt, hvilket AstraZeneca antager beror på observeret prævalens i PAOLA-1 og PRIMA studierne.

AstraZeneca har følgende kommentarer til algoritmen:

- Vi anerkender, at den observerede prævalens af mutationer i BRCA 1- eller 2-genet i PAOLA-1 studiet er ~30%, men vurderer at denne relativt høje prævalens er en konsekvens af selektionsbias. I følge Marth et al (2022) præsenterer 17% af nydiagnosticerede Stadium 3-4 high-grade serous eller endometroid patienter med kræft i æggestokkene sig med mutation i BRCA 1- eller 2-genet. En prævalens i området af hvad Medicinrådet nævner andet steds i rapporten, jf. afsnit 1.2.

- Vi mener ikke at incidensen af stadie 3 og 4 i god performance stadie er 520. Dels fremgår det ikke hvordan god performance status defineres, og dels rapporteres der andet steds i vurderingsrapporten til 520 som værende incidensen for æggestokkræft **samlet,** jf. afsnit 1.2. Vi henviser til den præsenterede patientmodel i ansøgningen, som blandt andet tager udgangspunkt i tidligere vurderinger på PRIMA og SOLO1 fra Medicinrådet. Af den vurderes det, at der årligt nydiagnostiseres ~260 Stadie III/IV High-Grade Epithelial patienter med kræft i æggestokkene, hvoraf 80-90 % vil respondere på platinholdig kemoterapi.

Baggrund for den valgte sundhedsøkonomiske analyse:
Valget af en omkostningsminimeringsanalyse til den sundhedsøkonomiske analyse er et pragmatisk valg snarere end en erkendelse af, at de to behandlinger (olaparib + bevacizumab og niraparib) har samme effekt i HRD+ BRCAwt populationen. Der er to hovedårsager til, at en omkostningseffektivitetsanalyse ville være svær at udføre:

- Den første er manglen på offentliggjorte samlede overlevelsesdata fra PRIMA-studiet (se ovenfor). Da offentliggjorte data for samlet overlevelse således kun er tilgængelige fra PAOLA-1-studiet, er det ikke muligt at udføre en indirekte behandlingssammenligning, hvilket ville være nødvendigt for at modellere den relative effektivitet i en omkostningseffektivitetsanalyse.

- Den anden grund er, at PRIMA-studiet kun blev udført i en højrisiko-population, dvs. patienter, der ikke blev fuldstændigt resekteret eller som ikke kan resekteres, og som har en høj risiko for tilbagefald. Det ville derfor ikke være muligt at sammenligne studierne som helhed, da den sammenlignende effekt kun kan estimeres for højrisikogruppen, også selvom data for samlet overlevelse var tilgængelige.

Endelig ønsker AstraZeneca at gøre opmærksom på, at omkostningsminimeringsanalysen udført af Medicinrådet er mere konservativ, end den AstraZeneca har fremsendt. De fleste af de forudsætninger Medicinrådet har anvendt, anser vi for at være realistiske, dog er AstraZeneca ikke enige i Medicinrådets valg om at udelukke lavrisiko-gruppen fra omkostningsminimeringsanalysen.

Indikationerne for både olaparib + bevacizumab og for niraparib omfatter både patienter med høj og lav risiko for tilbagefald. Patienter med lav risiko for tilbagefald bliver i gennemsnit behandlet i længere tid end højrisiko-patienter, da de har lavere risiko for at seponere behandlingen på grund af sygdomsprogression. Derfor vil forskellen i omkostninger mellem en PARP-hæmmerbehandling med 2-års stopregel (olaparib + bevacizumab) og en behandling med en 3-års stopregel (niraparib) være større for lavrisiko-gruppen end for højrisiko-gruppen gruppe, hvilket indebærer større omkostningsbesparelser for olaparib + bevacizumab sammenlignet med forskellen i omkostninger for højrisiko-gruppen. Kun medtagelse af højrisiko-gruppen vil derfor undervurdere besparelsen med olaparib + bevacizumab vs. niraparib på AIP-niveau sammenlignet med en analyse baseret på både højrisiko- og lavrisikopatient-populationen.

Vi ser frem til at modtage Medicinrådets endelige afgørelse på vores ansøgning.

Med venlig hilsen
AstraZeneca A/S

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20.03.2024
DBS/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	Revurdering
Leverandør	AstraZeneca
Lægemiddel	Lynparza (olaparib)
Ansøgt indikation	Olaparib i kombination med bevacizumab til 1. linje vedligeholdelsesbehandling af avanceret kræft i æggestokkene, æggelederne eller primær kræft i bughinden. For patienter med epitelcelle highgrade karcinom og homolog rekombinationsdefekt (HRD+) men uden BRCA 1/2-mutation
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende aftalepris på Lynparza (olaparib):

Tabel 1: Aftalepris

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP (DKK)	SAIP (DKK)	Rabatprocent ift. AIP
Lynparza	100 mg	56 stk.	15.337,06	[redacted]	[redacted]	[redacted]
Lynparza	150 mg	56 stk.	15.343,55	[redacted]	[redacted]	[redacted]

Den nye pris er betinget af Medicinrådets anbefaling.
[redacted]

Aftaleforhold

Amgros har en aftale med leverandøren, som gælder frem til den 31.03.2025 med mulighed for forlængelse.

Konkurrencesituationen

Der er i dag en behandlingsvejledning til behandling af patienter med BRCA-mutation i både 1. og 2. linje. Der er ingen behandlingsvejledning til patienter uden BRCA-mutation. Patienterne til den ansøgte population med avanceret HRD+ kræft i æggestokkene, som ikke har BRCA-mutation, modtager i dag vedligeholdelse behandling med niraparib.

Tabel 2: Lægemiddeludgifter pr. patient for et års behandling

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Lynparza	150 mg	56 stk.	300 mg 2 gange dagligt	[redacted]	[redacted]	[redacted]
Bevacizumab	25mg/ml	1*16 ml	810 mg hver 3. uge	[redacted]	[redacted]	
Niraparib	100 mg	84 stk.	200 mg dagligt	[redacted]		[redacted]

*Patientvægt 72 kg

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til anbefaling
England	Anbefalet	Link til anbefaling
Sverige	Anbefalet	Link til anbefaling

Konklusion

[redacted]

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

A comparison vs Zejula (niraparib)

- Submitted by AstraZeneca November 2nd , 2022
- 1st validation received September 7th ,2023
- Additional comments received September 20th ,2023
- Application re-submitted by AstraZeneca October 13th 2023
- 2nd validation received October 19th 2023
- Updated application submitted by AstraZeneca November 2nd 2023
- 3rd validation received November 20th, 2023
- Updated application submitted by AstraZeneca November 28th, 2023
- 4th validation received December 13th and 18th, 2023
- Updated application submitted by AstraZeneca December 21st, 2023
- 5th validation received January 17th, and 24th, and 29th 2024
- Updated application submitted by AstraZeneca January 31th, 2024
- Further questions received February 20th and 21st 2024 and update submitted by AZ Feb 26th 2024

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Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
	Confidential information

1. Basic information

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Overview of the pharmaceutical	
Proprietary name	Lynparza
Generic name	Olaparib
Marketing authorization holder in Denmark	AstraZeneca AB
ATC code	L0XK01
Pharmacotherapeutic group	poly [ADP-ribose] polymerase inhibitors (PARPi),
Active substance(s)	Olaparib
Pharmaceutical form(s)	Tablets 150 mg and 100 mg
Mechanism of action	Olaparib is an oral potent inhibitor of PARP1, PARP2, and PARP3. These PARP enzymes are required for the efficient repair of DNA single-strand breaks. During the repair process, after chromatin modification, PARP auto-modifies itself and dissociates from the DNA to facilitate access for base excision repair (BER) enzymes. Olaparib, when bound to the active site of DNA-associated PARP, prevents dissociation from DNA, blocking repair of the single-strand break
Dosage regimen	2 tablets twice daily.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	• Maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a *BRCA1/2* mutation and/or genomic instability.

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

Overview of the pharmaceutical	
Combination therapy and/or co-medication	Olaparib plus bevacizumab
Packaging – types, sizes/number of units, and concentrations	100mg and 150 mg pack. 56 tablets per pack
Orphan drug designation	No

2. Abbreviations

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

Abbreviations	
AESI	Adverse Events of Special Interest
EMA	European Medicines Agency
ENGOT	European Network of Gynaecological Oncological Trials
EOC	Epithelial ovarian cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer life questionnaire 30
EORTC QLQ-OV28	European Organisation for Research and Treatment of Cancer life questionnaire-ovarian cancer module 28
EoT	End of treatment
EQ-5D-5L	European Profile of Quality of Life (EuroQoL) 5 dimensions, 5 level
ESMO	European Society for Medical Oncology
EuroQoL	European Profile of Quality of Life
FACT	Functional Assessment of Cancer Therapy
FACT-O	Functional Assessment of Cancer Therapy – Ovarian
FAS	Full analysis set
FSD	Fixed Starting Dose
FUP	Follow-up
gBRCA	Germline (mutation in) breast cancer susceptibility gene
HGEC	High-grade endometroid carcinoma
HGSC	High-grade serous carcinoma
HGSOC	High-grade serous ovarian cancer
HR	Hazard ratio
HRD	Homologous recombination deficiency
HRQoL	Health-related quality of life
HRR	Homologous recombination repair
IDS	Interval Debulking Surgery
ISD	Individual Starting Dose
ITC	Indirect treatment comparison
ITT	Intent-to-treat
LGEC	Low-grade endometroid carcinoma
LGSC	Low-grade serous carcinoma

Abbreviations	
MMRM	Mixed model for repeated measures
NS	Not significant
OC	Ovarian cancer
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PDS	Primary Debulking Surgery
PARP	Poly (ADP-ribose) polymerase
PARPi	Poly (ADP-ribose) polymerase inhibitor
PFS	Progression-free survival
PFS2	Time to second progression or death
PPS	Post-progression survival
PR	Partial response
PRO	Patient-reported outcome
PRR	Platinum resistant/refractory
PS	Performance status
PSR	Platinum-sensitive recurrent
QoL	Quality of life
RCT	Randomised clinical trial
RECIST	Response Evaluation Criteria in Solid Tumours
RR	Relative Risk
SAE	Serious adverse event
SAS	Safety analysis set
sBRCA	Somatic (mutation in) breast cancer susceptibility gene
SD	Standard deviation
SE	Standard error
SST	Second subsequent therapy
TDT	Time to discontinuation of treatment
TFST	Time to first subsequent therapy or death
TNM	Tumour (T), Node (N), Metastasis (M)

Abbreviations	
TSST	Time from randomisation to second subsequent therapy or death
TTP	Time to progression
VUS	Variants of unknown significance
Wt	Wild-type

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4. Summary (Danish)

AstraZeneca indsendte i februar 2021 ansøgning om anbefaling af olaparib i kombination med bevacizumab til 1. linje vedligeholdelsesbehandling af HRD+ ovarie cancer. Ansøgningen (merværdi) var baseret på PAOLA1 studiet og var en sammenligning med olaparib monotherapy (BRCAm), bevacizumab vedligelsesholdelse behandling for high-risk populationen af HRD positive ekskluderende BRCA muterede og placebo for low-risk populationen af HRD positive ekskluderende de BRCA muterede. Ansøgning blev afvist den 23. juni 2021 på grund af ubalance mellem effekt og omkostninger. Den BRCA muterede subgruppe blev vurderet til ingen merværdi mens de to andre subgrupper blev evalueret til at have en lille merværdi:

- 1. linje vedligeholdelsesbehandling af HRD+, BRCAwt hos gruppen af patienter defineret som enten "higher" eller "lower"-risk

Senere var AstraZeneca i dialog med Amgros og Medicinrådet idet AstraZeneca efterfølgende havde valgt at reducere prisen på olaparib blandt andet som følge af afslaget. I mellemtiden var Zejula (niraparib) blevet anbefalet af Medicinrådet i HRD+, BRCAwt patientgruppen, og bør ifølge Medicinrådet nu betragtes som komparator i stedet for bevacizumab. Medicinrådet har således specifikt bedt om en evaluering af kombinationen af olaparib plus bevacizumab versus niraparib monoterapi til patientgruppen karakteriseret ved HRD+ excl BRCAm status.

Data i denne ansøgning tager dermed udgangspunkt i PAOLA-1 og PRIMA studierne. Begge studier undersøger rollen af vedligeholdelsesbehandling med PARPi, men adskiller sig markant ved at niraparib i PRIMA studiet blev sammenlignet mod placebo, mens tillæg af olaparib til bevacizumab blev sammenlignet med aktiv bevacizumab behandling i PAOLA-1 studiet. I forhold til inklusionskriterierne i PAOLA-1 og PRIMA var der flere væsentlige forskelle studierne i mellem uagtet at begge studier tillod inklusion af patienter uanset HRD status.

Gruppen af stadium III patienter uden residual sygdom (≤1 cm efter primær kirurgi (efterfølgende benævnt *lower-risk*) var ekskluderet fra PRIMA studiet. Denne patientgruppe udgjorde 26,2% af ITT populationen i PAOLA-1 studiet.

For at adressere spørgsmålet om tillæg af olaparib til en aktiv vedligelsesholdelsesbehandling med bevacizumab versus PARPi behandling med niraparib til undergruppen af HRD positive ekskludernde BRCA muterede patienter med avanceret æggestok kræft indeholder ansøgningen følgende data:

- Overlevelsesdata for den specificerede subgruppe af HRD positive patienter ekskluderende BRCA muterede patienter. Ansøgningen indeholder ikke en formel MAIC på overlevelsesdata da disse ikke er publiceret for PRIMA og dermed tilgængelige for AstraZeneca
- Gennemgang af overlevelsedata for 1. linie studier for at belyse rollen af vedligelsesholdelse behandling med PARPi (hvis data er tilgængelige). Dette for at perspektivere overlevelsessignalet for de HRD positive patienter ekskluderende de BRCA muterede fra PAOLA-1 og give Medicinrådet et bedre beslutningsgrundlag
- Data fra formel PAIC sammenligning af HRD-positive patienter fra PAOLA-1 studiet og PRIMA studiet. Det er ikke muligt at gennemføre en PAIC for gruppen af HRD+ ekskludernede BRCAm, da baseline karakteristika ikke er publicerede for denne specifikke subgruppe i PRIMA studiet
- Populationen af primært opererede stadium III patienter uden residual sygdom efter operation diskuteres særskilt på baggrund af deskriptive data da disse patienter er ekskluderede fra PRIMA studiet
- Medicinrådet har bedt om en særskilt analyse af stadium IV patienter. AstraZeneca adresserer dette ved dels:

    - ✓ At belyse den kliniske aktivitet af bevacizumab for gruppen af Stadium IV patienter illustrerende bevacizumabs rolle som aktiv komparator
    - ✓ At belyse at tillæg af olaparib til bevacizumab behandling af disse patienter ved at præsentere upublicerede data for HRD positive stadium IV patienter

I gennemgang af uønskede hændelser inddrages data fra olaparib monoterapi studier (SOLO-1 og SOLO-2) for blandt andet at perspektivere data fra PAOLA.

En række punkter er centrale for denne ansøgning:

- Medicinrådet har godkendt niraparib til alle HRD positive patienter på baggrund af PRIMA studiet. I den sammenhæng er det vigtigt at notere sig, at man med udgangpunkt i real-world data fra DGCGs database og RESPONSE trial (Marth 2022) kan estimere at patient populationen i PRIMA studiet repræsenterer ~40% af stadium III/IV patienter i klinisk praksis i Danmark

- Af denne grund vil en formel indirekte sammenligning ikke alene være fyldestgørende, da effekten af den givende intervention således ikke bliver evalueret i alle klinisk relevante patientgrupper. Af den grund vil deskriptive data indgå i ansøgningen. Disse data vil blive søgt perspektiveret med data fra andre subgrupper for at give fagudvalget og medicinrådet et kvalificeret beslutningsgrundlag

Siden evalueringen af AstraZenecas initiale ansøgning er der for PAOLA-1 studiet præsenteret endelig overlevelses analyse baseret på DCO3 med data maturity på 55% og en median opfølgningstid på ~62 måneder. For den HRD positive population var median overlevelse forlænget for olaparib + bevacizumab sammenlignet med bevacizumab med en større andel af patienter i live efter 5 år (5-års OS rate: 65.5% versus 48.4%; median OS 75.2 versus 57.3 åneder; HR 0.62; 95% CI 0.45-0.85).

Overordnet kan følgende konkluderes for sammenligningen af olaparib plus bevacizumab versus niraparib for HRD positive patienter uden BRCA mutation:

OS:

- En 10,5 %-points forbedering i 5-års overlevelsen blev observeret i PAOLA-1 studiet. Dette kan ikke sammenlignes med data fra PRIMA studiet, da disse ikke er frigivet. En 29 % reduktion i risikoen før død (HR 0.71 95% CI 0.45-1.13).

PSF:

- Baseret på en PAIC mellem PRIMA og gruppen af patienter i PAOLA-1 ekskluderende primært opererede stadium III patienter uden rest sygdom fandtes:

  - ✓ Absolut forskel i mPFS på 14 måneder til fordel for kombinationen, der opfylder Mindste Kliniske Relavante Forskel(MKRF) som tidligere blev anvendt i "Merværdi" evaluering.

  - ✓ PFS rate ved 24 måneder svarende til 11 %-points forskel til fordel for kombinationen , der opfylder MKRF på 10 %-points forskel

- For gruppen af ekskluderende primært opererede stadium III patienter uden rest sygdom fandtes følgende:

  - ✓ 82.1 % (61.8 – 92.2) af patienter behandlet med olaparib plus bevacizumab var progressionfri efter 24 måneder sammenlignet med 46.2 % (21.3 – 67.9) for patienter behandlet med bevacizumab

  - ✓ En 81 % reduktion i risikoen for progression eller død blev observeret (HR= 0.19 95% CI 0.06-0.55). Denne reduktion er på niveau med data fra den BRCA muterede subgruppe i PAOLA-1, men lavere en generelt observeret for PARPi monoterapi behandling

Bivirkninger:

- I PAOLA1 studiet var der en sammenlignelig frekvens af Grad 3-4 bivirkninger de to studier i mellem men der var variationer i typen af bivirkninger. Grad ≥3 bivirkninger var 57,6% i kombinationsarmen og 50.9% i placebo-gruppen. Alvorlig bivirkninger så hos 31% i begge arme. I HRD+ patientgruppen var bivirkningsfrekvensen identisk med ITT populationen

- Den indirekte sammenligning mellem PAOLA1 og PRIMA viste at næste alle patienter oplevede bivirkning(any grade): 100% olaparib plus bevacizumab; 96% placebo plus bevacizumab; 99% niraparib og 92% placebo. Frekvensen af grad ⩾3 bivirkninger var højere for vedligeholdelsesbehandling med niraparib (70%) vs. olaparib plus bevacizumab (60%)

Livskvalitet:

- I PAOLA var EORTC QLQ-C30 baseline scores var høje og end i begge arme og forblev stabile i den 24 måneders behandlingsperiode. Desuden var der ikke klinisk betydelige forskelle mellem de to arme målt på henholdvis EORTC QLQ-C30, QLQ-OV2 og EQ-5D-5L. Det har ikke været muligt at sammenligne livskvalitet data studierne i mellem.

Tillige bad Medicinrådet om en separat analyse af **stadium IV patienter**:

- Bevacizumabs rolle i behandling af stadium IV patienter er belyst i ICON-7 og GOG-218. 26%/25% reduktion i risikoen for død blev demonstreret i henholdsvis ICON-7 og GOG-218. I GOG-218 studiet viste en forbedring i 5-års overlevelse på 12,6 %-point

- Bevacizumabs rolle er yderligere blevet undersøgt i RESPONSE studiet, et real-world retrospektivt observationelt studie. Det viste en 50% reduktion i riskoen for død ved tillæg af bevacizumab for stadium IV patienter der kan tolerere behandling med platin-holdig kemoterapi

- Sammenholdt understreger det relevansen af bevacizumab som aktiv komparator i randomiserede studier

- For ITT grupperne i PAOLA-1 og PRIMA fandtes følgende PFS HR for tillæg af olaparib til bevacizumab og niraparib

    - ✓ PAOLA-1: HR 0.49 95% CI 0.36-0.67
    - ✓ PRIMA: HR 0.79 95% CI 0.55-1,12

- For gruppen af HRD positive patienter i PAOLA-1 studiet sås en 31% reduktion i risikoen for død ved tillæg af olaparib til den aktive komparator bevacizumab (HR 0.69 95% CI 0.42 – 1.13)

Med bagrund i ovenstående har AstraZeneca derfor udarbejdet en ny og opdateret ansøgning vs niraparib baseret på:

- Nyligt publicerede overlevelsesdata fra PAOLA-1 og SOLO-1til at underbygge OS diskussionen

- Indirekte sammenligning af PAOLA-1 og PRIMA for HRD+ higher-risk subpopulationen

- Deskriptiv beskrivelse af PAOLA-1 data for HRD+ excl BRCAm lower-risk subpopulationen, da der for nærværende ikke er data tilgængelige for niraparib

4.1 Samlet konklusion effekt og bivirkninger

Medicinrådet har accepteret at der var belæg for, at AstraZeneca genansøgte på PAOLA indikationen dog med en ny komparator. Vi mener at det er vist, at kombinationen af olaparib og bevacizumab er et veldokumenteret alternativ til niraparib baseret på indirekte sammenligninger af effekt og bivirkninger.

Den sundhedsøkomiske del af ansøgningen udgøres af en omkostningsminimeringsanalyse mellem olaparib + bevacizumab og niraparib. Der er forskelle i patientpopulationerne i PAOLA-1 og PRIMA og desuden fravær af modne OS-data fra PRIMA. I højrisikopopulationen viste resultaterne af gennemsnitsomkostninger pr. patient, at for patienter behandlet med olaparib + bevacizumab er omkostningerne over 10 år DKK 981 652, sammenlignet med DKK 1 281 025 for niraparib monoterapi, dvs. en forskel på DKK – 299 373 (olaparib + bevacizumab omkostningsbesparende). I lavrisikopopulationen viste resultaterne af gennemsnitsomkostninger pr. patient, at for patienter behandlet med olaparib + bevacizumab er omkostningerne over 10 år 1 202 730 kr. mod 1 882 626 kr. for niraparib monoterapi, dvs. en forskel på kr. – 679 897 (olaparib + bevacizumab omkostningsbesparende).

De direkte Lægemiddelomkostninger udgør hovedparten af omkostningerne, og derfor var resultaterne mest følsomme over for ændringer i disse for olaparib og niraparib (og behandlingsvarigheden af niraparib) og relativt ufølsomme over for andre variabler. Antagelsen vedrørende behandlingsvarighed for niraparib følger danske retningslinjer, dvs. 36 måneder.

Budgetkonsekvensberegningerne omfatter omkostningsimplikationer for introduktion af olaparib + bevacizumab i dansk klinisk praksis. I den højrisiko HRD-positive BRCAwt-population viste hovedanalysen, at en sådan introduktion i gennemsnit ville føre til en budgetnedgang på 3 % i år 2024, 5 % i år 2025, 13 % i 2026, 17% i år 2027 og 19 % i år 2028. I lav-risiko HRD-positive BRCAwt-population var der budgetnedgang på 3 % i år 2024, 5 % i år 2025, 14 % i 2026, 19% i år 2027 og 22 % i år 2028.

Omkostningerne pr. patient og budgetpåvirkning for bevacizumab + olaparib varierede på en forudsigelig måde afhængigt af subpopulation og andre variabler. Analysen er meget konservativ, da olaparib + bevacizumab har vist signifikant effekt i forhold til aktiv komparator og behandlingen med niraparib er til progression i produktresuméet: "It is recommended that treatment should be continued until disease progression or toxicity" (Zejula produktresumé, EMA 2022).

5. The patient population, the intervention and choice of comparator(s)

5.1 The medical condition and patient population

Ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer, hereafter ovarian cancer, is the fourth most common cause of cancer-related deaths in women in Denmark. According to Cancerregistered the number of new cases in 2021 were 516. This is a decline in case compared to previous years. Persons living with the diagnosis at the end of 2021 (prevalence) were 4931 (file:///C:/Users/ktgp476/Downloads/Kraefttilfaelde%202021.pdf)

5.1.1 Patient populations relevant for this application

Lynparza has obtained several therapeutic indications. This specific application is based on the EMA-approved indication *" Lynparza in combination with bevacizumab is indicated for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a BRCA1/2 mutation and/or genomic instability "*

For this application an incidence of 235 high-grade Epithelial Ovarian Cancer patients responding to platinum-based chemotherapy with concomitant bevacizumab are estimated as representative in Denmark, of which about 65 would be HRD positive (excl. BRCAm). The analysis for this estimation are presented below. Epithelial ovarian cancer is the most common type of ovarian cancer. DGCGs Annual Report estimates that 90 % of tumors of the ovary are epithelial. Further it is estimated that ~80% of the Epithelial Carcinomas have a high-grade coding, hence approximately 370 out of the 516 annually diagnosed ovarian cancer patients belong to the High-Grade Epithelial Ovarian cancer subgroup. Approximately 70 % of patients are diagnosed with FIGO stage III/IV disease, leading to the estimation that ~260 patients are being diagnosed as Stage III/IV High-Grade Epithelial Ovarian Cancer Patients annually in Denmark. Therapeutic indication for both olaparib in combination with bevacizumab and niraparib states, that patients must be in response following completion of first-line platinum-based treatment (with or without bevacizumab). Real-World data from the RESPONSE trial [Marth 2022] suggests that ~80% of Stage III/IV High-Grade epithelial ovarian cancer patients present with No Evidence of Disease (NED), complete response or partial response following completion of 1st line therapy. These definitions resemble inclusion criteria in the PAOLA-1 study making **~215** eligible for addition of maintenance olaparib. However, it can be speculated that the percentage of responders would be higher in the HRD+ patients' subgroup of patient, further enhanced by the concomitant usage of bevacizumab and finally by clinical variation in assessment criteria. Therefore, and for the remainder of this application, an incidence of 235 high-grade Epithelial Ovarian Cancer patients responding to platinum-based chemotherapy with concomitant bevacizumab are estimated as representative in Denmark. Based on data from PAOLA-1 (Ray-Coquard 2019) it is further estimated that ~30% (n≈65) would be defined as homologous recombination deficiency (HRD) positive (excluding BRCA ½ mutated) according to Myriad MyChoice HRD test (Table 1).

Table 1. Estimation of incidence of relevant patient population – HRDpos excl. BRCA mutated

	Ovarian Cancer	Epithelial Ovarian Cancer	High-Grade	Stage III/IV	Responding to platinum based Chemotherapy	HRD positive excluding BRCA 1/2
Subgroup - Relative Proportion	100 %	90 %	80 %	70 %	80 – 90 %	~30%
Incidence in Denmark	516	~465	~372	~260	208– **234**	62 - **70**

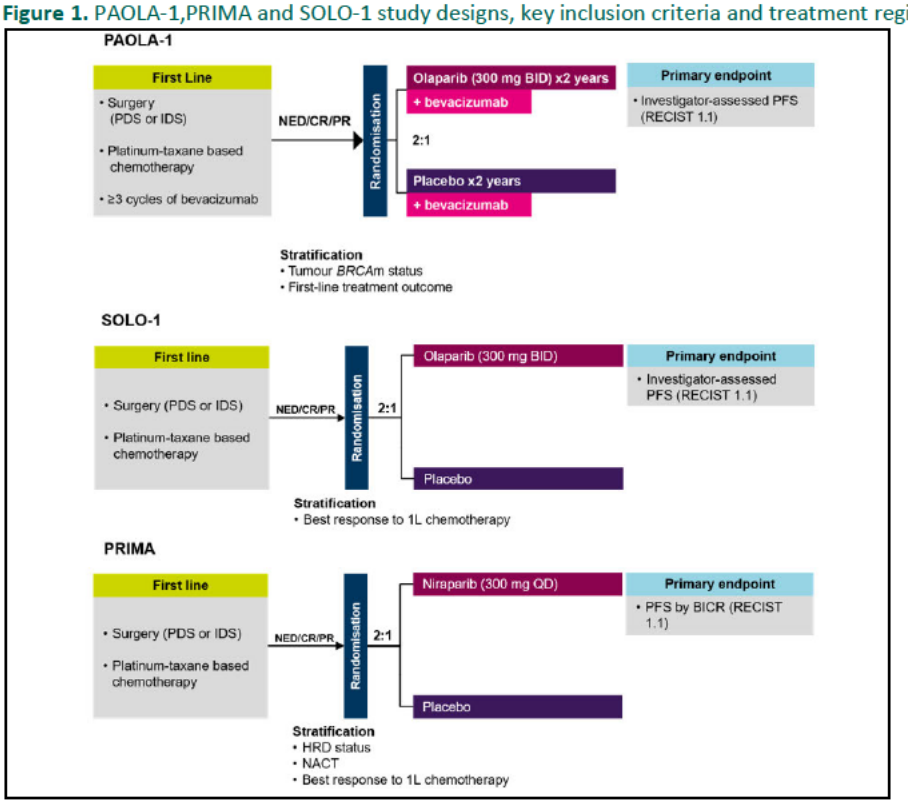
5.1.1.1 Study populations in PAOLA-1,PRIMA and SOLO-1

PAOLA-1 included patients with newly diagnosed stage III/IV high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer or fallopian-tube cancer irrespective of previous surgical outcome. In contrast, PRIMA included patients with newly diagnosed stage III/ IV high-grade serous or endometrioid ovarian cancer, peritoneal

cancer or fallopian-tube cancer in which patients with stage III disease required incompletely resected cancer after primary debulking surgery or inoperable disease or receipt of neoadjuvant chemotherapy.

Figure 1 and Table 2 summarizes the study designs of PAOLA-1 [ClinicalTrials.gov identifier: NCT 02477644],PRIMA (Gonzalez-Martin 2019) [ClinicalTrials.gov identifier: NCT02655016] and SOLO-1 (NCT01844986) including the randomized double-blind design, key patient inclusion criteria and treatment regimens. We have included SOLO-1 in this section since it was requested by DMC.

Figure 1. PAOLA-1,PRIMA and SOLO-1 study designs, key inclusion criteria and treatment regimens



Main characteristics of the two studies and SOLO-1 is shown below in Table 2 where relative distribution is calculate out ITT population. Data presented in highlights the impact of variation in baseline population when calculating relative distribution.

Table 2. Patient characteristics SOLO-1, PAOLA-1 and PRIMA.

	SOLO-1	PAOLA-1	PRIMA
Study size	N=391	N=806	N=727
Arms	Olaparib vs placebo as maintenance therapy	Olaparib + bevacizumab vs placebo + bevacizumab as maintenance therapy	Niraparib vs placebo as maintenance therapy

	SOLO-1	PAOLA-1	PRIMA
Patients included	*BRCA*m	All-comers HRD testing (Myriad myChoice® HRD plus, ≥42 and ≥33 cut-offs) *BRCA* testing	All-comers HRD testing (Myriad myChoice® HRD, ≥42 cut-off) *BRCA* testing
Includes patients with NED following primary surgery?	Yes	Yes	Stage IV patients were eligible irrespective of residual disease Stage III patients were required to have residual disease and <2cm tumour volume at baseline
Disease stage	Stage III: 85% Stage IV: 15%	Stage III: 70% Stage IV: 30%	Stage III: 65% Stage IV: 35%
Surgery	PDS: 62% IDS: 36% None: 2%	PDS: 51% IDS: 42% None: 7%	PDS: 24%[a] IDS: 67%[b] Unknown: 9%[c]
1L treatment outcome	CR: 82% PR: 18%	CR: 73% PR: 27%	CR: 69% PR: 31%

Footnotes: *[a]The proportion of patients who had PDS was only reported for patients with stage III disease. Some patients with stage IV disease may also have had PDS. [b]Based on the proportion of patients reported to have NACT. [c]The proportion of patients for whom surgical status was not reported.* ***Source:*** *AstraZeneca Data on File (SOLO-1 CSR), AstraZeneca Data on File (PAOLA-1 CSR), Ray-Coquard et al. 2019, González-Martín et al. 2019, Coleman et al. 2019*

Main differences between the 3 studies

Putting the patient populations from PAOLA-1, SOLO-1 and PRIMA into context of a real-world patient population, such as described in the RESPONSE trial [Marth et al. 2022] clearly demonstrates that the PAOLA-1 study population to a larger extent resembles the population met in clinical practice. Compared with PRIMA, patients from PAOLA-1 represent a broader population with less restrictive criteria for eligibility based on surgical outcomes and the requirement to demonstrate a response to treatment with platinum-based chemotherapy.

This difference is important to acknowledge in order to assess and compare the clinical outcome in PAOLA-1 and PRIMA, and thereby addressing the clinical question in this application. Out of the 806 total patients randomized in PAOLA- 1, 595 patients enrolled in PAOLA-1 would have met the staging and surgical eligibility criteria for PRIMA (referred to as "higher-risk in Table 3 [Hettle et al. 2021]. The remainder 211 patients, who would have been excluded from PRIMA based on eligibility criteria included those with stage III disease and no evidence of disease following primary debulking surgery . While all PAOLA-1 patients were at high risk of progression, these patients represent a "lower-risk group" and referred to as such in Table 3 [Hettle et al. 2021] The "higher-risk" subgroup of PAOLA-1 patients, matching the staging and surgical eligibility criteria for PRIMA, were patients with any stage IV disease; stage III disease and residual disease after primary debulking surgery; inoperable stage III disease; and patients with stage III disease who had received neoadjuvant chemotherapy.

Table 3. Relative distribution of "higher-risk" and "lower-risk" subgroups in key 1st line studies and Real World study.

	PAOLA-1[1] N = 806	PRIMA[2] N=733	SOLO-1[3] N=391	RESPONSE Trial[4] (Clinical practice) N=1.119
"Lower-risk" subgroup [% (n/N)]				
- **stage III disease and no evidence of disease following primary debulking surgery**	26,2 % (211/806)	0 % (0/733)	44,0 % (172/391)	24,5 % (274/1.119)
"Higher-risk" subgroup [% (n/N)]				
- **any stage IV disease** - **stage III disease & residual disease after primary debulking surgery;** - **patients with stage III disease who had received neoadjuvant chemotherapy** - **inoperable stage III disease**	73,8 % (595/806)	100 % (733/733)	56,0 % (219/391)	75,5 % (845/1.119)

1 Ray-Coquard NEJM 2019; 2. Gonzalez-Martin NEJM 2019; 3. Moore NEJM 2018; Marth et al Cancer 2022

Table 3 further highlights why it is important to address the comparison between the PAOLA-1 study and the PRIMA study in two step in this application as depicted below:

- **For the Higher-risk subgroup:** The comparison will be based on an unanchored population-adjusted indirect treatment comparison (PAIC), thereby adjusting for variations in this heterogenous subgroup of patients

- **For the Lower-risk subgroup:** This subset of HRD+ excluding BRCAm patients has been excluded from the PRIMA study. It will therefore not be possible for AstraZeneca to perform an indirect treatment comparison versus niraparib for this subset of patients. Since the PAOLA-1 study provides the only dataset on Caucasian patients utilizing a Myriad HRD test, AstraZeneca will discuss this subgroup with descriptive data contextualize with data from SOLO-1

5.1.1.2 Higher-risk subgroup in PAOLA-1 vs ITT population in PRIMA

Comparison of trial results are confounded by differences in the design of the studies including use of an active background treatment in PAOLA-1. Table 4 outlines relative distribution of baseline characteristics in PAOLA-1 ITT population, PAOLA-1 higher risk population and PRIMA ITT population often referred to as a subgroup of patients characterized by a higher risk profile. However naïve comparison of the relative distribution of baseline characteristic reveals that the PAOLA-1 "higher-risk subgroup" contains a higher proportion of patients with known negative characteristics:

- ✓ Higher proportion of stage IV patients
- ✓ Higher proportion of inoperable patients
- ✓ Higher proportion of patients with Baseline CA-125 >ULN (%)
- ✓ Higher proportion of patients with PR after first line therapy

Table 4. Relative distribution of baseline characteristics in PAOLA-1 (ITT & Higher-risk) and PRIMA

	PAOLA-1 ITT		PAOLA-1 "Higher-risk"		PRIMA ITT	
	Olaparib + Bevacizumab	Bevacizumab	Olaparib + Bevacizumab	Bevacizumab	Niraparib	Placebo
N	537	269	399	196	487	246
Median age (range) years	61	60	62	61	62	62
% BRCAm	30	30	28,3	27,6	31,2	28,9
FIGO stage IV (%)	30	31	39,8	42,3	34,7	35,8
ECOG 0 (%)	70	70	68,9	68,4	69,2	70,7
ECOG 1 (%)	28	28	29,8	30,1	30,8	29,3
ECOG ≥2 (%)						
Inoperable (%)	7	8	9,5	10,7	1,2	0,4
NACT (%)	42	41	57,1	56,1	66	68
Baseline CA-125 ≤ULN (%)	86	87	83,5	84,2	92,4	91,9
Baseline CA-125 >ULN (%)	14	13	16,5	15,3	7	7,3
Baseline CA-125 missing (%)	0	0,3	0	0,5	0,6	0,8
Response after first line therapy, n (%)						
- **NED/Clinical CR**	74	72	64,9	62,8	69,2	69,9
- **PR**	26	28	35,1	37,2	30,8	30,1

For that reason an unanchored population-adjusted indirect treatment comparison (PAIC) has been performed in order to adjust for the imbalance between patient populations. For this application focus will be on the HRD population in PAOLA-1 and PRIMA with baseline characteristics pre- and post-matching being displayed in Table 5**Error! Reference source not found.**. Result of the PAIC will be discussed in Chapter 7.

Table 5. Relative distribution of baseline characteristics for the HRD population in PAOLA-1 (pre- & post-matching) and PRIMA

	PAOLA-1 HRD population (pre-matching)		PAOLA-1 HRD population (post-matching)		PRIMA HRD population	
	Olaparib + Bevacizumab	Placebo + Bevacizumab	Olaparib + Bevacizumab	Placebo + Bevacizumab	Niraparib	Placebo
			ESS		Target	
N	177	89	164[1]	79[1]	247	126
FIGO Stage IV, %	41,2	47,2	34,8	34,8	34,8	38,1
Neoadjuvant Chemotherapy, %	62,1	59,6	63,2	63,2	63,2	63,5
Inoperable, %	9,5	10,7	NA	NA	0	0
Partial response to prior chemotherapy, %	27,1	29,2	25,1	25,1	25,1	26,2
BRCAm, %	63,8	58,4	61,5	61,5	61,5	56,3
Positive HRD test, %	100	100	100	100	100	100
Age, Years*	58,5	58,5	58,0	58,0	58	58
CA-125≤ULN, %	87,6	88,8	95,5	95,5	95,5	95,2
CA-125>ULN, %	12,4	11,2	4,5	4,5	4,5	4,8
ECOG performance status 0, %	74,6	76,4	73,7	73,7	73,7	77,0

[1]Effective sample size *Mean for PAOLA-1, median for PRIMA. Source: [Hettle 2021]

5.1.1.3 Lower-risk subgroup in PAOLA-1

In PAOLA-1 and SOLO-1 lower-risk patients were those with FIGO stage III disease who had undergone upfront surgery and had complete resection, and constitute a relative homogenous patient population compared to the higher-risk population. In the PRIMA study this subgroup has been excluded limiting the possibility for PAIC or naïve comparison for this specific patient population.

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

Based on DMC recommendations for olaparib and niraparib in addition to DGCGs clinical guideline the following treatment options are generally recommended for treatment of advanced ovarian cancer patients (Figure 2 and Figure 3).

Figure 2. Current treatment options in Denmark based on DMCs recommendation and DGCGs Guidelines

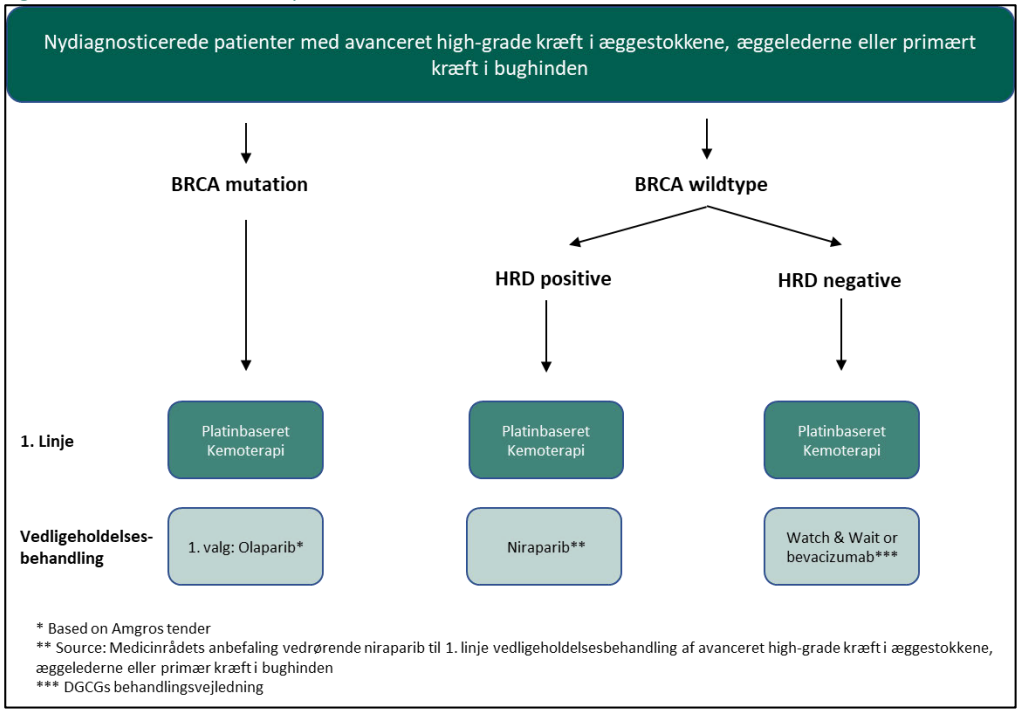
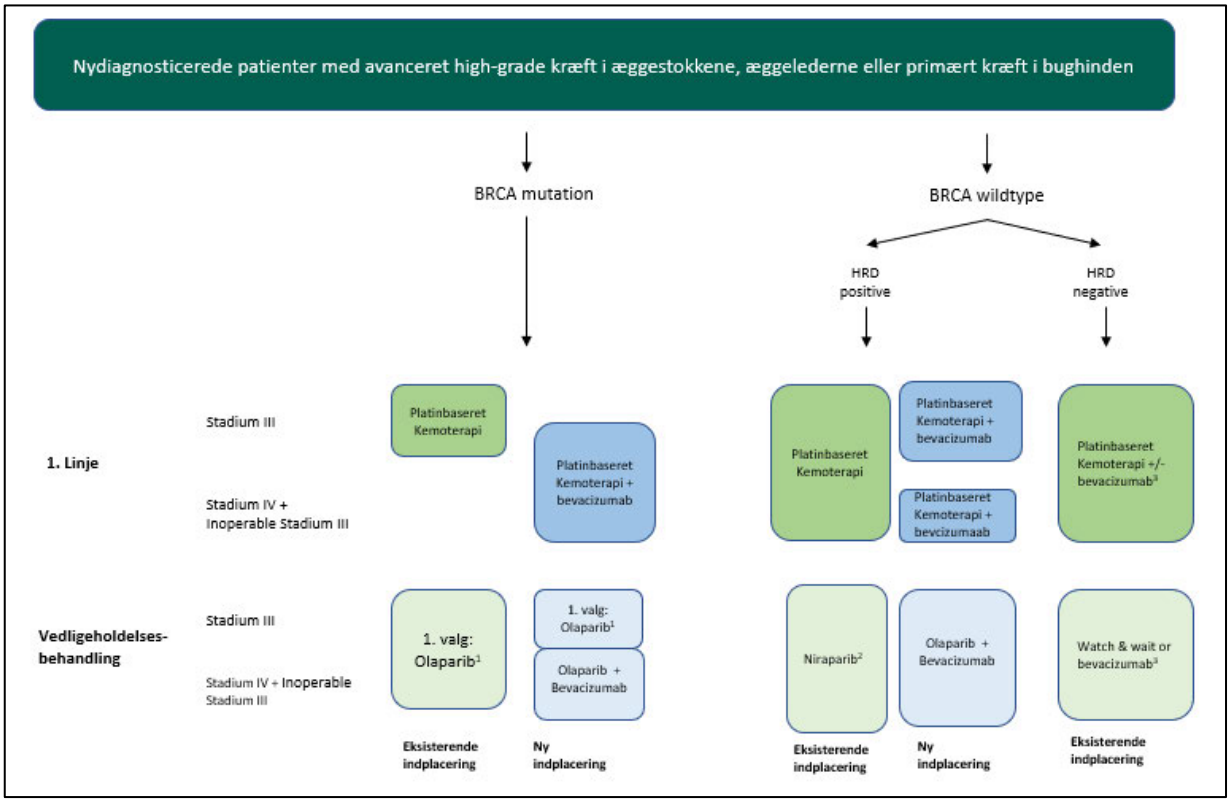


Figure 3. Treatment options based on a DMCs recommendation of the combination of olaparib plus bevacizumab

Source: *[1] baseret på Amgros udbud og behandlingsvejling inkl. Rekommandation. [2] Medicinrådet anbefaling af niraparib [3] DGCG retningslinjer*



5.2.2 Choice of comparator(s)

The first application submitted to DMC in 2020/2021 was based on bevacizumab as comparator(PAOLA study). In the meantime Zejula (niraparib) has been recommended by DMC in the HRD segment. Due to it's recommendation by DMC this application for patients with a HRD+ excl BRCAm profile will be compared with niraparib monotherapy.

Proprietary name
Zejula

Generic name
Niraparib

ATC code
L01XK02

Pharmacotherapeutic group
Other antineoplastic agents

Mechanism of action
Niraparib is an inhibitor of poly(ADP ribose) polymerase (PARP) enzymes, PARP-1 and PARP-2, which play a role in DNA repair. In vitro studies have shown that niraparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes resulting in DNA damage, apoptosis and cell death. Increased niraparib-induced cytotoxicity was observed in tumour cell lines with or without deficiencies in the Breast Cancer (BRCA) 1 and 2 tumour suppressor genes. In orthotopic high-grade serous ovarian cancer patient-derived xenograft tumours (PDX) grown in mice, niraparib has been shown to reduce tumour growth in BRCA 1 and 2 mutant, BRCA wildtype but homologous recombination deficient, and in tumours that are BRCA wildtype and without detectable homologous recombination deficiency.

Dosage regimen
The recommended starting dose of niraparib is 200 mg (two 100-mg tablets), taken once daily. However, for those patients who weigh ≥77 kg and have baseline platelet count ≥150,000/µL, the recommended starting dose of niraparib is 300 mg (three 100-mg tablet), taken once daily.

Approved therapeutic indications

Zejula is indicated:

- as monotherapy for the maintenance treatment of adult patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.
- 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

Packaging – types, sizes/number of units, and concentrations
Unit dose blisters in cartons of 84 × 1 and 56 × 1 tablets.

5.3 The interventions

Proprietary name
Lynparza

Generic name
Olaparib

ATC
L01XK01

Pharmaceutical form
Lynparza is available as 100 mg and 150 mg tablets for oral administration.

Administration and dosing
Olaparib is recommended at a dose of 300 mg (2 × 150 mg tablets) taken twice daily with or without food, equivalent to a total daily dose of 600 mg. The 100 mg tablet is available for dose reductions.

Mechanism of action
Olaparib is a potent inhibitor of human PARP enzymes (PARP-1, PARP-2 and PARP-3) that are required for the efficient repair of DNA single strand breaks. Through binding to the active site of the PARP enzymes, 28laparib prevents the dissociation of the PARP enzyme from the DNA, blocking repair and, in replicating cells, causing a double strand break (DSB). In normal cells, DSBs are efficiently repaired by the HRR pathway; however, in HRR-deficient cells e.g. HRR-mutated cancer cells, DSBs cannot be accurately or effectively repaired resulting in the activation of alternative and error-prone pathways. Following several rounds of replication, the genomic stability of cancerous cells becomes compromised leading to cellular death, in part due to the already high DNA damage load compared with normal cells.

Indication and proposed position in treatment sequence

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

Lynparza is approved for several indications. These are listed in the early sections of this application

Restrictions of use
The safety and efficacy of 28laparib in children and adolescents have not been established.

Proprietary name
Avastin. Generic/biosimilars are available.

Generic name
Bevacizumab

ATC:
L01FG01

Pharmaceutical form
25 mg/ml concentrate for solution for infusion

Administration and dosing

Front-line treatment:
Avastin is administered in addition to carboplatin and paclitaxel for up to 6 cycles of treatment followed by continued use of Avastin as single agent until disease progression or for a maximum of 15 months or until unacceptable toxicity, whichever occurs earlier. The recommended dose of Avastin is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.
Treatment of platinum-sensitive recurrent disease:
Avastin is administered in combination with either carboplatin and gemcitabine for 6 cycles and up to 10 cycles or in combination with carboplatin and paclitaxel for 6 cycles and up to 8 cycles, followed by continued use of Avastin as single agent until disease progression. The recommended dose of Avastin is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.
Treatment of platinum-resistant recurrent disease:
Avastin is administered in combination with one of the following agents – paclitaxel, topotecan (given weekly) or pegylated liposomal doxorubicin. The recommended dose of Avastin is 10 mg/kg of body weight given once every 2 weeks as an intravenous infusion. When Avastin is administered in combination with topotecan (given on days 1-5, every 3 weeks), the recommended dose of Avastin is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion. It is recommended that treatment be continued until disease progression or unacceptable toxicity.
The initial dose should be delivered over 90 minutes as an intravenous infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

Mechanism of action
Bevacizumab binds to vascular endothelial growth factor (VEGF), the key driver of vasculogenesis and angiogenesis, and thereby inhibits the binding of VEGF to its receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells. Neutralising the biological activity of VEGF regresses the vascularisation of tumours, normalises remaining tumour vasculature, and inhibits the formation of new tumour vasculature, thereby inhibiting tumour growth.

Indication and proposed position in treatment sequence

- Bevacizumab, in combination with carboplatin and paclitaxel is indicated for the front-line treatment of adult patients with advanced (FIGO stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer.
- Bevacizumab, in combination with carboplatin and gemcitabine or in combination with carboplatin and paclitaxel, is indicated for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents.
- Bevacizumab in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin is indicated for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary

peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents.

Bevacizumab is indicated in several other indication. See Summery Of Product Characteristics for full overview: https://www.ema.europa.eu/en/documents/product-information/avastin-epar-product-information_en.pdf

Conclusion

Based on the data from the PAOLA-1 study the intervention addressed in this application is the combination of 30laparib and bevacizumab for HRD+ excl BRCAm advanced ovarian cancer patients. DMC has previously stated that they see no added benefit of the combination of 30laparib + bevacizumab versus 30laparib monotherapy.
In that context it is worth highlighting the updated OS data from both the PAOLA-1 study (Ray-Coquard 2022) and SOLO-1 study (DiSilvestro 2022).
Despite that PAOLA-1 study represents a patient population with a worse prognosis, a 5-year OS rate of 73% is reached representing a 20 %-point increase in 5-year OS rate. A 5-year OS rate of 73 % is also reached in SOLO-1 but only representing a 10 %-point increase.

AstraZeneca urge DMC and Fagudvalget to take these newly released OS data into consideration.

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted using PubMed and the Cochrane Library to identify phase 2 and phase 3 randomised controlled trials (RCTs) that evaluate efficacy, safety, and quality of life data of maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status. Searches were conducted up to 7/10/2022. The results were filtered according to the parameters of this report and included studies are listed below (Table 6**Error! Reference source not found.**). The entire SLR and excluded studies can be found in appendix A.

As there has passed 8 months since AstraZeneca submitted the application and the arrival of the first validations several updates has been published in oncology journals. We have updated Table 6 below to includes these publications.

6.2 List of relevant studies

Table 6. Relevant studies

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant endpoints
1) Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. K. Moore, N. et al. N Engl J Med 2018; 379:2495-2505 https://www.nejm.org/doi/full/10.1056/nejmoa1810858 **2)** DiSilvestro, P., et al. (2020). "Efficacy of Maintenance Olaparib for Patients With Newly Diagnosed Advanced Ovarian Cancer With a BRCA Mutation: Subgroup Analysis Findings From the SOLO1 Trial." J Clin Oncol **38**(30): 3528-3537' https://ascopubs.org/doi/10.1200/JCO.20.00799?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed **3)** DiSilvestro P., et al. Efficacy of Maintenance Olaparib for Patients With Newly Diagnosed Advanced Ovarian Cancer With a BRCA Mutation: Subgroup Analysis Findings From the SOLO1 Trial. J Clin Oncol. 2020 Oct 20;38(30):3528-3537. Doi: 10.1200/JCO.20.00799. Epub 2020 Aug 4. **Erratum** in: J Clin Oncol. 2021 Apr 20;39(12):1414. **4)** Maintenance Olaparib for patients with newly diagnosed advanced ovarian cancer and a BRCA mutation (SOLO1/GOG	SOLO-1	NCT01844986	Enrolment between August 2013 and May 17th 2016. Subgroup update 2020 by Di Silvestro et al. 2020 OS update at ESMO Subgroup Analysis Findings From the SOLO1 Trial	OS, PFS, Discontinuations, AE grade 3 or more. HRQoL

3004): 5-year follow-up of a randomised, double-blind, placebo-controlled, phase 3 trial. Banerjee S. VOLUME 22, ISSUE 12, P1721-1731, DECEMBER 2021 https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(21)00531-3/fulltext **5)** Overall Survival With Maintenance Olaparib at a 7-Year Follow-Up in Patients With Newly Diagnosed Advanced Ovarian Cancer and a BRCA Mutation: The SOLO1/GOG 3004 Trial J Clin Oncol. 2023 Jan 20;41(3):609-617 https://ascopubs.org/doi/10.1200/JCO.22.01549?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed				
6) Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer Ray-Coquard I, et al. *N Engl J Med* 2019;381:2416–28 https://www.nejm.org/doi/full/10.1056/nejmoa1911361 **7)** Efficacy of maintenance Olaparib plus bevacizumab according to clinical risk in patients with newly diagnosed, advanced ovarian cancer in the phase III PAOLA-1/ENGOT-ov25 trial. Harter P., et al Gynecol Oncol. 2022 Feb;164(2):254-264. https://www.sciencedirect.com/science/article/pii/S0090825821016735?via%3Dihub	PAOLA-1	NCT02477644	Inclusion between July 2015 and September 2017 OS update at ESMO 2022 PFS by clinical risk and biomarker status (2021).	OS, PFS, Discontinuations, AE grade 3 or more. HRQoL

8) PAOLA1/ENGOT-Ov 25 investigators. Maintenance olaparib plus bevacizumab in patients with newly diagnosed advanced high-grade ovarian cancer: Main analysis of second progression-free survival in the phase III PAOLA-1/ENGOT-ov25 trial. González-Martín A., et al. Eur J Cancer. 2022 Oct;174:221-231. https://www.ejcancer.com/article/S0959-8049(22)00447-6/fulltext **9)** Olaparib plus bevacizumab first-line maintenance in ovarian cancer: final overall survival results from the PAOLA-1/ENGOT-ov25 trial. Ray-Coquard I. Annals of Onc. Vol. 34. 8. https://www.annalsofoncology.org/action/showPdf?pii=S0923-7534%2823%2900686-5			Analysis of second progression-free survival in the phase III PAOLA-1/ENGOt-ov-25 (2022)	
10) Niraparib in patients with newly diagnosed advanced ovarian cancer. González-Martín A et al; for the PRIMA/ENGOT-OV26/GOG3012 Investigators. N Engl J Med. 2019 https://www.nejm.org/doi/full/10.1056/NEJMoa1910962 **11)** Progression-free survival and safety at 3.5 years of follow-up: results from the randomised phase 3 PRIMA/ENGOT-OV26/GOG-3012 trial of niraparib maintenance treatment in patients with newly diagnosed ovarian cancer	PRIMA	NCT02655016	Inclusion between July 2016 And May 17th 2019 Estimated trial completion Mar-2024	OS, PFS, Discontinuations, AE grade 3 or more. HRQoL

Gonzales-Martin A. European Journal of Cancer 189 (2023) https://www.ejcancer.com/article/S0959-8049(23)00225-3/fulltext				
12) Mirza MR et al. Prospective evaluation of the tolerability and efficacy of niraparib dosing based on baseline body weight and platelet count: Results from the PRIMA/ENGOT-OV26/GOG-3012 trial. Cancer. 2023 Jun 15;129(12):1846-1855. https://acsjournals.onlinelibrary.wiley.com/doi/10.1002/cncr.34706				
13) A phase III trial in Ovarian Cancer. Perren TJ, et al. N Engl J Med 2011; 365:2484-2496 3) Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial.. Oza AM, Cook AD, Pfisterer J, et al. Lancet Oncol. 2015 https://www.nejm.org/doi/full/10.1056/nejmoa1103799	ICON7	ISRCTN91273375.	December 2006 to February 2009. 1528 patients randomized. Bevacizumab: 7.5 mg per kilogram of body weight, given concurrently every 3 weeks OS update by Oza et al. 2015	OS, PFS, Discontinuations, AE grade 3 or more
14) Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, Mannel RS, Homesley HD, Fowler J, Greer BE, Boente M, Birrer MJ, Liang SX; Gynecologic Oncology Group. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med. 2011 https://www.nejm.org/doi/full/10.1056/nejmoa1104390		NCT00262847	December 2005 to the last update in July 2019	OS, PFS, Discontinuations, AE grade 3 or more

15) Tewari KS, Burger RA, Enserro D, Norquist BM, Swisher EM, Brady MF, Bookman MA, Fleming GF, Huang H, Homesley HD, Fowler JM, Greer BE, Boente M, Liang SX, Final Overall Survival of a Randomized Trial of Bevacizumab for Primary Treatment of Ovarian Cancer. J Clin Oncol. 2019 Sep 10;37(26):2317-2328. https://ascopubs.org/doi/full/10.1200/JCO.19.01009				OS
16) Vergote I., et al. Population-adjusted indirect treatment comparison of the SOLO1 and PAOLA-1/ENGOT-ov25 trials evaluating maintenance olaparib or bevacizumab or the combination of both in newly diagnosed, advanced BRCA-mutated ovarian cancer. Eur J Cancer. 2021 Nov;157:415-423. https://www.ejcancer.com/article/S0959-8049(21)00550-5/fulltext	SOLO1 and PAOLA-1/ENGOT-ov25	NCT02477644	June 2015 to August 2022	OS, PFS, AE grade 3
17) Population-adjusted indirect treatment comparison of maintenance PARP inhibitor with or without bevacizumab versus bevacizumab alone in women with newly diagnosed advanced ovarian cancer Hettle et al. Ther Adv Med Oncol. 2021; 13: Comments to the author https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10126591/	Indirect treatment comparison (ITC) of PAOLA-1 and PRIMA			OS, PFS, AE grade 3 or more

For detailed information about the key studies, refer to appendix B.

7. Efficacy and safety

In June 2021 DMC recommended niraparib as 1st line maintenance treatment for patients with advanced high-grade Ovarian Cancer and whose cancer is associated with positive homologous recombination deficiency (HRD) status defined by either a BRCA1/2 mutation and/or genomic instability. AstraZeneca's first PAOLA application was initially rejected by DMC in 2021 but following a re-evaluation AZ were allowed to reapply for an assessment of the added value of olaparib in combination with bevacizumab for maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab **and whose cancer is associated with homologous recombination deficiency (HRD) positive status excluding patients with BRCA mutation**. Comparison should be made against new standard of care being niraparib monotherapy.
As stated in chapter 4, this re-application will overall address the question:

1) Is there an added benefit with the combination of olaparib and bevacizumab maintenance therapy vs. niraparib monotherapy for the maintenance treatment adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with **homologous recombination deficiency (HRD) positive status excluding patients with BRCA mutation**

In addition and based on request from DMC, AstraZeneca's reapplication will also address the question:

2) Does concomitant bevacizumab to chemotherapy followed by olaparib plus bevacizumab maintenance therapy provide an added benefit versus olaparib monotherapy (BRCAm) or niraparib monotherapy (HRD positive) **for the group of stage IV and inoperable stage III/IV** adult patients with advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with **homologous recombination deficiency (HRD) positive status**

AstraZeneca will address the first question with the following data:

OS:

- Descriptive data from final OS analysis for the group of HRD+ excl BRCAm patients from the PAOLA-1 study
- Discuss the OS signal for HRD+ excl BRCAm patients from PAOLA-1 in context of OS results from other PARPi trial in first line advanced ovarian cancer patients

PFS

- PAIC of homologous recombination repair deficiency (HRD)-positive populations excluding patients with Stage III disease and no evidence of disease following primary debulking (PRIMA vs PAOLA-1)
- Descriptive PAOLA-1 data from the subgroup of Stage III disease patients with no evidence of disease following primary debulking surgery. PFS signal analyzed in context of signal observed in SOLO-1

Safety

- Naïve comparison of safety signal observed in PAOLA-1 and PRIMA

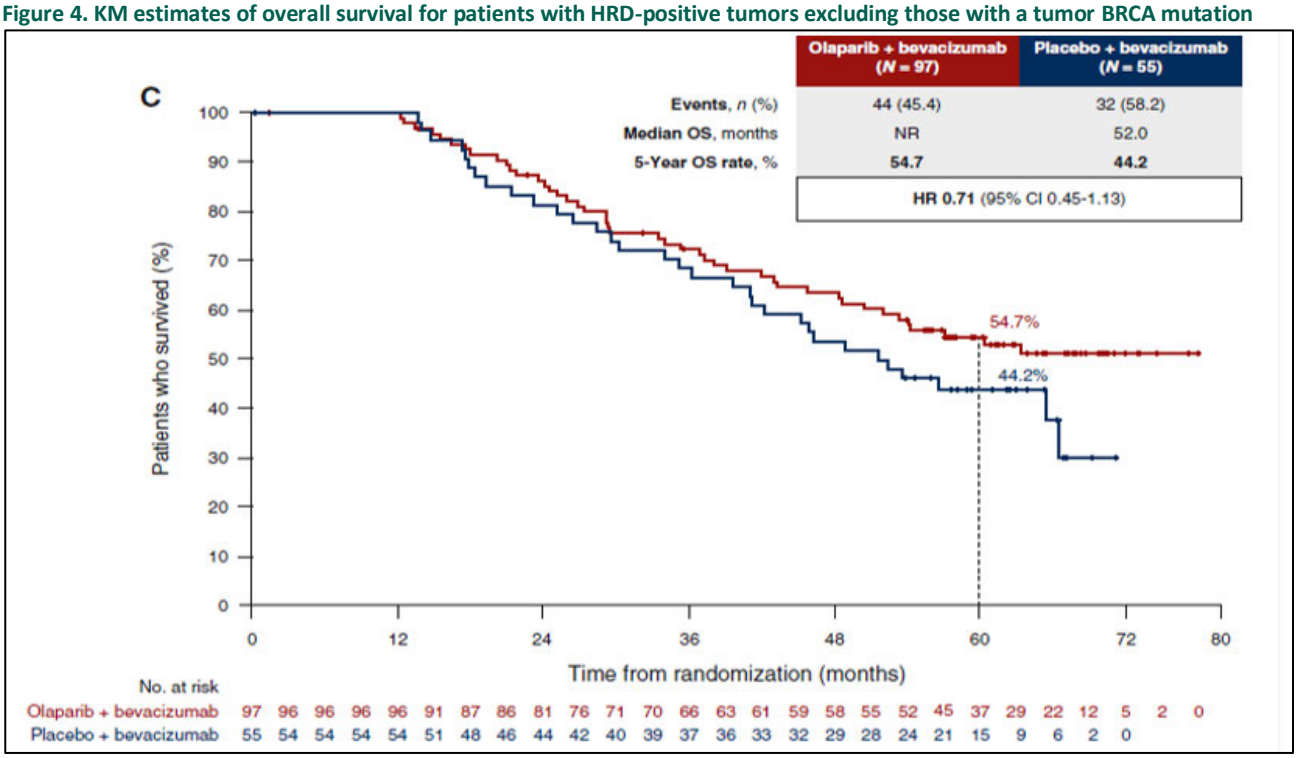
7.1 Question 1

7.1.1 OS: Olaparib + bevacizumab compared to niraparib for HRD+ without BRCAm Ovarian Cancer patients

The final OS analysis in the PAOLA-1 study was carried out 3 years after the primary PFS analysis, at 55% data maturity (data cut-off: 22 March 2022). The median duration of follow up for OS was 61.7 months [interquartile range (IQR): 57.5-67.0 months] versus 61.9 months (IQR 58.1-66.8 months) in the olaparib and placebo groups, respectively. [Ray-Coquard et al (2023)].

An OS benefit with olaparib plus bevacizumab was observed in patients with HRD-positive tumors without a BRCA mutation (by Myriad) with 54,7 % of patients for the olaparib + bevacizumab arm versus 44,2 % for the bevacizumab arm being alive at 5 years (median OS, not reached versus 52 months; HR 0.71; 95% CI 0.45-1.13) (Table 7 and Figure 4).

Figure 4. KM estimates of overall survival for patients with HRD-positive tumors excluding those with a tumor BRCA mutation



Source: Ray-Coquard et al (2023).

Table 7. OS signal in HRD positive patients excluding BRCA mutated

PAOLA-1: OS in patients with HRD-positive tumors excluding those with a tumor BRCA mutations			
	Active arm (n=97)	Control arm (n=55)	
Events, n (%)	44 (45,4)	32 (58,2)	
Median Overall Survival (months)	NR	52,0	
OS-rate at 60-months (%)	54,7	44,2	10,5 %-point difference
HR (95% CI)	0,71 (0,45-1,13)		

The observed 10,5 % point difference in 5-year OS rate for HRD-positive tumors without a BRCA mutation is in line with the observed 5-year OS benefit observed in SOLO-1 [DiSilvestro 2022], despite that the population in SOLO-1 consisted of BRCA mutated patients (9,7 % point difference; 73,1 % vs 63,4 %). For the BRCA mutated population in PAOLA-1 a difference of 19,4 %-points(73,2 % vs 53,8%) were observed.

The numerical OS benefit observed in PAOLA-1 for patients with HRD-positive tumors without BRCA mutations (HR 0.71; 95% CI 0.45-1.13) might be explained by the relatively small subgroup size (n=97 and n= 55 in the olaparib plus bevacizumab and placebo plus bevacizumab arms, respectively) resulting in the large CIs observed.

A formal Matching-Adjusted Indirect Comparison of OS data from PAOLA-1 study and PRIMA study for patients with HRD-positive tumors excluding those with a BRCA mutations would be the preferred tool for indirect comparison of treatment across separate trial. This however requires insights into OS data from the trials being compared.

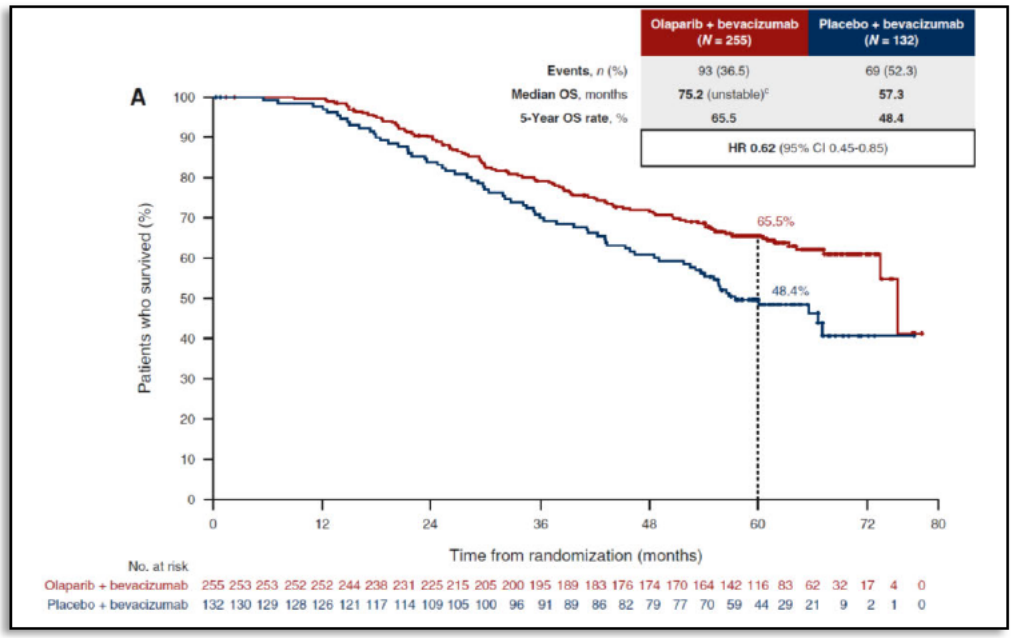
For the PRIMA study no OS data has been reported for the subset of first line patients with HRD-positive tumors excluding those with a tumor BRCA mutations, and therefore **AstraZeneca cannot perform a formal MAIC for this subgroup of patients**. AstraZeneca would support the development of a formal MAIC, if DMC has access to updated OS data from PRIMA study.

7.1.2 Overview of OS results for PARPi approved for treatment of first line advanced ovarian cancer patients by EMA

Due to lack of OS data for the group **HRD-positive tumors excluding those with a BRCA mutations** from the PRIMA study, AstraZeneca find it important to contextualize the observed OS result in section 7.1.1 from the discussed subgroup in the PAOLA-1 study, with additional OS data from PAOLA-1 and observed OS signal from SOLO-1 and PRIMA. Final OS analysis from the PAOLA-1 study and 7-year OS follow-up from the SOLO-1 study was presented at ESMO 2022 and later published in Annals of Oncology [Ray-Coquard 2023] and JCO [Di Silvestro 2022] respectively. Table 8 summarizes observed 5-year OS rate and %-points difference observed with PARP inhibitors approved for first line treatment of advanced ovarian cancer. The largest numerical improvement were observed with the addition of olaparib to bevacizumab for BRCA mutated patients in the PAOLA-1 study resulting in a 19.4 %-points improvement in 5-year OS rate. For the entire population of patients with HRD-positive tumors, the median duration of OS was prolonged with olaparib plus bevacizumab versus placebo plus bevacizumab and a greater proportion of patients were

alive at 5 years (5-year OS rates, 65.5% vs. 48.4%; median 75.2 vs. 57.3 months; HR=0.62; 95% CI 0.45-0.85) despite 50.8% of patients in the placebo arm receiving a PARP inhibitor during subsequent therapy (versus 17.3% in the olaparib arm)(Table 8 and Figure 5).

Figure 5. KM estimates (PAOLA1) of overall survival for Patients with HRD-positive tumors

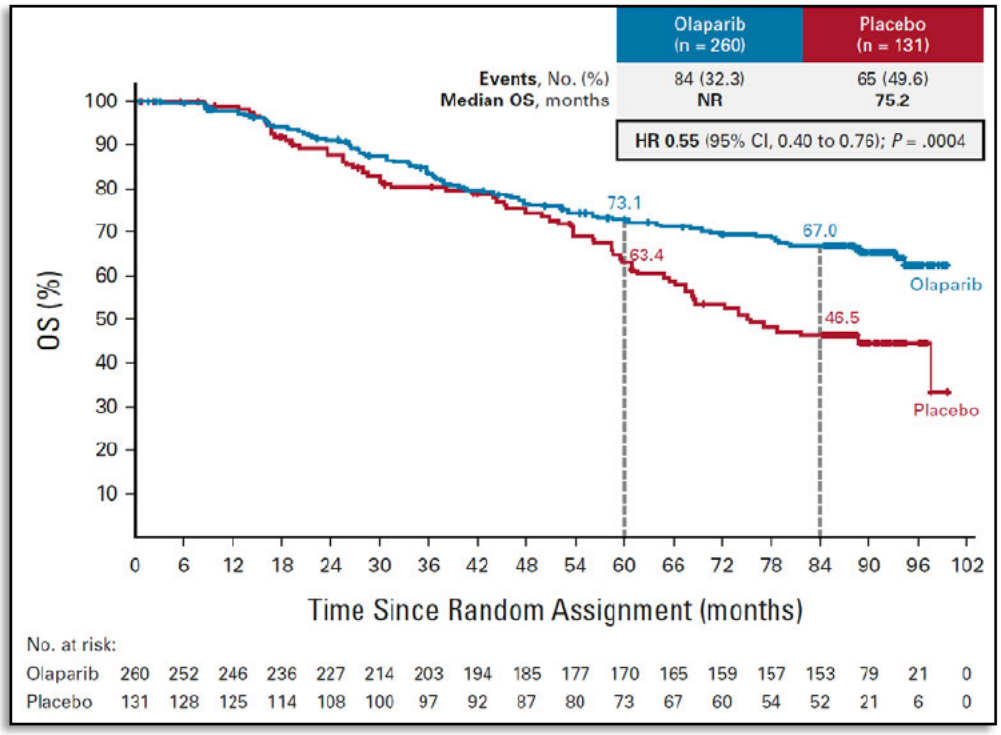


Source: [Ray-Coquard 2023]

A HR of 1.19 (95% CI 0.88–1.63) was observed for the HRDneg/unknown population reinforcing that the activity of the combination is restricted to the HRD positive population.

In SOLO-1 a descriptive OS analysis (DCO: March 7, 2022) took place 7 years after the last patient was randomly assigned. At the DCO, 149 of 391 patients had died (data maturity 38.1%). The median OS was not reached (95% CI, not reached to not reached) in the olaparib group compared with 75.2 months (95% CI, 65.4 to not reached) in the placebo group, with an HR of 0.55 (95% CI, 0.40 to 0.76; P=0004 [P<0001 required to declare statistical significance]. 5-Year OS rate was 73.1 % in the olaparib arm versus 63.4 % in the placebo arm (see Table 8).

Figure 6. Kaplan Meier estimates of OS for patients with BRCA mutated tumors in SOLO-1



Source: [Di Silvestro 2022]

This analysis was unadjusted for subsequent therapy, and the OS benefit was achieved despite 44.3% of patients in the placebo group having received a PARP inhibitor in a subsequent line of therapy. These results indicate a clinically meaningful improvement in OS with maintenance olaparib in patients with newly diagnosed advanced ovarian cancer and a BRCA mutation, albeit not statistically significant according to prespecified criteria.

According to the niraparib assessment report (assessed at https://www.ema.europa.eu/en/documents/product-information/zejula-epar-product-information_en.pdf), the estimated survival in the overall population at two years after randomization was 84% for patients receiving niraparib, as compared to 77% for patients receiving placebo. For the HRD positive population, the observed 2-year OS rate were 91.1 % (87.5-94.6 %) in the niraparib-arm and 84.9 % (78.7-91.2 %) in placebo-arm. The above is based on DCO at the time of primary PFS analysis (May 17, 2019). Event rate reported for the niraparib arm were 6.5% and 7.9% for the placebo arm in the HRD positive population and a median duration of follow-up at the time of the data cutoff was 13.8 months (range, <1.0 to 28.0).

Gonzales-Martin A et al (2023) reported updated PFS and safety update with a median duration of follow-up of ≈ 3.5 years. At the time of the data cutoff (November 17, 2021) OS remained immature at 30.8% for the HRD population and 41.2% for the overall population, and updated OS data were not presented in the publication.

Table 8. 5-Year OS rate in first line PARPi maintenance studies

5-year OS rate and Hazard ratios observed with PARPi in first line advanced ovarian cancer patients							
Study	Study	SOLO-1[1]		PAOLA1[2]		PRIMA[3]	
	Study population	Active arm	Control arm	Active arm	Control arm	Active arm	Control arm
Population (n) **OS-rate at 60-months** **%-points difference** **Hazard Ratio**	Overall Population	(BRCAm only)		537 47,3 % **5,8 %-point** **HR 0.92** (95% CI 0.76-1.12)	269 41,5 %	Updated data based on data maturity of 41,2% not reported[4]	
	HRD positive	Not evaluated	Not evaluated	255 65,5 % **17,1 %-point** **HR 0.62** (95% CI 0.45-0.85)	132 48,4 %	Updated data based on data maturity of 30,8% not reported[5]	
	HRD positive **with** a BRCAm	260 73,1 % **9,7 %-point** **HR 0.55** (95% CI, 0.40 to 0.76)	131 63,4 %	157 73,2 % **19,4 %-point** **HR 0.60** (95% CI 0.39-0.93)	80 53,8 %		
	HRD positive **without** a BRCAm	Not evaluated	Not evaluated	97 54,7 % **10,5 %-point** **HR 0.71** (95% CI 0.45-1.13)	55 44,2 %		
	HRD negative excl unknown	Not evaluated	Not evaluated	192 25,7 % **-6,6 %-point** **HR 1.19** (95% CI 0.88-1.63)	85 32,3 %		

1) *DCO: 22MAR2022/ Data maturity: 55%/ Median follow-up time of 61,7 months versus 61,9 months*
2) *DCO: 17NOV2021/ Data maturity: 41,2%/ Median follow-up time 41,6 months versus 41,9 months*
3) *2-year OS-rate of 84% vs 77% (ITT population) based on DCO1 (see text for further details)*
4) 2-year OS-rate of 91,1 vs 84,1% (HRD positive population) based on DCO1 (see text for further details)

7.1.3 PFS: Olaparib + bevacizumab compared to niraparib for HRD+ without BRCAm Ovarian Cancer patients

The section will divide into two subsections due to exclusion of patients with Stage III disease and no evidence of disease following primary debulking surgery in the PRIMA study.

7.1.3.1 PFS: Olaparib + bevacizumab compared to niraparib for HRD+ without BRCAm Ovarian Cancer patients excluding patients with Stage III disease and no evidence of disease following primary debulking surgery

PFS

The **PAOLA-1 study** included patients with newly diagnosed stage III/IV high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer or fallopian-tube cancer **irrespective of previous surgical outcome.**
In contrast the **PRIMA study** included patients with newly diagnosed stage III/ IV high-grade serous or endometrioid ovarian cancer, peritoneal cancer or fallopian-tube cancer in which patients with stage III disease required incompletely resected cancer after primary debulking surgery or inoperable disease or receipt of neoadjuvant chemotherapy, **but excluded patients with Stage III disease and no evidence of disease following primary debulking surgery**.

Table 9 displays the observed PFS from the population of patients with HRD-positive tumors excluding those with a tumor BRCA mutation suggesting a longer mPFS for patients treated with the combination of olaparib plus bevacizumab. However due to the significant differences between study populations, a formal indirect treatment comparison between the two studies should be performed.

Table 9. Naive comparison of PFS results for the population of HRD positive excluding BRCAm in PAOLA-1 and PRIMA

	Naïve comparison of PFS Signal in HRD patients with HRD-positive tumors excluding those with a tumor BRCA mutations Median PFS		
		Active arm	Control arm
PRIMA[1]	Population (n)	95	55
	mPFS (months)	19,6	8,2
	HR (95% CI)	**0.66 (0,44 – 1.00)**	
PAOLA-1[2]	Population (n)	97	55
	mPFS (months)	30,0	16,6
	HR (95% CI)	**0.47 (0,32 – 0,70)**	

1) *Based on DCO2; Gonzales-Martin 2023*
2) *Based on final OS DCO (DCO3) presented at ESMO Gynaecological Cancers 2023 as mini-oral by Gonzales-Martin*

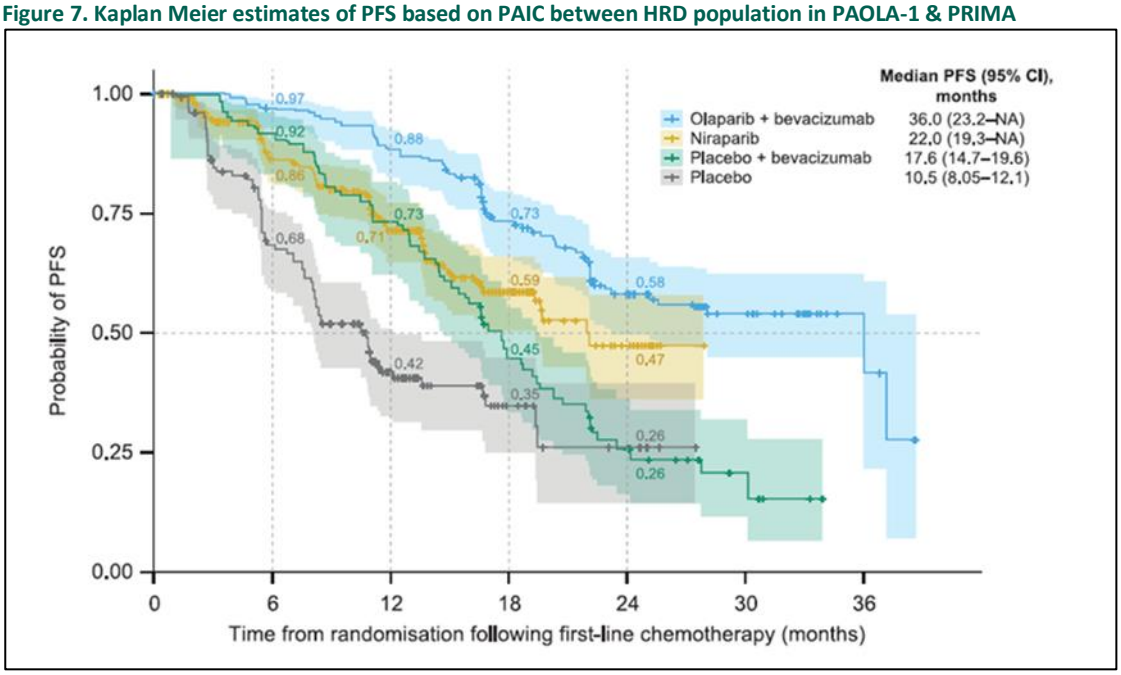
Indirect comparison of PAOLA-1 and PRIMA

As previous discussed in chapter 5, variations in baseline characteristics exist between the study population in PRIMA and the "high-risk" population in PAOLA-1. An unanchored matching-adjusted indirect comparison (MAIC) was performed to assess the comparative efficacy of olaparib + bevacizumab (based on data from PAOLA-1 DCO1) vs niraparib, bevacizumab + placebo, and placebo in the maintenance treatment of women with HRD+ advanced Ovarian Cancer. At the time of analysis, there was insufficient data available from the HRD+ population of the PRIMA study on PFS2 and OS endpoints, and on post-baseline prognostic variables or effect modifiers (e.g. use of subsequent PARP-inhibitor or bevacizumab-therapy after disease progression, which could have been imbalanced) to enable the comparison of these endpoints. Therefore, the MAIC focuses on PFS only.
The MAIC methodology closely followed the recommendations of the NICE decision support unit review (TSD18) of the use of population-adjusted indirect comparisons (PAIC) for technology appraisals (Phillippo et al. 2016). Following TSD18, an unanchored comparison was performed due to the lack of a common comparator arm across studies. The unanchored MAIC included the adjustment of all relevant prognostic and effect modifiers (whether in imbalance or not) between the HRD+ populations of PAOLA-1 and PRIMA.
The matching analysis was performed on the subset of the HRD+ population of PAOLA-1 who met the more restrictive FIGO disease staging and surgical outcome inclusion criteria of PRIMA. This involved excluding those HRD+ patients from PAOLA-1 who had FIGO stage III disease and no residual tumour after primary debulking surgery (n=211). The population used in the matching analysis (referred to as the PRIMA-modified dataset hereafter) comprised stage III patients with inoperable disease or residual disease after primary debulking surgery or those who had received neoadjuvant chemotherapy, as well as any patients with stage IV disease.
The matching analysis was performed on any baseline characteristics reported in PRIMA that was found to be potentially prognostic or an effect-modifier for PFS with olaparib + bevacizumab or bevacizumab + placebo. This was established via a series of Cox proportional hazards regression analyses that included covariates for baseline factor, randomized treatment, and an interaction term between randomized treatment and baseline covariate. The results of these analyses were used to determine if factors were potentially prognostic and/or effect-modifiers of PFS in PAOLA-1 using a 20% significance level. Any factor that was considered as a stratification variable in either PRIMA or PAOLA-1, and for which baseline data were reported in PRIMA, was also considered in the matching analysis. The final list of variables was reviewed by an external statistician with experience in ovarian cancer and compared against the published literature reporting prognostic factors for PFS in newly-diagnosed advanced ovarian cancer.
Following TSD18, the matching of PAOLA-1 to PRIMA was achieved through propensity score weighting (Phillippo et al. 2016). The matching was performed separately for each arm of PAOLA-1 and using the baseline characteristics of the niraparib arm of PRIMA as the target for matching. The matched PAOLA-1 dataset was then combined with pseudo patient-level data from PRIMA, recreated from the published Kaplan-Meier graphs for the HRD+ population. All results were then summarized via weighted Cox regression and Kaplan-Meier methods.

As mentioned the remaining group of patients in PAOLA1 excluding the patients with **Stage III disease and no evidence of disease following primary debulking surgery (n=595)**, can be characterized as a relative heterogenous population compared to the population of patients with Stage III disease and no evidence of disease following primary debulking surgery. Since baseline characteristics for the population of HRD positive excluding BRCA mutated patients in the PRIMA study is unknown for AstraZeneca the indirect comparison have been performed on ITT and HRD positive population. Results presented in the following represents data from the comparison of HRD positive patients.

Results from the PAIC Kaplan-Meier curves after matching are displayed in Figure 7 with corresponding median PFS values shown in Table 10.

Figure 7. Kaplan Meier estimates of PFS based on PAIC between HRD population in PAOLA-1 & PRIMA



Source: Hettle 2021

Table 10. Absolute differences in mPFS between PAOLA-1 and PRIMA

Population-Adjusted Indirect Comparison (PAIC) Median PFS			
		Active arm	**Control arm**
Population (n)[1] **mPFS (months; CI)**	PRIMA	247	126
		22,0 (19,3; NR)	10,5 (8,05; 12,1)
	PAOLA-1	164	79
		36,0 (23,2; NR)	17,6 (14,7; 19,6)

[1] See table 5 for further details. For PAOLA-1 population represent ESS with target population being presented for PRIMA

Based on the MAIC an absolute difference of 14,0 months with the addition bevacizumab to olaparib versus niraparib were observed (Table 10). In the former "Merværdi" assessment an absolute difference (MKRF) of 6 months was required to show a clinical meaningful benefit. The 14 months advantage more than fulfill this goal.

In addition, an 11 %-points difference were observed for PFS-rate at 24 months (Table 11) meeting previous defined MKRF of 10 %-point. These data suggests a maintained benefit of the addition of bevacizumab to olaparib versus niraparib, since identical PFS rates at 24 months were observed in the control arm in the two studies.

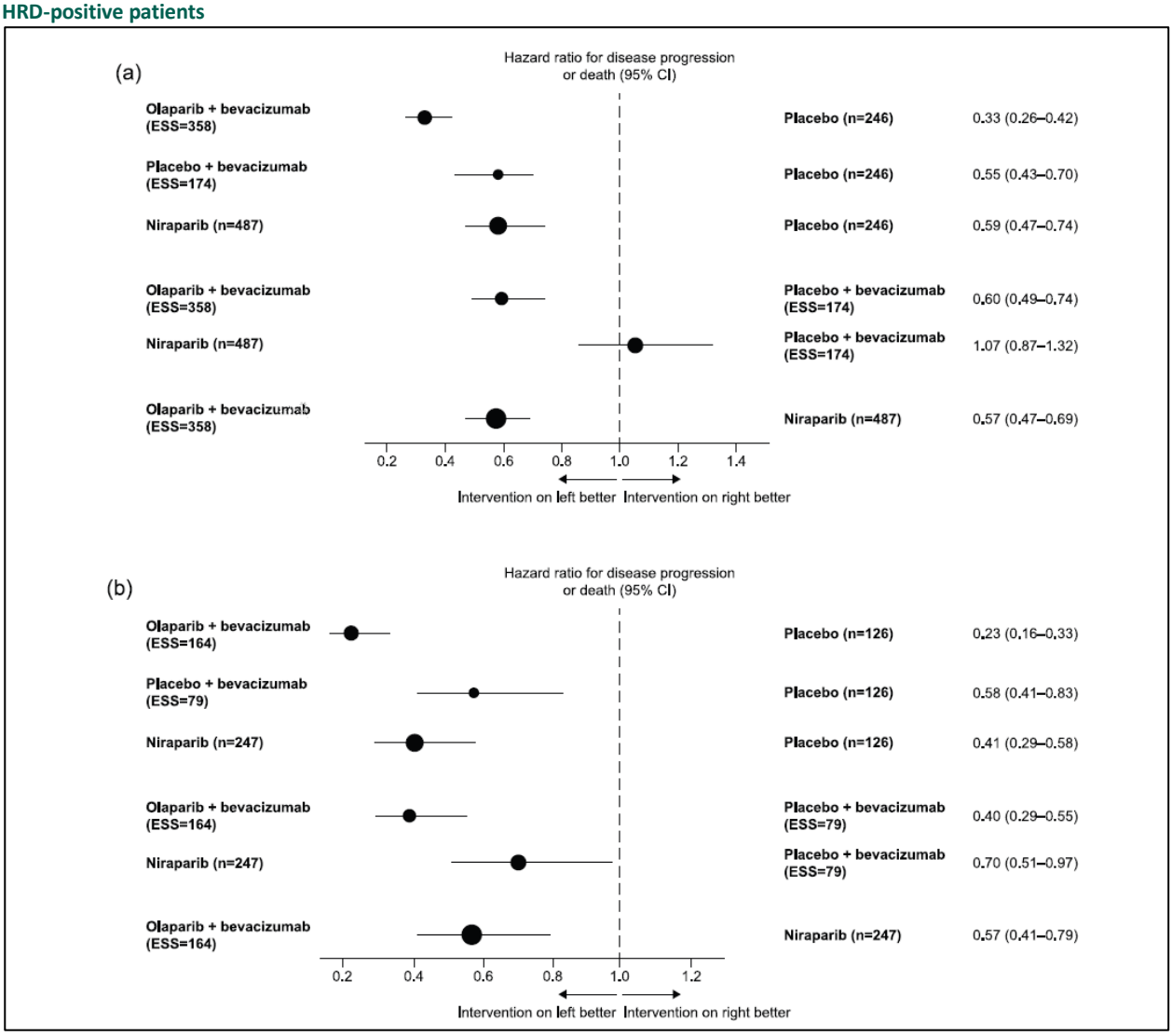
Table 11. PFS-rate at 24-months in PRIMA and PAOLA-1 study

		Population-Adjusted Indirect Comparison (PAIC) PFS rate at 24 months	
		Active arm	Control arm
Population (n)[1] PFS-rate (24-months) (%)	PRIMA	247	126
		47	**26**
	PAOLA-1	164	79
		58	**26**
Addition of Bevacizumab %-point difference		**11**	**0**

[1] See table 5 for further details. For PAOLA-1 population represent ESS with target population being presented for PRIMA

For HRD-positive patients, maintenance olaparib plus bevacizumab was associated with statistically significant improvements in PFS compared with either placebo plus bevacizumab, niraparib or placebo alone, reducing the risk of disease progression by 43% for the HRD positive patients treated with olaparib plus bevacizumab versus niraparib (HR=0,57 95% CI 0,41-0,79) (Figure 8).

Figure 8. PAIC comparison of progression-free survival. Forest plot showing results in (a) biomarker-unselected patients and (b) HRD-positive patients



In summary the PAIC suggest an added benefit of the combination olaparib plus bevacizumab versus niraparib for the HRD+ subpopulation investigated.

7.1.3.2 PFS: Olaparib + bevacizumab compared to niraparib for HRD+ excluding BRCAm for Ovarian Cancer patients with Stage III disease and no evidence of disease following primary debulking surgery

Unlike in the PRIMA study **patients with Stage III disease and no evidence of disease following primary debulking surgery** were eligible in the PAOLA-1 study. This population constitutes 26 % of the population in the PAOLA-1 study, which correspond to the observed frequency in Real-World populations (Marth 2022).

A total of 121 patients in the PAOLA-1 study were defined as being HRD positive in addition to having stage III disease with no evidence of disease following primary debulking surgery (Harter et al 2022). Out of those, 51 patients were defined as HRD positive without a BRCA mutation (Table 12)

Table 12. Distribution of Stage III patients and no evidence of disease following Primary debulking surgery in PAOLA-1 according to BRCA/HRD status

Treatment arm	PAOLA-1[1] (HRD positive)	PAOLA-1 (BRCAm positive)	PAOLA-1 (HRD+ excl BRCAm)
Olaparib + bevacizumab (n)	78	48	33
Bevacizumab (n)	43	25	18
All (n)	121	73	51

1) Numbers provided in table reflects data provided in Harter et al 2022 however 3 additional patients are being allocated to HRD+ excl BRCAm active arm. AZ refer to Harter et al 2022 Figures S4 in appendix for further details

An 81% reduction in the risk of progression or death were observed for the group of HRD positive patients without BRCA mutation (HR 0,19 95% CI 0,06-0,55) (Table 13) well in line with the observed HR for the BRCAm subgroup (HR 0,11 95% CI 0,03-0,31).

Comparison with niraparib maintenance treatment cannot be made, but it is worth noticing that observed HR for addition of PARPi maintenance (mono) treatment range between ~0,3 - 0,45. As an example, a HR of 0,38 (95% CI 0,25; 0,59) were observed for addition of olaparib monotherapy for BRCAm patients with Stage III disease and no evidence of disease following primary debulking in the SOLO-1 study (ref Banerjee 2021].

The specific subpopulation of BRCA mutated patients with Stage III disease and no evidence of disease following primary debulking surgery is a homogenic group of patients with several known prognostic variables being identical (BRCA status, timing and extent of surgery and staging) increasing comparability between these subpopulations in different studies.

Based on previously observed clinical signals from ICON-7 and GOG-218, these data from PAOLA-1 and SOLO-1, numerical suggesting an enhanced signal for the combination of Olaparib and bevacizumab versus olaparib in this specific subpopulation is surprising.

Harter et al. (2022) hypothesized that the apparent difference in this group of stage III patients, undergoing primary debulking surgery with no residual disease, unexpectedly reveal the main difference of the combination compared to the more PRIMA-like population. Amongst other underlying pathophysiological factors they suggested the following: removal of poorly vascularized tumor with elimination of pharmacological sanctuaries; higher growth fraction in better perfused, small residual tumor masses, favoring increased cell kill with cytotoxic therapy; less opportunity for induced drug resistance with small tumor masses requiring fewer chemotherapy cycles; and enhanced host immunocompetence following removal of large tumor bulk [Harter 2022].

Subgroup analysis further demonstrated that a PFS rate at 24 months of 82 % for the HRD+ excl BRCAm treated with olaparib + bevacizumab compared to 46% for patients treated with bevacizumab. Corresponding numbers for the total HRD positive population of patients with Stage III disease and no evidence of disease following primary debulking surgery were 90% for the combination of olaparib and bevacizumab versus 43% of the patients treated with bevacizumab. For the BRCAm subgroup corresponding numbers were 96%/44% respectively (Table 13)

[redacted]

Table 13. HR and PFS-rates at 24 months for various Biomarker subgroups in Stage III patients without residual disease following Primary Debulking Surgery[1]

Population	Biomarker status	PAOLA-1 (HRD positive)[2]		PAOLA-1 (BRCAm)[2]		[redacted]
		HR (95% CI)	mPFS (m) PFS rate 24 months	HR (95% CI)	mPFS (m) PFS rate 24 months	[redacted]
Stage III patients with no evidence of disease following primary debulking surgery	Olaparib + bevacizumab	0,15 (0,07;0,30)	NR 89,7 % (79,4-95,0)	0,11 (0,03-0,31)	NR 95,5 % (83,1-98,1)	[redacted]
	Bevacizumab		22,1 42,6 % (26,2-58,1)		22,2 43,7 % (21,4-64,1)	[redacted]

[1] Population size displayed in table 12 [2]*Harter et al 2022;* [3]*AZ data on file*

The dataset from the PAOLA-1 study on HRD positive excluding BRCA mutated patients suggest clinical relevant activity of the combination of Olaparib and bevacizumab. Direct comparison with niraparib monotherapy can be made due to lack of evidence for niraparib monotherapy in this subgroup of patients.

7.2 Question 2

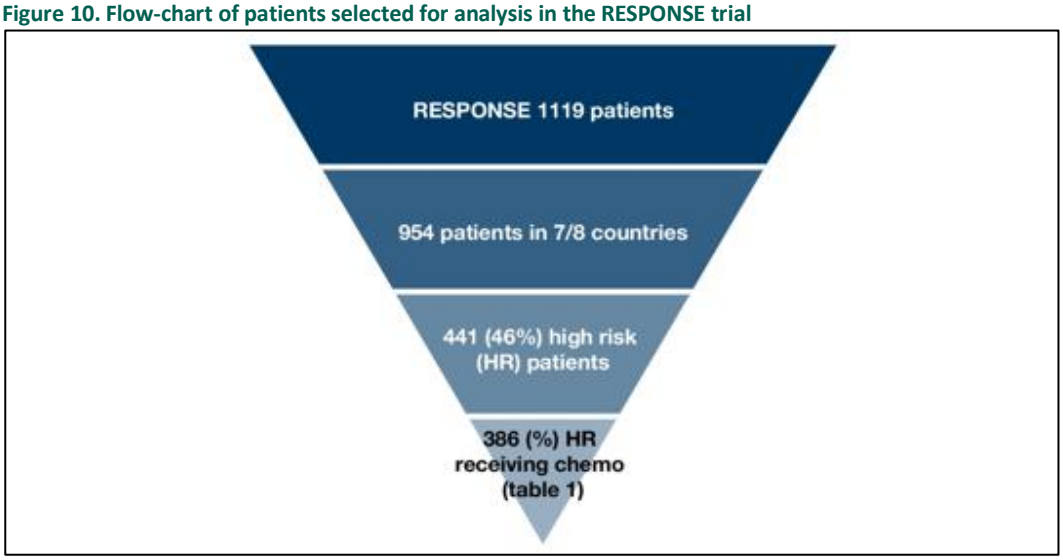
Following a meeting with Fagudvalget, DMC has requested that AstraZeneca address the role of bevacizumab added to PARPi maintenance treatment for the subpopulation of stage IV patients. AstraZeneca will address the question in two steps:

- Can bevacizumab be considered an active comparator for Stage IV patients based on current clinical evidence (Section 7.2.1)?
- Will the addition of olaparib to bevacizumab improve outcome for the subgroup of Stage IV HRD+ patients (section 7.2.2)?

In addition AstraZeneca will discuss the role of bevacizumab in the treatment of inoperable patients however due to a very low number of subjects presenting as inoperable HRD+ in PAOLA-1 a firm conclusion is not possible.

The role of bevacizumab in clinical practice were assessed as a secondary objective in the RESPONSE trial [Marth 2022]. In a 7 country analysis set of this trial, [Lindemann et al 2023] reported subgroup analysis of the "higher-risk" subgroup per ICON-7 definition. In the analysis set (n=954), 46% (n=441) belonged to high-risk subgroup (Figure 10)

Figure 10. Flow-chart of patients selected for analysis in the RESPONSE trial



***Source**: RESPONSE*

This proportion of high-risk patients in a Real-World setting were higher than seen in the ICON-7 population, with high-risk population constituting of 33% of the total ICON-7 population (Table 14).

Table 14. The High-risk patient population in the RESPONSE study and ICON-7 study

	RESPONSE Trial – 7 country analysis set		ICON-7	
ITT population	954		1528	
		% of ITT		% of ITT
High-Risk*	441	46%	502	33%
High-Risk + chemo	386	% of High-Risk		% of High-Risk
Stage IV	239	62	182	36
No surgery stage III	83	21	30	6
>1cm Stage III	64	17	290	58

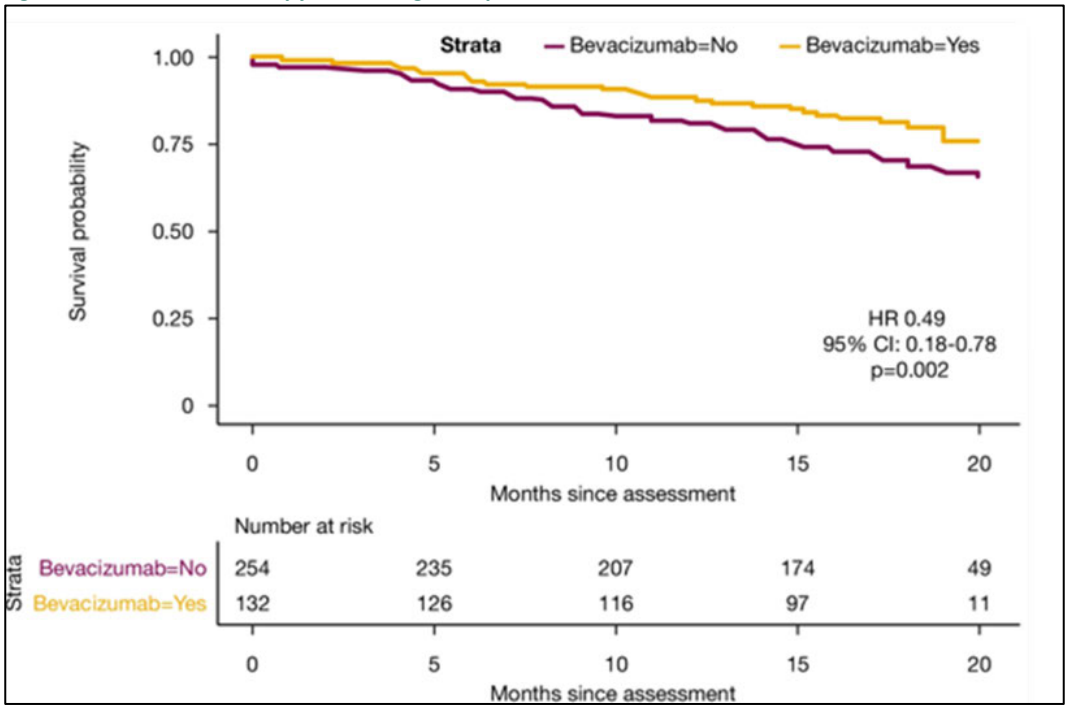
* High risk of progression was defined as stage IV disease, stage III disease with no surgery, or suboptimally debulked (>1 cm) stage III disease according to ICON-7

***Source**: RESPONSE and ICON-7*

In addition, data from this real-world population demonstrated that the proportion of stage IV patients and inoperable Stage III patients were significant higher than seen in ICON-7 (Stage IV: 62 % vs 36%; inoperable stage III patients: 21% vs 6%; (Table 14) highlighting the relevance of interpreting results from RCT and MAIC in the context of a real-world population. In order to limit bias, the effect of bevacizumab in treatment of high-risk patients were further investigated in the subgroup of patients receiving chemotherapy. Of the 441 high risk patients, 386 (88%) received chemotherapy.

A 51% reduction in risk of death (HR of 0,49 (95% CI 0,18-0,78; p=0.002) was observed for patients receiving bevacizumab versus patients treated without addition of bevacizumab (Figure 11).

Figure 11. OS in chemotherapy treated high-risk patients

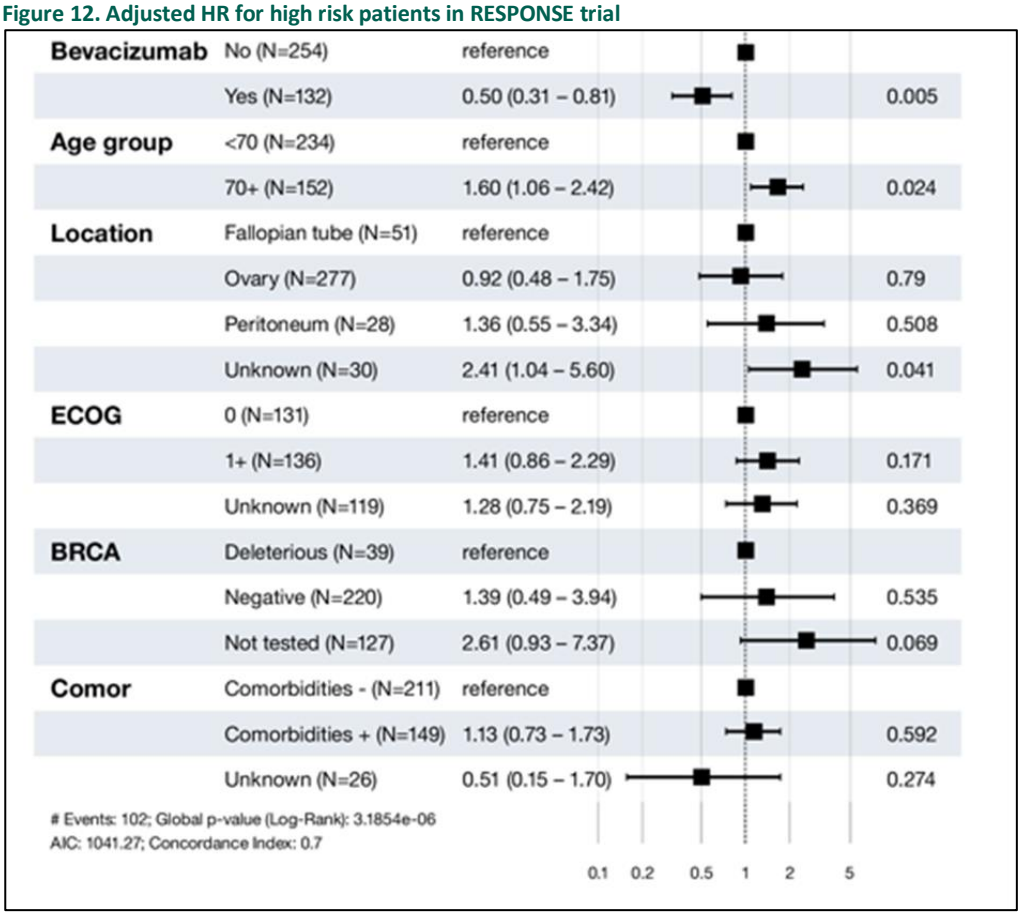


***Source:** RESPONSE*

In ICON-7 a 22% reduction in the risk of death were oberserved (HR 0,78 95% CI 0,63 – 0,97). Evidence of non-proportionality rendered a hazard ratio difficult to interpret in ICON-7 (Oza et al 2015). For that reason and due to variation in assessment point and assessment period, an adjusted HR associated with bevacizumab use were estimated, based on individual patient data from the published Kaplan-Meier survival curves in the ICON-7 study for the period 5 months since diagnosis and with a follow-duration of 20 months. The HR for the Bevacizumab group was 0.60 with 95% CI 0.43-0.85 compared to those not receiving Bevacizumab comparing favourably with observed data from a real-world population in the RESPONSE trial

Further when adjusting for patient and disease characteristics in the RESPONSE trial (Figure 12) the effect of bevacizumab remained significant with a HR of 0,50 (95 CI 0,31-0,81).

Figure 12. Adjusted HR for high risk patients in RESPONSE trial



In conclusion, data from both RCT and real-world setting suggest clinical meaningful activity of bevacizumab in a high-risk population highlighting the relevance as an active comparator.

7.2.1 Stage IV patients

According to DGCG data Annual report Stage IV patients constitute 45 - 51% % of Stage III-IV patients. The relative distribution of stage IV patients in RCT varies significantly, but it is important to reflect on the denominator in these calculations. As an example stage IV patients constituted 17% of the ITT population in SOLO-1, but 30% of the High-risk population with corresponding numbers for PAOLA-1 being 30%/41% respectively. In the PRIMA study – often being characterized as a population of high-risk patients – stage IV patients constituted 35% of this high-risk population (Table 15).

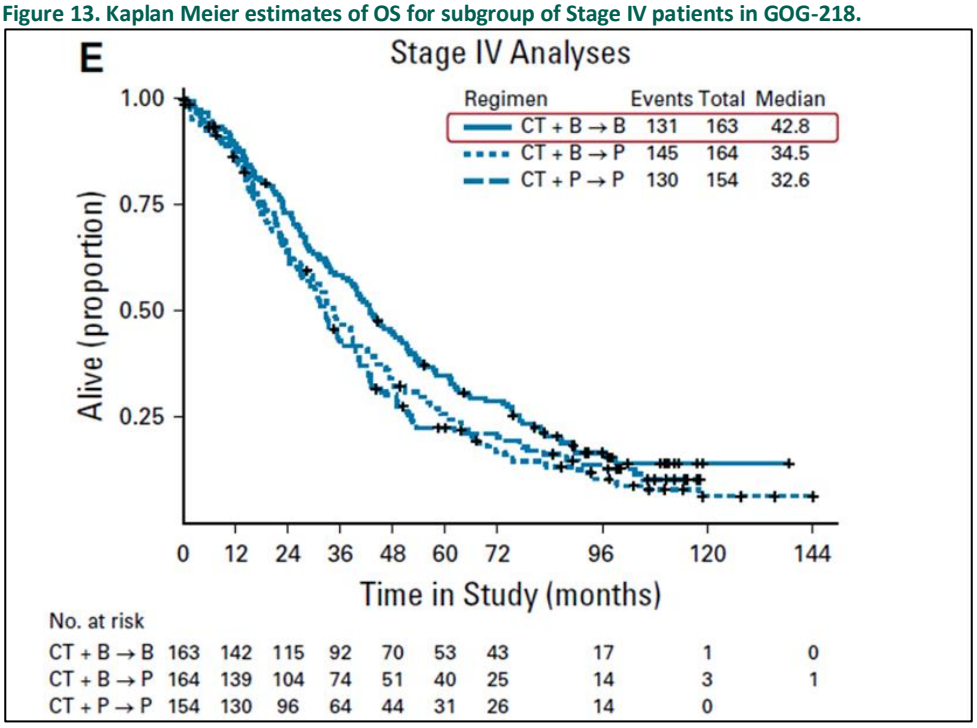
Table 15. Relative distribution of Stage IV patients in selected studies investigating interventions in 1. line advanced OC

	Stage IV							
Population	PAOLA-1 (n=806)	SOLO-1 (n=391)	PRIMA (n=733)	PRIMA HRD (n=373)	ICON-7 (n=1528)	GOG-218 (n=1873)	RESPONSE (n=1.119)	DGCG database (n=364/351/ 338))[1]
Stage IV n (%)	242 (30)	66 (17)	257 (35)	134 (36)	201 (13)	482 (26)	370 (33)	187 (51)/ 159 (45)/ 179 (53)
Stage IV % of High-risk	41	30	35	36	33	26	62[1]	Not Estimated

[1] *Data from year 19/20; 20/21; 21/22 . Percentage estimated out of total number of stage III/IV patients*

Results from the GOG-218 study first presented in NEJM in 2011 by Burger et al, and after a median follow-up 102.9 months [Tewari et al 2019] a median OS of 42,8 months in the bevacizumab concurrent followed by bevacizumab maintenance arm versus a median OS of 32,6 months in the placebo arm [Δ of 10,2 months] for patients with stage IV disease were reported. A corresponding HR of 0.75 [95% CI, 0.59 to 0.95] were observed, and based on image analysis (Figure 13) the observed 5-year OS rate for patients with stage IV disease in the bevacizumab-concurrent plus maintenance arm were 34,9 % versus 22,3 % in the placebo arm yielding an 12,6 %-point improvement in 5-year OS rate.

Figure 13. Kaplan Meier estimates of OS for subgroup of Stage IV patients in GOG-218.



***Source**: GOG-218*

In ICON-7, a similar HR for overall survival (HR 0,74 95% CI 0,53-1,05) was demonstrated for stage IV patients, with data from RESPONSE trial demonstrating a 50% reduction in the risk of death [HR 0,50 95% CI 0,28-0,91] for stage IV patients receiving chemotherapy (Table 16 and Table 18).

Table 16. Effect estimates on overall survival (OS) in patients receiving platinum-based chemotherapy with or without bevacizumab

Analysis set	Chemotherapy with bevacizumab (no. of pts)	Chemotherapy without bevacizumab (no. of pts)	Events N	HR 95% CI	p-value
High-risk* (n = 386)	132	254	102	0.49 (0.31 – 0.77)	0.002
Inoperable (stage III/IV) (n = 151)	34	117	62	0.37 (0.18 – 0.78)	0.009
Stage IV (n = 239)	89	150	56	0.50 (0.28 – 0.91)	0.023
Stage III inoperable (n= 83)	15	68	28	0.33 (0.10 – 1.10)	0.069
Stage III >1cm residual (n = 64)	28	36	18	0.63 (0.25 – 1.6)	0.324

* High risk of progression was defined as stage IV disease, stage III disease with no surgery, or suboptimally debulked (>1 cm) stage III disease according to ICON-7

***Source**: GOG-218*

The above data clearly demonstrates a clinical meaningful effect of bevacizumab in the subgroup of stage IV patients both in RCT and an in Real-world population resembling clinical practice. The 12,6 %-point improvement in 5-year OS rate observed in GOG-218 corresponds to the improvement in 5-year OS rate observed in SOLO-1 and in PAOLA-1 for the HRD+ patients without a BRCA mutations.
These data further highlights the importance of the PAOLA-1 study, where the effect of a PARPi (Olaparib) were investigated as an **addition** to an already active treatment (bevacizumab). Neither of PARPi monotherapy studies addresses this question.
In PAOLA-1 the primary PFS analysis (DCO1) demonstrated that addition of Olaparib to bevacizumab versus bevacizumab for stage IV patients led to a 51 % reduction in the risk of progression or death in the ITT population [HR 0.49 CI 95% 0.36–0.67].

In PRIMA a 21%/12% reduction in risk of progression or death were observed for Stage IV patients at DCO1 and DCO2 respectively for the ITT population. Results from the study also demonstrated a 55% reduction in risk of progression or death for the group of Stage IV patients being HRD positive [HR 0.45 95% CI 0.27-0.77; EPAR], which is in line with data from SOLO-1, where a 51% reduction in risk of progression or death were observed for BRCAm Stage IV patients (Table 17).

Table 17. PFS and PFS2 HR for Stage IV patients in PAOLA-1, SOLO-1 & PRIMA

Stage IV subgroup				
Study	Population (n)	DCO	PFS HR (95% CI)	PFS2 HR (95 % CI)
PRIMA	ITT (n=257)	(DCO1)[1]	0.79 (0.55-1.12)	
	ITT (n=257)	(DCO2)[2]	0.88 (0.65-1.18)	
	HRDpos (n=134)	(DCO1)[3]	0.45 (0.27-0.77)	
SOLO-1	BRCAm (n=66)	(DCO1)[4]	0.49 (0.25-0.94)	
PAOLA-1	ITT (n=242)	(DCO1)[5]	0.49 (0.36-0.67)	
	ITT (n=242)	(DCO2)[6]		0.71 (0.52 – 0.99]

1) Gonzales Martin el (2019) 2) Gonzales Martin et al (2023) 3) Zejula EPAR (figure 38) assessed at https://www.ema.europa.eu/en/documents/variation-report/zejula-h-c-003943-ii-0019-epar-assessment-report-variation_en.pdf 4) Moore K et al (2018) Ray-Coquard et al (2019) 5) Gonzales-Martin et al (2022)

[redacted]

Table 18. OS HRs for addition of bevacizumab and for addition of olaparib to bevacizumab in Stage IV advanced ovarian cancer patients from ICON-7, GOG-218, RESPONSE Trial and PAOLA-1

Population	ICON-7 (n=201)	GOG-218 (n=481)	RESPONSE (n=239)[1]		PAOLA-1 (n=242/115)
	OS HR (95% CI)	OS HR (95% CI)	OS HR (95% CI)		OS HR (95% CI)
ITT Addition of bevacizumab to Placebo	0,74 (0,53 – 1,05)	0,75 (0,59 – 0,95)	0,50[2] (0,28 – 0,91)		
HRD positive (n = 115) Addition of Olaparib to bevacizumab					[redacted]

[1] For the ITT population reported in RESPONSE trial (Marth 2022) Stage IV patients constituted 370 patients (33,1%). For the 7 country analysis set (n=954) 239 stage IV patients who have received chemotherapy were included and represents the population for this analysis
[2] Assessment point varies between studies

7.2.2 Inoperable patients

According to DGCG's Annual Report 2021-2022 the percentage of stage IIIC-IV without operation range from 32,8% in 2019/20 to 37,3% in 2021/22. This percentage is higher than reported in the RESPONSE Trial, being a Real-World observational study including data from Norway, Finland, Denmark, Austria, Netherlands, Belgium, Portugal and Israel where 19,9 % of advanced ovarian cancer were reported inoperable.

In general (see Table 19), the subgroup of inoperable advanced ovarian cancer patients is underrepresented in a group representative randomized clinical trials enrolling advanced ovarian cancer patients, ranging from 0% in GOG-218 to 7% in the PAOLA-1 study. For the HRD positive subgroup in the PRIMA study all patients had surgery procedures related to the study indication.

Table 19. Proportion of Inoperable patients in Randomized clinical Trials and Clinical Practice

Inoperable patients								
Population	PAOLA-1 (n=806)	SOLO-1 (n=391)	PRIMA (n=733)	PRIMA HRD (n=373)	ICON-7 (n=1528)	GOG-218 (n=1873)	RESPONSE (n=1.119)	DGCG database (n=292)[1]
No Surgery n (%)	59 (7)	7 (2)	7 (1)	0 (0)	30 (2)	0 (0)	223 (20)	109 (37)

[1] Data represents stage IIIC-IV in 2021-22

Limited data exist investigating the role of bevacizumab for this group of patients constituting a third of IIIC-IV patients in clinical practice in Denmark. ICON-7 enrolled 30 inoperable patients corresponding to 2 % of ITT population. Final OS analysis from ICON-7 were reported by Oza et al in 2015 (data maturity of 49% and a median follow-up of 48,8 in bevacizumab arm vs 48,6 months in control arm).

For the group of inoperable patients a 48% reduction in the risk of death were reported [HR 0,52 95% CI 0,21-1,27]. The numerical OS benefit observed for this patient group is most likely explained by the relative small subgroup size (n=30) resulting in the large CIs observed.

The role of bevacizumab for inoperable patients were assessed in the subgroup of High-Risk patients receiving chemotherapy in the RESPONSE trial. Of the 386 patients high-risk patients receiving chemotherapy 151 had no surgery procedure performed. Addition of bevacizumab resulted in a 63 % reduction in the risk of death [HR 0,39 95% CI 0,18-0,78] supporting the findings in ICON-7 (Table 16).

These data suggest a significant effect of bevacizumab in the subgroup of inoperable patients, and AZ believe that bevacizumab has an important role in the treatment of this specific subgroup of patients.

Addition of olaparib to bevacizumab were investigated for a small subset of patients in PAOLA-1 (n=59). Due to the limited size of the subgroup further split into HRD positive subgroup without BRCA mutations is considered inappropriate, but in the result from primary PFS analysis in PAOLA-1, a HR of 0,57 [95% CI 0,32 – 1,01] were demonstrated regardless of HRD or BRCA status.

AstraZeneca support further Real-world evidence generating activities in this setting, and are funding the HERO study, a prospective observational study in advanced ovarian cancer sponsored by NSGO-CTU.

7.3 Safety – PAOLA-1 ITT population

An important aspect of introducing new treatment modalities is to consider the risk-benefit ratio of the treatment. Efficacy signal of the PAOLA regimen has been addressed in section 7.1 and 7.2 with section 7.3 being dedicated to safety.

7.3.1 Safety PAOLA-1

Overall, nearly all patients included in the PAOLA-1 study experienced one or more AE (99.3% vs 95.9 %) (Table 20). All patients had discontinued treatment by the data cut-off for PFS2 (DCO2) and safety data were reported by Gonzales-Martin et al (2022). No new safety signals were observed at DCO3 (ref Ray-Coquard et al 2023). Data on MDS/AML/AA, new primary malignancies, and pneumonitis were collected up to the OS data cut-off (DCO3), and are included in Table 27.

Table 20. Summary of AEs, ITT population, DCO2

AEs	Olaparib + bevacizumab (N=535)	Placebo + bevacizumab (N=267)
Any AEs, n (%)	531 (99.3)	256 (95.9)
Any AE of Grade ⩾3 , n (%)	306 (57.2)	137 (51.3)
Any SAEs, n (%)	168 (31.4)	84 (31.5)
Any AE with outcome of Death, n (%)	1 (0.2)	4 (1.5)
Any AE leading to dose interruptions n (%)	290 (54.2)	65 (24.3)
Any AE leading to dose reductions n (%)	223 (41.7)	21 (7.9)
Any AE leading to Discontinuation of trial intervention n (%)	112 (20.9)	15 (5.6)

Footnotes: *Dose interruptions, reductions and discontinuations reported are from olaparib and placebo.*
Source: *Ray-Coquard et al. 2019, ESMO Congress Presentation*

Though AEs of any grade occurred in almost all patients, and Grade ≥3 AEs occurred in over 50% of patients, there was no detrimental impact of treatment on HRQoL. This suggests that the AEs experienced during treatment did not have a negative effect of patient QoL. More patients in the olaparib plus bevacizumab arm experienced discontinuation due to AE compared to the bevacizumab arm (20.9 % vs 5.6 %).

Common AEs ITT

At DCO2, the most common AE experienced in the olaparib arm was nausea (285/535 patients [53.3%]) whereas the most common AE in the placebo arm was hypertension (161/267 patients [60,3%]).
Although nausea was reported more frequently in olaparib-treated patients than placebo-treated patients, the severity of nausea was similar across the treatment arms. Nausea AEs were mostly low-grade (<Grade 3) and could be resolved with antiemetic therapy (Table 21).

Table 21. Summary of AEs in PAOLA1 at DCO2

AEs[a]	n (%) of patients with AEs[b]			
	Olaparib + bevacizumab (N=535)		Placebo + bevacizumab (N=267)	
	All grades	Grade ≥3	All grades	Grade ≥3
Nausea	285 (53.3)	13 (2.4)	58 (21.7)	2 (0.7)
Fatigue or asthenia	284 (5319)	28 (5.2)	86 (32.2)	4 (1.5)
Hypertension	244 (45.6)	100 (18.7)	161 (60.3)	82 (30.7)
Anaemia	219 (40.9)	94 (17.6)	27 (10.1)	1 (0.4)
Lymphopenia	128 (23.9)	38 (7.1)	25 (9.0)	3 (1.1)
Vomiting	119 (22.2)	8 (1.5)	29 (10.9)	5 (1.9)
Arthralgia	117 (21.9)	3 (0.6)	65 (24.3)	4 (1.5)
Abdominal pain	118 (22.1)	8 (1.5)	59 (22.1)	5 (1.9)
Diarrhoea	98 (18.3)	12 (2.2)	46 (17.2)	5 (1.9)
Leukopenia	95 (17.8)	11 (2.1)	26 (9.7)	4 (1.5)
Urinary tract infection	79 (14.8)	1 (0.2)	27 (10.1)	1 (0.4)
Headache	73 (13.6)	2 (0.4)	36 (13.5)	2 (0.7)
Muscoloskeletal pain	62 (11.6)	5 (0.9)	28 (10.5)	1 (0.4)
Neuropathy peripheral	59 (11.0)	3 (0.6)	18 (6.7)	3 (1.1)
Neutropenia[c]	98 (18.3)	33 (6.2)	42 (15.7)	8 (3.0)
Constipation	54 (10.1)	0	27 (10.1)	1 (0.4)
Thrombocytopenia	42 (7.9)	9 (1.7)	9 (3.4)	1 (0.4)
Proteinuria	31 (5.8)	5 (0.9)	40 (15.0)	1 (0.4)
Intestinal obstruction	21 (3.9)	12 (2.2)	9 (3.4)	6 (2.2)

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

Safety in HRD+ patients

In the HRD+ population (assessed at DCO1), a similar level of AEs was observed in both study arms at DCO1 (Table 22). Although Grade ≥3 AEs occurred in a greater proportion of patients in the olaparib + bevacizumab arm, the difference was minimal vs the placebo + bevacizumab arm (56.5% vs 49.6%, respectively). In total there were four fatal AEs; one in the olaparib-treated arm and three in the placebo-treated arm.

Table 22. Summary of AEs, HRD+ population, DCO1

AEs	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
All grade AEs, n (%)	255 (100)	127 (96.9)
Grade ⩾3 AEs, n (%)	144 (56.5)	65 (49.6)
SAEs, n (%)	72 (28.2)	44 (33.6)
Deaths, n (%)	1 (0.4)	3 (2.3)
Dose interruptions due to AEs, n (%)	144 (56.5)	28 (21.4)
Dose reductions due to AEs, n (%)	111 (43.5)	9 (6.9)
Discontinuations due to AEs, n (%)	48 (18.8)	8 (6.1)

Footnotes: *Dose interruptions, reductions and discontinuations reported are from olaparib and placebo.*

Source: *AstraZeneca Data on File (HRD+ Data)*

7.3.2 Safety PRIMA trial

An overview of the safety and tolerability data reported for the PRIMA trial (niraparib monotherapy) is presented below:

- In the initial PRIMA trial protocol, all patients were to be given a fixed dose of 300 mg niraparib once daily. The trial protocol was amended after the trial start such that patients with a baseline body weight of >77 kg, a platelet count of >150,000/cm3, or both, started on a niraparib dose of 200 mg once daily. This dosing regimen was found to improve the safety profile.
- Dose reductions were reported for 70.9% of patients.
- PRIMA has reported no treatment-related deaths.
- Grade ≥3 AEs were reported in 70.5% of niraparib treated patients, compared to 18.9% of placebo-treated patients
- The most common Grade ≥3 AEs reported in the PRIMA study were anaemia (31% of patients), thrombocytopenia (39% of patients) and neutropenia (21% of patients)., The preferred term 'platelet count decreased' was included as a separate AE in this analysis, with 13% of patients experiencing this AE at Grade ≥3. This implies that if data for grouped thrombocytopenia terms were included in this publication, this would be the most common AE of Grade ≥3.
- No reduction in HRQoL benefits was identified in the PRIMA trial.

7.3.3 Comparison of safety in PAOLA-1 and PRIMA

Table 23 assess comparison of safety signal in PAOLA-1 higher-risk population post-matching verus ITT population in PRIMA regardless of ISD or FSD. Table 24 further assess the difference between Individual Starting Dose and Fixed Starting dose.

Table 23. Safety in biomarker-unselected group in post-matching PAOLA-1 population and PRIMA[1]

AEs[a]	Post-matching			
Intervention	**Olaparib + bevacizumab**	**Placebo + bevacizumab**	**Niraparib[2]**	**Placebo[2]**
Sample Size (n) **Effective Sample Size (ESS)**	398 357	194 172	484	244
Adverse event, % (n)				
Any grade: all causes	100	96	99	92
Grade ⩾3	60	53	70	19
Haematological				
Anaemia				
Any Grade	42	10	64	18
Grade ⩾3	18	0	31	2
Neutropenia				
Any Grade	18	16	42	80
Grade ⩾3	6	3	21	1
Thrombocytopenia				
Any Grade	9	5	66	5
Grade ⩾3	2	1	39	<1
Non-Haematological				
Nausea				
Any Grade	51	23	57	28
Grade ⩾3	2	1	1	1
Vomiting				
Any Grade	20	11	22	12
Grade ⩾3	2	2	1	1
Fatigue				
Any Grade	52	30	51	41
Grade ⩾3	5	2	3	1
Hypertension				
Any Grade	46	64	18	7
Grade ⩾3	19	33	6	

[1] Table based on table 2 in Hettle et al (2021)

Most patients experienced adverse events (any grade: 100% olaparib plus bevacizumab; 96% placebo plus bevacizumab; 99% niraparib and 92% placebo). The frequency of adverse events of grade ⩾3 was higher for maintenance niraparib (70%) versus olaparib plus bevacizumab (60%) (Table 23).

Haematological adverse events (any grade) of anaemia (42% olaparib plus bevacizumab; 64% niraparib), neutropenia (18% olaparib plus bevacizumab; 42% niraparib) and thrombocytopenia (9% Olaparib plus bevacizumab; 66% niraparib) were all more common with niraparib compared with Olaparib plus bevacizumab.
Hypertension (any grade) were more commonly observed with combination of olaparib plus bevacizumab (46% vs 18%) whereas no apparently difference in nausea & vomiting was observed between the treatment. Frequency of Grade ≥3 fatigue were numerical higher with niraparib.

For Individual Starting Dose (ISD), the following adverse events (grade 3 & 4) were observed with an increased frequency (>10%) in comparison of olaparib + bevacizumab and niraparib (ISD):

- **Niraparib:** Neutropenia; thrombocytopenia
- **Olaparib + bevacizumab:** hypertension

No increased frequency (<10%) was observed for the following AEs

- Anemia; nausea, vomiting, fatigue

In order to assess safety profile of the combination of olaparib and bevacizumab the absolute difference in grade 3 & 4 versus niraparib and olaparib monotherapy are displayed in Table 24.

Table 24. Frequency of Grade 3 & 4 Adverse Events in various 1. & 2. line PARPi maintenance studies

Frequency of Grade 3 & 4 Adverse Events and absolute differences[1]						
	PARPi	Study Population	Active arm	Placebo arm	Absolute difference (%-point)	
2nd Line						%-point difference vs SOLO-2
	Olaparib	SOLO-2 (n=295)	36,0 %	18,0 %	18,0 %-point	
	Niraparib	NOVA (n=553)	74,1 %	22,9 %	51,2 %-point	**38,1 %-point**
1st Line mono						%-point difference vs SOLO-1
	Olaparib	SOLO-1 ITT(n=391) SOLO-1 Higher Risk (n = 219)	39,2 % 45,0 %	18,5 % 18,0 %	20,7 %-point 27,0 %-point	
	Niraparib	PRIMA ITT (n=733) PRIMA FSD (n=475) PRIMA ISD (n=258) PRIMA ISD (n=258)	70,5 % 75,9 % 60,4 % 60,4 %	18,9 % 18,9 % 18,9 % 18,9 %	51,6 %-point 57,0 %-point 41,5 %-point 41,5 %-point	31,5 %-point 36,9 %-point **21,4 %-point** **15,4 %-point** vs SOLO-1 higher-risk
1st Line Combo						%-point difference vs PRIMA ITT/ISD[2]
	Olaparib + bevacizumab	PAOLA-1 ITT(n=806)	57,6 %	51,0 %	6,6 %-point	**÷ 12,9/ ÷2,8 %-point**
1st Line Combo						%-point difference vs SOLO-1
	Olaparib + bevacizumab	PAOLA-1 ITT(n=806) PAOLA-1 ITT (n=806)	57,6 % 57,6 %	51,0 % 51,0 %	6,6 %-point 6,6 %-point	**18,4 %-point** **12,6 %-point**

[1] Data based on initial data cut-off in respective studies[2] ISD: Individualized starting dose

- In the PRIMA study a frequency of grade 3-4 AE's of 70,5% (ITT population) were observed. For patients on Fixed Starting Dose (FSD) a frequency of 75,9 % were reported compared with a frequency of 60,4% for patients on Individualized Starting Dose (ISD).
- In PAOLA-1 ITT, a frequency of grade 3 & 4 AE's of 57,6% were observed. Observed absolute difference compared to PRIMA IIT/ISD population is ÷ 12,9/ ÷2,8 %-point hence below the MKRF defined by DMC leading to the conclusion that the two treatment options do not differ in terms of frequency of Grade 3 & 4 AEs.

However the profile of the side effects suggest a difference between the two treatment options which is supported by the PAIC. An increased risk of hematological toxicity is observed with niraparib, however hypertension more often reported with or without addition of olaparib.

Adverse events in BRCAm populations vs non-BRCAm

Based on DCO1 safety data(Clinical study report) from PAOLA-1, we do not see significant differences between SAS and SAS split on tBRCAm population and non-tBRCAm population with regards to addition of olaparib to bevacizumab (Table 25).

AstraZeneca have not been able to identified published safety data from PRIMA study where SAS has been spilt on tBRCAm and non-tBRCAm population. However safety data from NOVA trial assessing the role of niraparib in platinum sensitive Ovarian Cancer patients reveal no difference in any AE, AE≥3, SAE, Any AE leading to discontinuation or death between gBRCAm cohort and non-gBRCAm cohort hence suggesting identical safety profile (Table 26).

Table 25. Observed safety profile from PAOLA-1 split on tBRCAm population and non-tBRCAm population

Population[1]	SAS[2] Olaparib + bevacizumab N=535	Non-tBRCAm Olaparib + bevacizumab N=378	tBRCAm Olaparib + bevacizumab N=157	SAS Placebo + bevacizumab N=267	Non-tBRCAm Placebo + bevacizumab N=187	tBRCAm Olaparib + bevacizumab N=80
Any AE n (%)	531 (99.3)	374 (98.9)	157 (100)	256 (95.9)	178 (95.2)	78 (97.5)
Any AE of CTCAE grade 3 or higher, n (%)	308 (57.6)	216 (57.1)	92 (58.6)	136 (50.9)	99 (52.9)	37 (46.3)
Any AE of CTCAE grade 3 or higher, causally related to olaparib or placebo, n (%)	183 (34.2)	127 (33.6)	56 (35.7)	28 (10.5)	23 (12.3)	5 (6.3)
Any AE leading to discontinuation of olaparib or placebo, causally related to olaparib or placebo	95 (17.8)	71 (18.8)	24 (15.3)	6 (2.2)	5 (2.7)	1 (1.3)
Any AE leading to dose interruption of olaparib or placebo, causally related to olaparib or placebo	234 (43.7)	158 (41.8)	76 (48.4)	24 (9.0)	21 (11.2)	3 (3.8)
Any AE leading to dose reduction of olaparib or placebo, causally related to olaparib or placebo	203 (37.9)	140 (37.0)	63 (40.1)	17 (6.4)	14 (7.5)	3 (3.8)

1) *Source: Clinical Study Report AstraZeneca Olaparib-D0817C00003 (GINECO-OV125b); data from DCO1*
2) *SAS: Safety Analysis Set*

Table 26. Data from NOVA trial split on gBRCAmut and non-gBRCAm cohort

Population[1]	gBRCAm Niraparib N=136	Non-gBRCAm Niraparib N=231	gBRCAm Placebo n=65	Non-gBRCAm placebo N=114
Any AE n (%)	136 (100)	231 (100)	61 (94)	110 (96)
Any AE of CTCAE grade 3 or higher, n (%)	108 (80)	164 (71)	14 (22)	27 (24)
SAE	42 (31)	68 (29)	7 (11)	20 (18)
Any AE leading to discontinuation	18 (13)	36 (16)	1 (2)	3 (3)
Any AE leading to death	0	0	0	0

1) *FDA Assessment report of NOVA trial; table 11-27*

Adverse events of Special Interest(AESI). PAOLA-1

With DCO3 re-assessment of adverse events of special interest were performed. Incidence of MDS/AML and new primary malignancies remained low and balanced between arms (Table 27).

Table 27. Incidence of AESI at DCO 1, 2 & 3 in PAOLA-1

	Primary PFS analysis (DCO: 22 March 2019)		Final PFS2 analysis (DCO: 22 March 2020)		Final OS analysis (DCO: 22 March 2022)	
	Olaparib + bevacizumab (N=535)	Placebo + bevacizumab (N=267)	Olaparib + bevacizumab (N=535)	Placebo + bevacizumab (N=267)	Olaparib + bevacizumab (N=535)	Placebo + bevacizumab (N=267)
MDS/AML/AA, n (%)	6 (1.1)	1 (0.4)	7 (1.3)	4 (1.5)	9 (1.7)	6 (2.2)
New primary malignancies, n (%)*	7 (1.3)	3 (1.1)	13 (2.4)	5 (1.9)	22 (4.1)	8 (3.0)
Pneumonitis/ILD/bronchiolitis, n (%)†	6 (1.1)	0 (0.0)	6 (1.1)	0 (0.0)	7 (1.3)	2 (0.7)

7.4 HRQoL PAOLA-1 ITT and HRD+ population

7.4.1 EORTC QLQ ITT population

EORTC QLQ-C30 baseline scores were generally high and similar in both arms (68.64 in the olaparib + bevacizumab arm and 67.14 in the placebo + bevacizumab arm) and remained stable across the 24-month treatment period. No clinically meaningful difference in HRQoL was observed between the treatment arms over the 24-month treatment period (Table 28) or across individual timepoints. Adjusted mean change from baseline over 24 months was 0.13 points for the olaparib + bevacizumab arm and -0.46 points for the placebo + bevacizumab arm, with the threshold for a meaningful difference being a 10 point change. Similar results were observed for the physical and role functioning scales of the QLQ-C30. A transient worsening in the mean nausea/vomiting score for patients in the olaparib +

bevacizumab arm was observed at 12 weeks, and an improvement in mean social functioning score for patients in the placebo + bevacizumab arm was observed at 96 weeks. Otherwise, there were no clinically meaningful changes from baseline in any QLQ-C30 functioning or symptom subscales at any timepoint on treatment over 24 months. This demonstrates that treatment with the combination of olaparib + bevacizumab does not have a detrimental effect on the HRQoL of AOC patients. As EORTC QLQ-C30 baseline scores were generally high (>10 points higher than the ovarian cancer stage III/IV reference value of 56.3, and approximately three points lower than the general population reference value of 71.2)[ref European Organisation for Research and Treatment of Cancer. EORTC Reference Values Manual. Available at https://qol.eortc.org/manuals/2008].

Patients undergoing treatment with olaparib + bevacizumab have a generally high HRQoL, which is not meaningfully different from that of the general population. The high baseline score for patients in the PAOLA-1 trial may however have led to a ceiling effect in which meaningful increases in HRQoL were not possible.

Table 28. Change from baseline in QLQ-C30 GHS/QoL score, MMRM, ITT population

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

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

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

7.4.2 EQ-5D-5L ITT population

The compliance rates for the planned on-treatment visits of EQ-5D-5L were high (above 80%) from baseline to Week 96 in both treatment arms reflecting the treatment cap of 2 years. Overall the data supported no meaningful deterioration from baseline for patients in the olaparib/bevacizumab arm relative to patients in the placebo/bevacizumab arm as measured by the weighted health state index score (Figure 14).

The visual analogue scale score also did not support a meaningful deterioration from baseline for patients in the olaparib/bevacizumab arm relative to patients in the placebo/bevacizumab arm (Figure 15).

7.4.3 PAOLA1 EQ-5D-5L HRD+ population

Mean EQ-5D-5L scores and change from baseline in HRD+ subgroup is shown below in Figure 16 and Figure 17.

7.4.4 PAOLA1 EORTC QLQ-C30 ITT and HRD+ population

PROs for HRQoL were gathered using the EORTC Quality of Life Questionnaire Core 30 (QLQ-C30) and the ovarian cancer specific module (QLQ-OV28), every 12 weeks for two years from first study drug administration. Change from baseline in EORTC QLQ-C30 GHS was regarded as the key analysis of the PROs; this was analysed using a mixed model for repeated measures (MMRM) analysis of the change from baseline (defined as prior to first dose) in QLQ-C30 global health status (GHS) for each visit. At DCO1, in the HRD+ population, HRQoL remained stable across the 24-month treatment period in both the olaparib + bevacizumab and placebo + bevacizumab arms (Table 29).(ref AstraZeneca Data on File 219) No clinically meaningful changes from baseline in GHS/QoL score were observed across timepoints in either treatment arm (Figure 18). Similar results were also observed in the following EORTC QLQ-C30 functional scales: role functioning, physical functioning, emotional functioning and social functioning [ref AstraZeneca Data on File 219]. Collectively, these data show that the addition of olaparib to bevacizumab does not negatively impact on the HRQoL of HRD+ patients and are consistent with the manageable safety profile of olaparib + bevacizumab treatment. Furthermore, GHS/QoL scores as well as role, social, and emotional functioning scores remained stable in the olaparib + bevacizumab group in the follow-up period, although these data should be interpreted with caution given small sample sizes, and EORTC QLQ-C30 summary data in the HRD+ group were consistent with that in the ITT population, confirming the robustness of the HRD+ data.

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7.4.5 HRQoL SOLO-1

FACT-O

Patient-reported HRQoL was assessed using the FACT-O questionnaire, while patient health status was measured through the EQ-5D-5L questionnaire. The FACT-O is composed of several subscales: physical, social/family, emotional, and functional well-being scales, as well as the additional concerns scale consisting of specific ovarian cancer symptoms. The primary HRQoL analysis in SOLO1 was the TOI, change from baseline over the first 24 months in the TOI score, an established single targeted index derived from the FACT-O questionnaire. The TOI targets the most relevant symptoms and functional and physical well-being that can be directly related to symptoms and AEs. The TOI is composed of the following scales of the FACT-O: physical and functional well-being and additional concerns. Baseline scores for the TOI and FACT-O were high with no differences between treatment arms for all patients. Mean TOI scores at baseline were 73.6 and 75.0 for patients in the olaparib and placebo arms, respectively.

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

The adjusted mean change from baseline in TOI score over 24 months for patients in the olaparib arm was 0.30 (95% CI −0.717, 1.318) and 3.30 (95% CI 1.839, 4.758) for patients in the placebo arm. The estimated difference in treatment arms was -3.00 (95% CI −4.779, −1.216; *P*=0.001)(Figure 19). The observation of no clinically meaningful worsening in TOI of olaparib relative to placebo in HRQoL was supported by a sensitivity analysis using area under the curve (AUC) over all visits. This analysis found that up to 24 months there were no statistically significant or clinically relevant differences between the treatment arms (estimated difference −2.05; 95% CI −5.596, 1.501; *P*=0.2573).
The primary measure of HRQoL, the FACT-O TOI score, did not decrease and there was no clinically significant deterioration in TOI of olaparib relative to placebo or baseline in HRQoL.

EQ-5D-5L

The impact of treatment and disease state on health state utility was assessed by the EQ-5D-5L using a weighted health state index score over time (until the treatment cap). Overall, there was no worsening or deterioration in HRQoL for patients in the olaparib arm compared with patients in the placebo arm (Figure 20).
The EQ-5D-VAS records the respondent's self-rated health on a vertical, VAS where the endpoints are labelled 'best imaginable health state' and 'worst imaginable health state'. The VAS score also did not support a worsening or deterioration of patients in the olaparib arm relative to patients in the placebo arm (Figure 21**Error! Reference source not found.**).

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[redacted]

7.4.6 HQRoL PRIMA

In PRIMA PROs (FOSI, EQ-5D-5L, EORTC-QLQ-C30, EORTC-QLQ-OV28) were collected every 8 weeks (±7 days) for 56 weeks beginning on cycle 1/day 1, then every 12 weeks (±7 days) thereafter while the patient received study treatment. Once a patient discontinued treatment, PRO evaluations were performed at the time of treatment discontinuation and then at 4, 8, 12, and 24 weeks (±1 week for each timepoint) after the end of treatment, regardless of the status of subsequent treatment (Table 30) . A mixed effects model for repeated measures (MMRM) was performed to compare between-treatment difference adjusting for correlations across multiple time points within a patient and controlling for the baseline value. Adjusted mean difference and 95% CIs were presented to illustrate the effect of treatment. Adjusted means and standard error bars were plotted over time.

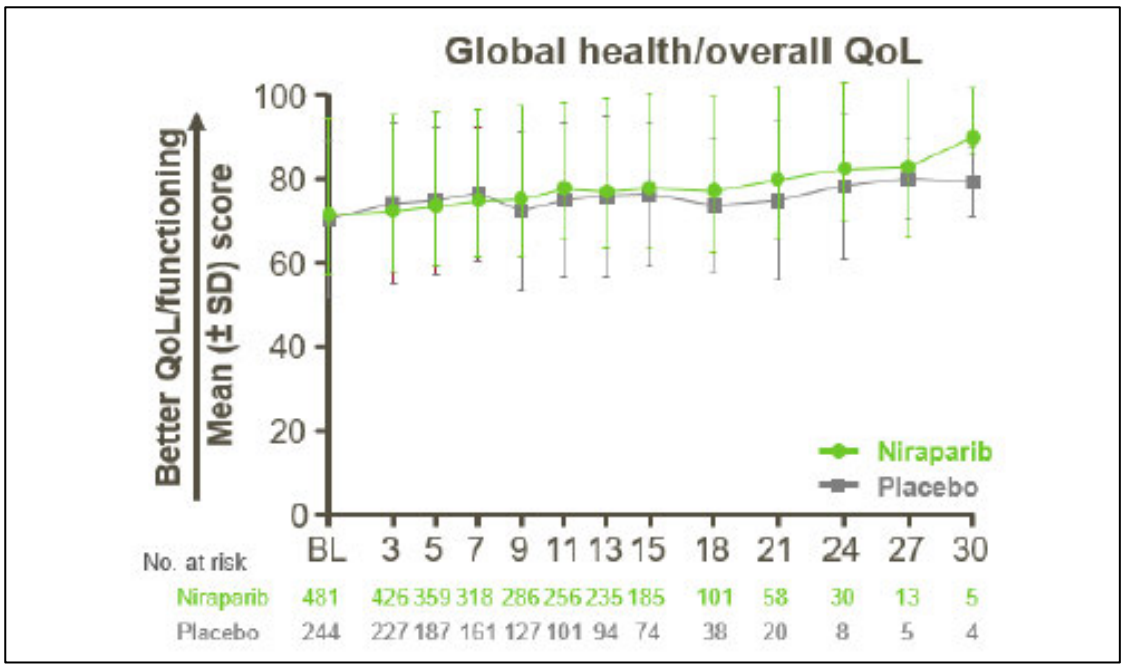
Table 30. Functional Assessment of Cancer Therapy-Ovarian Symptom Index (FOSI) Completion Status by Visit.

Timepoint	Niraparib (N=487)		Placebo (N=246)	
	N	%	N	%
Screening	483/487	99.2	242/246	98.4
Cycle 3	424/441	96.1	221/232	95.3
Cycle 5	352/375	93.9	185/196	94.4
Cycle 7	316/344	91.9	158/177	89.3
Cycle 9	254/266	95.5	125/138	90.6
Cycle 11	254/266	95.5	99/109	90.8
Cycle 13	231/249	92.8	97/98	99.0
Cycle 15	185/198	93.4	74/83	89.2
Cycle 18	100/109	91.7	38/39	97.4
Cycle 21	56/61	91.8	21/22	95.5
Cycle 24	30/33	90.9	8/8	100
Cycle 27	13/16	81.3	5/5	100

For the PRIMA ITT population patient-compliance rates for the HRQoL questionnaires were high for all HRQoL tools and remained consistently >80% throughout the trial.
The average scores for abdominal/GI symptoms and other chemotherapy side effects were maintained or slightly improved during the trial and were largely comparable in both treatment groups throughout the trial.
EORTC QLQ-C30:The average global health/overall QoL and individual domain scores were comparable for niraparib and placebo groups throughout the trial. The average score for global health/overall QoL was maintained or slightly

improved during the trial. Similarly, scores for physical function, fatigue and pain were maintained or improved during the trial (Figure 22).

Figure 22. Results of the EORTC QLQ-C30 in the full ITT population in PRIMA.

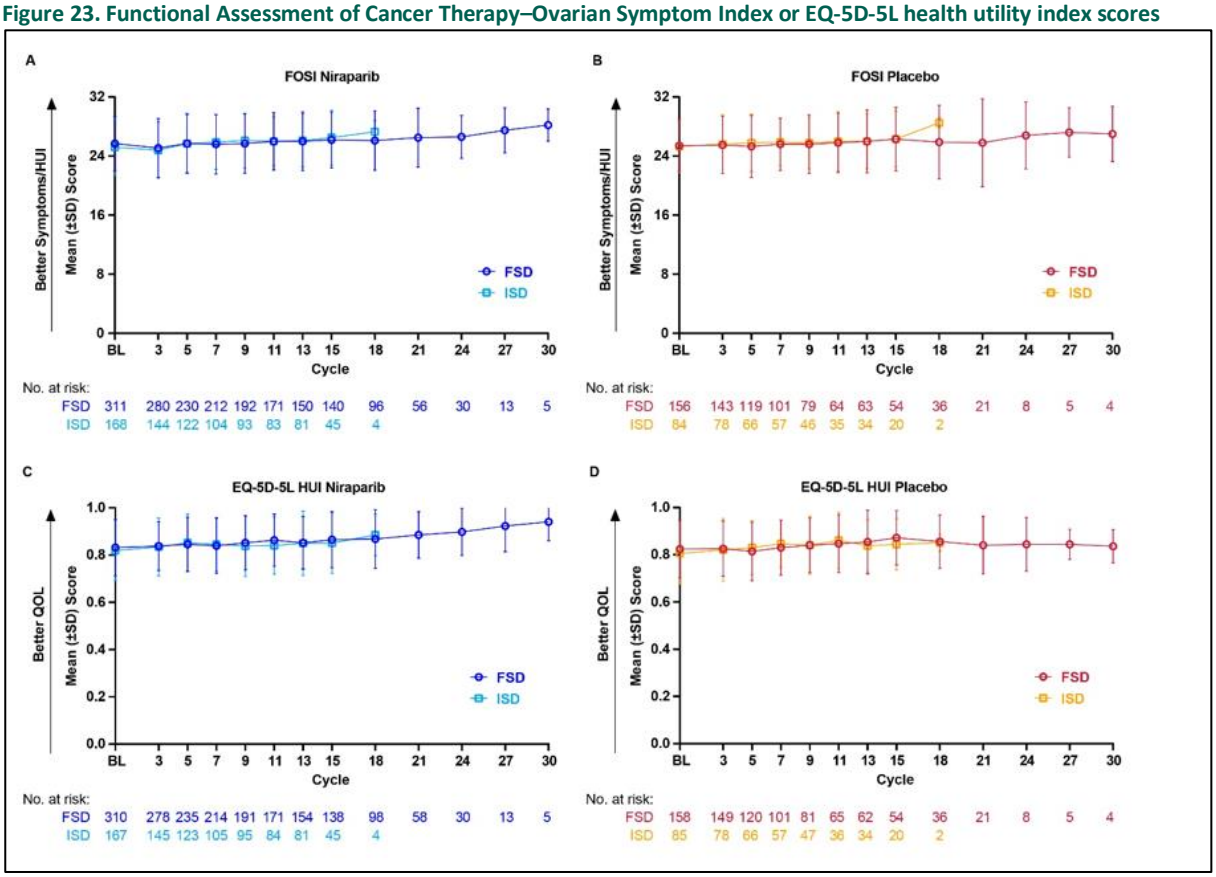


Source. Niraparib application DMC 2020

Data presented in abstract form (Freyer G, Int J Gynecol Cancer. 2020;30(Suppl 3):A12-A3) showed that there was no difference in HRQoL outcomes between the HRD and HRP subgroups.

Maria-Pilar Barretina-Ginesta(Ther. Adv Med Oncol. 2022; 14) published an update based on PRIMA results and measured on quality-adjusted PFS (QA-PFS) and quality-adjusted time without symptoms of disease or toxicity (Q-TWiST). They concluded that in patients with advanced OC, first-line maintenance therapy with niraparib was associated with longer QA-PFS and Q-TWiST compared with placebo. Significant benefit was seen in both the HRD and overall ITT populations, confirming the benefit of niraparib in genetically diverse patients with OC. "Collectively, these findings demonstrate that niraparib maintenance treatment is associated with a PFS improvement and that treatment benefit is maintained even when HRQoL and/or toxicity data are combined with PFS in a single measure". Further a recently publication on fixed dose(FSD) and Individual dosing(ISD) reported data on EQ-5D-5L [Mirza et al. 2023]. In this publication no differences were seen in mean Functional Assessment of Cancer Therapy–Ovarian Symptom Index or EQ-5D-5L health utility index scores between patients receiving niraparib and placebo in the ISD and FSD subgroups (Figure 23)

Figure 23. Functional Assessment of Cancer Therapy–Ovarian Symptom Index or EQ-5D-5L health utility index scores



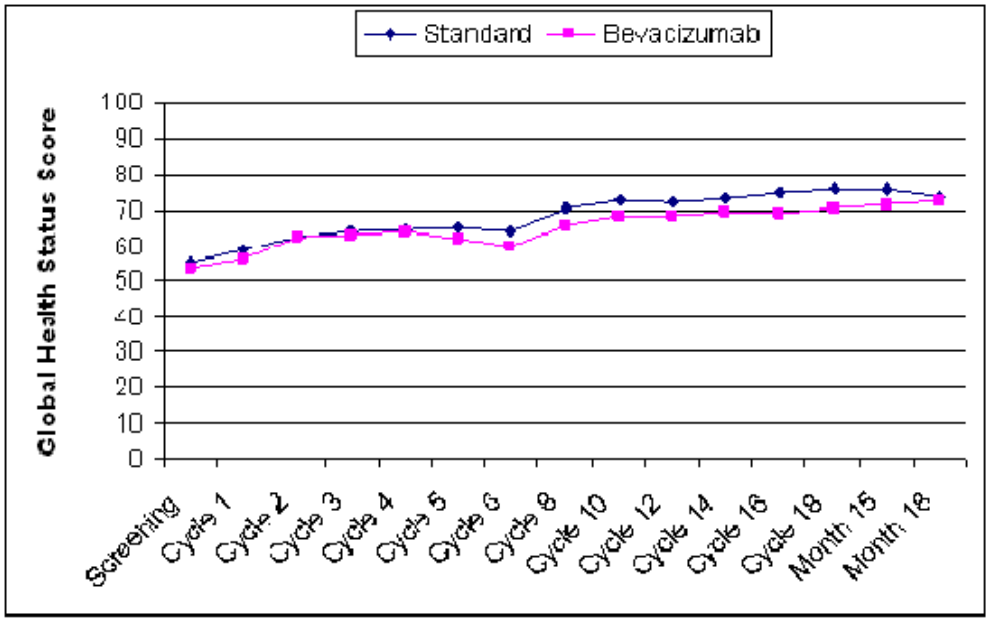
Source: Mirza et al. Cancer, June 2023. This figure is from the supplementary appendix. AstraZeneca has copyrights to this publication

7.4.7 HQRoL bevacizumab trials

In the GOG-0218 trial, the FACT-O TOI score prior to treatment was 67.4 (66.1; 68.7) in the bevacizumab maintenance group and 68.2 (66.9; 69.5) in the placebo group. Prior to cycle 21 the scores had increased to 78.6 (77.3; 79.9) in the bevacizumab maintenance group and 77.6 (76.2; 79.0) in the placebo group. Thus, in both treatment groups, HRQoL improved during the trial and there was no obvious difference between the groups.

In the ICON7 trial, the EOCTC QLQ-C30 global HRQoL score was 55.1 (53.5; 56.7) at baseline in the bevacizumab group and 58.6 (57.1; 60.1) in the control group. At the end of bevacizumab maintenance treatment, the global HRQoL scores increased to 69.7 (68.0; 71.4) in the bevacizumab group and 76.1 (74.3; 77.9) in the control group indicating that HRQoL improved in both groups during the trial. The difference between groups at week 54 was small but statistically significant (-6.4 [-9.0; 3.7], P<0.0001), indicating a greater improvement in the control group (Figure 24).

Figure 24. Global health status score over time ICON7



Source: Perren et al 2011. AstraZeneca has copyrights

In summary, based on available data from the GOG-0218 and ICON7 trials, bevacizumab treatment was associated with a small improvement in HRQoL, but improvements were more pronounced in the control group.

7.4.8 Comparative HRQoL PAOLA-1, PRIMA, SOLO-1 and bevacizumab studies

Indirect or narrative comparisons of niraparib, olaparib, olaparib + bevacizumab and bevacizumab within the HRQoL will not be meaningful due to differences in patient-groups and HRQoL methods. In the "bilag til medicinrådet anbefaling af niraparib. 2020" it was also concluded that "indirect or narrative comparisons of niraparib, olaparib and bevacizumab are not considered meaningful. However based on the clinical trial data described , treatment with niraparib and bevacizumab seemed to be associated with small improvements in HRQoL, whereas treatment with olaparib was not. None of the 3 medicines were associated with any deterioration in HRQoL; "Niraparibs effekt på livskvalitet overfor bevacizumab og olaparib kan ikke kategoriseres".

In the same report Fagudvalget concludes "Fagudvalget vurderer, at der ikke er grund til at antage, at nogen af behandlingerne har klinisk relevant effekt på livskvaliteten ved de anvendte målemetoder".

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

8. Health economic analysis

8.1 Model

8.1.1 Modelling approach

The model presents a cost-minimization analysis, including both average costs per patient and budget consequences, for olaparib + bevacizumab compared with niraparib for patients within the BRCAwt (non-BRCAm positive) part of the HRD-positive indication for olaparib + bevacizumab.

Ideally, the health economic analysis should be a full cost-effectiveness analysis with the incremental cost per QALY as measure, according to Medicinrådet guidelines. However, there are limitations in the data availability that makes a full cost-effectiveness analysis unattainable in this case:

- No mature OS data have as yet been presented from the PRIMA study, which would be required for an indirect comparison. Interim OS data were presented in the EPAR (EMA 2020), but with less than 10% maturity and no significant outcome (HR HRDpos: 0.61; 95% CI: 0.265 – 1.388). No OS data at all have been published specifically for the HRDpos BRCAwt subpopulation in PRIMA.
- The PRIMA study only covers a high-risk population, i.e. patients with residual disease after surgery. Hence, it would be theoretically impossible to compare olaparib + bevacizumab with niraparib in the low-risk population.

For these reasons, the approach taken here is a cost-minimization analysis between olaparib + bevacizumab and niraparib. This approach builds on the assumption that the efficacy is the same for olaparib + bevacizumab and niraparib and that only difference is in the costs. We would like to emphasize very strongly that the cost-minimization approach used in this application does not mean that we think that these treatments are equal from the efficacy standpoint, but we have taken a pragmatic and conservative approach given the availability and the comparability of the data from the PAOLA-1 and PRIMA clinical trials.

The results of a population-adjusted indirect treatment comparison suggested that combination treatment with olaparib plus bevacizumab as maintenance treatment improves PFS for women with newly diagnosed advanced ovarian cancer compared with niraparib alone in a high-risk population. Maintenance olaparib plus bevacizumab reduced the risk of disease progression or death by 43% (HR 0.57; 95% CI: 0.41-0.79) vs. niraparib in the HRD-positive population (Hettle et al., 2021). See also section 7.1.3, Figure 8.

Comparative PFS data are not sufficient for a cost-utility analysis. However, no indirect treatment comparison of OS has yet been conducted between PAOLA-1 and PRIMA due to limited data availability. Overall survival data in PRIMA are not yet regarded as mature based on the prespecified analysis plan (https://www.gsk.com/en-gb/media/press-releases/zejula-niraparib-shows-durable-and-sustained-long-term-progression-free-survival-benefit-in-the-prima-study-of-first-line-platinum-responsive-advanced-ovarian-cancer/).

A naïve comparison of the OS HR for the whole HRD positive population would indicate similar hazard ratios for OS, although the comparators are different. In the final OS analysis of PAOLA-1, there was a 38% reduction in risk of death for olaparib + bevacizumab vs bevacizumab alone (HR 0.62; 95% CI 0.45–0.85). In the HRDpos BRCAwt population, there was a 29% reduction in risk of death for olaparib + bevacizumab vs bevacizumab alone (HR 0.71; 95% CI 0.45–1.13). The

niraparib OS HR for the HRDpos group is 0.61 as mentioned above, with 95% CI: 0.265 – 1.388. Hence, olaparib + bevacizumab has a similar OS HR compared with bevacizumab alone as niraparib has with placebo for the HRDpos population.

Given that olaparib + bevacizumab shows as good relative efficacy versus an active comparator arm (bevacizumab) as niraparib showed versus placebo, it reasonable to assume that the efficacy regarding for olaparib + bevacizumab is at least as good as for niraparib monotherapy. Hence, a cost-minimization approach is both feasible and very conservative.

8.1.2 Other basic modelling assumptions

The model includes both a calculation on the average cost per patient over the time horizon, and a calculation on budget impact. The model structure follows the standard format for calculating the budget impact of new treatments and is closely aligned with other budget impact models (BIMs) in oncology that have been presented and accepted by health technology appraisal (HTA) authorities. The cost per patient analysis has been adapted to follow Medicinrådet guidelines. The model was populated with patient numbers (for the budget impact), relevant treatments (intervention, comparator, subsequent therapies), healthcare resource use, and cost data that are relevant in a Danish setting.

Market share data for niraparib in the current scenario (without olaparib + bevacizumab) and with olaparib + bevacizumab (if the combination would be recommended) are based on AstraZeneca's internal estimations. Data on eligible patients, market shares and duration of treatments were combined to estimate the number of patients on each treatment per year. The cost analyses include costs for drug acquisition, monitoring, administration, patient time and transport, and treatment-related adverse event (AE) costs.

First line treatment for ovarian cancer starts with chemotherapy, or chemotherapy in combination with bevacizumab. Olaparib can then be used as maintenance therapy after chemotherapy, either as monotherapy or in combination with bevacizumab. (However, olaparib monotherapy is only indicted for BRCAm-positive patients in first line advanced ovarian cancer and is not included here). The cost of chemotherapy at the start of first-line treatment, i.e. before olaparib treatment is initiated as maintenance therapy, is assumed to be same in all arms and is therefore not included in the estimated costs.

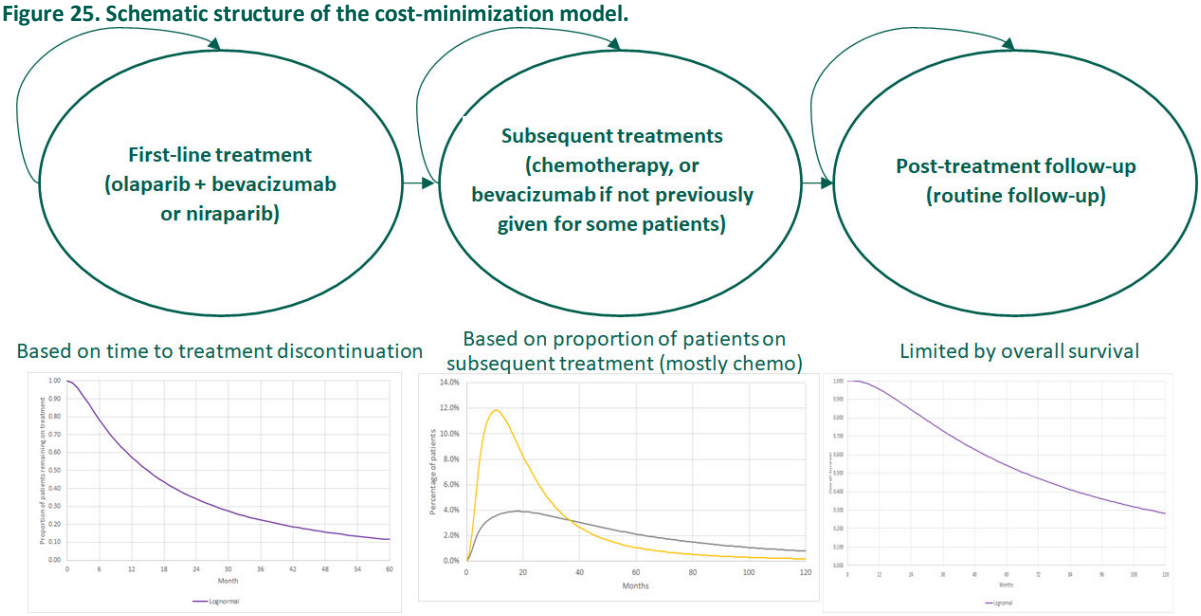
Hence, the treatment initiation of olaparib occurs after chemotherapy and defines the starting point of the cost model. Treatment with bevacizumab includes two phases, first the concomitant phase in which bevacizumab is given in combination with chemotherapy, which implies more frequent administrations and monitoring, and thereafter the maintenance phase in which patients receive treatment with only bevacizumab. Thus, the treatment with bevacizumab starts earlier than treatment with olaparib. Since the total cost for bevacizumab must be considered for a fair comparison, the costs for bevacizumab occurring prior to the bevacizumab maintenance phase is included as if the two treatments had the same starting point.

8.1.3 Model structure

The model is similar to a partitioned survival model used for oncology treatments in general, but it builds on the time to treatment discontinuation rather than progression-free survival and post-progression survival. Overall survival is only used to limit the long-term costs of routine disease monitoring and follow-up, but are otherwise not used in the model. In Figure 25 below there is a schematic description of the model.

- The most important aspect is the time-to-treatment discontinuation modelling (TTD) modelling. That is just a straightforward extrapolation of the TTD KM curves from the PAOLA-1 study. As we have noted before, we do not have a separate TTD KM curve for niraparib for this patient population (non-BRCA HRD+), and in any case the PRIMA study only included high-risk patients. Therefore, the non-BRCA HRD+ low-risk TTD has to be modelled based on olaparib + bevacizumab data in any case.
- The subsequent therapy is modelled based on time to first subsequent therapy from either the SOLO1 trial or the PAOLA-1 trial. However, TFST is not used directly, as it cannot just be tagged on to the TTD curve. Instead, the TFST data is transformed into a distribution of patients on subsequent therapy over time, as is described in the file.
- Patients who are no longer on treatment may still have some follow-up costs for disease monitoring. These costs are limited by the overall survival.

Figure 25. Schematic structure of the cost-minimization model.



8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

8.2.1 Time horizon and discount rate

AstraZeneca proposes a time horizon of 10 years for the base-case analysis of average costs per patient and year. The time horizon for the cost per patient is long enough to capture the cost per patient for both olaparib and niraparib, as well as relevant subsequent therapies. A 5-year time horizon and a 25-year time horizon for the cost per patient are tested in scenario analysis. A 5-year time horizon is used for the total budget impact, based on Medicinrådet guidelines. This might not be long enough to capture all subsequent therapies fully, but an even longer time perspective is also associated with more uncertainty regarding for example future market shares.

A discount rate of 3.5% was used in the cost per patient analysis according to the latest recommendations from the Ministry of Finance (https://fm.dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021.pdf).

8.2.2 Presentation of input data used in the model and how they were obtained

As a cost-minimization approach was used, no comparative efficacy data are used in the model. The model is based on time-to-treatment discontinuation (TTD) data from PAOLA-1 for the relevant subgroups and also OS data for PAOLA-1 to take costs for resource use over time into account.

8.2.3 Relationship between the clinical documentation, data used in the model and Danish clinical practice

8.2.3.1 Patient population

The model uses the total female population in Denmark as a starting point and the specific target population is estimated based on the disease characteristics of patients in the indication, such as stage, proportion with high-grade serous disease, epithelial ovarian cancer, HRD and BRCA positive status, receiving and responding to platinum-based first-line chemotherapy.

Given the epidemiology and an assumption of the proportion of patients who receive and respond to 1st line chemotherapy, it is estimated that around 75 patients per year would be eligible for treatment with olaparib + bevacizumab in the ovarian HRD positive non-BRCA setting (Table 31,Figure 26).

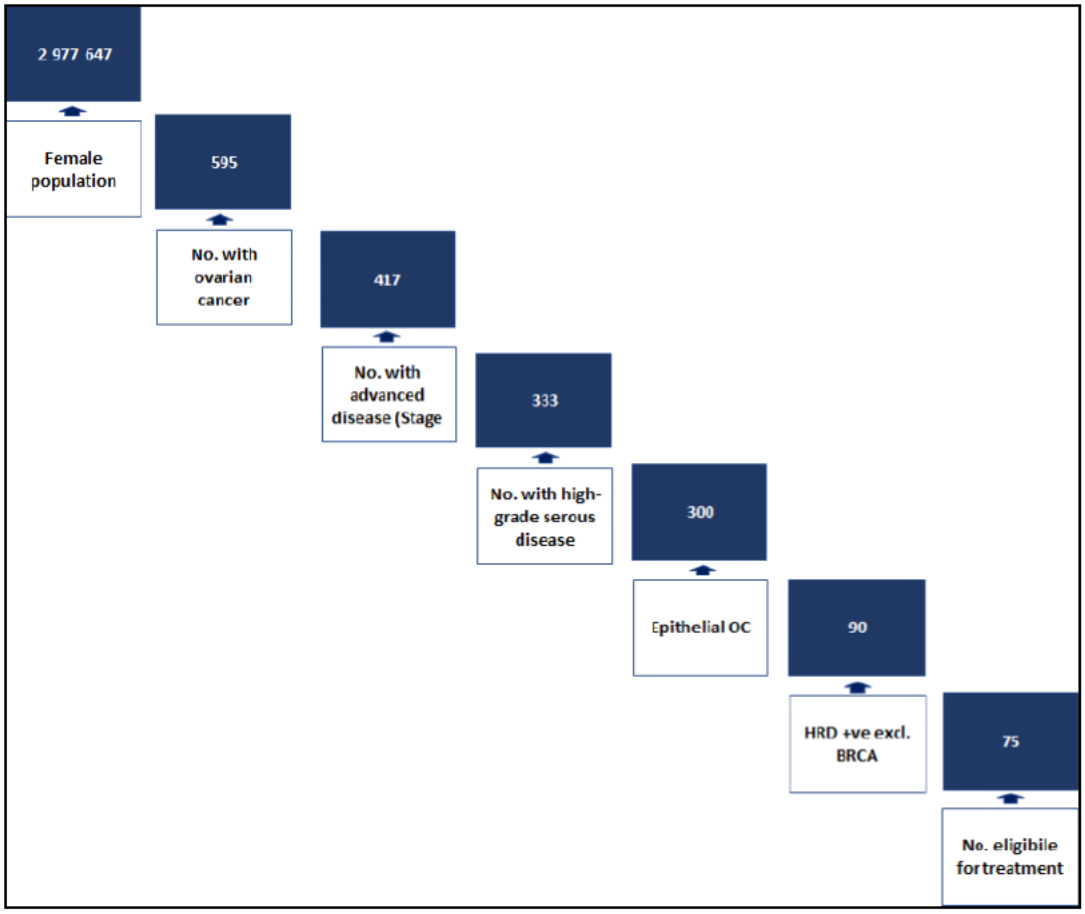
The eligible population (Table 31) refers to adult patients who have HRDpos BRCA positive advanced (FIGO stage III and IV) ovarian cancer (OC), who are in response (complete or partial) after first-line platinum-based chemotherapy (Lynparza SPC, EMA 2020).

The AZ patient funnel estimates that around 75 patients would be eligible for treatment with olaparib + bevacizumab. In our base case, we are thus assuming around 75 new patients per year eligible for the treatment (see also section 5.1.1).

Table 31. Model inputs used to estimate the number of patients eligible for treatment with olaparib

Parameter	Figure	Source
Total female population in Denmark	2 977 647	Statistics Denmark, retrieved October 2022
Incidence of OC (per 100 000)	19.99	The Nordcan project (based on crude rate in 2020)
Proportion with advanced OC: Stage IIb to IV	70%	DGCD 2017. National Årsrapport 2016/2017
Proportion of with high-grade serous OC	80%	Romero et al. (2012)
Proportion with epithelial OC	90%	DGCG Årsrapport 2010-12
Proportion with positive HRD status excl. BRCA	30%	PAOLA-1 (Ray-Coquard 2019)
Patients who receive and respond (CR/PR) to 1st line chemotherapy	83%	Receive 1L: 92% (AstraZeneca's internal assumption); complete or partial response: 90%

Figure 26. Estimation of population eligible for treatment with olaparib + bevacizumab in first-line ovarian cancer.



8.2.3.2 Intervention

The first application based to Medicine Council was based on bevacizumab as comparator (PAOLA-1 study). In the meantime Zejula (niraparib) has been recommended by Medicine Council in the HRD segment. Based on the approval of niraparib this application is for the "higher" and "lower" risk subgroups of patients with an HRD+ BRCAwt profile. Hence, the comparator for this application will be niraparib monotherapy (see section 5.2.2). The intervention and the comparator are described with regard to posology, dosing, time on treatment, criteria for discontinuation and clinical practice in Table 32 and Table 33.

Table 32. Intervention: Lynparza (olaparib) + bevacizumab

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology	The recommended dose of Lynparza in monotherapy or in combination with bevacizumab or endocrine therapy is 300 mg (two 150 mg tablets) taken twice daily,	Bevacizumab: Mix of 15 mg/kg and 7.5 mg/kg bevacizumab based on Danish clinical practice (15 mg/kg in SmPC but 7.5	The dosing in the SmPCs is bevacizumab 15 mg/kg for both olaparib + bevacizumab and bevacizumab alone. However, the 7.5 mg/kg

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
	equivalent to a total daily dose of 600 mg. The 100 mg tablet is available for dose reduction. (EMA 2020, EPAR Product Information – Lynparza) When Lynparza is used in combination with bevacizumab for the first-line maintenance treatment of high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer following completion of first-line platinum-based therapy with bevacizumab, the dose of bevacizumab is 15 mg/kg once every 3 weeks. (EMA 2020, EPAR Product Information – Lynparza)	mg/kg common based on ICON7. Base case 50% 15 mg/kg and 50% 7.5 mg/kg	dosing is preferred by many clinicians based on the results of the ICON7 study. It is not expected that the combination therapy would lead to changed dosing of bevacizumab in the 1st line setting.
Length of treatment (time on treatment) (mean/median)	Max 2 years	Max 2 years – length of treatment based on TTD from PAOLA-1	
Criteria for discontinuation	Patients can continue treatment with Lynparza until radiological disease progression, unacceptable toxicity or for up to 2 years if there is no radiological evidence of disease after 2 years of treatment. Patients with evidence of disease at 2 years, who in the opinion of the treating physician can derive further benefit from continuous Lynparza treatment, can be treated beyond 2 years. (EMA 2020, EPAR Product Information – Lynparza) Bevacizumab: the recommended overall duration of treatment of a maximum of 15 months including the periods in combination with chemotherapy and as maintenance (EMA 2020, EPAR Product Information – Lynparza)	As very few patients continue beyond 2 years, a 2-year limitation is used in the model. For bevacizumab the 15-month limitation is used	The 2-year limitation for olaparib and the 15-month limitation for bevacizumab for most patients is expected to be in line with Danish clinical practice (DGCG 2021)
The pharmaceutical's position in Danish clinical practice	Olaparib and bevacizumab is a well-documented treatment that is reimbursed and recommended	Assumed to be used according to the indication, with the exception of the bevacizumab dose with a	

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
	in for example Finland, Norway and Sweden	mix between 7.5 and 15 mg/kg	

8.2.3.3 Comparator

Table 33. Comparator: Zejula (niraparib)

Comparator	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
Posology	The recommended starting dose of Zejula is 200 mg (two 100-mg tablets), taken once daily. However, for those patients who weigh ≥ 77 kg and have baseline platelet count ≥ 150,000/µL, the recommended starting dose of Zejula is 300 mg (three 100-mg capsules/tablets), taken once daily (EMA 2022. Zejula EPAR – Product Information). Zejula capsules was withdrawn from medicinpriser.dk 03.04.2023 and replaced by the tablet formulation	In PRIMA, 21.8% of patients fulfilled the criteria for the 300 mg starting dose (Zejula EPAR 2020). In the model, the dose is assumed to be a mix of 72.8% starting on 200 mg and 21.8% starting on 300 mg.	The Danish clinical practice is expected to be in line with the PRIMA study.
Length of treatment	It is recommended that treatment should be continued until disease progression or toxicity (EMA 2022. Zejula EPAR – Product Information)	Treatment duration limited to 36 months in the base case. As the indication is treatment to progression, longer treatment duration is tested in the sensitivity analysis.	DGCG guidelines recommend 36 months of maintenance treatment (DGCG 2023)
The comparator's position in the Danish clinical practice			Recommended in DGCG (2023) guidelines

8.2.3.4 Relative efficacy outcomes

As the health economic analysis is based on a cost-minimization approach, relative efficacy outcomes are not used.

8.2.3.5 Adverse reaction outcomes

The model uses the probability of AEs of grade 3 or higher with a frequency of at least 2% in one of the arms in PAOLA-1 (Ray-Coquard 2019: Table 2). For niraparib monotherapy, the AEs were reported in the PRIMA publication (González-Martín 2019: Table 2 & Table S9). See section 8.9 for further details.

8.2.4 Treatment duration for olaparib + bevacizumab

The treatment duration was based on the time to treatment discontinuation for olaparib + bevacizumab and in PAOLA-1. As there is a 2-year treatment cap on olaparib and 15-month treatment cap on bevacizumab, the time to treatment discontinuation curves are used directly as a basis for the treatment duration.

Figure 27 shows the time to treatment discontinuation (TTD) for the high-risk population and Figure 28 for the low-risk population. Patients in the high-risk group tend to be at higher risk of disease recurrence, as reflected by shorter PFS (and treatment duration) compared with those in the low-risk group.

As we do not have a separate time-to-treatment discontinuation (TTD) curve for bevacizumab from start to finish (i.e., bevacizumab infusions given pre- and post-randomization, including those given in combination with chemotherapy before the initiation of olaparib), we had to make some simplifying assumptions. We have assumed that the treatment duration for bevacizumab from start to finish would be approximately the same as the treatment duration from start to finish for olaparib. Given the numbers available, this is a reasonable assumption. According to the Clinical Study Report (CSR) for PAOLA-1, the mean TTD for olaparib + bevacizumab was 15.2 months. The mean TTD for the bevacizumab component of the olaparib + bevacizumab arm post-randomization was 10.0 months and the median number of infusions during this time period was 15. The PAOLA-1 CSR also states that the median number bevacizumab infusions from start to finish was 21 (including pre- and post-randomization). If the mean is approximately proportional to the median number of infusions, this would imply a mean TTD from start to finish of around 21/15*10.0 = 14 months. This is quite close to the mean TTD for olaparib + bevacizumab. Hence, it seems to be a good approximation that the total TTD from start to finish is similar for olaparib and bevacizumab. (The maximum recommended number of cycles of bevacizumab is 22, which corresponds to around 15 months. The CSR notes that that most patients in the PAOLA-1 study received close to the number of recommended cycles). The indication for bevacizumab in first line epithelial ovarian, fallopian tube and primary peritoneal cancer is the following: “Avastin is administered in addition to carboplatin and paclitaxel for up to 6 cycles of treatment followed by continued use of Avastin as single agent until disease progression or for a maximum of 15 months or until unacceptable toxicity, whichever occurs earlier”.

The PAOLA-1 trial used 15 mg/kg dosing as this is in line with the indication for bevacizumab, but the model can use both 7.5 mg/kg and 15 mg/kg based on the ICON7 and the GOG-0218 trials, respectively. Both of these studies are referred to in the Danish ovarian cancer guidelines (DGCG 2023):

"På baggrund af de to ovennævnte undersøgelser har Sundhedsstyrelsen efter ansøgning fra DGCG d. 25. juni 2012 godkendt bevacizumab 15 mg/kg hver 3. uge givet fra 2. serie og sammenlagt 15 måneders behandling som 1. linje behandling til ovariecancer patienter med restsygdom. På grundlag af GOG218 og ICON7 studierne som anført ovenfor, og i lyset af, at ICON7 studiet med dosering på 7,5 mg har vist en overlevelsesgevinst på 7,8 måneder hos patienter med residual tumor efter primær kirurgi (post hoc analyse), er det ovariecancergruppens opfattelse, at 7,5 mg/kg og 15 mg/kg er ligeværdige doseringer. Standard behandling af patienter med restsygdom kan derfor bestå i carboplatin, taxan og bevacizumab."

8.2.5 Treatment duration for niraparib monotherapy

The treatment duration for niraparib monotherapy was also based on PAOLA-1. As PRIMA only included high-risk patients, the PAOLA-1 trial is the best source in this comparison. In addition, we did not have access to patient data on TTD in the PRIMA trial and to our knowledge there are no published data on the treatment duration in the HRD-positive BRCAwt subgroup. The Norwegian Medicines Agency has published an assessment of niraparib for the BRCAwt subgroup. However, the Norwegian assessment also included HRD-negative patients and the BRCAwt TTD curve in PRIMA is not included, as it is unpublished and confidential (SLV 2022). PRIMA has a longer treatment duration than olaparib + bevacizumab in PAOLA-1, as the indication for niraparib is treatment to progression while PAOLA-1 had a 2-year stopping rule. A 3-year stopping rule has been introduced as recommended practice in Danish guidelines (DGCG 2023). Hence, the TTD data needs to be extrapolated beyond 2 years. This was performed with standard parametric distributions. Extrapolations for the high-risk population are included in Figure 29 and for the low risk population in [redacted] See Appendix G (section G1) for further details.

8.2.6 Treatment duration in the model

To be consistent, the extrapolated curves were used for both olaparib + bevacizumab and for niraparib (up to 2 years for olaparib + bevacizumab and up to 3 years in the base case for niraparib). For the high-risk group, the lognormal distribution was chosen based on best statistical fit according to AIC and BIC (Table 34) and for the low-risk group, Weibull distribution was chosen based on best statistical fit according to AIC and BIC (Table 35). Alternative distributions are tested in sensitivity scenarios. Most of the distributions had reasonably good fit during the period for which data are available, with the exception of the Gompertz distribution for the TTD curve in the high-risk HRD+ BRCAwt subgroup. In terms of clinical plausibility of the extrapolations, the risk of progression is highest at the beginning and will tend to decrease over the long run [Banerjee 2021, Ray-Coquard 2023]. As treatment discontinuation is correlated with progression, that would suggest that a lognormal distribution or Weibull distribution with decreasing risk would fit the TTD data in the long run (at least if treatment would have continued beyond 24 months for olaparib + bevacizumab).

Table 34. Parametric fit according to Akaike and Bayesian information criteria (TTD in the high-risk group, olaparib + bevacizumab arm)

Model	AIC	BIC
Exponential	481.76	483.91
Weibull	442.87	447.16
Loglogistic	436.57	440.86
Lognormal	428.41	432.70
Gompertz	461.43	465.72
Gamma	443.71	448.00

Table 35. Parametric fit according to Akaike and Bayesian information criteria (TTD in the low-risk group, olaparib + bevacizumab arm)

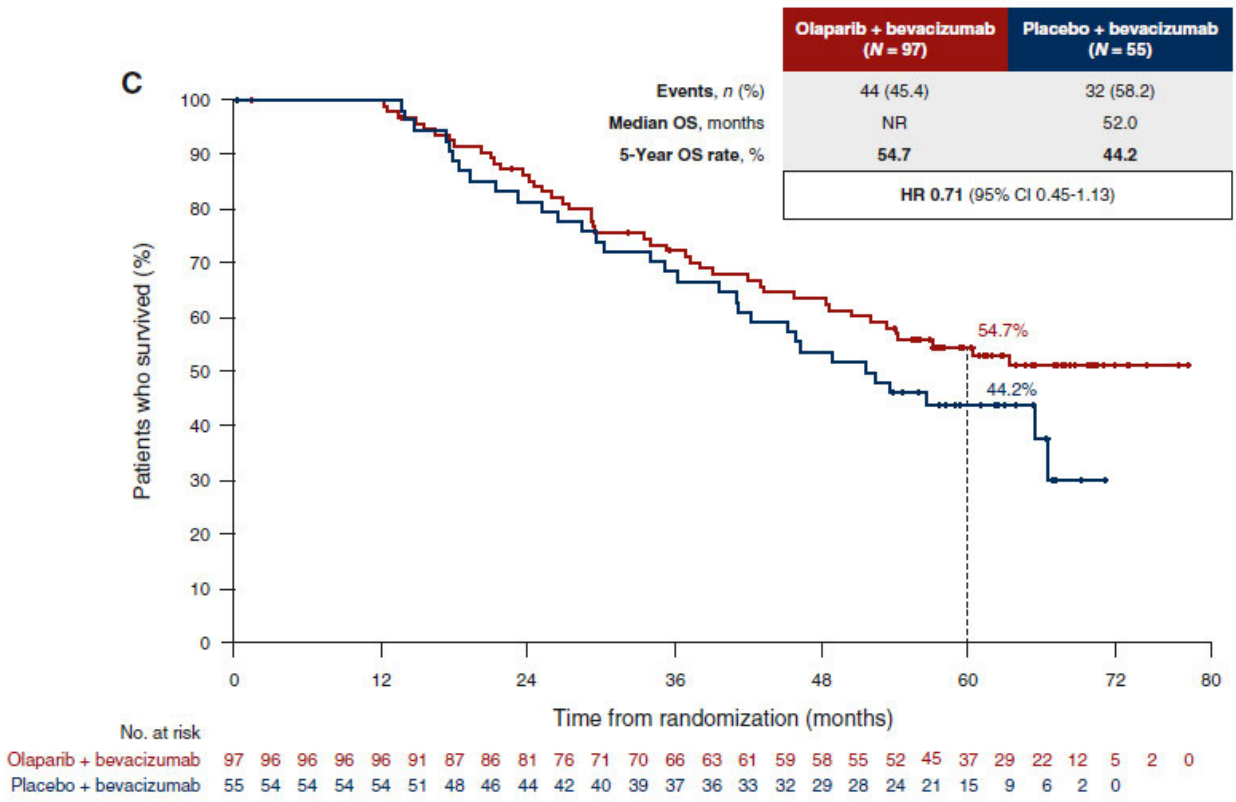
Model	AIC	BIC
Exponential	245.93	248.08
Weibull	228.56	232.85
Loglogistic	229.21	233.50
Lognormal	229.81	234.10
Gompertz	257.56	261.85
Gamma	229.14	233.43

8.2.7 Overall survival

Overall survival is not used in the model as an efficacy measure, only to estimate the correct resource use over time (i.e. the proportion of patients still alive using resources). For this reason, no subgroup analyses of OS have been performed specifically for the high-risk and low-risk HRD+ BRCAwt subgroups.

OS in the HRD positive BRCAwt subgroup in shown in Figure 31.

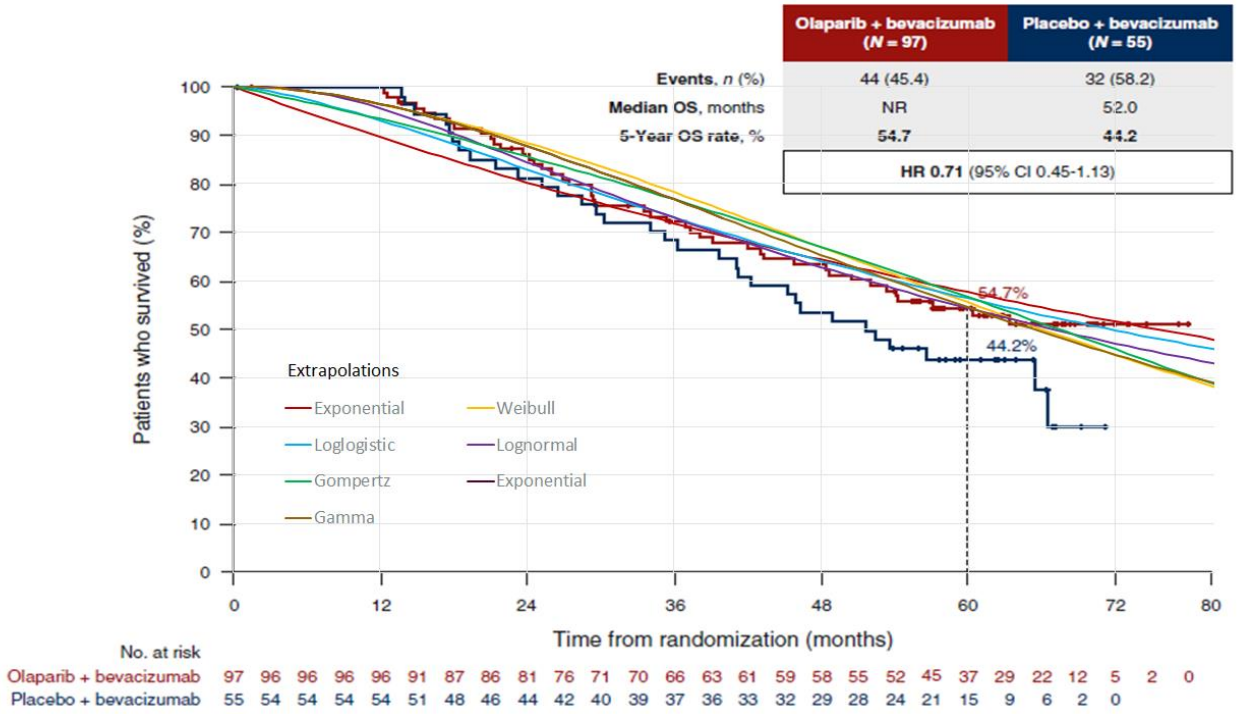
Figure 31. Kaplan Meier overall survival curve per arm for the HRD positive BRCAwt subgroup



Source: Ray-Coquard (2023)

OS extrapolations were performed with standard parametric distributions Figure 32). The models are plotted with the KM data to illustrate how well they capture the trends. Most distributions have relatively good visual fit, with some having better fit for the first 24 months and other better fit between 24 and 60 months.

Figure 32. Kaplan-Meier plot of OS in HRD+ BRCAwt with extrapolations



The lognormal distribution was chosen based on best statistical fit according to AIC and BIC (Table 36). Alternative distributions are tested in sensitivity scenarios. A corresponding figure with longer time axis is included in Appendix G (section G2) as Figure G28. In terms of clinical plausibility of the extrapolations, the risk of death will tend to decrease over the long run [DiSilvestro 2022]. That would also suggest that a lognormal distribution would be suitable for extrapolating the OS data in the long run.

Table 36. Parametric fit according to Akaike and Bayesian information criteria (OS in HRD+ BRCAwt (olaparib + bevacizumab arm)

Model	AIC	BIC
Exponential	814.83	825.18
Weibull	819.48	829.83
Loglogistic	806.43	816.78
Lognormal	805.29	815.64
Gompertz	817.55	827.90
Gamma	814.70	825.05

8.2.8 Subsequent treatments

A summary of subsequent treatments in the model in included in Table 37.

Table 37. Assumptions regarding subsequent treatments in the model

Patient population	Subsequent therapy by treatment group
HRD+ non-BRCAm high-risk group, who are candidates for bevacizumab	• Olaparib + bevacizumab group: Chemotherapy only • Niraparib group: Chemotherapy with addition of bevacizumab maintenance ➢ Treatment duration chemotherapy: 6 three-week cycles corresponding to 3.5 months ➢ Treatment duration bevacizumab: 11.7 months on average based on the time to treatment discontinuation in the OCEANS study (Roche 2012)
HRD+ non-BRCAm low-risk group, who are not candidates for bevacizumab	• Olaparib + bevacizumab group: Chemotherapy only • Niraparib group: Chemotherapy and in addition bevacizumab for a proportion of the patients (12.5%), as it is assumed that some relapsed patients could become eligible for bevazizumab ➢ Treatment duration chemotherapy: 6 three-week cycles corresponding to 3.5 months ➢ Treatment duration bevacizumab: 11.7 months on average based on the time to treatment discontinuation in the OCEANS study (Roche 2012)

For time to first subsequent chemotherapy, data was based on the SOLO-1 trial, as these data were more mature and included more information on subsequent chemotherapies. In addition, the comparator arm in PAOLA-1 is bevacizumab rather than watch and wait, but SOLO-1 are providing a watch and wait arm. For consistency, the same approach is used in the HRD+ non-BRCA patients who are candidates for bevacizumab. However, the time to first subsequent therapy is longer in SOLO-1 than in PAOLA-1, as there are differences in the patients populations with , on average, slightly more severe disease in PAOLA-1 than in SOLO-1. In practice, the time to first subsequent chemotherapy is transformed to a proportion on treatment in each monthly cycle in the model. Those proportions are renormalized so that all subsequent therapy is assumed to occur within 10 years, as will be described in more detail below. This is completely reasonable, as late relapses beyond 5 years are increasingly unlikely. In that respect, extrapolations with "thick tails", such as lognormal and loglogistic, are not realistic for the long run. Due to the renormalization, it does not matter that much if data from SOLO-1 or PAOLA-1 are used for subsequent chemotherapy. The cost results will be similar.

A summary of median and mean time to subsequent therapy in PAOLA-1 and SOLO-1 is shown in Table 38.

Table 38. Summary of median and mean time to first subsequent therapy.

Endpoint	Median (months)	Mean (months) (RMST)	Extrapolated mean (months)
Time to first subsequent therapy SOLO-1			
• Olaparib	52	38	104[1]
• Placebo	15	23	32[1]
Time to first subsequent therapy PAOLA-1			
• Olaparib + bevacizumab	25	26	44[1]
• Bevacizumab	18	20	26[1]

RMST: Restricted mean survival time (to the end of follow up) [1] Loglogistic; [2] Lognormal; [3] Weibull (extrapolation)

Subsequent chemotherapy

The cost of subsequent chemotherapies are calculated based on the total cost of each therapy (medication acquisition and administration), the share of patients receiving each therapy (informed by the SOLO-1 appraisal for olaparib), and an average number of treatment lines.

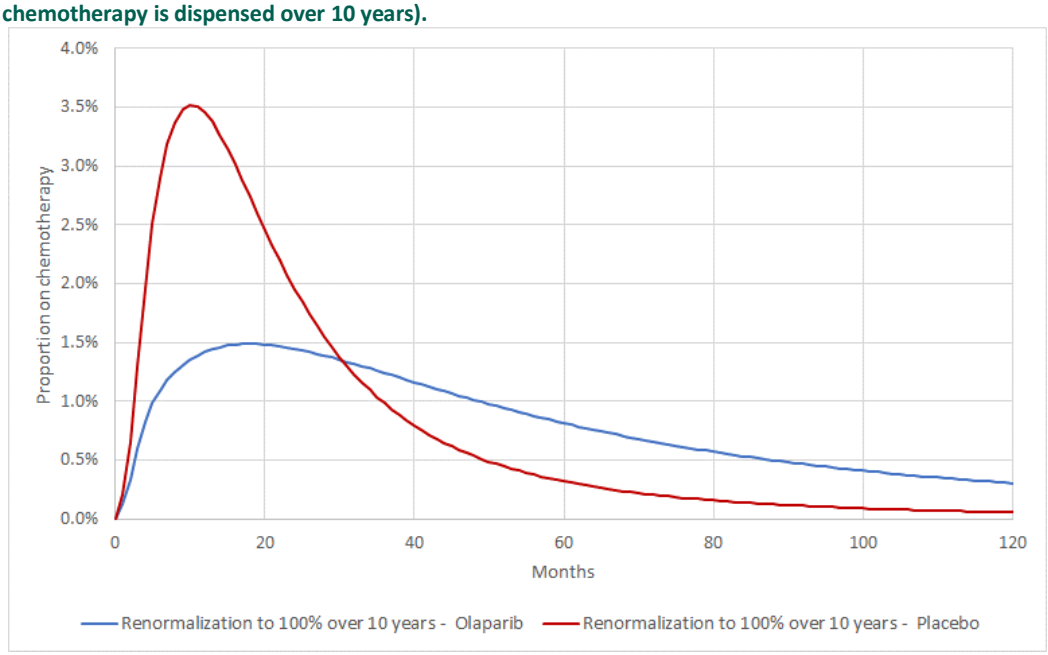
The start time for subsequent chemotherapy treatments was based on time to first subsequent therapy. However, the time to subsequent therapy curves are not used directly in the budget impact model, as the curves need to be transformed into the proportion of patients on subsequent therapy during each time period. This can be calculated based on the proportion of patients new on chemotherapy each month, in combination with the treatment duration, which is assumed to be 6 three-week cycles corresponding to 3.5 months (15 weeks) of treatment. For example, if 1% of the population is initiated on chemotherapy each month, then 3.5 * 1% = 3.5% of patients will be on treatment with chemotherapy each month in the steady state. In reality, the proportion initiated on chemotherapy varies over time. The percentage on subsequent treatment in a patient cohort will increase over time to a peak as more and more patients get further lines of therapy and then decline over time (Figure 33).

It is assumed that all chemotherapy is dispensed within 10 years, which we refer to as renormalization. According to the SOLO-1 TFST curve, 77.4 % in the olaparib group and 96.5% in the control group have had subsequent therapy within 10 years. In PAOLA-1, the corresponding probabilities are for olaparib + bevacizumab 94% and 98% for bevacizumab alone. Renormalization means that the probability in each month for being on treatment in the unadjusted data are divided by the cumulative probability of getting treatment within 10 years. Hence, the probability of getting subsequent therapy within 10 years adds up to 100%, which is clinically more plausible than subsequent therapy beyond 10 years. Note that for the control arm in SOLO-1 and for both arms in PAOLA-1, the renormalized data will differ little from the original data, as the probability of getting subsequent therapy is at least 94% for all of these groups.

As the time to progression is long for both olaparib + bevacizumab in PAOLA-1 and for olaparib monotherapy in SOLO-1, it is plausible to assume that a proportion of the patients will never have any relapse at all. In the first line, the treatment has curative intent, and a majority of the patients in PAOLA-1 and SOLO-1 had no residual disease after surgery (Moore 2018, Ray-Coquard 2019). Therefore, it is assumed that patients undergo on average 3 lines of subsequent chemotherapy after olaparib+bev / olaparib and 4 after bevacizumab or watch and wait within this time frame. In Study 19, a trial investigating olaparib as 2nd line treatment and beyond, on average 4 subsequent lines of chemotherapy were used within a time frame of 6.5 years of median follow up (Friedlander 2018).

Overall, at the time of the data cut-off for the PFS analysis in SOLO-1, the proportion of patients in the placebo arm that had started a first subsequent therapy was 72% compared with 35% the olaparib arm, i.e. twice as much for watch and wait. A large part of this difference is driven by PARP inhibitors as first subsequent therapy in the placebo arm, but chemotherapy was also used as subsequent therapy at some point by 58% in the placebo arm vs. 36% in the olaparib arm (AZ data on file 2018). On the other hand, over the whole follow-up time in Study 19, the average number of chemotherapy lines was very similar in both arms, 4.1 in the olaparib arm vs 4.2 in the placebo arm (Friedlander 2018). This means that olaparib is adding a treatment line rather than replacing chemotherapy in the second-line setting and beyond. In the first-line setting, however, there is a possibility a proportion of the patients with no residual disease after surgery will not relapse in a long time, which could diminish the use of subsequent chemotherapy, in particular in the olaparib + bev arm in PAOLA-1 and the olaparib arm of SOLO-1, compared with Study 19 (2nd line treatment and beyond). Therefore, three subsequent lines of chemotherapy seems like a reasonable assumption in this setting for olaparib + bev and olaparib, while 4 would be a plausible assumption for bevacizumab or watch and wait. The number of subsequent lines of chemotherapy is varied in a sensitivity scenario.

Figure 33. Proportion of patients on chemotherapy as subsequent therapy over time (estimated so that 100% of the chemotherapy is dispensed over 10 years).



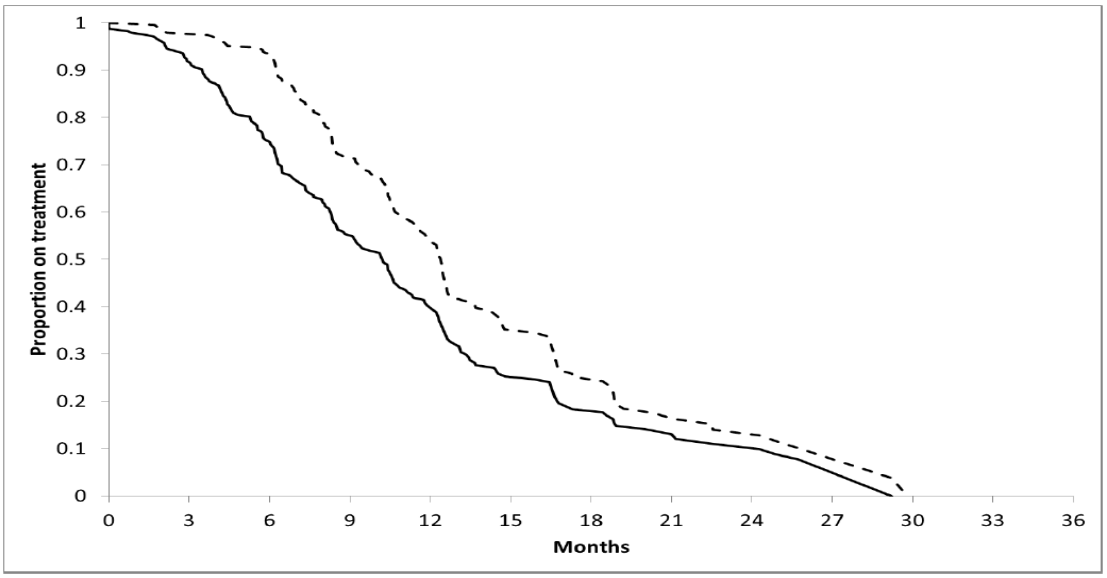
Subsequent bevacizumab

Subsequent bevacizumab is limited as it is used in the treatment arm and also for one of the comparisons in the cost analysis. Subsequent bevacizumab was used for the niraparib arm. SOLO-1 is used as data source for subsequent bevacizumab, as PAOLA-1 did not include an olaparib monotherapy arm or a watch and wait arm. It is assumed that a proportion of these patients would quality for bevacizumab use in later lines. As for subsequent chemotherapy, the start time for subsequent bevacizumab treatments was based on time to first subsequent therapy.

However, the time to subsequent therapy curves are not used directly in the budget impact model, as the curves need to be transformed into the proportion of patients on subsequent therapy during each time period. This can be calculated based on the proportion of patients new on chemotherapy each month, in combination with the treatment duration, which for bevacizumab is assumed to be 11.7 months on average based on the time to treatment discontinuation in the OCEANS study (Roche 2012) (Figure 34). OCEANS was a randomized, double-blind, phase III trial, comparing the efficacy and safety of chemotherapy (gemcitabine and carboplatin) plus bevacizumab (bevacizumab arm) and gemcitabine and carboplatin plus placebo (placebo arm) in patients with platinum-sensitive relapsed ovarian cancer (Aghajanian 2012).

Apart from the longer mean treatment duration, the calculation is performed in the same way as for chemotherapy. For example, if 1% of the population is initiated on chemotherapy each month, then 11.7 * 1% = 11.7% of patients will be on treatment with bevacizumab each month in the steady state. In reality, the proportion initiated on chemotherapy and bevacizumab varies over time. The percentage on subsequent treatment in a patient cohort will increase over time to a peak as more and more patients get further lines of therapy and then decline over time. It is assumed that all chemotherapy and bevacizumab is dispensed within 10 years after diagnosis.

Figure 34. Proportion of patients in OCEANS remaining on bevacizumab (solid line) compared to progression (dotted line)



Source: Roche (2012).

In SOLO-1, 9 patients in the olaparib arm (8.8% of patients who progressed in olaparib arm [9/102]) and 12 patients in watch and wait arm (12.5% of patients receiving who progressed in watch and wait arm [12/96]) received bevacizumab in addition to chemotherapy in the relapsed disease setting (second and further lines). These are also the proportions of subsequent bevacizumab used in the base case. The proportion of patients receiving bevacizumab in the relapsed disease setting in current Danish clinical practice is probably higher than that. Hence, the proportion of patients receiving subsequent bevacizumab therapy sourced from SOLO1 may be a conservative assumption. We used SOLO1 as the base case for the proportion of patients receiving subsequent therapy with bevacizumab but tested higher proportions of second line bevacizumab in sensitivity scenarios. It is notable that even though PAOLA-1 included bevacizumab as first line treatment in both arms, 48 patients in the olaparib + bevacizumab arm (8.9%) and 33 patients in watch and wait arm (12.3%) received antiangiogenic therapy, presumably mostly with bevacizumab, in addition to chemotherapy in the relapsed disease setting (second and further lines).

A summary of the percentage with subsequent therapy, the treatment mix, the time to subsequent therapy and the treatment duration is presented in Table 39.

Table 39. Summary of the subsequent therapy.

	Olaparib + bevacizumab	Niraparib	Source
Percentage with subsequent therapy in the base case	Chemotherapy 77.4%	Chemotherapy 77.4% Bevacizumab 12.5%	Chemo: SOLO1 TFST with loglogistic extrapolation Bev: SOLO1 PARPi arm
Percentage with subsequent therapy in sensitivity scenario with chemotherapy based on PAOLA-1 (bevacizumab still based on SOLO1)	Chemotherapy 94%	Chemotherapy 94% Bevacizumab 12.5%	Chemo: PAOLA-1 TFST with loglogistic extrapolation Bev: SOLO1 PARPi arm
Treatment mix in subsequent therapy (incl. doses and frequencies)			
Platinum chemotherapy	• Carboplatin AUC5, 6 cycles, 50% • Cisplatin 75 mg/m², 6 cycles, 50%	• Carboplatin AUC5, 6 cycles, 50% • Cisplatin 75 mg/m², 6 cycles, 50% • Bevacizumab 15 mg/m² add-on + maintemance for 12.5%	DGCG guidelines, frequencies based on assumption (or SOLO1 PARPi arm data for bevacizumab)
Non-platinum chemotherapy	• Gemcitabin 1000 mg/m², 6 cycles, 10% • Doxorubicin (pegylated liposomal) 30 mg/m², 6 cycles, 50% • Paclitaxel 175 mg/m², 6 cycles, 30% • Topotecan 1.5 mg/m²	• Gemcitabin 1000 mg/m², 6 cycles, 10% • Doxorubicin (pegylated liposomal) 30 mg/m², 6 cycles, 50% • Paclitaxel 175 mg/m², 6 cycles, 30% • Topotecan 1.5 mg/m2, 6 cycles,10%	DGCG guidelines, frequencies based on expert input
Time to subsequent therapy	Median time 54 months	Median time 54 months	
Treatment duration, subsequent chemotherapy	3.5 months chemotherapy	3.5 months chemotherapy	
Treatment duration, subsequent bevacizumab (in combination with chemo and as maintenance therapy	Not used	11.7 months bevacizumab	OCEANS study (Roche 2012)

8.3 Documentation of health-related quality of life (HRQoL)

Health-related quality of life is not covered as the health economic analysis is based on a cost-minimization approach.

8.4 Resource use and costs

The cost analysis includes:

- Drug acquisition costs
- Administration costs

- Monitoring costs
- Adverse event costs
- Patient and transport costs (for the cost per patient analysis)
- Cost of subsequent therapies

8.5 Drug acquisition costs

Drug acquisition costs were calculated based on available formulations; pack sizes, unit costs and price per mg for each (combination of) treatment included in the model. The dosing information was sourced from the European Medicines Agency (EMA) label for each treatment and the drug acquisition costs were sourced from medicinpriser.dk (AIP).

Table 40 summarizes the treatment dosing, administration frequency and drug acquisition costs for the treatments included in the base case. Bevacizumab has a weight-based dosing regimen. The average weight from PAOLA-1, 63.3 kg,1 is applied in the model and gives 712 mg bevacizumab per dose based on the assumption of 50% on 7.5 mg/kg and 50% on 15 mg per kg (7.5 mg/kg in ICON7 and 15 mg/kg in GOG-0218). For subsequent bevacizumab, 15 mg/kg is used based on the OCEANS trial (Aghajanian 2012).

Table 40. Treatment dosing, administration and drug acquisition costs for olaparib, niraparib and bevacizumab

Maintenance therapy	Available formulations	Pack size	Mg/ Daily dose	Doses/ month	Cost/ Pack (AIP) (DKK)	Cost/ Dose (DKK)	Cost/ month
Olaparib	150 mg	56	600	30.44	15 688.70	1 120.62	34 112
Niraparib	100 mg	84	221.79*	30.44	57 474.55	1517.57	46 195
Bevacizumab	25 mg/ml	4 ml	712	36	269.70	2 157.80*	3 129**
	25 mg/ml	16 ml	712	1.45	1 078.90		

*Assuming 21.8% >77 kg starting on 300 mg and the rest on 200 mg per day (EPAR Zejula, EMA 2000 (Table 4, p.18 & p.69); **Including wastage

Source: www.medicinpriser.dk and www.amgros.dk. Both accessed 22.09.2023

For bevacizumab the cheapest combination of the 4 ml and the 16 ml packs is used in the analysis, based on tender prices for bevacizumab (Aybintio). This generates a cost per 3-week cycle of DKK 2 158, which equals a cost per month of DKK 3 129.

Treatment dosing, administration frequency and drug acquisition costs for subsequent chemotherapy are summarized in Table 41.

[1] No information on average body weight is given in the ICON7 (Perren 2011) and GOG-0218 (Burger 2011) clinical trial publications.

Table 41. Treatment dosing, administration and drug acquisition costs for chemotherapy

Maintenance therapy	Formulation (mg/ml)	Vial size (ml)	Cost/ pack (DKK)	Average cost / mg (DKK)	Dose (mg)	Cost/ cycle (DKK)	Doses / month***	Cost/ month
Doxorubicin (Caelyx)	2	10	3700	185	30/m²	240*	1.09	12 099
Carboplatin	10	45	226	0.50	AUC 4 (472)	11 100**	1.45	328
Paclitaxel	6	50	201.50	0.67	175/m²	201.50*	1.45	292
Gemcitabin	10	200	385	0.19	1000/m²	693*	2.9	1 005
Topotecan	1	4	290	72.5	1.5/m²	870*	4.35	1 262
Cisplatin	1	100	200	2.00	75/m²	300*	1.45	435

Based on a body surface are of 1.69m²; **Based on area under the curve concentration AUC 4 mg/mL•min, Calvert formula: Dose (mg) = target AUC x (GFR + 25);*Average number of days per months divided by cycle length of 3 or 4 weeks (30.44/21 = 1.45; 30.44/28 = 1.09).*

8.6 Drug administration costs

The administration frequency was based on the EMA licensed posology information for each treatment. For olaparib, which is an oral treatment, no cost of administration was applied. For bevacizumab and chemotherapy, it is assumed that the tariff for DRG 13MA98, i.e. MDC13 1-dagsgruppe, pat. mindst 7 år, represents the cost of chemotherapy administration. MDC 13 applies to Diseases and Disorders of the Female Reproductive System in ICD-10 and dagsgruppe represent ambulant care, as chemotherapy is administered in the outpatient setting.. The administration costs are outlined in Table 42.

Table 42. Drug administration unit costs

	Unit costs (DKK)	Code /description	Source
Chemotherapy administration	DKK 1 220	DRG 13MA98 MDC13 1-dagsgruppe, pat. mindst	DRG takster 2023*

* DRG Takster 2023 (https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2023)

The total administration cost per month for bevacizumab and chemotherapy is summarized in Table 43.

Table 43. Monthly drug administration costs per treatment

	Unit costs (DKK)	Administrations / month	Administration cost/ month (DKK)
Bevacizumab	1 220	1.45	1 769
Carboplatin	1 220	1.45	1 769
Cisplatin	1 220	1.45	1 769
Paclitaxel	1 220	1.45	1 769

	Unit costs (DKK)	Administrations / month	Administration cost/ month (DKK)
Gemcitabin	1 220	2.9	3 538
Doxorubicin (Caelyx)	1 220	1.09	1 330
Topotecan	1 220	4.35	5 307

8.7 Drug monitoring costs

The monitoring unit costs are found in Table 44. The cost of blood tests is not included, as one blood test is assumed to be included in doctor visits.

Table 44. Unit costs for monitoring

Cost item	Cost* (DKK)	Code	Code description	Source
Doctor or nurse visit	1 220	13MA98	MDC13 1-dagsgruppe, pat. mindst 7 år	DRG takster 2023*
CT scan	2 440	30PR06	CT-scanning, kompliceret	DRG takster 2023*
Vaginal ultrasound	1 949	30PR10	UL-scanning, kompliceret	DRG takster 2023*

*DRG Takster 2023 (https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2023)

Since there is an absence of drug monitoring information and frequency data in the respective EMA summary of product characteristics for the included treatments, the estimates are based on AstraZeneca's assumptions from the medical department which in turned are based on discussion with clinicians. Table 45 shows the resource use in terms of the average number of visits and diagnostic procedures per month for olaparib + bevacizumab, niraparib, chemotherapy and off-treatment routine follow-up. For example, a health care contact occurring once every third month corresponds to a quantity of 1/3 = 0.33 per month.

Table 45. Monitoring frequency and total monthly costs for olaparib, niraparib, and chemotherapy

Cost unit	Olaparib+ Bevacizumab	Niraparib	Chemotherapy	Off-treatment routine follow-up
Doctor visit	1	1	1	0.33
Nurse visit	1.45	1	0.78	0.33
CT scan	0.33	0.33	0.33	0.33
Vaginal ultrasound	0.2	0.2	0.2	0.2
Total monthly cost per patient	**DKK 4 572**	**DKK 3 953**	**DKK 3 643**	**DKK 2 124**

8.8 Adverse event costs

AE costs were included to account for the potential cost of experiencing AEs whilst on treatment. AE costs are applied to patients receiving treatment each year. These costs are calculated by multiplying the rate AEs by the unit cost of treating the AE. Since AEs usually are more frequent in the beginning of a treatment the AE costs are applied at treatment initiation.

The costs for AEs are likely to differ depending on grade. The model uses the probability of AEs of grade 3 or higher with a frequency of at least 2% in one of the arms in PAOLA-1. For niraparib monotherapy and watch and wait the AEs reported in the PRIMA publication (González-Martín 2019).

The resource utilization related to AEs are presented in Table 46. The cost items were sourced from the Danish DRG/DAGS codes recommended in Medicinrådet guidelines. Overall, the assumption is that the medicines associated with AE treatment are not costly and therefore excluded.

Table 46. Cost items related to AEs

AE associated to cost item	Cost item	Cost* (DKK)	Code	Code description	Source
Several AEs**	Doctor or nurse visit	1 220	13MA98	MDC13 1-dagsgruppe, pat. mindst 7 år	DRG takster 2023*
Nausea / vomiting / diarrhoea	Hospitalization	26 929	DRG06MA14	Andre sygdomme i fordøjelsesorganerne, pat. mindst 18 år	DRG takster 2023*
Anemia	Blood transfusion	3 969	16PR02	Transfusion af blod, øvrig	DRG takster 2023*
Hypertension	Hospitalization	17 304	DRG05MA11	Hypertension	DRG takster 2023*

*DRG Takster 2023 (https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2023); **Fatigue or asthenia, lymphopenia, neutropenia, thrombocytopenia.

The cost items in Table 46 are combined for each AE, the resulting unit cost with the associated justification are presented in Table 47.

Table 47. Unit costs for AEs for olaparib, bevacizumab, and watch and wait

Treatment	Unit cost (DKK)	Justification
Diarrhea	1 392.58	70% of patients have one additional doctor visit, 2% of patients are hospitalized
Anemia	3 419.20	80% of these patients get blood transfusions. The 20% without need for transfusion have 1 extra nurse visit in the outpatient clinic
Hypertension	8 652.00	50% of patients get hospitalized
Neutropenia	1 220.00	One additional doctor visit
Fatigue or Asthenia	1 220.00	One additional doctor visit
Thrombocytopenia	1 220.00	One additional doctor visit
Lymphopenia	1 220.00	One additional doctor visit

AEs were incorporated into the economic model through applying the proportion of patients expected to experience an AE per year for each treatment as reported in PAOLA-1. The model includes grade 3 or above adverse events considered to have a large impact on patient HRQoL and/or are associated with significant costs. Grade ≥3 AEs taken into consideration are listed in Table 48. The AE incidence rates for niraparib monotherapy and watch and wait in Table 18 were sourced from PRIMA (González-Martín et al. 2019; Table 2 & Table S9). The incidence rates were derived from treatment-related AEs of grade ≥3 according to the Common Terminology Criteria for Adverse Events (CTCAE).

Table 48. Incidence rates and costs for grade 3 or 4 adverse events for olaparib + bevacizumab, and niraparib.

AEs/Treatment	Olaparib + bevacizumab (N = 535)	Niraparib (n = 484)
Anemia	17.4%	31.0%
Diarrhea	2.2%	0.6%
Hypertension	18.7%	5.6%
Neutropenia	6.4%	12.8%
Fatigue or Asthenia	5.2%	1.9%
Thrombocytopenia	1.7%	28.7%
Lymphopenia	5.9%	2.5%
Total cost / patient	**DKK 2 487**	**DKK 2 121**

8.9 Patient time and patient transport

Patient costs were estimated based on Medicinrådet guidelines. The patient costs are calculated based on drug monitoring visits, thus AE related visits are excluded. The average time for each health care visit includes the effective time in the health care unit (Table 49), and the associated waiting time and transport time is included as patient transport time. The estimated time for CT scan is the same as the values accepted by Amgros in the evaluation of alectinib.

Table 49. Patient time associated with drug monitoring visits

Cost unit	Patient time (minutes)
Consultation (office visit)	20
CT scan	30
Vaginal ultrasound	30

Table 50 shows the costs for patient time and transport. This includes the average number of visits to the health care clinic per month for olaparib, bevacizumab, watch and wait, and associated patient time and patient costs. The estimate for total time cost per month, off treatment, is the same as for watch and wait.The doctor visit and vaginal ultrasound

is assumed to occur in the same visit, when applicable. CT-scans are always assumed to require separate visits as these diagnostic investigations are performed in separate facilities.

The patient time for visits is multiplied with the monetary value for patient time according to Medicinrådet guidelines, DKK 203 per hour. The transport cost to and from visits to the health care clinic is set to DKK 140, also based on DMC guidelines. The total patient costs are the sum of the patient time costs and the transport costs.

Table 50. Estimated patient costs for time and transport for olaparib, niraparib, and chemotherapy

Cost unit	Olaparib+ Bevacizumab	Niraparib	Chemotherapy
Number of visits per month	2.78	2.33	2.33
Patient time, visits (hours)	1.08	0.93	0.86
Patient time cost (DKK)	220	189	174
Transport time (hours)	5.57	4.67	4.22
Transport cost (DKK)	779	653	591
Total patient cost per month, patient time + transport (DKK)	**999**	**843**	**765**

8.10 HRD testing costs

HRD tests could for most patients be expected to be performed prior to treatment with olaparib and are therefore not included in the current cost analyses. HRD testing is expected to have a cost similar to BRCA testing. The cost for an HRD test is included in the sensitivity analysis and is estimated to be between 6000 – 8000 DKK per test in Denmark. In the sensitivity analysis, 7000 DKK is used.

8.11 Results

8.11.1 Base case overview

The basic assumptions from the base case analysis are summarized in Table 51.

Table 51. Basic assumptions for the base case analysis

Variable	Assumption	Comment
Type of model	Cost-minimization model	Due to lack of OS data from PRIMA and differences in patient populations between PAOLA-1 and PRIMA, it is not possible to perform an indirect treatment comparison that would be needed for a full health economic evaluation (costs and QALYs). Instead, a cost-minimization approach is chosen as a fallback option, although it is very conservative given that

Variable	Assumption	Comment
		olaparib + bevacizumab has shown an OS benefit vs. active comparator (bevacizumab alone) in PAOLA-1, while niraparib is compared with watch and wait in PRIMA
Time horizon	10 years	Time horizon long enough to capture the major costs. Longer time horizon would go far beyond patent expiry for olaparib and would not be very meaningful. 5-year and 25-year time horizons are tested in scenario analysis.
Discount rate	3.5%	Based on latest recommendations from the Danish Finance ministry. 2.5% and 4.5% tested in sensitivity analysis.
Included costs	• Pharmaceutical costs • Administration costs • Monitoring costs • Adverse event costs • Patient and transport costs • Subsequent therapies	Standard cost elements
Comparator	• Niraparib	Recommended in Danish guidelines in this setting (DGCG 2021)
Dose	• Lynparza (olaparib): 600 mg (2 x 300 mg) per day as in SmPC • Bevacizumab: Mix of 15 mg/kg and 7.5 mg/kg bevacizumab based on Danish clinical practice (15 mg/kg in SmPC but 7.5 mg/kg common based on ICON7. • Base case 50% 15 mg/kg and 50% 7.5 mg/kg • Zejula (niraparib): 200 mg (2 x 100 mg) for 78.2% of patients and 300 mg (3 x 100 mg) for 21.8% of patients based on Zejula EPAR (1L OC PRIMA), EMA 2020 (Table 4, p.18 & p.69)	The dosing in the SmPCs is bevacizumab 15 mg/kg for both olaparib + bevacizumab and bevacizumab alone. However, the 7.5 mg/kg dosing is preferred by many clinicians based on the results of the ICON7 study. It is not expected that the combination therapy would lead to changed dosing of bevacizumab in the 1st line setting. According to the SmPC for niraparib, the recommended starting dose of Zejula is 200 mg (two 100-mg capsules), taken once daily. However, for those patients who weigh ≥ 77 kg and have baseline platelet count ≥ 150,000/µL, the recommended starting dose of Zejula is 300 mg (three 100-mg capsules), taken once daily. In PRIMA, 21.8% of patients fulfilled the criteria for the 300 mg starting dose (EPAR Zejula, EMA 2020 [Table 4, p.18 & p.69]).
Treatment line	1st line	As per indication and protocol
Subsequent therapies included	Yes	As the choice of initial 1st line therapy affects subsequent therapies.
Time on treatment for olaparib + bevacizumab and comparators	Based on extrapolated KM data from PAOLA-1 for time to treatment discontinuation (TTD) to make the data comparable between olaparib + bevacizumab and niraparib.	Need to extrapolate as KM data does not covers the relevant time horizon for niraparib (treatment to progression in the Zejula SmPC; 3-year limitation recommended in DK guidelines)

Variable	Assumption	Comment
	TTD extrapolations were chosen based on best statistical fit according to AIC and BIC TTD HRD+ BRCAwt high-risk: Lognormal extrapolation used as base case. Mean duration olaparib + bevacizumab 14.8 months (treatment limited to 2 years). Mean duration niraparib estimated to 18.1 months (treatment limited to 3 years). TTD HRD+ BRCAwt high-risk: Weibull extrapolation used as base case. Mean duration olaparib + bevacizumab 20.3 months (treatment limited to 2 years). Mean duration niraparib estimated to 28.7 months (treatment limited to 3 years).	
Overall survival	Based on parametric extrapolations based on statistical fit and clinical plausibility. Lognormal extrapolation used as base case.	Only used for estimation of monitoring costs and patient time costs over time. Treatment and administration costs are covered by time-to-treatment discontinuation data from PAOLA-1.
Subsequent PARP inhibitors	Not included	Not reused after olaparib in the first line and not recommended for non-BRCAm patients
Subsequent chemotherapy	Included	Based on time to first subsequent therapy (TFST). In the base case TFST from SOLO-1.
Subsequent bevacizumab	Included	Included for the comparison with niraparib monotherapy (BRCAm population). Mean treatment duration 11.7 months based on the OCEANS trial.
Inclusion of wastage	Yes, for bevacizumab and chemotherapy	Vial sharing is possible as an option for bevacizumab and chemotherapy
Cost for HRD testing included	No	Genetic testing is not only driven by treatment, but is of wider interest for physicians and patients. Hence, thorough genetic testing should be performed at diagnosis and the cost for this should not be allocated to a specific treatment

8.12 Base case results - Average cost per patient: Olaparib + bevacizumab vs. niraparib in the high-risk HRD+ BRCAwt subpopulation

The results of the cost analysis for patients with HRD positive BRCAwt high-risk platinum-sensitive ovarian cancer show the average costs per patient over 10 years, including subsequent therapy (Table 52, Figure 35). The drug acquisition costs constitute the major part of the total costs for all treatments. Costs for drug administration and patient monitoring and follow-up are the second or third largest costs, while patient time and travel costs and in particular costs for adverse events are smaller. For adverse events, however, only costs for first-line treatments have been included.

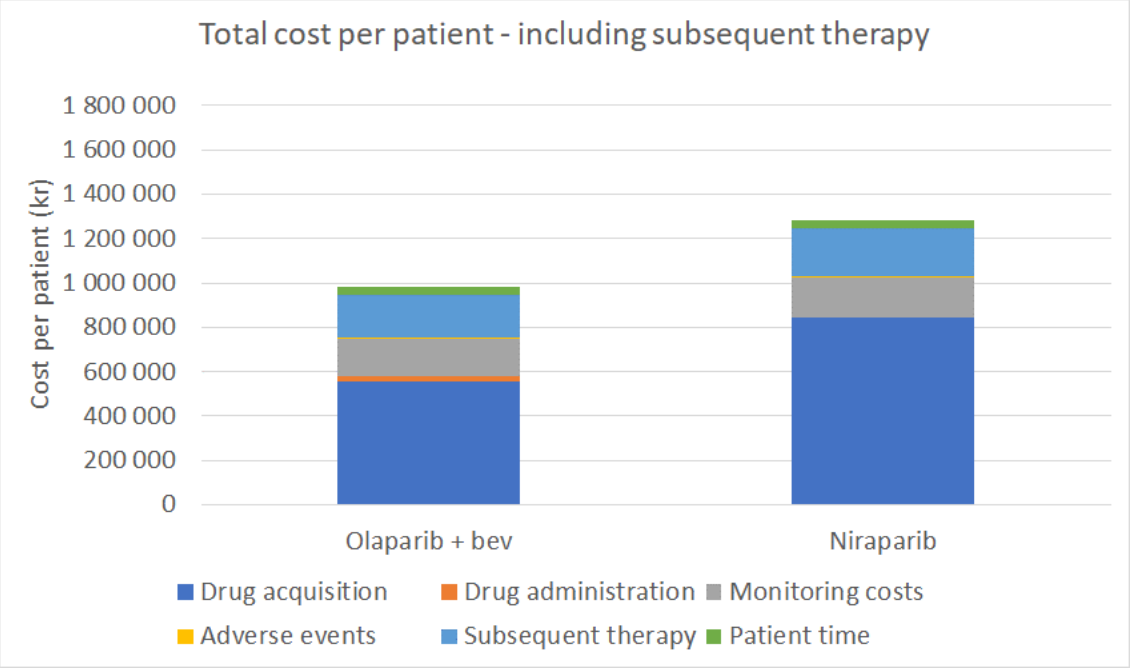
The total costs per patient over ten years show that treatment with olaparib + bevacizumab is DKK 299 373 less expensive than niraparib monotherapy. This is primarily due to a higher acquisition cost for niraparib (Table 52).

Table 52. Average costs per patient for olaparib + bevacizumab vs niraparib, year 1, year 2, years 3-10, and total over 10 years, base case (DKK)

Treatment	Cost item	Year 1 (2024)	Year 2 (2025)*	Year 3 to 10 * (2026 - 2033)	Total - Year 1 to 10* (2024 - 2033)
Olaparib + bevacizumab	Drug acquisition	361 060	185 752	10 887	557 699
	Drug administration	17 153	3 662	0	20 814
	Monitoring costs	48 924	35 180	89 459	191 981
	Adverse events	2 487	0	0	2 487
	Subsequent therapy	22 371	36 452	131 821	190 645
	Patient time	10 630	10 916	15 898	37 443
	Total	**462 625**	**271 963**	**247 064**	**981 652**
Niraparib	Drug acquisition	447 875	242 780	155 543	846 198
	Drug administration	0	0	0	0
	Monitoring costs	42 925	31 928	105 556	198 827
	Adverse events	2 121	0	0	2 121
	Subsequent therapy	24 999	41 427	150 819	217 245
	Patient time	8 335	6 498	20 221	35 053
	Total	**526 254**	**322 632**	**432 139**	**1 281 025**
Difference		***-63 629***	***-50 670***	***-185 075***	***-299 373***

* Discount rate of 3.5% used based on latest recommendation from the Danish Ministry of Finance (https://fm.dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021.pdf).

Figure 35. Average costs per patient for olaparib + bevacizumab vs olaparib monotherapy over 10 years, base case



8.13 One-way sensitivity analysis: Olaparib + bevacizumab vs. niraparib in the high-risk HRD+ BRCAwt subpopulation

A one-way sensitivity analysis was also performed for key variables in the model. The variables included in the one-way sensitivity analysis were the discount rate, drug acquisition costs, administration costs, monitoring costs, patient time and transport costs, and AE costs (Table 53). A positive % change means higher savings with olaparib + bevacizumab compared with niraparib.

Except for the discount rate, time frame, maximum treatment duration for niraparib, proportion of patients treated with subsequent bevacizumab (bev) in the niraparib arm and the TTD and OS extrapolation methods, all variables were varied with ±20%. The results were most sensitive to drug acquisition costs for olaparib and niraparib and the niraparib treatment duration, but relatively insensitive to other variables, with the exception of the proportion of patients treated with subsequent bev in the niraparib arm and TTD extrapolation method. It is notable that the method for OS extrapolation has almost no impact at all, as most of the costs occur within the first few years and the OS extrapolations are quite similar for the first 6 years or so.

Table 53. Sensitivity analysis: Difference in average costs per patient over 10 years (DKK)

Parameter	Variation	Total cost year 1 to 10		Olaparib + bev vs niraparib monotherapy	
		Olaparib + bevacizumab	Niraparib monotherapy	Difference	% Change
Base case	-	981 652	1 281 025	-299 373	-
Discount rate	2.5%	994 969	1 299 434	-304 465	1.7%
	4.5%	969 026	1 263 499	-294 473	-1.6%
Time frame	5 years	881 958	1 166 647	-284 689	-4.9%
	25 years	1 020 653	1 320 026	-299 373	0.0%
Treatment duration: Niraparib	Max 5 years	981 652	1 438 339	-456 687	52.5%
	Max 10 years	981 652	1 577 064	-595 411	98.9%
Proportion subsequent bev in niraparib arm	30%	981 652	1 291 728	-310 076	3.6%
	60%	981 652	1 310 076	-328 423	9.7%
TTD extrapolation	Loglogistic	972 502	1 300 264	-327 763	9.5%
	Weibull	982 826	1 250 039	-267 212	-10.7%
	Gamma	983 692	1 250 944	-267 252	-10.7%
OS extrapolation	Loglogistic	984 867	1 284 240	-299 373	0.0%
	Gamma	978 171	1 277 544	-299 373	0.0%
	Exponential	985 020	1 284 393	-299 373	0.0%
Drug acquisition cost: Olaparib	-20%	877 475	1 281 025	-403 551	34.8%
	+20%	1 085 830	1 281 025	-195 195	-34.8%
Drug acquisition cost: Bevacizumab	-20%	974 290	1 281 025	-306 735	2.5%
	+20%	989 014	1 281 025	-292 011	-2.5%
Drug acquisition cost: Niraparib	-20%	981 652	1 111 786	-130 133	-56.5%
	+20%	981 652	1 450 265	-468 612	56.5%
Monitoring cost	-20%	967 689	1 261 474	-293 786	-1.9%
	+20%	995 616	1 300 576	-304 960	1.9%
Administration cost	-20%	977 489	1 281 025	-303 536	1.4%
	+20%	985 815	1 281 025	-295 210	-1.4%
Patient time and transport cost	-20%	974 280	1 272 864	-298 584	-0.3%
	+20%	989 050	1 289 846	-300 796	0.5%
AE cost	-20%	981 155	1 280 601	-299 446	0.02%
	+20%	982 150	1 281 449	-299 300	-0.02%

The proportion of patients receiving subsequent bevacizumab therapy in the olaparib monotherapy arm was sourced from SOLO-1, but this may be a conservative assumption. The bevacizumab use in 2nd and further lines of therapy

could be expected to increase with more mature data. In this scenario analysis, 30% and 60% 2nd line bevacizumab use is tested for the olaparib monotherapy arm. It is assumed that there would be no retreatment with bevacizumab for patients treated with olaparib + bevacizumab in the first line. In the scenario with 60% subsequent bevacizumab use for olaparib monotherapy, the results show that the difference for olaparib + bevacizumab vs olaparib monotherapy is DKK - 328 423 over 10 years (Table 53), compared with a difference of DKK – 299 373 in the base case. Hence, a higher and presumably more realistic percentage of subsequent bevacizumab use in the olaparib arm leads to a higher difference in costs and making olaparib + bevacizumab more cost saving.

8.13.1 Scenario analysis: Excluding subsequent therapy

In this scenario treatments with olaparib + bevacizumab and niraparib monotherapy are included, and all costs related to subsequent therapy are excluded. Since subsequent PARP inhibitors are not recommended for patients who used these in the first line and chemotherapy will be used in clinical practice in both the arms, this scenario does not differ hugely from the base case. The difference for olaparib + bevacizumab vs niraparib monotherapy is DKK 270 234 over 10 years (Table 54), compared with a difference of DKK 299 373 in the base case, i.e. slightly smaller savings with olaparib + bevacizumab.

Table 54. Average costs per patient for olaparib + bevacizumab vs niraparib monotherapy, year 1, year 2, years 3-10, and total over 10 years, base case – excluding all costs related to subsequent therapy

Treatment	Cost item	Year 1 (2021)	Year 2 (2022)	Year 3 to 10 (2023 - 2030)	Total - Year 1 to 10 (2021 - 2030)
Olaparib + bevacizumab	Drug acquisition	361 060	185 752	10 887	557 699
	Drug administration	17 153	3 662	0	20 814
	Monitoring costs	48 924	35 180	88 459	172 564
	Adverse events	2 487	0	0	2 487
	Patient time	10 565	7 663	15 898	34 126
	Total	**440 189**	**232 258**	**115 243**	**787 690**
Niraparib	Drug acquisition	447 875	242 780	155 543	846 198
	Drug administration	0	0	0	0
	Monitoring costs	42 925	31 928	105 556	180 410
	Adverse events	2 121	0	0	2 121
	Patient time	4 565	4 410	20 221	29 196
	Total	**497 485**	**279 118**	**281 320**	**1 057 924**
Difference		***-57 296***	***-46 861***	***-166 077***	***-270 234***

8.13.2 Scenario analysis: Time to subsequent therapy from PAOLA-1 rather than SOLO-1

PAOLA-1 did not include an olaparib monotherapy arm or a wait and wait arm, but could be seen as more relevant for time to subsequent therapy in the olaparib + bevacizumab arm. For consistency, SOLO-1 data was used in the base case for all comparisons, but the PAOLA-1 data are also tested for all comparisons in the sensitivity scenarios. In the scenario with PAOLA-1 data for subsequent chemotherapy, the results show that the difference for olaparib + bevacizumab vs niraparib monotherapy is DKK - 300 409 over 10 years, compared with a difference of DKK – 299 373 in the base case. Hence, the use of PAOLA-1 for time to subsequent therapy had a minor impact on the cost difference (+0.3%).

8.13.3 Scenario analysis: Vial sharing

The base case does not assume vial sharing, but vial sharing could occur at some clinics for chemotherapy and also for bevacizumab. In the scenario with vial sharing, the results that the difference for olaparib + bevacizumab vs olaparib monotherapy is DKK - 301 658 over 10 years, compared with a difference of DKK – 299 373 in the base case. Hence, vial sharing had a minor impact on the cost difference (+0.8%).

8.14 Base case results - Average cost per patient: Olaparib + bevacizumab vs. niraparib in the low-risk HRD+ BRCAwt subpopulation

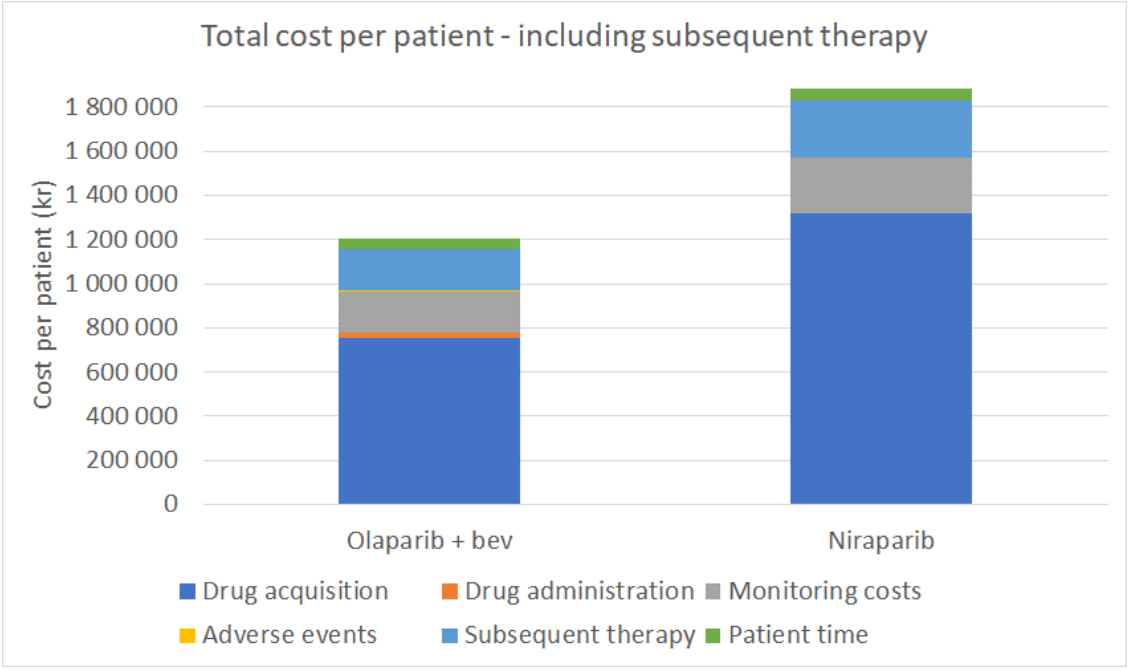
The results of the cost analysis for patients with HRD positive BRCAwt low-risk platinum-sensitive ovarian cancer show the average costs per patient over 10 years, including subsequent therapy. The drug acquisition costs constitute the major part of the total costs for all treatments (Table 55, Figure 36). Costs for drug administration and patient monitoring and follow-up are the second or third largest costs, while patient time and travel costs and in particular costs for adverse events are smaller. For adverse events, however, only costs for first-line treatments have been included. The total costs per patient over ten years show that treatment with olaparib + bevacizumab is DKK 679 897 less expensive than niraparib monotherapy. This is primarily due to a higher acquisition cost for niraparib.

Table 55. Average costs per patient for olaparib + bevacizumab vs niraparib, year 1, year 2, years 3-10, and total over 10 years, base case (DKK). Low-risk HRD+ BRCAwt subpopulation

Treatment	Cost item	Year 1 (2024)	Year 2 (2025)	Year 3 to 10 (2026 - 2033)	Total - Year 1 to 10 (2024 - 2033)
Olaparib + bevacizumab	Drug acquisition	408 314	322 839	23 557	754 709
	Drug administration	19 397	5 640	0	25 037
	Monitoring costs	52 030	44 766	89 368	186 164
	Adverse events	2 487	0	0	2 487
	Subsequent therapy	22 372	36 452	131 821	190 645
	Patient time	11 415	15 763	16 508	43 687
	Total	**516 015**	**425 460**	**261 254**	**1 202 730**
Niraparib	Drug acquisition	506 490	423 688	391 175	1 321 353
	Drug administration	0	0	0	0
	Monitoring costs	45 246	39 091	163 454	247 790
	Adverse events	2 121	0	0	2 121
	Subsequent therapy	29 978	49 540	180 158	259 676
	Patient time	8 823	8 004	34 860	51 687
	Total	**592 658**	**520 322**	**769 646**	**1 882 626**
Difference		***-76 642***	***-94 862***	***-508 392***	***-679 897***

**Discount rate of 3.5% used based on latest recommendation from the Danish Ministry of Finance (https://fm.dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021.pdf).*

Figure 36. Average costs per patient for olaparib + bevacizumab vs bevacizumab alone over 10 years, base case



8.15 One-way sensitivity analysis: Olaparib + bevacizumab vs. niraparib in the low-risk HRD+ BRCAwt subpopulation

A one-way sensitivity analysis was also performed for key variables in the model. The variables included in the one-way sensitivity analysis were the disco unt rate, drug acquisition costs, administration costs, monitoring costs, patient time and transport costs, and AE costs (Table 56). A positive % change means higher savings with olaparib + bevacizumab compared with niraparib. Except for the discount rate, time frame, maximum treatment duration for niraparib, proportion of patients treated with subsequent bevacizumab (bev) in the niraparib arm and the TTD and OS extrapolation methods, all variables were varied with ±20%. The results were most sensitive to drug acquisition costs for olaparib and niraparib and the niraparib treatment duration, but relatively insensitive to other variables. It is notable that the method for OS extrapolation has almost no impact at all, as most of the costs occur within the first few years and the OS extrapolations are quite similar for the first 6 years or so. It is also notable that treatment to progression with niraparib in the low-risk population could lead to very high treatment costs. As treatment to progression is in line with the Zejula SmPC, it is a relevant scenario.

Table 56. Sensitivity analysis: Difference in average costs per patient over 10 years (DKK). Low-risk HRD+ BRCAwt subpopulation.

Parameter	Variation	Total cost year 1 to 10		Olaparib + bev vs olaparib monotherapy	
		Olaparib + bevacizumab	Niraparib monotherapy	Difference	% Change
Base case	-	**1 202 730**	**1 882 626**	-679 897	-
Discount rate	2.5%	1 217 832	1 912 747	-694 915	2.2%
	4.5%	1 188 356	1 853 889	-665 533	-2.1%
Time frame	5 years	1 102 884	1 716 108	-613 224	-9.8%
	25 years	1 241 730	1 922 194	-680 464	0.1%
Treatment duration: Niraparib	Max 5 years	1 202 730	2 467 131	-1 264 401	86.0%
	Max 10 years	**1 202 730**	**3 405 415**	**-2 202 685**	**224.0%**
Proportion subsequent bev in niraparib arm	30%	1 202 730	1 893 329	-690 599	1.6%
	60%	1 202 730	1 911 677	-708 947	4.3%
TTD extrapolation	Gamma	1 203 728	1 863 052	-659 323	-3.0%
	Loglogistic	1 201 987	1 902 083	-700 096	3.0%
	Lognormal	1 203 633	1 887 302	-683 669	0.6%
OS extrapolation	Loglogistic	1 205 945	1 885 841	-679 897	0.0%
	Gamma	1 199 249	1 879 145	-679 897	0.0%
	Exponential	1 206 097	1 885 994	-679 897	0.0%
Drug acquisition cost: Olaparib	-20%	1 060 643	1 882 626	-821 983	20.9%
	+20%	1 344 816	1 882 626	-537 810	-20.9%
Drug acquisition cost: Bevacizumab	-20%	1 193 874	1 882 626	-688 752	1.3%
	+20%	1 211 585	1 882 626	-671 041	-1.3%
Drug acquisition cost: Niraparib	-20%	1 202 730	1 618 356	-415 626	-38.9%
	+20%	1 202 730	2 146 897	-944 167	38.9%
Monitoring cost	-20%	1 165 937	1 807 806	-641 868	-5.6%
	+20%	1 239 774	1 970 551	-730 776	7.5%
Administration cost	-20%	1 197 722	1 882 626	-684 904	0.7%
	+20%	1 207 737	1 882 626	-674 889	-0.7%
Patient time and transport cost	-20%	1 193 854	1 866 772	-672 918	-1.0%
	+20%	1 211 710	1 901 274	-689 565	1.4%
AE cost	-20%	1 202 232	1 882 202	-679 970	0.01%
	+20%	1 203 227	1 883 050	-679 823	-0.01%

8.15.1 Scenario analysis: Excluding subsequent therapy

In this scenario, treatment with olaparib + bevacizumab and niraparib monotherapy are included, but all costs related to subsequent therapy are excluded. Since subsequent PARP inhibitors are not recommended for patients who used these in the first line, and chemotherapy will be used in clinical practice in both the arms, this scenario does not differ hugely from the base case. The difference for olaparib + bevacizumab vs niraparib monotherapy is DKK -609 884 over 10 years (Table 57), compared with a difference of DKK -679 897 in the base case.

Table 57. Average costs per patient for olaparib + bevacizumab vs niraparib, year 1, year 2, years 3-10, and total over 10 years, excluding subsequent therapy (DKK). Low-risk HRD+ BRCAwt subpopulation

Treatment	Cost item	Year 1 (2021)	Year 2 (2022)	Year 3 to 10 (2023 - 2030)	Total - Year 1 to 10 (2021 - 2030)
Olaparib + bevacizumab	Drug acquisition	408 314	322 839	23 557	754 709
	Drug administration	19 397	5 640	0	25 037
	Monitoring costs	52 030	44 766	89 368	186 164
	Adverse events	2 487	0	0	2 487
	Patient time	11 351	10 087	16 508	37 946
	Total	**493 579**	**383 331**	**129 433**	**1 006 343**
Niraparib	Drug acquisition	506 490	423 688	391 175	1 321 353
	Drug administration	0	0	0	0
	Monitoring costs	45 246	39 091	163 454	247 790
	Adverse events	2 121	0	0	2 121
	Patient time	4 949	5 154	34 860	44 963
	Total	**558 806**	**467 932**	**589 489**	**1 616 227**
Difference		***-65 227***	***-84 601***	***-460 055***	***-609 884***

**Discount rate of 3.5% used based on latest recommendation from the Danish Ministry of Finance (https://fm.dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021.pdf).*

8.15.2 Scenario analysis: Time to subsequent therapy from PAOLA-1 rather than SOLO-1

PAOLA-1 did not include an olaparib monotherapy arm or a wait and wait arm, but could be seen as more relevant for time to subsequent therapy for the olaparib + bevacizumab arms. For consistency, SOLO-1 data was used in the base case for all comparisons, but the PAOLA-1 data are also tested for all comparisons in the sensitivity scenarios. In the scenario with PAOLA-1 data for subsequent chemotherapy, the results show that the difference for olaparib + bevacizumab vs niraparib is DKK – 682 634 over 10 years, compared with a difference of DKK – 679 897 in the base case (0.4% higher cost savings).

8.15.3 Scenario analysis: Vial sharing

The base case does not assume vial sharing, but vial sharing could occur at some clinics for chemotherapy and also for bevacizumab. In the scenario with vial sharing, the results that the difference for olaparib + bevacizumab vs niraparib is DKK - 678 008 over 10 years, compared with a difference of DKK – 679 897 in the base case. The effect of vial sharing is very small as expected.

8.15.4 Scenario analysis: Including the cost of HRD testing

The cost of HRD testing was excluded from the base case, as most patients would be expected to be tested at the time of diagnosis. The testing cost is thus not driven by the introduction of first-line olaparib and bevacizumab. In a scenario where the HRD testing cost is only applied to first-line olaparib + bevacizumab, difference for olaparib + bevacizumab vs niraparib is DKK – 651 784 over 10 years, vs DKK – 679 897 in the base case, i.e. a decreased cost difference (- 4.1%).

8.16 Probabilistic sensitivity analysis

The probabilistic sensitivity analysis (PSA) is a method that can be used to estimate the parametric uncertainty surrounding the results of the cost analysis. It is conducted through the repeated re-sampling of all major input parameters using probability distributions (e.g., normal) to generate a series of sampled estimates of the cost results under uncertainty. For treatment duration, overall survival and adverse events, the standard errors were estimated based on study data. For resource use, the SE was estimated based on the assumption that the SE was 20% of the parameter value. The 20% is a modelling assumption, but should be capturing the overall uncertainty well. The resource use estimates (e.g., frequency of follow-up visits) are to a large extent based on routines schedules for follow-up visits. Usually, patient monitoring is dependent on the patient status (on treatment or off treatment), and it is expected to be quite standard over time. The variables included in the PSA are listed in Appendix J.

8.16.1 PSA results for the high-risk HRD+ BRCAwt subpopulation

Probabilistic results for the total cost over the time horizon (10 years in the base case) and the difference in total costs are shown in Table 58, based on 3000 simulations On average, olaparib + bevacizumab leads to cost savings of DKK 291 913 versus niraparib. This is similar to the deterministic base case, which estimated savings of DKK 299 373 for olaparib + bevacizumab versus niraparib.

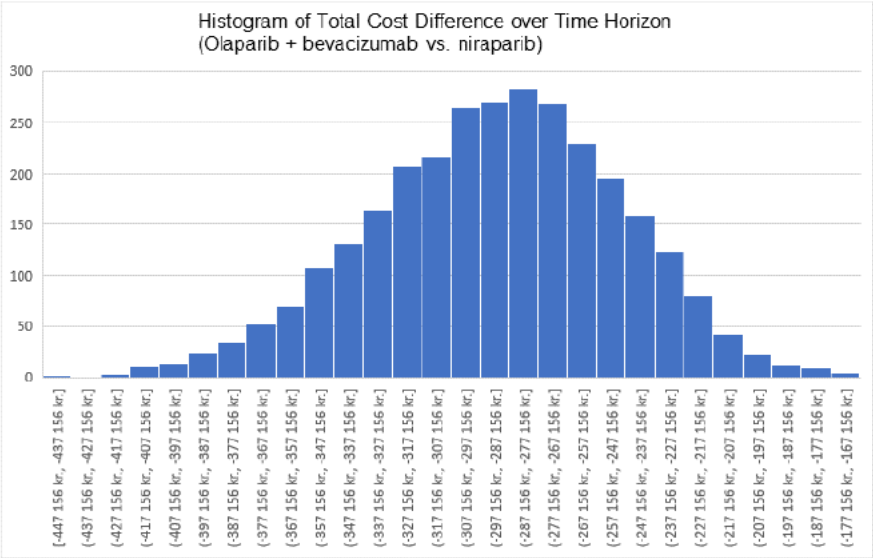
Table 58. Summary of PSA results for the high-risk HRD+ BRCAwt subpopulation (DKK)

	Total cost per patient Olaparib + bevacizumab	Total cost per patient Niraparib	Cost difference
Mean	990 653 kr.	1 282 566 kr.	-291 913 kr.
St.Dev.	70 616 kr.	87 352 kr.	42 856 kr.
95% CI LCL	988 127 kr.	1 279 441 kr.	-293 447 kr.
95% CI UCL	993 180 kr.	1 285 692 kr.	-290 380 kr.
Min	777 958 kr.	997 716 kr.	-447 156 kr.
Max	1 237 603 kr.	1 624 255 kr.	-167 431 kr.

CI: Confidence interval, LCL: Lower confidence limit; UCL: Upper confidence limit; St.Dev.: Standard deviation

The results are illustrated as a histogram in Figure 37, which shows how the cost differences were distributed in the PSA simulation.

Figure 37. Distribution of total cost differences for olaparib + bevacizumab versus niraparib in the high-risk HRD+ BRCAwt subpopulation



8.16.2 PSA results for the low-risk HRD+ BRCAwt subpopulation

Probabilistic results are shown in Table 59, based on 3000 simulations On average, olaparib + bevacizumab leads to cost savings of DKK 647 289 versus niraparib. This is fairly similar to the deterministic base case, which was savings of DKK 679 897 for olaparib + bevacizumab versus niraparib.

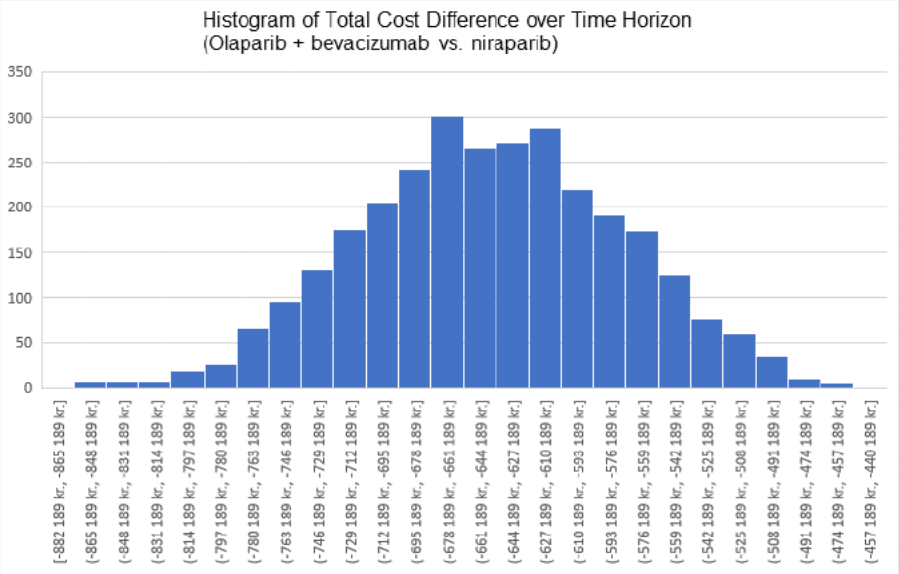
Table 59. Summary of PSA results for the low-risk HRD+ BRCAwt subpopulation (DKK)

	Total cost per patient Olaparib + bevacizumab	Total cost per patient Niraparib	Cost difference
Mean	1 170 232	1 817 522	-647 289
St.Dev.	45 627	89 696	68 409
95% CI LCL	1 168 599	1 814 312	-649 737
95% CI UCL	1 171 865	1 820 731	-644 841
Min	1 011 074	1 479 879	-882 189
Max	1 337 213	2 141 939	-446 013

CI: Confidence interval, LCL: Lower confidence limit; UCL: Upper confidence limit; St.Dev.: Standard deviation

The results are illustrated as a histogram in Figure 38, which shows how the cost differences were distributed in the PSA simulation.

Figure 38. Distribution of total cost differences for olaparib + bevacizumab versus niraparib in the low-risk HRD+ BRCAwt subpopulation



9. Budget impact analysis

9.1 Market shares

Market shares have been estimated separately for each subpopulation identified by Medicinrådet. Niraparib is recommend in the 1st line advanced HRD+ non-BRCA+ ovarian cancer setting. Hence it is assumed that gained market shares for olaparib + bevacizumab would be in replacement of niraparib if recommended.

9.1.1 Olaparib + bevacizumab vs. niraparib in the HRD+ non-BRCAm high-risk subpopulation

At peak-years sales, around 75% are estimated to get the combination therapy in the high-risk group (**Table 61**). The combination therapy could be expected to take market shares from niraparib monotherapy.

Table 60. Scenario without olaparib + bevacizumab

Year	Olaparib+bev	Niraparib mono
2021	0%	100%
2022	0%	100%
2023	0%	100%
2024	0%	100%
2025	0%	100%

Table 61. Scenario with olaparib + bevacizumab

Year	Olaparib+bev	Niraparib mono
2021	20%	80%
2022	35%	65%
2023	50%	50%
2024	65%	35%
2025	75%	25%

9.1.2 Olaparib + bevacizumab vs. niraparib in the HRD+ non-BRCAm low-risk subpopulation

As niraparib is the only comparator, it is assumed that olaparib + bevacizumab will take market shares from niraparib only (Table 62). At peak-years sales, around 60% are estimated to get the combination therapy in the low-risk group (Table 63).

Table 62. Scenario without olaparib + bevacizumab

Year	Olaparib+bev	Niraparib mono
2021	0%	100%
2022	0%	100%
2023	0%	100%
2024	0%	100%
2025	0%	100%

Table 63. Scenario with olaparib + bevacizumab

Year	Olaparib+bev	Olaparib mono
2021	20%	80%
2022	30%	70%
2023	40%	60%
2024	50%	50%
2025	60%	40%

9.2 Budget impact analysis

Olaparib + bevacizumab is assumed to take market shares from niraparib. The budget impact calculations include cost implications for the included comparators, i.e. olaparib + bevacizumab, and niraparib, and for subsequent bevacizumab and chemotherapy. The costs for drug acquisition and administration, monitoring and adverse events were also included. Based on the epidemiology, the patient numbers are expected to be 55 in the high risk HRD+ BRCAwt subpopulation, and 20 in the low-risk HRD+ BRCAwt subpopulation (Table 64). (See also section 5.1.1 for discussion on patient numbers).

Table 64. Number of patients per year in the model for the subpopulations

Year	BRCAwt HRD+ HR	BRCAwt HRD+ LR	All HRD+
2023	55	20	75
2024	55	20	75
2025	55	20	75
2026	55	20	75
2027	56	20	76

Table 65 and Table 66 present a summary of the budget impact results for the two subpopulations.

9.2.1 Olaparib + bevacizumab vs. niraparib in high-risk HRD+ BRCAwt subpopulation

The incremental total cost for the 55 patients eligible for treatment with olaparib + bevacizumab per year decreases from savings 0.7 million DKK in 2024 to a maximum of 12.6 million DKK in 2028 (Table 65).

Table 65. Summary of the incremental results: Base case for olaparib + bevacizumab vs. niraparib in the high-risk HRD+ BRCAwt subpopulation

Budget year	Scenario with olaparib+bev (DKK)	Scenario without olaparib+bev (DKK)	Incremental total cost (DKK)	Budget impact of new scenario vs. current scenario (%)
2024	27 654 906	28 377 315	-722 409	-3%
2025	44 021 624	46 382 689	-2 361 065	-5%
2026	51 083 095	58 718 691	-7 635 596	-13%
2027	51 836 053	62 459 242	-10 623 188	-17%
2028	52 541 132	65 096 581	-12 555 449	-19%

9.2.2 Olaparib + bevacizumab vs. niraparib in low-risk HRD+ BRCAwt subpopulation

The incremental total cost for the 20 patients eligible for treatment with olaparib + bevacizumab per year decreases from savings of 0.3 million DKK in 2024 to maximum savings of 7.8 million DKK in 2028 (Table 66).

Table 66. Summary of the incremental results: Base case for olaparib + bevacizumab vs. vs. niraparib in the low-risk HRD+ BRCAwt subpopulation

Budget year	Scenario with olaparib+bev (DKK)	Scenario without olaparib+bev (DKK)	Incremental total cost (DKK)	Budget impact of new scenario vs. current scenario (%)
2024	11 316 586	11 632 322	-315 736	-3%
2025	21 119 144	22 228 903	-1 109 760	-5%
2026	27 111 886	31 708 794	-4 596 908	-14%
2027	27 509 777	33 820 601	-6 310 824	-19%
2028	27 257 022	35 104 032	-7 847 010	-22%

9.2.3 Scenario analysis: Increased/decreased market shares for olaparib + bevacizumab

The sensitivity analyses and scenarios would have a similar impact on budgets as on the cost per patient, but market shares are also important for the total budget impact. Hence, the sensitivity analysis for the budget impact focuses on market shares. Since the market shares for olaparib + bevacizumab in the new scenarios may differ from the base case estimates, scenario analyses were created with higher and lower market shares for olaparib. Table 67 and Table 68 show budget impact results where market shares for olaparib + bevacizumab have been either increased or decreased by 10 percentage points compared with the base case market shares in section 9.1.

The results are as expected with relatively modest changes in the budget impact, but increased saving with a higher market share for olaparib + bevacizumab.

Table 67. Summary of the incremental results: Scenario analyses with increased market shares (+10 percentage points)

Budget year	Olaparib + bevacizumab vs. niraparib in the high-risk HRD+ BRCAwt subpopulation			
	Scenario with olaparib (DKK)	Scenario without olaparib (DKK)	Incremental total cost (DKK)	Budget impact of new scenario vs. current scenario (%)
2024	27 293 701	28 377 315	-1 083 613	-4%
2025	43 347 034	46 382 689	-3 035 655	-7%
2026	49 555 976	58 718 691	-9 162 715	-16%
2027	50 201 717	62 459 242	-12 257 525	-20%
2028	50 867 073	65 096 581	-14 229 508	-22%
Budget year	Olaparib + bevacizumab vs. niraparib in the low-risk HRD+ BRCAwt subpopulation			
	Scenario with olaparib (DKK)	Scenario without olaparib (DKK)	Incremental total cost (DKK)	Budget impact of new scenario vs. current scenario (%)
2024	11 158 718	11 632 322	-473 604	-4%
2025	20 749 224	22 228 903	-1 479 680	-7%
2026	25 962 659	31 708 794	-5 746 136	-18%
2027	26 247 612	33 820 601	-7 572 989	-22%
2028	25 949 187	35 104 032	-9 154 845	-26%

Table 68. Summary of the incremental results: Scenario analyses with decreased market shares (-10 percentage points)

Budget year	Olaparib + bevacizumab vs. niraparib in the high-risk HRD+ BRCAwt subpopulation			
	Scenario with olaparib (DKK)	Scenario without olaparib (DKK)	Incremental total cost (DKK)	Budget impact of new scenario vs. current scenario (%)
2024	28 016 110	28 377 315	-361 204	-1%
2025	44 696 214	46 382 689	-1 686 475	-4%
2026	52 610 215	58 718 691	-6 108 477	-10%
2027	53 470 390	62 459 242	-8 988 852	-14%
2028	54 215 192	65 096 581	-10 881 389	-17%
Budget year	Olaparib + bevacizumab vs. niraparib in the low-risk HRD+ BRCAwt subpopulation			
	Scenario with olaparib (DKK)	Scenario without olaparib (DKK)	Incremental total cost (DKK)	Budget impact of new scenario vs. current scenario (%)
2024	11 474 454	11 632 322	-157 868	-1%
2025	21 489 064	22 228 903	-739 840	-3%
2026	28 261 113	31 708 794	-3 447 681	-11%
2027	28 771 942	33 820 601	-5 048 659	-15%
2028	28 564 857	35 104 032	-6 539 175	-19%

10. Discussion on the submitted documentation

The cost-minimization analyses present the incremental costs of introducing olaparib + bevacizumab as a first line treatment for platinum-sensitive ovarian cancer patients with HRD mutations excluding BRCA in Denmark, compared with niraparib. The cost-minimization analyses included treatment acquisition, monitoring costs, patient-related costs and treatment-related AE costs. The treatment acquisition cost is by far the largest for all treatments in the base case analysis.

Two subpopulations of the HRD positive BRCAwt population were included:

1. Olaparib + bevacizumab vs. niraparib in high-risk patients.
2. Olaparib + bevacizumab vs. niraparib in low-risk patients.

In the high-risk population, the results on average cost per patient showed that for patients treated with olaparib + bevacizumab, the costs over 10 years are DKK 981 652, compared with DKK 1 281 025 niraparib monotherapy, i.e. a difference of DKK - 299 373 (olaparib + bevacizumab cost saving). The drug acquisition constitutes the major part of the

costs, and therefore results were most sensitive to changes in drug acquisition costs for olaparib, niraparib and the treatment duration of niraparib, and relatively insensitive to other variables.

In the low-risk population, the results on average cost per patient showed that for patients treated with olaparib + bevacizumab, the costs over 10 years are DKK 1 202 730, compared with DKK 1 882 626 for niraparib monotherapy, i.e. a difference of DKK - 679 897 (olaparib + bevacizumab cost saving). The drug acquisition constitutes the major part of the costs, and therefore results were most sensitive to changes in drug acquisition costs for olaparib, niraparib and the treatment duration of niraparib, and relatively insensitive to other variables.

As mentioned in the introduction, bevacizumab has a concomitant phase with chemotherapy, while olaparib treatment is initiated after platinum-based chemotherapy. However, the earlier start of bevacizumab treatment is not a problem in practice for the cost analysis. Bevacizumab is discounted more with the same starting point as olaparib compared with a slightly earlier start, but this discounting effect is very small and can be neglected for practical purposes.

The budget impact calculations include cost implications for introducing olaparib + bevacizumab in Danish clinical practice. In the high-risk HRD positive BRCAwt population, the base case results showed that such an introduction would on average lead to a budget decrease of 3% in year 2024, 5% in year 2025, 13% in 2026, 17% in 2027 and 19% in year 2028. In the low-risk HRD positive BRCAwt population, there was budget decrease 3% in year 2024, 5% in year 2025, 14% in 2026, 19% in 2027, and 22% in year 2028.

The cost per patient and budget impact for olaparib + bevacizumab varied in a predictable way depending on subpopulation and other variables. The analysis is conservative as the treatment with niraparib is to progression in the SmPC: “It is recommended that treatment should be continued until disease progression or toxicity” (Zejula Summary of Product Characteristics, EMA 2022). With treatment to progression for niraparib, the difference in cost would increase considerably and the cost savings with olaparib + bevacizumab would be even larger. It is also notable that olaparib + bevacizumab has shown superior efficacy vs. an active comparator arm in PAOLA-1, while niraparib has showed efficacy vs. watch and wait in PRIMA. Hence, the cost-minimization approach itself is also conservative.

11. List of experts

Not relevant

12. References

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Version log		
Version	**Date**	**Change**

Version log		
1.0	27 November 2020	Application form for assessment made available on the website of the Danish Medicines Council.
1.1	9 February 2022	Appendix K and onwards have been deleted (company specific appendices) Color scheme for text highlighting table added after table of contents Section 6: Specified requirements for literature search Section 7: Stated it explicitly that statistical methods used need to be described Section 8.3.1: Listed the standard parametric models Section 8.4.1: Added the need for description of quality of life mapping Appendix A: Specified that the literature search needs to be specific for the Danish context and the application Appendices B and D: Stated it explicitly that statistical methods need to be described in the tables in the appendices
1.2	20 June 2022	Clarification of the introduction, including instructions on how to complete the form.

Appendix A Literature search for efficacy and safety of intervention and comparator(s)

Objective of the literature search:

To conduct a systematic literature review (SLR) to evaluate efficacy, safety, and quality of life data of maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status. Intervention is Lynparza(olaparib +/- bevacizumab(Avastin). Comparator is Zejula(niraparib) 3 x 100 mg and 2 x 100 mg (capsules/tablets). Endpoints are OS, PFS, AE's, HRQoL and dicontinuations.

Databases:

A systematic search of PubMed, and the Cochrane Library was conducted by an information specialist and peer-reviewed by another senior information specialist using the Peer Review of Electronic Search Strategies (PRESS) checklist. Publication dates from database inception through October 10, 2022 are included in this report. Bibliographies of previously published SLRs, and the ClinicalTrials.gov website were searched to ensure inclusion of all relevant clinical trials. Study selection was performed in duplicate and standardized data extraction templates were used to collect data on study and patient characteristics and outcomes of interest.

Table A1: Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
PubMed	PubMed.com	E.g. 1970 until today	10/10/2022
Cochrane Library	CENTRAL	2005 until 10/10/2022	10/10/2022

Table A2: Registers included in the search

Database	Platform	Search strategy	Date of search
US NIH registry & results database	https://clinicaltrials.gov	See below	22.03.2021

Table A3: Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched
ESMO 2022	Conference website	Manual search	ESMO 2022

Search strategy

The search string is an extension of the last submitted search string from the original application to the Medicines Council.

The following electronic databases were interrogated on the 10th October 2022: PubMed, and Cochrane Central Register of Controlled Trials (CENTRAL). Additional hand-searching of conferences proceedings from the last 3 years, HTA websites, trial registries and additional sources were conducted to identify relevant evidence. Hand-searching of conferences proceedings, HTA websites, trial registries and additional sources were also re-searched to ensure sufficient background knowledge.

Table A4: Search string for PubMed

Search	Query	Results	Time
#19	Search: **#14 NOT #18**	95	08:06:23
#18	Search: **#15 OR #16 OR #17**	12,348,209	08:06:17
#17	Search: **Review[pt] OR Systematic Review[pt] OR Meta-Analysis[pt] OR review[ti] OR meta-analys*[ti]**	3,392,101	08:06:11
#16	Search: **Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR case report[ti]**	4,439,772	08:06:04
#15	Search: **Animals[mh] NOT Humans[mh]**	5,047,136	08:05:52
#14	Search: **#12 AND #13**	186	08:04:14
#13	Search: **Randomized Controlled Trial[pt] OR Controlled Clinical Trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR Clinical Trials as Topic[mh:noexp] OR randomly[tiab] OR trial[ti]**	1,532,246	08:04:06
#12	Search: **#10 AND #11**	485	08:03:57
#11	Search: **olaparib[nm] OR olaparib[tiab] OR Lynparza*[tiab] OR Bevacizumab[mh] OR bevacizumab[tiab] OR Avastin*[tiab] OR Mvasi*[tiab] OR HRD[tiab] OR homologous recombination[tiab] OR niraparib[nm] OR niraparib[tiab] OR Niraparib*[tiab] OR Zejula**	45,741	08:03:50
#10	Search: **#7 AND (#8 OR #9)**	4,166	07:57:52
#9	Search: **1L[tiab] OR firstline[tiab] OR first-line[tiab] OR frontline[tiab] OR front-line[tiab] OR primary treatment[tiab] OR primary therapy[tiab]**	143,259	07:57:38
#8	Search: **newly diagnosed[tiab]**	59,087	07:57:31
#7	Search: **#1 OR #2 OR #3 OR #4 OR #5 OR #6**	140,052	07:57:20
#6	Search: **(peritoneal[ti] OR peritoneum[ti] OR serous surface papillary[ti] OR extra-ovarian serous[ti] OR primary serous papillary[ti]) AND (cancer[ti] OR carcinoma*[ti] OR neoplasm*[ti] OR tumor*[ti] OR tumour*[ti])**	7,285	07:57:12
#5	Search: **Peritoneal Neoplasms[mh]**	17,646	07:57:03
#4	Search: **(fallopian tube*[ti] OR tubal[ti] OR oviduct[ti] OR tuba[ti]) AND (cancer[ti] OR carcinoma*[ti] OR neoplasm*[ti] OR tumor*[ti] OR tumour*[ti])**	1,913	07:56:51
#3	Search: **Fallopian Tube Neoplasms[mh]**	3,088	07:56:31
#2	Search: **(ovary[ti] OR ovari*[ti]) AND (cancer[ti] OR carcinoma*[ti] OR neoplasm*[ti] OR tumor*[ti] OR tumour*[ti])**	64,571	07:56:11
#1	Search: **ovarian neoplasms**	113,448	07:55:07

Table A5: Search string for CENTRAL

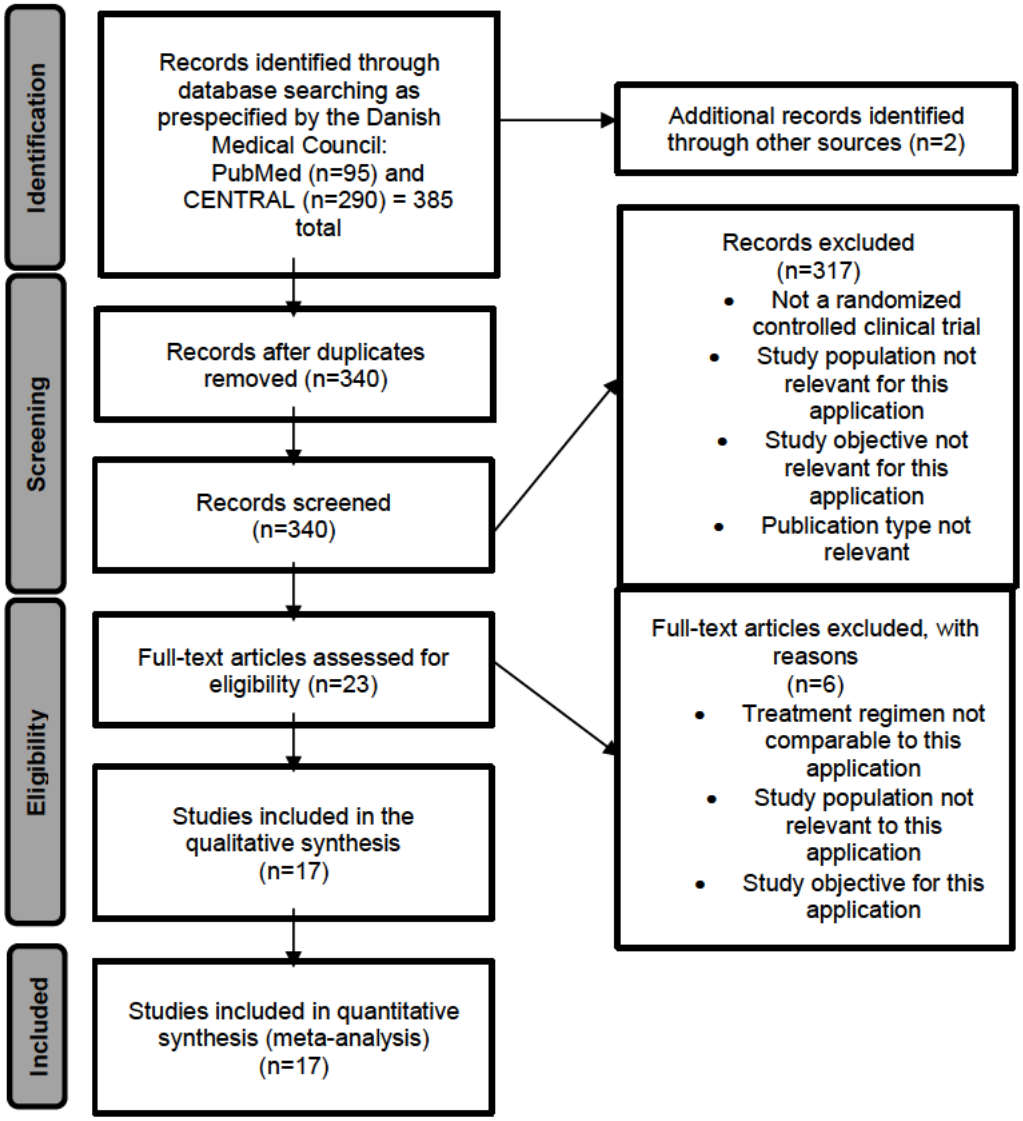
ID	Search	Hits
1	[mh "Ovarian Neoplasms"]	2217
2	((ovary OR ovari*) AND (cancer OR carcinoma* OR neoplasm* OR tumor* OR tumour*)):ti,kw	7902
3	[mh "Fallopian Tube Neoplasms"]	274
4	((fallopian next tube* OR uterine next tube* OR tubal OR oviduct OR tuba) AND (cancer OR carcinoma* OR neoplasm* OR tumor* OR tumour*)):ti,kw	781
5	[mh "Peritoneal Neoplasms"]	372
6	((peritoneal OR peritoneum OR serous surface papillary OR extra-ovarian serous OR primary serous papillary) AND (cancer OR carcinoma* OR neoplasm* OR tumor* OR tumour*)):ti,kw	1827
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	8928
8	("newly diagnosed"):ti,ab	13816
9	(1L OR firstline OR first-line OR frontline OR front-line OR "primary treatment" OR "primary therapy"):ti,ab	29248
10	#7 AND (#8 OR #9)	1303
11	(olaparib OR Lynparza* OR bevacizumab OR Avastin* OR Mvasi* OR HRD OR "homologous recombination" OR niraparib OR Zejula*):ti,ab,kw	8209
12	#10 AND #11	398
13	("conference abstract" OR review):pt OR (abstract OR meeting OR review):ti OR (abstract OR meeting):so	157306
14	(clinicaltrials.gov OR trialsearch):so	433301
15	NCT*:au	233181
16	#13 OR #14 OR #15	590793
17	#12 NOT #16 in Trials	290

Table A6: Search string received from DMC ahead of initial application

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

Systematic selection of studies

Figure A1: PRISMA flow diagram



1)
Coleman RL, Fleming GF, Brady MF, Swisher EM, Steffensen KD, Friedlander M, Okamoto A, Moore KN, Efrat Ben-Baruch N, Werner TL, Cloven NG, Oaknin A, DiSilvestro PA, Morgan MA, Nam JH, Leath CA 3rd, Nicum S, Hagemann AR, Littell RD, Cella D, Baron-Hay S, Garcia-Donas J, Mizuno M, Bell-McGuinn K, Sullivan DM, Bach BA, Bhattacharya S, Ratajczak CK, Ansell PJ, Dinh MH, Aghajanian C, Bookman MA. Veliparib with First-Line Chemotherapy and as Maintenance Therapy in Ovarian Cancer. N Engl J Med. 2019 Dec 19;381(25):2403-2415. doi: 10.1056/NEJMoa1909707. Epub 2019 Sep 28. PMID: 31562800; PMCID: PMC6941439.
Excluded due to invervention

2)
Aghajanian C, Blank SV, Goff BA, Judson PL, Teneriello MG, Husain A, Sovak MA, Yi J, Nycum LR. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol. 2012 Jun 10;30(17):2039-45. doi: 10.1200/JCO.2012.42.0505. Epub 2012 Apr 23. PMID: 22529265; PMCID: PMC3646321.
Recurrent disease

3)
Moore KN, Bookman M, Sehouli J, Miller A, Anderson C, Scambia G, Myers T, Taskiran C, Robison K, Mäenpää J, Willmott L, Colombo N, Thomes-Pepin J, Liontos M, Gold MA, Garcia Y, Sharma SK, Darus CJ, Aghajanian C, Okamoto A, Wu X, Safin R, Wu F, Molinero L, Maiya V, Khor VK, Lin YG, Pignata S. Atezolizumab, Bevacizumab, and Chemotherapy for Newly Diagnosed Stage III or IV Ovarian Cancer: Placebo-Controlled Randomized Phase III Trial (IMagyn050/GOG 3015/ENGOT-OV39). J Clin Oncol. 2021 Jun 10;39(17):1842-1855. doi: 10.1200/JCO.21.00306. Epub 2021 Apr 23. Erratum in: J Clin Oncol. 2021 Jul 20;39(21):2420. PMID: 33891472; PMCID: PMC8189598.
Excluded due to invervention

4)
Monk BJ, Coleman RL, Fujiwara K, Wilson MK, Oza AM, Oaknin A, O'Malley DM, Lorusso D, Westin SN, Safra T, Herzog TJ, Marmé F, N Eskander R, Lin KK, Shih D, Goble S, Grechko N, Hume S, Maloney L, McNeish IA, Kristeleit RS. ATHENA (GOG-3020/ENGOT-ov45): a randomized, phase III trial to evaluate rucaparib as monotherapy (ATHENA-MONO) and rucaparib in combination with nivolumab (ATHENA-COMBO) as maintenance treatment following frontline platinum-based chemotherapy in ovarian cancer. Int J Gynecol Cancer. 2021 Dec;31(12):1589-1594. doi: 10.1136/ijgc-2021-002933. Epub 2021 Sep 30. PMID: 34593565; PMCID: PMC8666815.
Excluded due to invervention

5)
Mirza MR, Åvall Lundqvist E, Birrer MJ, dePont Christensen R, Nyvang GB, Malander S, Anttila M, Werner TL, Lund B, Lindahl G, Hietanen S, Peen U, Dimoula M, Roed H, Ør Knudsen A, Staff S, Krog Vistisen A, Bjørge L, Mäenpää JU; AVANOVA investigators. Niraparib plus bevacizumab versus niraparib alone for platinum-sensitive recurrent ovarian cancer (NSGO-AVANOVA2/ENGOT-ov24): a randomised, phase 2, superiority trial. Lancet Oncol. 2019 Oct;20(10):1409-1419. doi: 10.1016/S1470-2045(19)30515-7. Epub 2019 Aug 29. PMID: 31474354.
Excluded due phase II and recurrent disease.

6)
Aghajanian C, Goff B, Nycum LR, Wang YV, Husain A, Blank SV. Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or

without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. Gynecol Oncol. 2015 Oct;139(1):10-6. doi: 10.1016/j.ygyno.2015.08.004. Epub 2015 Aug 10. PMID: 26271155; PMCID: PMC4993045.
Excluded due to recurrent disease

Quality assessment

As previously described, the literature search was based on a literature search described by the Danish Medicines Council, and there was no significant risk of bias during the process.

Appendix B Main characteristics of included studies

Trial name: PRIMA	NCT number: NCT02655016
Objective	The primary objective of the trial was to test the efficacy and safety of niraparib maintenance therapy after a response to platinum-based chemotherapy in patients with newly diagnosed advanced ovarian cancer at high risk for relapse
Publications – title, author, journal, year	Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. González-Martín A et al; PRIMA/ENGOT-OV26/GOG-3012 Investigators. N Engl J Med. 2019 [2].
Study type and design	A phase 3, randomized, double-blind, placebo-controlled, multicenter study of niraparib maintenance treatment in patients with advanced ovarian cancer following response on front-line platinum-based chemotherapy (PRIMA/ENGOTOV26/GOG-3012)..
Sample size (n)	
Main inclusion and exclusion criteria	**Main inclusion criteria** • Patients with histologically confirmed, advanced (FIGO Stage III or IV) high-grade predominantly serous or endometrioid ovarian cancer, fallopian tube cancer or primary peritoneal cancer who had completed first-line platinum-based chemotherapy (neoadjuvant or adjuvant). • Patients with clinical complete or partial response following completion of chemotherapy course. • All stage IV patients were eligible, irrespective of residual disease, after primary or interval debulking. Stage III patients were required to have visible residual disease after primary surgery. Patients with inoperable stage III and IV disease were eligible. • Patients had to agree to undergo central tumour HRD testing. • Patients of childbearing potential had to have negative pregnancy serum test within 72 hours of being dosed. • Patients had to be randomised within 12 weeks of the first day of the last cycle of chemotherapy. **Main exclusion criteria** • Patients with mucinous or clear cell subtypes of epithelial ovarian cancer, carcinosarcoma or undifferentiated ovarian cancer. • Patients who had undergone more than 2 debulking surgeries. • Patients receiving bevacizumab as maintenance treatment. • Patients who were pregnant, breastfeeding or expecting to conceive children, while receiving study treatment and for 180 days after the last dose of study treatment. • Patients who had received prior treatment with a known PARP inhibitor. • Patients who had been diagnosed and/or treated for any invasive cancer (other than study disease) less than 5 years prior to study enrolment

Trial name: PRIMA	NCT number: NCT02655016
Intervention	Niraparib 200/300 mg once daily (N=487). The initial starting dose for niraparib patients was 300 mg once daily; however, subsequent analysis of niraparib in the relapsed setting indicated baseline body weight and platelet counts were predictors of early dose modification. The trial was amended on November 27, 2017, to incorporate an individualized starting dose of 200 mg once daily for patients with a baseline body weight of less than 77 kg, a platelet count of less than 150,000 per cubic millimetre, or both.
Comparator(s)	Placebo once daily (N=246)
Follow-up time	The patients were treated for 36 months or until disease progression.
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	Primary outcome measure PFS defined as the time from randomisation to the earliest date of objective disease progression on imaging (according to RECIST, version 1.1) or death from any cause in the absence of progression and determined based on BICR. Key secondary outcome measure OS, defined as the time from date of randomisation until the date of death from any cause. Secondary outcome measures included: • Safety and tolerability of niraparib versus placebo evaluated as number of participants with treatment-related AEs with severity assessed according to CTCAE version 4.03. • PROs were collected every 8 weeks for 56 weeks beginning on cycle 1/day 1, thereafter every 12 weeks while the patient received study treatment, at the time of treatment discontinuation and at 4, 8, 12 and 24 weeks after the end of treatment, regardless of the status of subsequent treatment. o FOSI o EQ-5D-5L o EORTC-QLQ-C30 o EORTC-QLQ-OV28

Trial name: PRIMA	NCT number: NCT02655016
Method of analysis	The statistical analyses were performed according to a statistical analysis plan, and the analyses were independently reviewed and approved by a statistician from the Nordic Society of Gynaecological Oncology (ENGOT lead group). Efficacy data were analysed in the overall population, defined as all randomised patients. Safety data were analysed in the safety population, which included all patients who received at least one dose of niraparib or placebo. An ENGOT statistician performed an independent analysis on pre-defined endpoints. The PFS analysis in the overall population included all PFS events observed at the time of the final analysis of PFS. PFS was analysed in a time-to-event analysis after disease progression or death had occurred in 154 patients with HRD and in 386 patients in the overall population. For the HRD and overall populations, PFS was analysed with a stratified log-rank test using randomisation stratification factors and summarised using Kaplan-Meier methodology. Hazard ratios with 95% CIs were estimated using a stratified Cox proportional hazards model, with the stratification factors used in randomisation. Secondary time-to-event endpoints (OS, time to first subsequent therapy, PFS2) were analysed in the same manner as PFS. Hierarchical testing was used to control for the overall type I error. First, the analysis of PFS was conducted in the HRD population at the one-sided 0.025 type I error rate. Because this result was positive, PFS analysis was conducted in the overall population at the one sided 0.025 type I error rate. Hierarchical testing was used to control for the overall type I error, and since the PFS analysis was positive in the overall population, the OS analysis was conducted according to the prespecified group sequential design with an interim analysis performed for the overall population at the time of final PFS analysis. A final OS analysis will be performed in the future when the number of OS events is reached. A final OS analysis will be performed in the future when the number of OS events has been reached. A Lan-DeMets alpha-spending function with the O'Brien-Fleming stopping boundaries was used to determine the significance levels for interim and final OS analyses. The ENGOT statistician independently performed an analysis of the primary endpoint. Analyses of other secondary endpoints were not adjusted for multiple comparisons. All P values are reported at a two-sided significance level of 0.05..

Trial name: PRIMA	NCT number: NCT02655016
Subgroup analyses	Subgroup analyses of the PFS endpoint were performed in the following prespecified subgroups: • Age (<65 years or ≥65 years) • ECOG score (0 or 1) • Stage of disease at initial diagnosis (III or IV) • Neoadjuvant chemotherapy (yes or no) • Best response to platinum therapy (complete or partial) • Geographical region (North America or other) • Homologous-recombination status (BRCA mutation, no BRCA mutation and HRD, homologous-recombination proficiency or not determined). The subgroup analyses were performed using a stratified Cox proportional hazards model in the prespecified subgroups. The stratification factors used in the primary analysis were used in the subgroup analyses when applicable. A statistical test for the presence of a treatment-by-subgroup interaction was performed by including the interaction term in the primary analysis model using Cox regression. If the treatment-by-subgroup interaction was found to be statistically significant at the10% level (P<0.10), this may have been taken as evidence of heterogeneity of the treatment effect across the subgroup categories.
Other relevant information	No

Trial name: SOLO1	NCT number: NCT01844986
Objective	The primary objective of the trial was to evaluate the efficacy of maintenance therapy with a PARP inhibitor (olaparib) in patients with newly diagnosed advanced ovarian cancer with a germline or somatic mutation in BRCA1, BRCA2, or both (BRCA1/2) who had a complete or partial clinical response after platinum-based chemotherapy.
Publications – title, author, journal, year	Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. Moore K, et al. N Engl J Med. 2018
Study type and design	A phase 3, randomised, double-blind, placebo-controlled, multicentre study of olaparib maintenance monotherapy in patients with BRCA mutated advanced (FIGO Stage III-IV) ovarian cancer following first--line platinum-based chemotherapy.
Sample size (n)	

Trial name: SOLO1	NCT number: NCT01844986

Main inclusion and exclusion criteria

Inclusion criteria:

- Female patients with newly diagnosed, histologically confirmed, high risk advanced (FIGO stage III - IV) BRCA mutated high grade serous or high grade endometrioid ovarian cancer, primary peritoneal cancer and / or fallopian - tube cancer who have completed first line platinum based chemotherapy (intravenous or intraperitoneal).
- Stage III patients must have had one attempt at optimal debulking surgery (upfront or interval debulking). Stage IV patients must have had either a biopsy and/or upfront or interval debulking surgery.
- Documented mutation in BRCA1 or BRCA2 that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function).
- Patients who have completed first line platinum (e.g. carboplatin or cisplatin), containing therapy (intravenous or intraperitoneal) prior to randomisation:
- Patients must have, in the opinion of the investigator, clinical complete response or partial response and have no clinical evidence of disease progression on the post treatment scan or rising CA-125 level, following completion of this chemotherapy course. Patients with stable disease on the post-treatment scan at completion of first line platinum-containing therapy are not eligible for the study.
- Patients must be randomized within 8 weeks of their last dose of chemotherapy

Exclusion criteria:

- BRCA1 and/or BRCA2 mutations that are considered to be non detrimental (e.g. "Variants of uncertain clinical significance" or "Variant of unknown significance" or "Variant, favor polymorphism" or "benign polymorphism" etc).
- Patients with early stage disease (FIGO Stage I, IIA, IIB or IIC)
- Stable disease or progressive disease on the post-treatment scan or clinical evidence of progression at the end of the patient's first line chemotherapy treatment.
- Patients where more than one debulking surgery has been performed before randomisation to the study. (Patients who, at the time of diagnosis, are deemed to be unresectable and undergo only a biopsy or oophorectomy but then go on to receive chemotherapy and interval debulking surgery are eligible).
- Patients who have previously been diagnosed and treated for earlier stage ovarian, fallopian tube or primary peritoneal cancer.
- Patients who have previously received chemotherapy for any abdominal or pelvic tumour, including treatment for prior diagnosis at an earlier stage for their ovarian, fallopian tube or primary peritoneal cancer. (Patients who have received prior adjuvant chemotherapy for localised breast cancer may be eligible, provided that it was completed more than three years prior to registration, and that the patient remains free of recurrent or metastatic disease).
- Patients with synchronous primary endometrial cancer unless both of the following criteria are met: 1) stage <2 2) less than 60 years old at the time of diagnosis of endometrial cancer with stage IA or IB grade 1 or 2, or stage IA grade 3 endometrioid adenocarcinoma OR ≥ 60 years old at the time of diagnosis of endometrial cancer with Stage IA grade 1 or 2 endometrioid adenocarcinoma. Patients with serous or clear cell adenocarcinoma or carcinosarcoma of the endometrium are not eligible.

Trial name: SOLO1	NCT number: NCT01844986
Intervention	Olaparib tablets 300 mg twice daily (N=260). Dose reduction of olaparib to 250 mg and subsequently 200 mg was permitted following confirmation of toxicity.
Comparator(s)	Placebo tablets twice daily (N=131).
Follow-up time	The patients were treated for up to 2 years or until objective radiological disease progression as per RECIST as assessed by the Investigator. Patients with evidence of stable disease (or those who had progressed), could continue on treatment beyond 2 years, if in the patient's best interest. At the DCO of SOLO1, the median follow-up time was 41 months
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	Primary endpoint • The primary endpoint was PFS as assessed by investigators. PFS was defined as the time from randomisation to objective disease progression on imaging (according to modified RECIST, version 1.1) or death from any cause. Objective disease progression on imaging was assessed using CT or MRI which was performed at baseline and every 12 weeks for up to 3 years and then every 24 weeks, until objective disease progression. Trial data collection was expected to last for approximately 7 years. Secondary endpoints included • OS assessed every 4 weeks until treatment discontinued or for 2 years (whichever was earlier), then assessed every 12 weeks. • Time to deterioration of health-related quality of life, which was assessed with the Trial Outcome Index score on the FACT-O questionnaire. FACT-O questionnaires were completed at baseline, on day 29, and every 12 weeks for 3 years and then every 24 weeks, until the time of data cut off for the primary efficacy analysis. • Safety and tolerability of olaparib. AEs were collected from informed consent until the post-treatment 30-day follow-up period. Laboratory parameter assessments were collected until trial treatment discontinued. AEs were graded with the use of CTCAE, version 4.0.

Trial name: SOLO1	NCT number: NCT01844986
Method of analysis	The primary analysis of PFS was to be performed when approximately 196 events had occurred (data maturity, approximately 50%) or when the last patient to undergo randomisation had done so at least 3 years earlier, whichever came first. The analysis of PFS was performed using a stratified log-rank test, with calculation of an HR, an accompanying 95% CI, and a P value. A sensitivity analysis of PFS as assessed by blinded independent central review was performed. The analysis of OS was performed using a similar method to that used for the analysis of PFS. The analysis of health-related quality of life evaluated the change from baseline in the Trial Outcome Index score for the first 2 years. Data on efficacy and health-related quality of life were summarised and analysed in the intention-to-treat population (all patients who underwent randomisation, regardless of the intervention that they actually received). The analysis of change from baseline in the Trial Outcome Index score was performed with a mixed-effects model for repeated measures. Data on safety were summarised in the safety population (all patients who received ≥1 dose of the trial intervention).
Subgroup analyses	Subgroup analyses will be conducted comparing PFS between treatments in the following subgroups of the full analysis set: • Response to previous platinum chemotherapy (clinical complete response or partial response) • ECOG performance status at baseline (0 or 1) • Baseline CA-125 value (≤ ULN vs > ULN) • Age at randomisation (<65 vs. >=65) • Stage of disease at initial diagnosis (III or IV)
Other relevant information	

Trial name: PAOLA-1	NCT number: NCT02477644
Objective	Evaluate maintenance therapy with a PARP inhibitor (olaparib) compared with placebo in patients with newly diagnosed advanced ovarian cancer who were receiving chemotherapy plus bevacizumab followed by bevacizumab, regardless of *BRCA* mutation status
Publications – title, author, journal, year	Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. **Ray-Coquard I**, Pautier P, Pignata S, Pérol D, González-Martín A, Berger R, Fujiwara K, Vergote I, Colombo N, Mäenpää J, Selle F, Sehouli J, Lorusso D, Guerra Alía EM, Reinthaller A, Nagao S, Lefeuvre-Plesse C, Canzler U, Scambia G, Lortholary A, Marmé F, Combe P, de Gregorio N, Rodrigues M, Buderath P, Dubot C, Burges A, You B, Pujade-Lauraine E, Harter P. *N Engl J Med* 2019;381:2416–28

Trial name: PAOLA-1	NCT number: NCT02477644

Study type and design

- Phase 3, randomised . Patients were randomisered 2:1 to olaparib + bevacizumab or placebo + bevacizumab
- The study included patients between July 2015 and September 2017
- Stratification: BRCA status and 1st line treatment success
- Tumor characteristics as assessed by the myChoice® HRD Plus assay (Myriad Genetic Laboratories, Inc
- HRQoL tool EORTC QLQ-C30
- Kaplan–Meier was used to estimate PFS.
- Hazard ratio(HR) and related 95% confidence intervals were calculated using stratified Cox proportional-hazards model.

Sample size (n)

806 patients underwent randomization. A total of 535 of the 537 patients assigned to olaparib plus bevacizumab (olaparib group) and 267 of the 269 patients assigned to placebo plus bevacizumab (placebo group) received the trial intervention; 2 patients in each group withdrew before receiving the trial intervention

Main inclusion and exclusion criteria

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

Intervention

Intervention:

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

Olaparib administrated as:

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

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

Trial name: PAOLA-1	NCT number: NCT02477644

Comparator(s)

Bevacizumab:

15 mg/kg every 3rd week(+ placebo DID) for up to 15 months including pre-randomisation period where the patient receiced **platinum-based chemotherapy**.

Follow-up time

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

[redacted]

Is the study used in the health economic model?

Yes

Primary, secondary and exploratory endpoints

Primary:

- PFS

Secondary:

- OS
- time to second disease progression or death
- time to start of first subsequent therapy or death (TFST)
- time to start of second subsequent therapy or death (TSST)
- QoL
- toxicity

Method of analysis

The trial was designed to detect a treatment effect (hazard ratio for disease progression or death) of 0.75, translating to an improvement in median progression-free survival from 15.8 months in the placebo group to 21.1 months in the olaparib group; 458 primary end-point events (disease progression or death) would give the trial more than 80% power at a two-sided significance level of 5% to show a significant difference in progression-free survival between the olaparib group and the placebo group.

Trial name: PAOLA-1	NCT number: NCT02477644

Subgroup analyses

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

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

All subgoups were predefined except for:

- HRD negative
- HRD unknown

Other relevant information	No

Appendix C Baseline characteristics of patients in studies used for the comparative analysis

Baseline characteristics are included in Table 2, Table 4, and Table 5 in section 5.1.1.

Appendix D Efficacy and safety results per study

Data from relevant clinical trials are included in the table below.

Efficacy and safety results are also discussed in chapter 7. In particular, see efficacy and safety results in Table 10**Error! Reference source not found.** - Table 13

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

Discontinuations HRD+	Placebo + bev	127	8 (6.1%)					1,46; 6,12		
AE of CTCAE grade 3 or Higher. HRD+	Olaparib + bev	255	144 (56.5%)	[redacted]	-5.9¸16.5	NA	RR=1.1	0,90; 1,35	NA	Calculated by AstraZeneca
	Placebo + bev	127	65 (51.1 %)							
OS HRD+ BRCAm	Olaparib + bev	255	NR(NR, NR)	NA	NA	NA	HR= 0.55	0.33, 0.92	0.0189	
	Placebo + bev	135	NR(NR, NR)							
Median OS	Olaparib + bev	537	56.5m	4.9m	NA	NA	HR=0.92	(0.76; 1.12)	0.418	2022 update
	Placebo + bev	269	51.6m							
Median OS HRD+ exBRCA	Olaparib + bev	97	NR	NA	NA	NA	HR=0.71	(0.45; 1.13)	NA	2022 update
	Placebo + bev	55	52m							
Median OS BRCAm	Olaparib + bev	157	75.2m	8.3m	NA	NA	HR=0.60	(0.39; 0.93)	NA	2022 update
	Placebo + bev	80	66.9m							
Median OS HRD+ incl. BRCAm	Olaparib + bev	255	46.8m	29.2m	NA	NA	HR=0.41	(0.32; 0.54)	NA	2022 update
	Placebo + bev	132	17.6m							
HQoL (QLQ-C30)	Olaparib + bev	537	0.13 (1.02, 1.27)	0.59	-1.40, 2.57	P = 0.5626	NA	NA	NA	The analysis was performed using an MMRM analysis of the change from baseline QLQ-C30 QoL score for all post-baseline visits (up to study treatment discontinuation) with treatment, visit and treatment by visit interaction included as explanator variables and the baseline QLQ-C30 QoL score included as a covariate along with the baseline QLQ-C30 QoL score by visit interaction.
	Placebo + bev	269	-0.46 (-2.08, 1.16)							
	Olaparib + bev	398	[redacted]	[redacted]	NA	RR=1.1	0.96; 1.33	NA	NA	

AE of CTCAE grade 3 Higher Risk	Placebo + bev	194	[redacted]							Supplement material Harter et al. 2022 Calculated by AstraZenca. DCO March 2019
Discontinuations HRD+ non- BRCAm Higher Risk	Olaparib + bev	398	[redacted]	[redacted]	NA	R=3.3	1.81; 6,11	NA	NA	Calculated by AstraZenca. DCO March 2019
	Placebo + bev	194	[redacted]							
AE of CTCAE grade 3 Lower Risk	Olaparib + bev	137	[redacted]	3,4%	NA	RR=4,53	1,67, 12,3	NA	NA	Calculated by AstraZenca. DCO March 2019
	Placebo + bev	73	[redacted]							
Discontinuations non- BRCAm Lower Risk	Olaparib + bev	137	[redacted]	18,3%	NA	RR=1.07	0.82;1.39	NA	NA	Calculated by AstraZenca. DCO March 2019
	Placebo + bev	73	[redacted]							

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

Median OS 7 years update in ()	Olaparib	260	NR.(NR (NR; NR)) 70.4 % alive (67 %)	0.9 %(20.5%)	NA	NA	HR=0.95 (HR=0.55)	(0.60; 1.53) ((0.40; 0.76))	*P*=0.8903 (p=0.004)	At the time of the DCO (17 May 2018), data were immature (82/391 events, 21.0% maturity). 7 years update was published in J. of Clinical Onc. September 2022. DCO (March 7, 2022). The median duration of treatment was 24.6 months with olaparib and 13.9 months with placebo, and the median follow-up was 88.9 and 87.4 months
	Placebo	131	NR (75.2 months (95% CI, 65.4, NR) 69.5 % alive (46.5%)							
3-year OS rate	Olaparib	260	84%	4 %	NA	NA	HR=0.95	(0.60; 1.53)	NA	At the time of the DCO (17 May 2018), data were immature (82/391 events, 21.0% maturity)
	Placebo	131	80%							
TFST	Olaparib	260	64.0 m (47.7; 93.2)	[redacted]	NA	NA	HR=0.37	(0.28; 0.48)	NA	7 years update was published in J. of Clinical Onc. September 2022. DCO (March 7, 2022). Data maturity 59.6%
	Placebo	131	15.1 m (12.7; 20.5)							
TSST	Olaparib	260	93.2 m (84.2; NR)	[redacted]	NA	NA	HR=0.50	(0.37; 0.67)	NA	7 years update was published in J. of Clinical Onc. September 2022. DCO (March 7, 2022) Data maturity 48.6%
	Placebo	131	40.7 m (32.9; 54.4)							
Discontinuations due to AEs. 7 years update in ()	Olaparib	260	11,5 % (11.9%)	[redacted]	(4.0 – 14.5)	NA	RR = 5.0 (3.9)	(1.56; 16,08) (1.4; 10.8)	NA	RR calculated by AstraZeneca
	Placebo	131	2,3 % (3.1%)							
HQoL 24 months	Olaparib	237	0.3 (-0.72, 1.32)	- 3.00	(-4.8 - -1.2)	*P*=0.001	NA	NA	NA	TOI scorer. Baseline 73.6 (SD 12.8) and 75 (SD 13.1)
	Placebo	125	3.3 (1.84, 4.76)							

Any AE	Olaparib	260	256 (98,5%)	[redacted]	NA	NA	RR=1.07	(1.01; 1.12)		7 years update was published in J. of Clinical Onc. September 2022. DCO (March 7, 2022) RR and CI intervals Calculated by AstraZeneca
	Placebo	130	120 (92.3%)							
AE of CTCAE grade 3 or higher. 7 years update in ()	Olaparib	260	39.2 % (39,6%)	[redacted]	(11.4 – 30.4)	NA	RR = 2,13 RR = 1.99	(1.44, 3.14) ((1.36; 2.88))	NA	7 years update was published in J. of Clinical Onc. September 2022. DCO (March 7, 2022) RR and CI intervals Calculated by AstraZeneca
	Placebo	130	18.5 % (20%)							

Table A3a Results of PRIMA

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
OS rate[1] (%) (HRD)	Niraparib	247	91.1 (87.5; 94.6)	6.2	-1.01; 13.36	0.0774	HR: 0.61	0.27; 1.39	0.237	All time-to-event endpoints were analysed with a stratified log-rank test using randomisation stratification factors and summarised using Kaplan-Meier methodology. HRs with 95% CIs were estimated using a stratified Cox proportional hazards model, with stratification factors used in randomisation.	González-Martin 2019
	Placebo	126	**17.4 (15.0–19.8)** months								
OS rate[1] (%) (BRCAwt, HRP)	Niraparib	169	81.1 (75.2; 87.0)	22.3	10.0; 34.6	0.0002	HR: 0.51	0.27; 0.97	0.039	See above	González-Martin 2019
	Placebo	80	58.7 (48.0; 69.5)								
Median PFS[2], BICR (months) (BRCAm)	Niraparib	152	22.1 (19.3; NE)	11.2	NE	NE	HR: 0.40	0.27; 0.62	<0.001	See above	González-Martin 2019
	Placebo	71	10.9 (8.0–19.4)								
PFS rate[2] BICR (%) (BRCAm)	Niraparib	152	67.8 (60.3; 75.2)	24.1	10.38; 37.82	0.0007	HR: 0.40	0.27; 0.62	<0.001	See above	González-Martin 2019
	Placebo	71	43.7 (32.1; 55.2)								

Table A3a Results of PRIMA

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
PFS[2], BICR (months) (BRCAwt, HRD)	Niraparib	95	19.6 (13.6; NE)	11.4	NE	NE	HR: 0.50	0.31; 0.83	0.006		González-Martin 2019
	Placebo	55	8.2 (6.7; 16.8)								
PFS rate[2], BICR (%) (BRCAwt, HRD)	Niraparib	95	66.3 (56.8; 75.8)	26.3	10.25; 42.38	0.0017	HR: 0.50	0.31; 0.83	0.006		González-Martin 2019
	Placebo	55	40.0 (27.1; 52.9)								
Median PFS2, BICR (months) (BRCAwt, HRP)	Niraparib	169	8.1 (5.7; 9.4)	2.7	0.2; 5.2	0.0328	HR: 0.68	0.49; 0.94	0.002		González-Martin 2019
	Placebo	80	5.4 (4.0; 7.3)								
PFS rate2, BICR (%) (BRCAwt, HRP)	Niraparib	169	34.3 (27.2; 41.5)	4.3	8.01; 16.65	0.4964	HR: 0.68	0.49; 0.94	0.020		González-Martin 2019
	Placebo	80	30.0 (20.0; 40.0)								

Table A3a Results of PRIMA

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion discontinued due to AE[3]	Niraparib	484[4]	12.0 (9.1; 14.9)	9.5	6.04; 13.01	<0.0001	RR: 4.87	2.13; 11.14	<0.0001		González-Martin 2019
	Placebo	244[4]	2.5 (0.5; 4.4)								
Proportion with CTCAE ADR ≥grade 3[5]	Niraparib	484[3]	65.3 (61.0; 69.5)	58.7	53.48; 63.99	<0.0001					González-Martin 2019
	Placebo	244[3]	6.6 (3.5; 9.7)								

[1] OS data maturity 10.8% in overall population. Median estimates were not reported due to low event rate and insufficient follow-up time. [2] The HRs for PFS are provided from the publication and there is only one HR per population. [3] Proportions of patients discontinued due to ADRs are not reported; instead, proportions discontinued due to AE are provided. [4] Proportions are calculated based on the safety set, which comprised all randomised patients who received at least one dose of trial treatment. [5] Proportions of patients with CTCAE grade 3-4 ADR are not reported; instead, proportions with CTCAE grade ≥3 ADR are provided.

Appendix E Safety data for intervention and comparator(s)

The safety for intervention and comparator is discussed in section **Error! Reference source not found.** .

Appendix F Comparative analysis of efficacy and safety

Comparative analysis of efficacy and safety is included in sections 7.1 - 7.3.

Table A4 Meta-analysis of studies comparing olarparib plus bevazimab to niraparib for Lower-Risk HRD+ OC patients

Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference	CI	*P* value	Difference	CI	*P* value		
Median PFS	**PAOLA1** **SOLO1**	*	NA	NA	NA	NA	NA	PAIC (Hettle 2021) *value of adding bevacizumab	Yes
PFS rate at 24m(%)	**PAOLA1** 81% vs 45 % **SOLO1** 95% vs 44%	*15 %	NA	NA	NA	NA	NA	PAIC (Hettle 2021) *value of adding bevacizumab	Yes

Table A4 Meta-analysis of studies comparing olaparib plus bevazimab to olaparib for Higher-Risk HRD+ OC patients									
Outcome	**Studies included in the analysis**	**Absolute difference in effect**			**Relative difference in effect**			**Method used for quantitative synthesis**	**Result used in the health economic analysis?**
		Difference	**CI**	***P* value**	**Difference**	**CI**	***P* value**		
Median PFS	**PAOLA** 36,0m (23,2; NA) vs 17,6m (14,7;19,6) **PRIMA** 22 m (19,3; NA) vs 10,5m (8,05; 12,1)	7.1m*	NA	NA	NA	NA	NA	PAIC *value of adding bevacizumab	Yes
PFS rate at 24m(%)	**PAOLA** 58 vs 26 **PRIMA** 47 vs 26	11%*	NA	NA	NA	NA	NA	PAIC *value of adding bevacizumab	Yes

Appendix G Extrapolation

G1. Parametric estimates of time-to-treatment discontinuation

As only the olaparib + bevacizumab arm is used in the extrapolations and not the control arm (bevacizumab alone), testing the proportional hazards assumption is of less relevance than if relative efficacy over time is considered.

Some standard statistics are still included, such as cumulative hazard plots, Cox-Snell residuals and Schoenfeld residuals.

G1.1 Kaplan Meier plot – High-risk HRD+ BRCAwt population

G1.2 Treatment duration – High-risk HRD+ BRCAwt population

G1.3 Logrank test(s) – High-risk HRD+ BRCAwt population

Table G1. Logrank test(s) – High-risk HRD+ BRCAwt population

row_names	Statistic	df	p-value
No stratification	3.686	1	0.055

G1.4 Restricted means – High-risk HRD+ BRCAwt population

Restricted means are calculated until the last time point where each arm has observations, using the area under KM curve with confidence interval at the 95% level.

Table G2. Restricted means

Arm	RMST	SE	Lower CI	Upper CI	p-value
Placebo bd	14.023	1.146	11.778	16.268	
Olaparib 300 mg bd	14.849	1.094	12.705	16.993	
Difference	0.826	1.584	-2.279	3.930	0.602

G1.5 Cumulative Hazards plots – High-risk HRD+ BRCAwt population

The following are diagnostic plots to check assumptions. Linear trends indicate that there are no clear violations to the model assumptions for the corresponding distribution In the exponential diagnostic plot, the gradient corresponds to the hazards and parallel lines indicate proportional hazards In the Weibull, parallel lines indicate proportional hazards and a gradient of 1 indicates exponential survival. In the Loglogistic diagnostic plot, parallel lines indicate proportional odds and in the Lognormal diagnostic plot, parallel lines indicate constant acceleration.

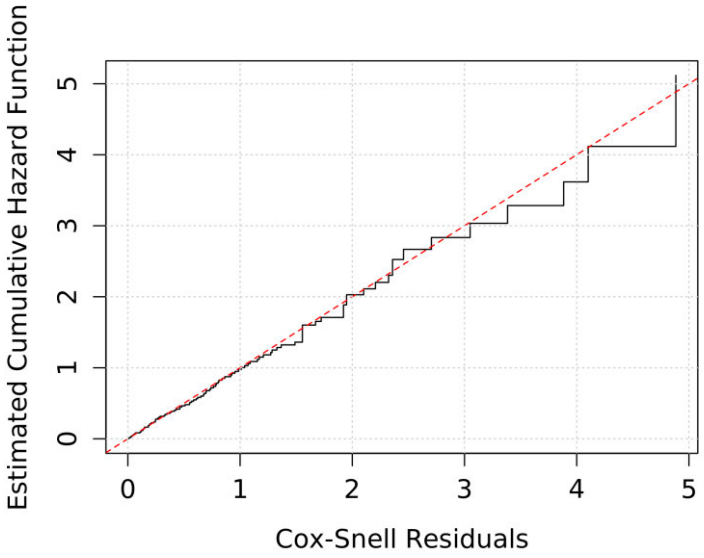
[redacted]

[redacted]

[redacted]

[redacted]

Figure G6. Cox Snell residuals



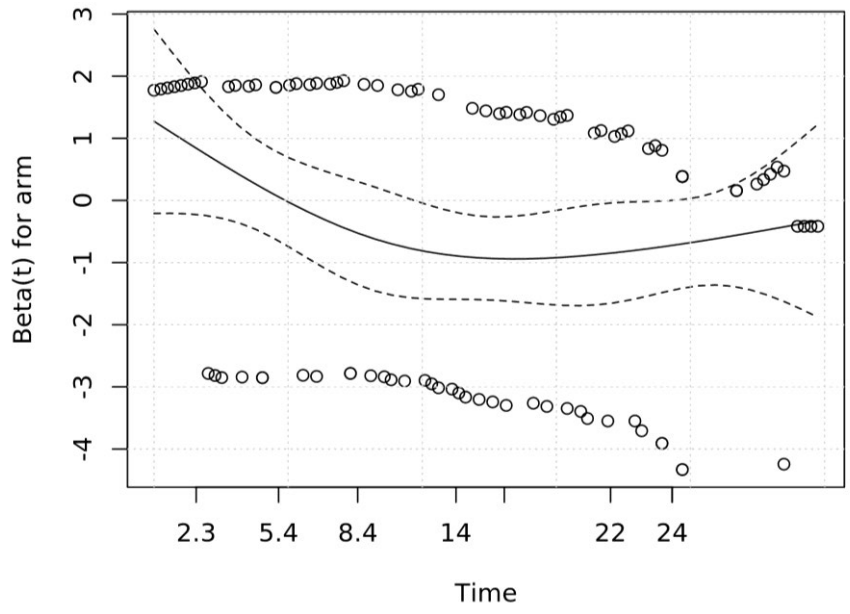
A straight line with slope=1 in the Cox Snell residuals plot indicates that a Cox model fits the data well.

Schoenfeld residuals have been calculated using the km transform.

Table G3. Chi square statistics for the Schoenfeld residuals

	chisq	df	p
Olaparib 300 mg bd	4.025	1	0.045

Figure G7. Schoenfeld residuals



The Schoenfeld residuals can be used to test the proportional hazard assumption. If PH, the plot of the residuals against time should show a linear trend with slope=0. The visual inspection of this

plot is more important than the test, however, a p-value is also output as the result of a test of non-negative slope (Therneau and Grambsch).

G1.6 AIC/BIC values – TTD distributions – High-risk HRD+ BRCAwt population

Akaike and Bayesian information criteria by treatment arm are shown in Table G4. The models with lower values fit data better. For olaparib + bevacizumab, the lognormal distribution has the lowest AIC and BIC values. (Only values for olaparib + bevacizumab are shown as bevacizumab monotherapy is not used in the model).

Table G4. Parametric fit according to Akaike and Bayesian information criteria – High-risk HRD+ BRCAwt population.

	Olaparib 300 mg bd*	
Model	**AIC**	**BIC**
Exponential	481.76	483.91
Weibull	442.87	447.16
Loglogistic	436.57	440.86
Lognormal	428.41	432.70
Gompertz	461.43	465.72
Gamma	443.71	448.00

*Olaparib should be understood as olaparib + bevacizumab (as bevacizumab is used in the control arm)

G1.7 Model parameter estimates – High-risk HRD+ BRCAwt population

Table G5. Model parameter estimates for time to treatment discontinuation – High-risk HRD+ BRCAwt population.

Exponential	**est**	**L95%**	**U95%**
rate	0.04399	0.03852	0.063121

Weibull	**est**	**L95%**	**U95%**
shape	1.121	0.911921	1.398532
scale	21.439	18.09398	25.40027

Loglogistic	**est**	**L95%**	**U95%**
shape	1.151	1.21419	1.841204
scale	15.191	11.27235	18.11691

Lognormal	**est**	**L95%**	**U95%**
meanlog	2.7036	2.345628	2.901882
sdlog	1.165	0.978392	1.387286

Gompertz	**est**	**L95%**	**U95%**
shape	0.0546	0.031188	0.068012

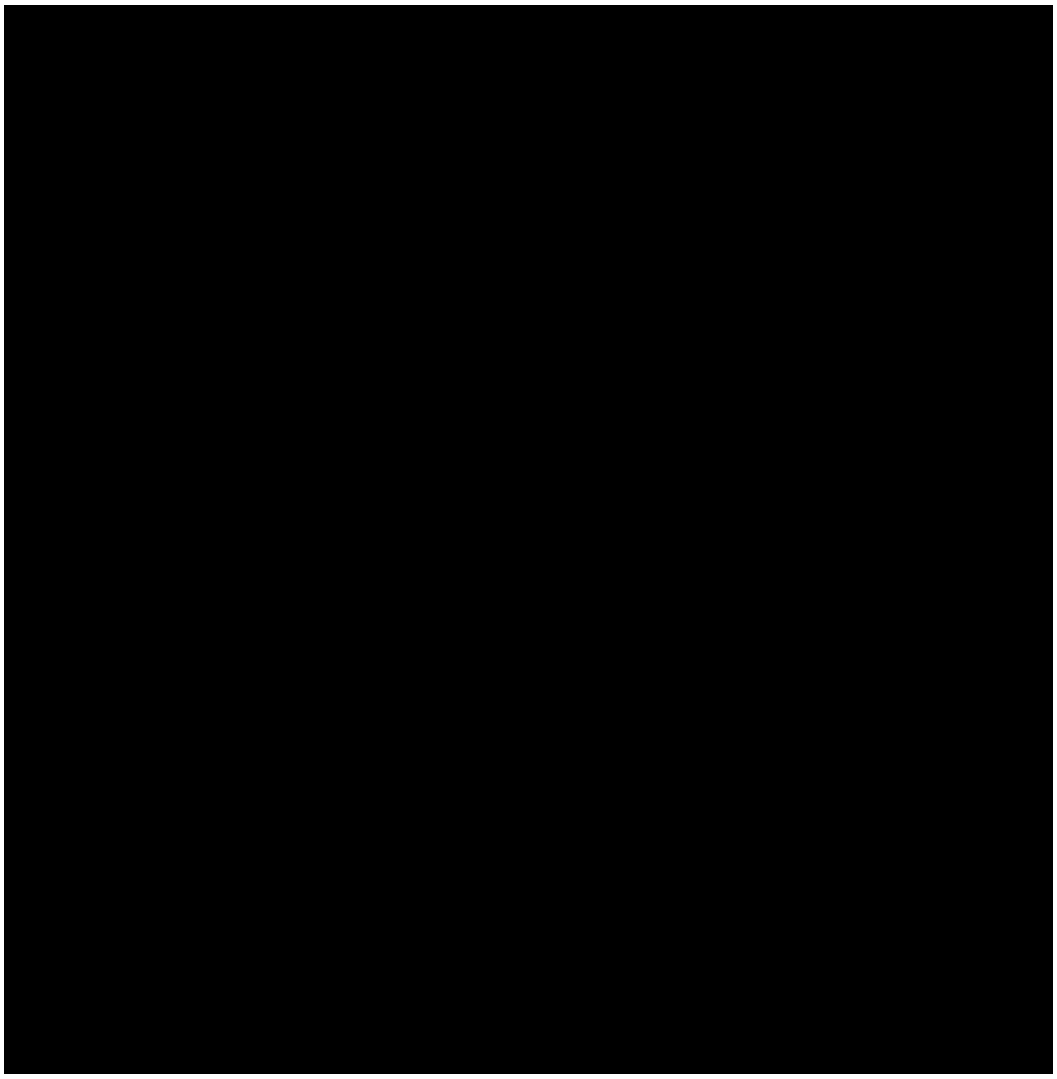
rate	0.027291	0.015848	0.046997

Gamma	est	L95%	U95%
alfa	1.2166	0.927637	1.757594
beta	17.035	11.71745	24.76729

G1.8 Parametric survival curves – High-risk HRD+ BRCAwt population

The models are plotted with the KM data to illustrate how well they capture the trends. Most distributions have relatively good visual fit, with some having better fit for the first 12 months and other better fit between 12 and 24 months.

The hazard rate plot for TTD KM in the high-risk group suggest that the hazard of discontinuing treatment is increasing in the olaparib + bevacizumab arm slowly but steadily for the first 23 months, then goes up very rapidly as patients stop treatment at around 24 months. Among the extrapolations, the Gompertz distribution is something of an outlier and does not seem to have the best fit for the 24-month period that is of most interest.



With the time period limited to 24 months, it is easier to perceive trends in the hazard rate for the extrapolations. The lognormal distribution was chosen for the extrapolation base case as it had the lowest AIC and BIC values. In terms of trends for the hazard rate, visual inspection would suggest that gamma and Weibull would capture the slowly increasing trend even better. These two were 3rd and 4th in terms of AIC and BIC values for the statistical fit and were also included in sensitivity analyses. However, what happens at the end of the curves close to 24 months should be interpreted with caution as there are fewer patients at risk and the treatment is stopping at 24 months. Hence, lognormal is still the most plausible choice for the base case.

G1.9 Kaplan Meier plot – Low-risk HRD+ BRCAwt population

G1.10 Treatment duration – Low-risk HRD+ BRCAwt population

G1.11 Logrank test(s) – Low-risk HRD+ BRCAwt population

Table G6. Logrank test(s) – Low-risk HRD+ BRCAwt population

row_names	Statistic	df	p-value
No stratification	7.96	1	0.006

G1.12 Restricted means – Low-risk HRD+ BRCAwt population

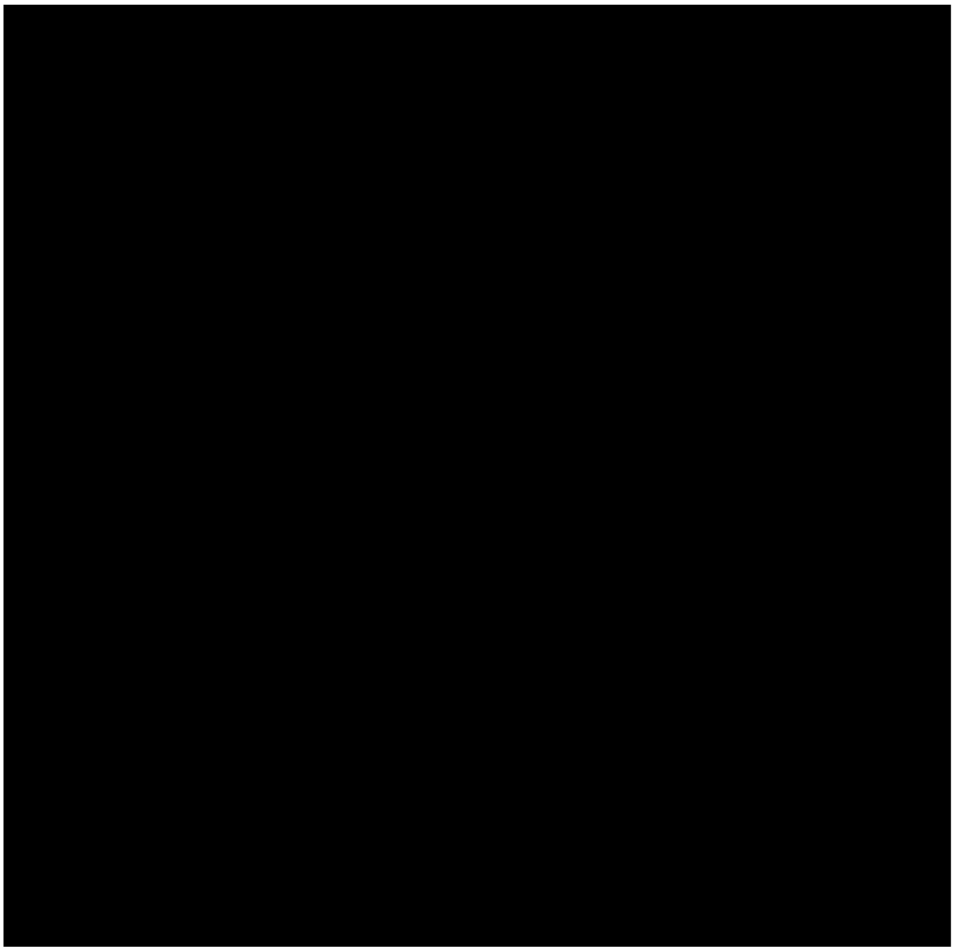
Restricted means are calculated until the last time point where each arm has observations, using the area under KM curve with confidence interval at the 95% level.

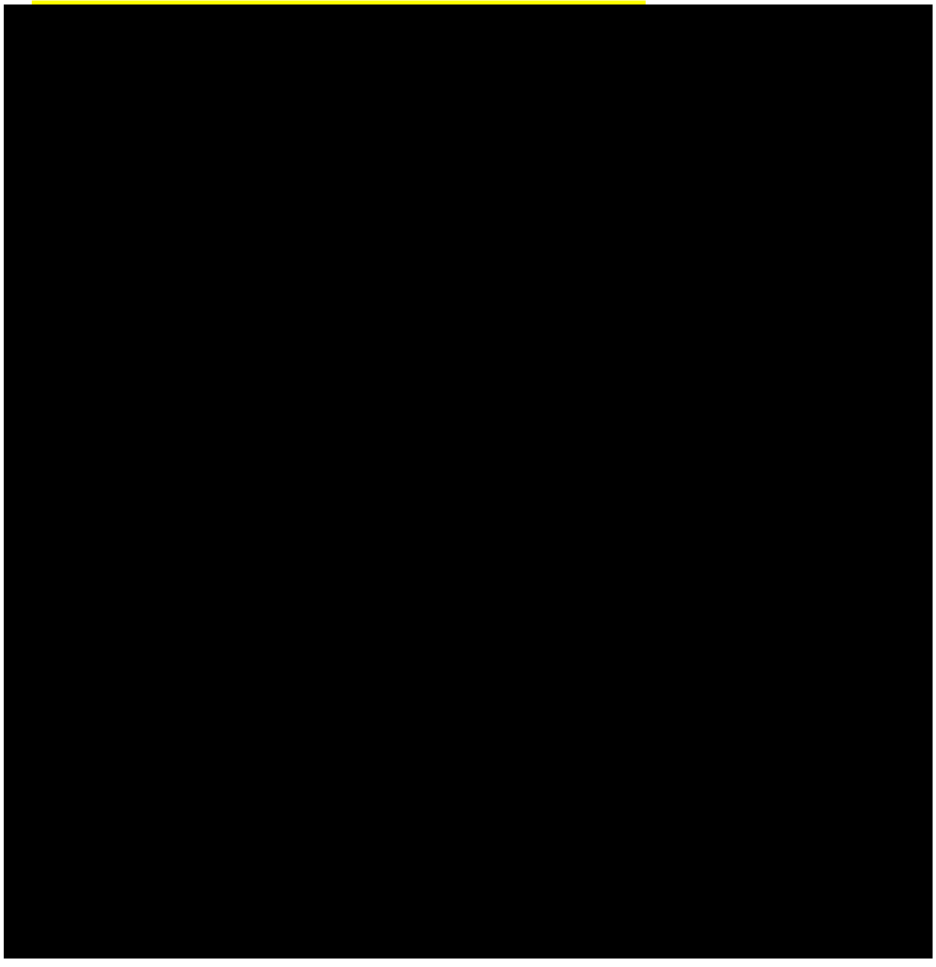
Table G7. Restricted means

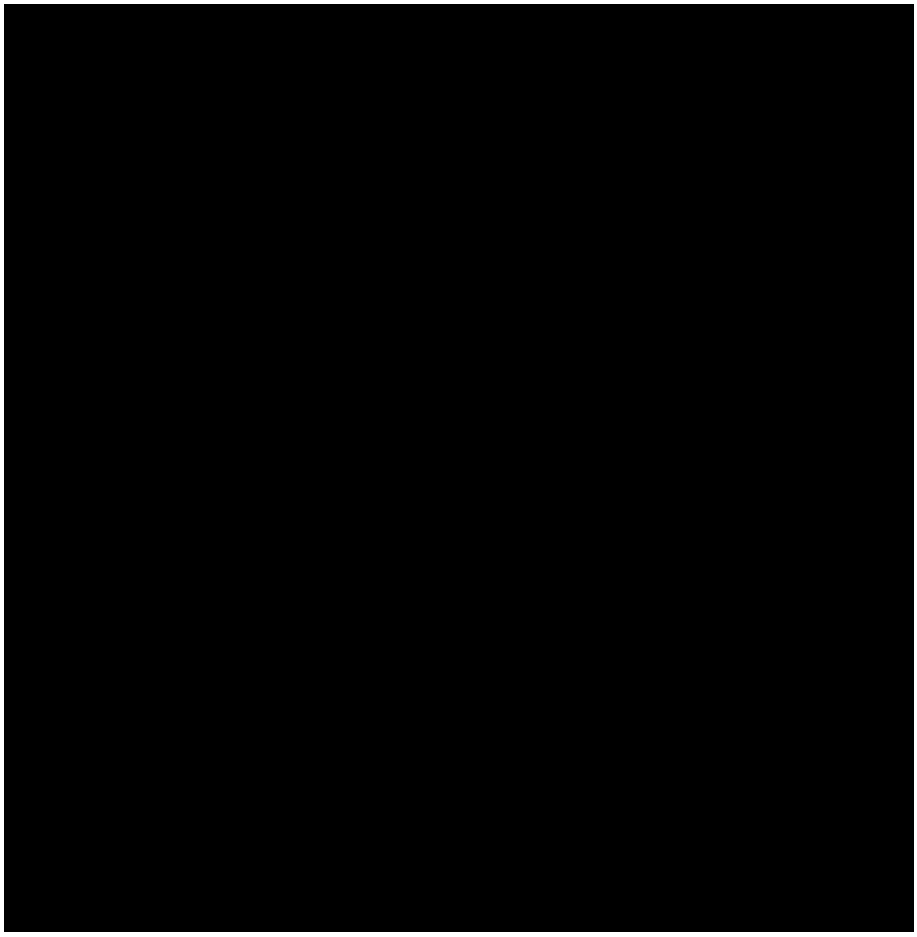
Arm	RMST	SE	Lower CI	Upper CI	p-value
Placebo bd	18.110	1.681	14.815	21.405	
Olaparib 300 mg bd	20.302	1.133	18.081	22.523	
Difference	2.192	2.0273	-1.782	6.166	0.438

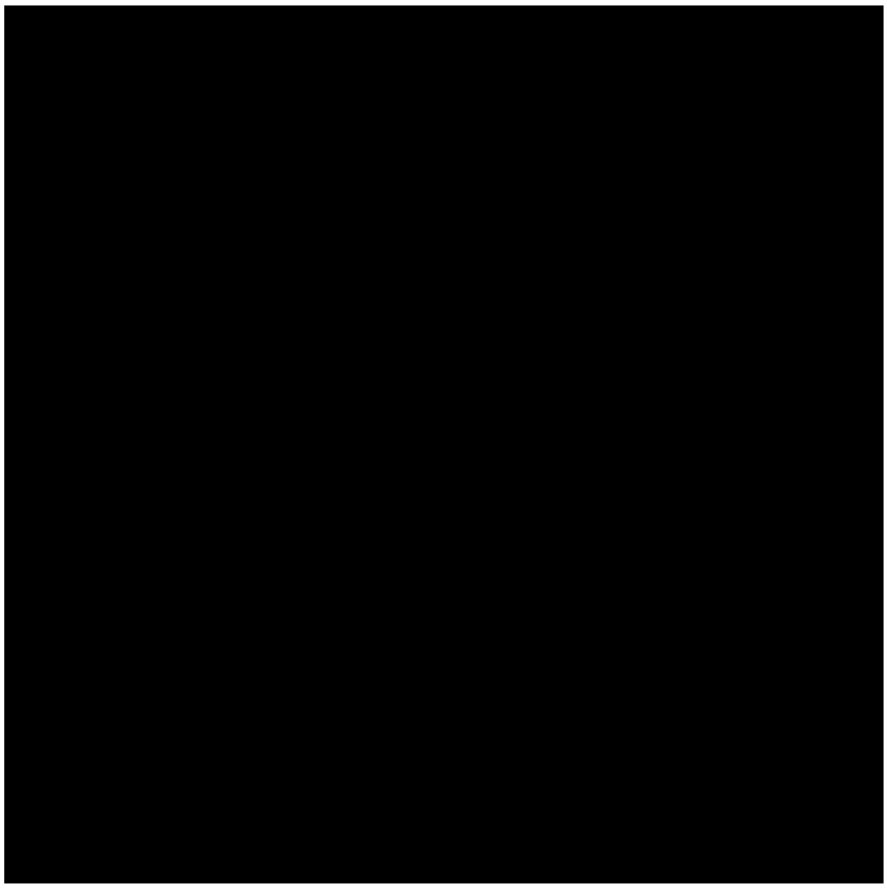
G1.13 Cumulative Hazards plots – Low-risk HRD+ BRCAwt population

The following are diagnostic plots to check assumptions. Linear trends indicate that there are no clear violations to the model assumptions for the corresponding distribution In the exponential diagnostic plot, the gradient corresponds to the hazards and parallel lines indicate proportional hazards In the Weibull, parallel lines indicate proportional hazards and a gradient of 1 indicates exponential survival. In the Loglogistic diagnostic plot, parallel lines indicate proportional odds and in the Lognormal diagnostic plot, parallel lines indicate constant acceleration.









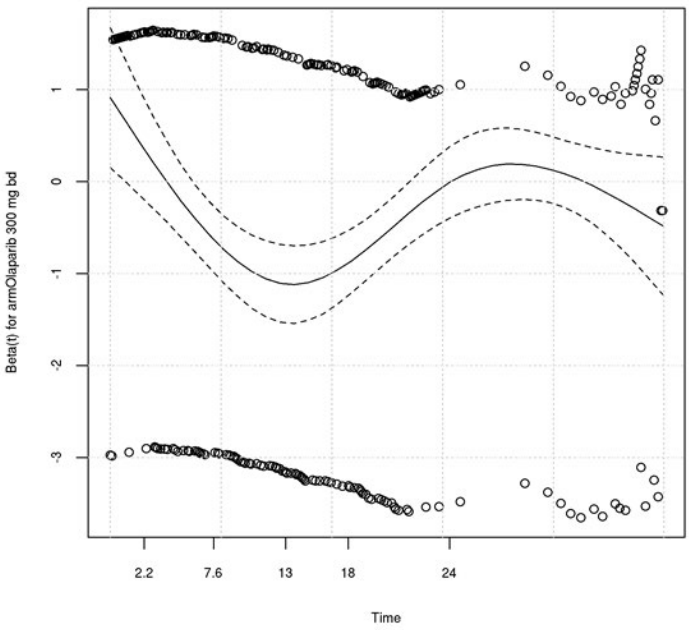
A straight line with slope=1 in the Cox Snell residuals plot indicates that a Cox model fits the data well.

Schoenfeld residuals have been calculated using the km transform.

Table G8. Chi square statistics for the Schoenfeld residuals

	chisq	df	p
Olaparib 300 mg bd	0.033	0.422	0.516

Figure G18. Schoenfeld residuals



The Schoenfeld residuals can be used to test the proportional hazard assumption. If PH, the plot of the residuals against time should show a linear trend with slope=0. The visual inspection of this plot is more important than the test, however, a p-value is also output as the result of a test of non-negative slope (Therneau and Grambsch).

G1.14 AIC/BIC values – TTD distributions – Low-risk HRD+ BRCAwt population

Akaike and Bayesian information criteria by treatment arm are shown in Table G9. The models with lower values fit data better. For olaparib + bevacizumab, the Weibull distribution has the lowest AIC and BIC values. (Only values for olaparib + bevacizumab are shown as bevacizumab monotherapy is not used in the model).

Table G9. Parametric fit according to Akaike and Bayesian information criteria.

	Olaparib 300 mg bd*	
Model	**AIC**	**BIC**
Exponential	245.93	248.08
Weibull	228.56	232.85
Loglogistic	229.21	233.50
Lognormal	229.81	234.10

Gompertz	257.56	261.85
Gamma	229.14	233.43

*Olaparib should be understood as olaparib + bevacizumab (as bevacizumab is used in the control arm)

G1.15 Model parameter estimates – Low-risk HRD+ BRCAwt population

Table G10. Model parameter estimates for time to treatment discontinuation.

Exponential	est	L95%	U95%
rate	0.0135	0.03852	0.063121

Weibull	est	L95%	U95%
shape	0.7771	0.911921	1.398532
scale	112.35	18.09398	25.40027

Loglogistic	est	L95%	U95%
shape	0.774	1.21419	1.841204
scale	98.52	11.27235	18.11691

Lognormal	est	L95%	U95%
meanlog	4.397	2.345628	2.901882
sdlog	1.948	0.978392	1.387286

Gompertz	est	L95%	U95%
shape	0.0051	0.031188	0.068012
rate	0.0135	0.015848	0.046997

Gamma	est	L95%	U95%
alfa	0.8503	0.927637	1.757594
beta	105.22	11.71745	24.76729

G1.16 Parametric survival curves – Low-risk HRD+ BRCAwt population

The models are plotted with the KM data to illustrate how well they capture the trends. Most distributions have relatively good visual fit up to 24 months.

The hazard rate plot for TTD KM in the low-risk group also suggest that the hazard of discontinuing treatment is increasing in the olaparib + bevacizumab arm slowly but steadily for the first 23 months, then goes up very rapidly as patients stop treatment at around 24 months. The extrapolations are more similar in terms of hazard development, with no clear outlier (Figure G20).

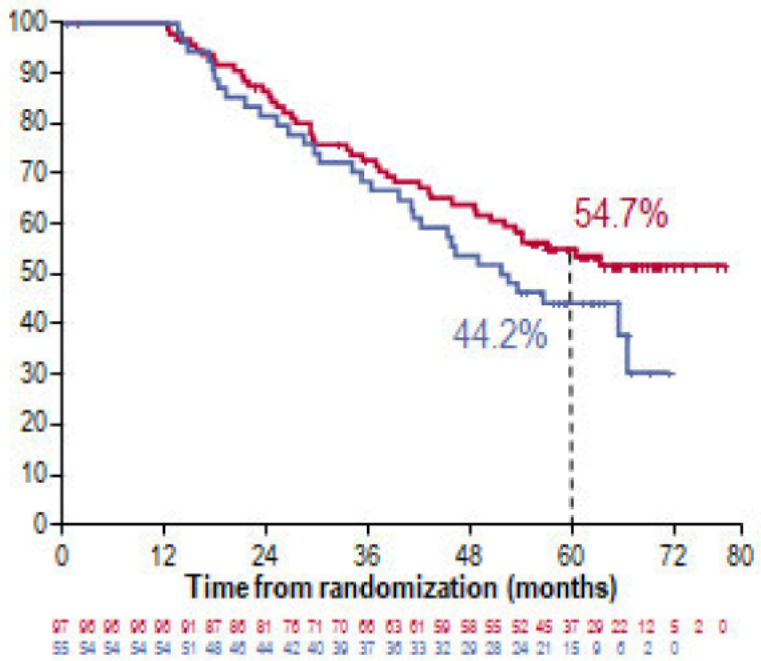
With the time period limited to 24 months, it is once again easier to perceive trends in the hazard rate for the extrapolations. The Weibull distribution was chosen for the extrapolation base case as it had the lowest AIC and BIC values. In terms of trends for the hazard rate, visual inspection would suggest that none of the distributions capture the slowly increasing trend really (Figure G21). As mentioned before, what happens at the end of the curves close to 24 months should be interpreted with caution as there are fewer patients at risk as the treatment is stopping at 24

months. Hence, Weibull is still the most plausible choice for the base case, as it captures the early increase in the hazard rate better than for example Gompertz or exponential. Gompertz and exponential also had the worst fit according to AIC and BIC.

G2. Parametric estimates of overall survival

G2.1 Kaplan Meier plot – HRD+ BRCAwt population

Figure G22. Kaplan Meier survival curve per arm for the HRD positive BRCAwt subgroup



Source: Ray-Coquard 2022

G2.2 Summary of outcomes

Key outcomes in the HRD positive BRCAwt subgroup are summarized in Table G11.

Table G11. Summary of outcomes for the HRD positive BRCAwt subgroup

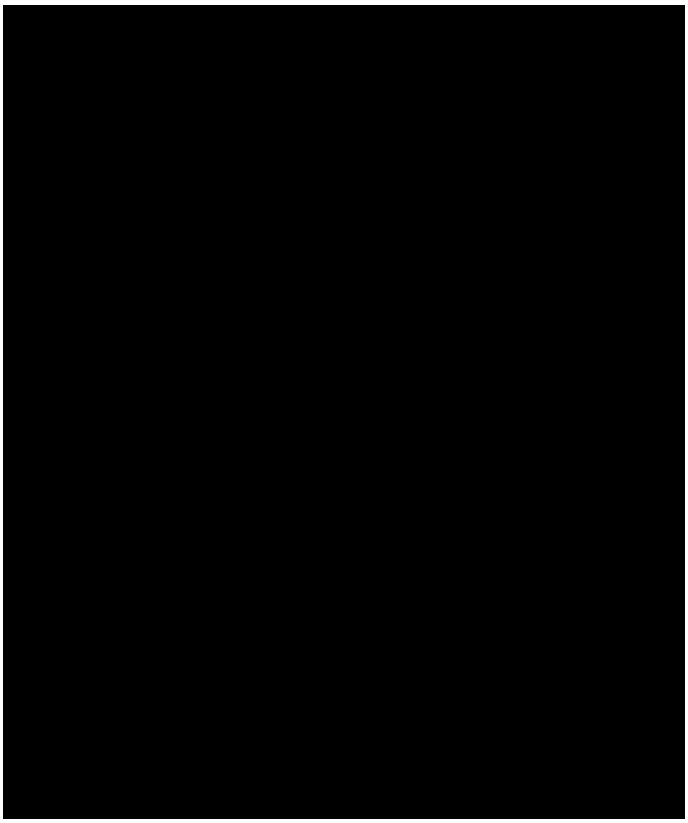
Outcome	Olaparib + bevacizumab (N=97)	Placebo + bevacizumab (N=55)
Events	44 (45.4)	32 (58.2)
Median OS, months	NR	52.0
5-year OS rate, %	**54.7**	**44.2**
PARPi as subsequent treatment, n (%)	9 (9.3)	23 (41.8)
OS hazard ratio (95% CI)	**HR 0.71** (0.45–1.13)	

Source: Ray-Coquard 2022

G2.3 Cumulative Hazards plots –HRD+ BRCAwt population

The following are diagnostic plots to check assumptions. Linear trends indicate that there are no clear violations to the model assumptions for the corresponding distribution In the exponential

diagnostic plot, the gradient corresponds to the hazards and parallel lines indicate proportional hazards. In the Weibull, parallel lines indicate proportional hazards and a gradient of 1 indicates exponential survival (Figure G23). In the Loglogistic diagnostic plot, parallel lines indicate proportional odds (Figure G24) and in the Lognormal diagnostic plot, parallel lines indicate constant acceleration (Figure G25). However, only the olaparib + bevacizumab arm is used in the model. Hence, the proportional hazard assumptions is of less interest for this analysis.



[redacted]

[redacted]

Schoenfeld residuals have been calculated using the km transform (Figure G26).

The Schoenfeld residuals can be used to test the proportional hazard assumption. If PH, the plot of the residuals against time should show a linear trend with slope=0.

G2.4 AIC/BIC values – OS distributions – HRD+ BRCAwt population

Akaike and Bayesian information criteria by treatment arm are shown in Table G12. The models with lower values fit data better. For olaparib + bevacizumab, the lognormal distribution has the lowest AIC and BIC values. (Only values for olaparib + bevacizumab are shown as bevacizumab monotherapy is not used in the model).

Table G12. Parametric fit according to Akaike and Bayesian information criteria –HRD+ BRCAwt population.

	Olaparib 300 mg bd*	
Model	**AIC**	**BIC**
Exponential	814.83	825.18
Weibull	819.48	829.83
Loglogistic	806.43	816.78
Lognormal	805.29	815.64
Gompertz	817.55	827.90
Gamma	814.70	825.05

*Olaparib should be understood as olaparib + bevacizumab (as bevacizumab is used in the control arm)

G2.5 Model parameter estimates – HRD+ BRCAwt population

Model parameters are presented in Table G13.

Table G13. Model parameter estimates for overall survival – HRD+ BRCAwt population.

Exponential	est	L95%	U95%
rate	0.009183	0.006960	0.011406

Weibull	est	L95%	U95%
shape	1.7080	1.348	2.068
scale	0.00054	0.00045	0.00063

Loglogistic	est	L95%	U95%
shape	1.44795	1.15081	1.74509
scale	71.601	54.926	88.276

Lognormal	est	L95%	U95%
meanlog	4.2036	3.7580	4.6492
sdlog	1.0140	0.839	1.189

Gompertz	est	L95%	U95%
shape	0.01843	0.01159	0.02527
rate	0.005185	0.002615	0.007755

Gamma	est	L95%	U95%
alfa	2.0622	1.4248	2.6996
beta	37.554	24.122	50.986

G2.6 Parametric survival curves – HRD+ BRCAwt population

The models are plotted with the KM data to illustrate how well they capture the trends. Most distributions have relatively good visual fit, with some having better fit for the first 24 months and other better fit between 24 and 60 months (Figure G27).

The long-term behavior of the OS extrapolations is shown in Figure G28. The timeframe is here 25 years (300 months), as it is the longest possible time for the cost per patient analysis in the model.

The hazard rate plot for OS KM in the HRD+ BRCAwt population suggest that the overall survival hazard has an increasing trend in the olaparib + bevacizumab arm (Figure G29). Among the extrapolations, the Gompertz distribution is an outlier.

With the time period limited to 120 months, i.e. the time horizon in the base case, it is as for TTD easier to perceive trends in the hazard rate for the extrapolations. The lognormal distribution was chosen for the extrapolation base case as it had the lowest AIC and BIC values. In terms of trends for the hazard rate, visual inspection would suggest that Weibull or gamma might capture the slowly increasing trend slightly better towards the end (Figure G30). As mentioned before, however, what happens at the end of the curve beyond 50 months should be interpreted with caution as there are fewer patients at risk at this point. Hence, lognormal is still the most plausible choice for the base case, as it has better fit up to 50 months when data are more reliable. In the long run, the risk would also be expected to decrease as the risk of long-term recurrence tend to decrease beyond 5 years.

G3. Parametric estimates of time to first subsequent therapy

The statistical analysis of time to subsequent therapy was conducted using the approach outlined in the Technical Support Document for survival analysis published by NICE Decision Support Unit (Latimer 2011). Following the selection of model type, the most plausible parametric models are selected based upon statistical and visual fit to the observed data and the clinical plausibility of the extrapolation. two types of models were considered:

- Independent survival models. (e.g. a separate model fitted to a dataset containing only one treatment group from SOLO1)
- Treatment covariate models (e.g. a model fitted to a dataset containing both treatment groups from SOLO1, and including a covariate for treatment that acts on the scale or related parameter)

The choice of model type was based on visual inspection of the cumulative event plots (e.g. log cumulative hazard plots) to assess the possibility of a proportional treatment effect. If the cumulative event curves plotted for each arm of the study were parallel, then a proportional effects model may be applied. If the curves are not parallel, then independent models may be more suitable.

Following Latimer et al, the best fitting models were chosen based on an assessment of the internal goodness of fit of the models using the Bayesian Information Criterion (BIC), Akaike Information Criterion (AIC), and visual inspection of the fit of the model to the Kaplan-Meier curves (Latimer 2011).

G3.1 Time to first subsequent therapy

G3.1.1 Semi-parametric analysis

The median time to first subsequent therapy is included in Table G14 and Figure G31.

Table G14. Total number of events and median time-to-event (if defined, otherwise NA).

	Placebo bd (total=131)	Olaparib 300 mg bd (total=260)
Total number of events	94	99
Median time to event (months)	15.15	51.78
95% lower CI	12.68	44.25
95% upper CI	20.53	NA

G3.1.2 Kaplan Meier plot

G3.1.3 Restricted means

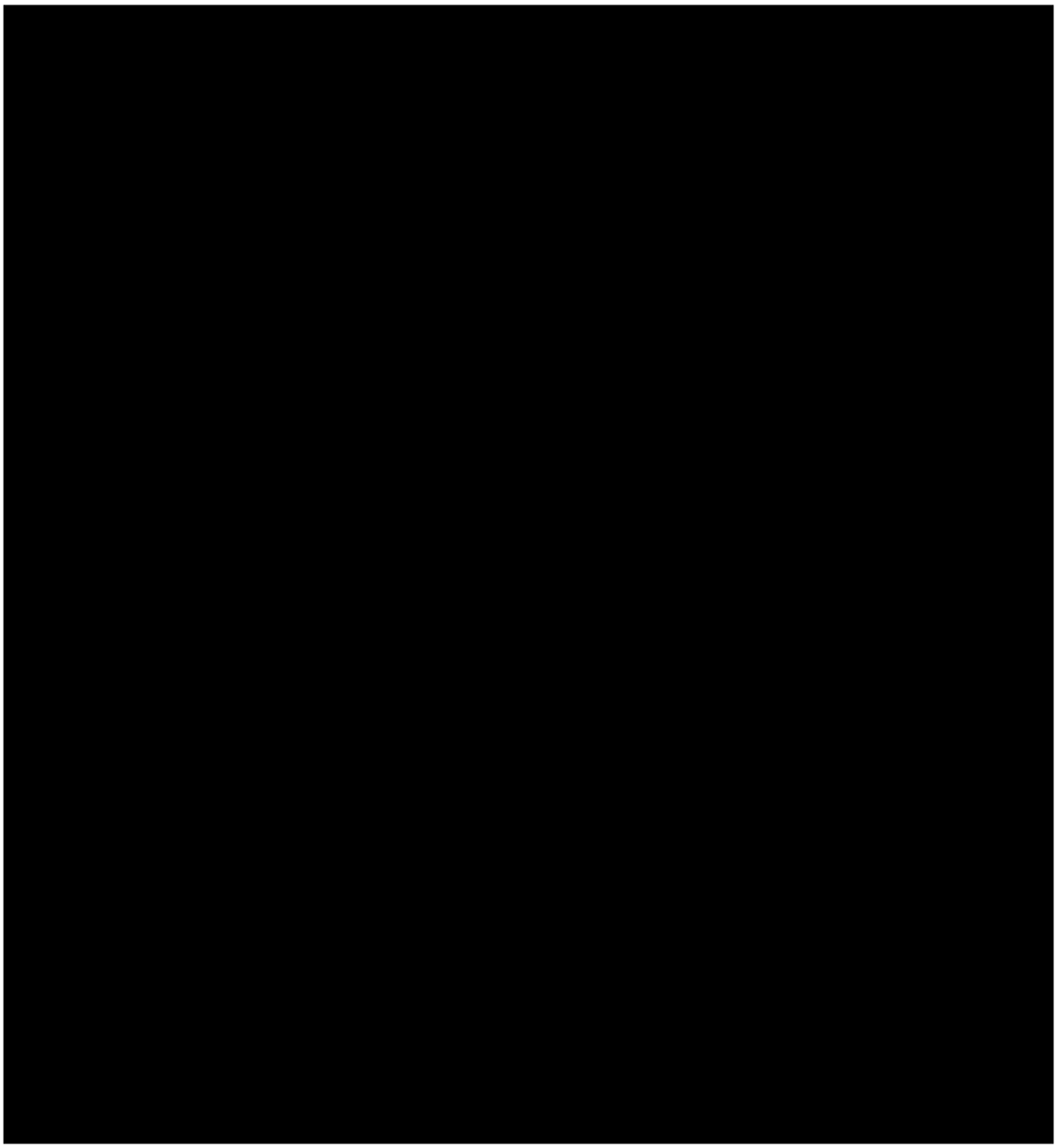
Restricted means are calculated until the last time point where each arm has observations, using the area under KM curve with confidence interval at the 95% level (Table G15).

Table G15. Restricted means for time to first subsequent therapy.

Arm	RMST	SE	Lower CI	Upper CI	p-value
Placebo bd	23.143	1.517	20.169	26.116	
Olaparib 300 mg bd	38.081	1.015	36.091	40.071	
Difference	14.938	1.825	11.361	18.516	< 0.001

G3.1.4 Cumulative Hazards plots

The following are diagnostic plots to check assumptions. Linear trends indicate that there are no clear violations to the model assumptions for the corresponding distribution. In the Loglogistic diagnostic plot, parallel lines indicate proportional odds (Figure G32). As lines are not parallel, this would suggest that hazards are not proportional and separate distributions fitted per arm are more suitable.



G3.2 Separate distributions fitted per arm

G3.2.1 AIC/BIC

Akaike and Bayesian information criteria by treatment arm are shown in Table G16. The models with lower values fit data better. For olaparib, the loglogistic distribution has the lowest AIC and BIC values. For placebo, generalized gamma has the lowest AIC and BIC values.

Table G16. Parametric fit according to Akaike and Bayesian information criteria.

	Olaparib 300 mg bd		Placebo bd	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	1076.60	1080.16	819.63	822.51
Weibull	1073.15	1080.28	817.87	823.62
Loglogistic	1071.38	1078.51	800.52	806.27
Lognormal	1071.50	1078.62	796.17	801.92
Gamma	1072.93	1083.61	786.02	794.64
Exponential	1076.60	1080.16	819.63	822.51

G3.2.2 Parametric survival curves

The models are plotted with the KM data to illustrate how well they capture the trends (Figure G33 and G34).

The best model is Loglogistic which had the lowest AIC and BIC values for the olaparib arm, as well as relatively good visual fit to the KM data (Table G17).

G3.2.3 Model parameter estimates

Table G17. Model parameter estimates for time to first subsequent therapy based on SOLO-1.

Distribution	Parameters - Olaparib 300 mg			Parameters - Placebo		
Exponential	est	L95%	U95%	est	L95%	U95%
rate	0.01195	0.00981	0.01455	0.035115	0.028688	0.042982
Weibull	est	L95%	U95%	est	L95%	U95%
shape	1.2517	1.0444	1.5001	1.1867	1.0049	1.4013
scale	0.004805	0.014248	0.001245	0.01896	0.04131	0.00729
Loglogistic	est	L95%	U95%	est	L95%	U95%
shape	1.4232	1.1946	1.6956	1.7222	1.4585	2.0335
scale	54.989	45.2290	66.8560	18.043	15.0680	21.6060
Lognormal	est	L95%	U95%	est	L95%	U95%
meanlog	4.068	3.841	4.295	2.9354	2.7603	3.1106
sdlog	1.295	1.107	1.513	0.9607	0.8254	1.1182
Gompertz	est	L95%	U95%	est	L95%	U95%
shape	0.01097	-0.00435	0.02629	-0.00438	-0.02174	0.01298
rate	0.00957	0.00655	0.01398	0.03750	0.02709	0.05191
Gamma	est	L95%	U95%	est	L95%	U95%
beta	44.81055	17.803413	26.555408	22.33854	17.8034	26.5554

G3.3 Time to first subsequent therapy in PAOLA-1

Data on subsequent therapy from PAOLA-1 was used for sensitivity analysis. For time to first subsequent therapy in PAOLA-1, the loglogistic distribution also had the best fit as in SOLO-1, but the other distributions are also included in Figure G35 and G36.

The median time to first subsequent therapy is included in Table G18.

Table G18. Total number of events and median time-to-event (if defined, otherwise NA).

	Olaparib/bevacizumab (N=537)	Placebo/bevacizumab (N=269)
Total number of events	275	190
Median time to event (months)	24.8	18.5
95% lower CI	23.4	17.2

	Olaparib/bevacizumab (N=537)	Placebo/bevacizumab (N=269)
95% upper CI	27.9	20.1

G3.3.1 AIC/BIC

Akaike and Bayesian information criteria by treatment arm are shown in Table G19. The models with lower values fit data better. For olaparib + bevacizumab, the loglogistic distribution has the lowest AIC and BIC values. For placebo, loglogistic also has the lowest AIC and BIC values.

Table G19. Parametric fit according to Akaike and Bayesian information criteria.

	Olaparib + bevacizumab		Bevacizumab	
Model	AIC	BIC	AIC	BIC
Exponential	1187.93	1196.81	936.47	929.14
Weibull	1185.31	1194.85	933.58	925.93
Loglogistic	1182.47	1192.01	931.72	924.07
Lognormal	1182.95	1192.49	931.91	924.26
Gompertz	1185.85	1195.39	934.46	926.81
Gamma	1183.69	1193.23	932.71	925.06

G3.3.2 Parametric survival curves

The models are plotted with the KM data to illustrate how well they capture the trends (Figure G35 and G36).

[redacted]

[redacted]

[redacted]

G3.3.3 Model parameter estimates

Table G20. Model parameter estimates for time to first subsequent therapy based on SOLO-1.

Distribution	Parameters - olaparib + bevacizumab			Parameters - bevacizumab		
Exponential	est	L95%	U95%	est	L95%	U95%

rate	0.02549046	0.020107	0.030874	0.04111252	0.032425	0.049791

Weibull	**est**	**L95%**	**U95%**	**est**	**L95%**	**U95%**
shape	1.6197	1.338439	1.900961	1.6295	1.347	1.913
scale	0.003371	0.002711	0.004031	0.00579419	0.00466	0.00693

Loglogistic	**est**	**L95%**	**U95%**	**est**	**L95%**	**U95%**
shape	1.8158	1.507750	2.123850	2.0731	1.72150	2.42491
scale	26.4513091	22.261422	30.641196	17.2159235	14.491	19.945

Lognormal	**est**	**L95%**	**U95%**	**est**	**L95%**	**U95%**
meanlog	3.2603176	2.530169	3.990466	2.86573882	2.2241	3.5077
sdlog	0.89625421	0.724801	1.067708	0.76016751	0.615	0.906

Gompertz	**est**	**L95%**	**U95%**	**est**	**L95%**	**U95%**
shape	0.02969405	0.022177	0.037211	0.04172512	0.03116	0.05229
rate	0.01637787	0.012713	0.020043	0.02409951	0.018708	0.029495

Gamma	**est**	**L95%**	**U95%**	**est**	**L95%**	**U95%**
alfa	1.52586133	1.192308	1.859415	1.76748339	1.3813	2.1540
beta	22.1794106	17.803413	26.555408	12.3861883	9.944	14.831

Appendix H – Literature search for HRQoL data

Health-related quality of life is not covered as the health economic analysis is based on a cost-minimization approach, as explained in section 8.1.1. The HRQoL results from relevant trials are covered in section 7.4.

Appendix I Mapping of HRQoL data

Mapping of HRQoL data is not covered as the health economic analysis is based on a cost-minimization approach.

Appendix J Parameters for the Probabilistic Sensitivity Analysis

Probabilistic sensitivity analysis (PSA) is a method for accounting for parameter uncertainty in health economic models. A probability distribution is assigned to each parameter, and samples are then repeatedly drawn from each distribution and used as model inputs. Beta distributions were used for frequencies and proportions, gamma distributions for resource use and normal distributions for patients characteristics, and parameters for treatment duration and overall survival (Table J1).

The results of the PSA are included in section 8.16.

Table J1. Parameters included in the probabilistic sensitivity analysis

Category	Parameter	PSA distribution	Motivation for distribution
Patient characteristics	BSA	Normal	Central limit theorem (CLT) – mean BSA
	Weight	Normal	CLT – mean weight
	GFR	Normal	CLT – mean GFR
Survival extrapolations	Survival model coefficients	Normal	Parameters are assumed to be normally distributed based on the CLT
AEs	Frequency of AEs	Beta	Binominal data – the beta distribution ensures values between 0-1
Proportions with subsequent therapy	Proportions with subsequent chemotherapy (Carboplatin, Cisplatin, Docetaxel, Doxorubicin, Topotecan, Paclitaxel)	Beta	Binominal data – the beta distribution ensures values between 0-1
	Proportions with subsequent bevacizumab	Beta	Binominal data – the beta distribution ensures values between 0-1
Resource use	CT scans	Gamma	Resource use variables are assumed to be right-skewed and non-
	Consultations	Gamma	

Category	Parameter	PSA distribution	Motivation for distribution
	Ultrasound	Gamma	negative values not possible.

For treatment duration, overall survival and adverse events, the standard errors were estimated based on study data. For resource use, the SE was estimated based on the assumption that the SE was 20% of the parameter value. The 20% is a modelling assumption, but should be capturing the overall uncertainty well. The resource use estimates (e.g., frequency of follow-up visits) are to a large extent based on routines schedules for follow-up visits. Usually, patient monitoring is dependent on the patient status (on treatment or off treatment), and it is expected to be quite standard over time. Parameters values (mean and standard error) are shown in Table J2.

Parameters excluded from the PSA are unit costs and discount rates. Individual resource use items are varied in the PSA, thus totals are excluded. Discount rates are given and are without uncertainty.

Table J2. Summary of base case variables applied in the economic model

Variables	Mean	SE	Distribution
Baseline characteristics			
Weight	63.30	3.20	Normal
BSA	1.69	0.34	Normal
GFR	73.30	14.66	Normal
AEs olaparib + bev			
Anaemia	0.174	0.016	Beta
Neutropenia	0.060	0.010	Beta
Diarrhoea	0.022	0.006	Beta
Hypertension	0.187	0.017	Beta
Fatigue or asthenia	0.052	0.010	Beta
Thrombocytopenia	0.017	0.006	Beta
Lymphopaenia	0.071	0.011	Beta
AEs niraparib			
Anaemia	0.310	0.021	Beta
Neutropenia	0.128	0.015	Beta
Diarrhoea	0.006	0.004	Beta
Hypertension	0.056	0.010	Beta
Fatigue or asthenia	0.027	0.007	Beta
Thrombocytopenia	0.287	0.021	Beta
Lymphopaenia	0.025	0.007	Beta
Proportion subsequent chemotherapy			
Carboplatin	0.500	0.100	Beta
Cisplatin	0.500	0.100	Beta

Variables	Mean	SE	Distribution
Docetaxel	0.100	0.020	Beta
Doxorubicin	0.500	0.100	Beta
Topotecan	0.100	0.020	Beta
Paclitaxel	0.300	0.060	Beta
Proportion subsequent bevacizumab			
Proportion in niraparib arm	0.125	0.025	Beta
Resource use - olaparib + bev (on treatment)			
CT scan	0.33	0.067	Gamma
Consultation	2.45	0.490	Gamma
Vaginal ultrasound	0.20	0.040	Gamma
Resource use - niraparib (on treatment)			
CT scan	0.33	0.067	Gamma
Consultation	2.00	0.400	Gamma
Vaginal ultrasound	0.20	0.040	Gamma
Resource use - subsequent chemotherapy/bev			
CT scan	0.33	0.066	Gamma
Consultation	1.78	0.356	Gamma
Vaginal ultrasound	0.20	0.040	Gamma
Resource use - routine surveillance (off treatment)			
CT scan	0.33	0.067	Gamma
Consultation	0.67	0.134	Gamma
Vaginal ultrasound	0.20	0.040	Gamma
Survival parameter			
TTD high risk parameters			Normal
TTD low risk parameters			Normal
OS parameters			Normal