Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende niraparib til 1. linje vedligeholdelsesbehandling af avanceret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden

Vers. 1.0

Bilagsoversigt

1. Medicinrådets sundhedsøkonomiske afrapportering vedr. niraparib, version 1.0
2. Forhandlingsnotat fra Amgros vedr. niraparib
3. Høringssvar fra ansøger, inkl. eventuel efterfølgende dialog vedr. lægemidlets værdi
4. Medicinrådets vurdering vedr. niraparib til 1. linje vedligeholdelsesbehandling af avanceret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden, version 1.0
5. Dissens til niraparib vurderingsrapport fra patientrepræsentanterne i fagudvalget, Birthe Lemley og Dorte Blou
6. Brev til Birthe Lemley og Dorte Blou vedr. niraparib fra Medicinrådet
7. Ansøgers endelige ansøgning
8. Ansøgers tekniske dokument til den sundhedsøkonomiske ansøgning
9. Medicinrådets protokol for vurdering af niraparib til 1. linje vedligeholdelsesbehandling af avanceret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden, version 1.0

Medicinrådet

Medicinrådets sundheds-økonomiske afrapportering

Niraparib

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

Version 1.0

Om Medicinrådet

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

Dokumentets formål

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

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

Dokumentoplysninger	
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Indholdsfortegnelse

1. Begreber og forkortelser

AIP	Apotekernes indkøbspris
DGCG	*Danish Gynaecological Cancer Group*
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
SAIP	Sygehusapotekernes indkøbspriser
BRCA	*Breast Cancer* (tumorsuppressorgen)
HRD	Homolog rekombinationsdefekt
OS	Samlet overlevelse
PFS	Progressionsfri overlevelse
TTD	Gennemsnitlige tid til behandlingsophør
SmPC	Produktresumé

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser

Patienter med BRCA-mutation

I det scenarie, Medicinrådet finder mest sandsynligt for patienter med BRCA-mutation, er de inkrementelle omkostninger for niraparib ca. [redacted] DKK pr. patient sammenlignet med olaparib. Når analysen er udført med apotekets indkøbspriser (AIP), er de inkrementelle omkostninger til sammenligning ca. 172.000 DKK pr. patient.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af niraparib som mulig standardbehandling vil være ca. [redacted] DKK i år 5. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 4,6 mio. DKK i år 5.

HRD-positive patienter uden BRCA-mutation (bevacizumabkandidater)

I det scenarie, Medicinrådet finder mest sandsynligt for HRD-positive patienter uden BRCA-mutation (bevacizumabkandidater), er de inkrementelle omkostninger for niraparib ca. [redacted] DKK pr. patient sammenlignet med ingen vedligeholdelsesbehandling. Når analysen er udført med AIP, er de inkrementelle omkostninger til sammenligning ca. 614.000 DKK pr. patient.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af niraparib som mulig standardbehandling vil være ca. [redacted] DKK i år 5. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 18,3 mio. DKK i år 5.

HRD-positive patienter uden BRCA-mutation (ikke-bevacizumabkandidater)

I det scenarie, Medicinrådet finder mest sandsynligt for HRD-positive patienter uden BRCA-mutation (ikke-bevacizumabkandidater), er de inkrementelle omkostninger for niraparib ca. [redacted] DKK pr. patient sammenlignet med ingen vedligeholdelsesbehandling. Når analysen er udført med AIP, er de inkrementelle omkostninger til sammenligning ca. 614.000 DKK pr. patient.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af niraparib som mulig standardbehandling vil være ca. [redacted] DKK i år 5. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 31,1 mio. DKK i år 5.

HRD-negative patienter uden BRCA-mutation (bevacizumabkandidater)

I det scenarie, Medicinrådet mener er mest sandsynligt for HRD-negative patienter uden BRCA-mutation (bevacizumabkandidater), er de inkrementelle omkostninger for niraparib ca. [redacted] DKK pr. patient sammenlignet med ingen vedligeholdelsesbehandling. Når analysen er udført med AIP, er de inkrementelle omkostninger til sammenligning ca. 426.000 DKK pr. patient.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af niraparib som mulig standardbehandling vil være ca. [redacted] DKK i år 5. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 17,9 mio. DKK i år 5.

HRD-negative patienter uden BRCA-mutation (ikke-bevacizumabkandidater)
I det scenarie, Medicinrådet finder mest sandsynligt for HRD-negative patienter uden BRCA-mutation (ikke-bevacizumabkandidater), er de inkrementelle omkostninger for niraparib ca. [redacted] DKK pr. patient sammenlignet med ingen vedligeholdelsesbehandling. Når analysen er udført med AIP, er de inkrementelle omkostninger til sammenligning ca. 426.000 DKK pr. patient.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af niraparib som mulig standardbehandling vil være ca. [redacted] DKK i år 5. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 29,5 mio. DKK i år 5.

For alle fem sammenligninger driver lægemiddelomkostningerne for niraparib de inkrementelle omkostninger.

3. Introduktion

Formålet med analyserne er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af niraparib som mulig standardbehandling på danske hospitaler til 1. linje vedligeholdelsesbehandling af avanceret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden. Analysen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra GlaxoSmithKline. Vi modtog ansøgningen den 25. februar 2021.

3.1 Patientpopulation

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

Mutationer i Breast Cancer (BRCA) 1- eller 2-genet er en væsentlig arvelig risikofaktor for udviklingen af kræft i æggestokkene [3]. BRCA er involveret i homolog rekombination, som er en vital celleproces til reparation af DNA-skader [4,5]. Tumorer med BRCA-mutation vil oftest også have homolog rekombinationsdefekt (HRD), men HRD kan også forekomme i ikke-BRCA-muterede tumorer. Det anbefales i dag, at alle patienter med kræft i æggestokkene udredes i forhold til BRCA-mutationsstatus [6], men der findes ingen nationale guidelines i forbindelse med udredning af HRD-status. Derfor vil det forventes, at en væsentlig gruppe af danske patienter uden påvist BRCA-mutation har tumorer, der udviser HRD.

Tilstedeværelsen af en patientgruppe uden BRCA-mutation men med HRD, gør det relevant at formulere kliniske spørgsmål for tre subpopulationer. Ud fra de tidligere data på forekomsten af BRCA-mutation og HRD forventes det, at omkring 300 patienter i alt vil have avanceret high-grade kræft i æggestokkene, og omkring 60 af disse vil have en

BRCA-mutation. Derudover forventes det, at omkring 100 vil have HRD-positive tumorer uden BRCA-mutation, ud fra forekomsten rapporteret i de kliniske studier med MYRIAD myChoice CDx. De resterende 140 vil have tumorer uden BRCA-mutation eller HRD.

Yderligere information om sygdomsområdet kan findes i Medicinrådets vurderingsrapport.

3.1.1 Komparator

Medicinrådet har vurderet den kliniske værdi af niraparib på baggrund af følgende kliniske spørgsmål:

Klinisk spørgsmål 1:

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

Klinisk spørgsmål 2:

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

Klinisk spørgsmål 3:

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

Klinisk spørgsmål 4:

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

Klinisk spørgsmål 5:

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

4. Vurdering af den sundhedsøkonomiske analyse

I sin ansøgning har ansøger indsendt en sundhedsøkonomisk analyse, der består af omkostningsanalyser og budgetkonsekvensanalyser til hvert klinisk spørgsmål. I omkostningsanalyserne estimeres de inkrementelle omkostninger pr. patient for niraparib sammenlignet med olaparib og ingen vedligeholdelsesbehandling. Medicinrådet vurderer nedenfor de sundhedsøkonomiske analyser, som ansøger har indsendt.

4.1 Antagelser og forudsætninger for model

Patienter med BRCA-mutation

Sammenligningen mellem niraparib og olaparib for patienter med BRCA-mutation (klinisk spørgsmål 1) er lavet på baggrund af data fra et klinisk fase III-studie, PRIMA [7]. PRIMA er et multicenter, randomiseret, dobbeltblindet studie, hvor patienterne er randomiseret 2:1 til hhv. niraparib og placebo. I PRIMA-studiet indgår olaparib ikke som komparator. Olaparib er derimod undersøgt overfor placebo i et klinisk fase III-studie, SOLO-1 [8], som ligeledes er et multicenter, randomiseret, dobbeltblindet studie. Dog er der væsentlige forskelle mellem populationerne i PRIMA-studiet og SOLO-1-studiet, hvorfor ansøger vurderer, at det ikke er muligt at lave en indirekte sammenligning mellem niraparib og olaparib. Derfor udarbejder ansøger en omkostningsminimeringsanalyse, idet ansøger antager, at effekten af niraparib og olaparib er ens. Data fra PRIMA-studiet anvendes til at modellere samlet overlevelse (OS), progression og behandlingsvarighed for både niraparib og olaparib.

HRD-positive eller HRD-negative patienter uden BRCA-mutation, som ikke kandiderer til bevacizumab

For patienter, som er HRD-positive eller HRD-negative uden BRCA-mutation, og som ikke kandiderer til behandling med bevacizumab, er sammenligningen mellem niraparib og ingen vedligeholdelsesbehandling lavet på baggrund af data fra en subpopulation i PRIMA-studiet, der direkte sammenligner niraparib mod placebo. Dog inkluderer denne subpopulation patienter, hovedsageligt patienter, som ville være kandidater til bevacizumab ifølge dansk klinisk praksis. Fagudvalget vurderer, at studiet kan anvendes til at udarbejde en sammenligning for klinisk spørgsmål 4 og 5.

HRD-positive eller HRD-negative patienter uden BRCA-mutation, som kandiderer til bevacizumab

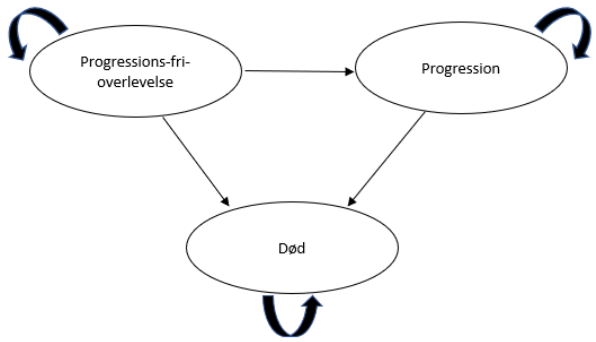
For patienter, som er HRD-positive eller HRD-negative uden BRCA-mutation, og som kandiderer til behandling med bevacizumab, er det ikke muligt at lave en indirekte sammenligningen mellem niraparib og bevacizumab grundet væsentlige forskelle mellem populationerne i PRIMA-studiet og studierne for bevacizumab, GOG-0218 [9–11] og ICON7 [12–14]. Derfor vælger ansøger at sammenligne niraparib med ingen vedligeholdelsesbehandling for både klinisk spørgsmål 2 og 3, velvidende at dette vil

overestimere omkostningerne for niraparib, idet omkostningerne til bevacizumab ikke inkluderes. Ligesom for klinisk spørgsmål 4 og 5 anvender ansøger data fra den samme subpopulation i PRIMA-studiet til at modellere OS og progression for ingen vedligeholdelsesbehandling.

4.1.1 Modelbeskrivelse

Patienter med BRCA-mutation

Ansøger har indsendt en omkostningsminimeringsanalyse for patienter med BRCA-mutation til at estimere omkostningerne for sammenligningen mellem niraparib og olaparib, idet ansøger antager, at effekten mellem niraparib og olaparib er ens. Modellen indeholder en række sygdomsstadier, som patienterne skifter mellem i takt med sygdomsprogression. Ansøgers model består af tre stadier: progressionsfri overlevelse (PFS), post-progression (PD) og død, se Figur 1. Alle patienter starter i sygdomsstadiet progressionsfri overlevelse, hvorfra deres bevægelse gennem modellen bestemmes ud fra ekstrapoleret time-to-event data. Som tidligere beskrevet anvender ansøger data fra PRIMA-studiet til at modellere OS, progression og behandlingsvarighed for både niraparib og olaparib.



Figur 1. Beskrivelse af modelstrukturen i omkostningsanalysen

Patientens tid i stadiet progressionsfri overlevelse bestemmes ud fra PFS-data for niraparib fra PRIMA-studiet. Fra progressionsfri overlevelse kan patienten bevæge sig videre til stadiet post-progression og til stadiet død. Patienter, der er progredieret, men ikke døde, vil befinde sig i post-progression. Tiden, patienterne befinder sig i dette stadie, estimeres ud fra PFS- og OS-data for niraparib fra PRIMA-studiet, som den andel af patienter, der hverken er i præ-progression eller død. Fra post-progression kan patienten udelukkende bevæge sig til det absorberende stadie død.

Modellen for patienter med BRCA-mutation har en cykluslængde på en måned, hvilket, ansøger argumenterer, er passende, da denne cykluslængde er i tråd med forløbsdata fra PRIMA-studiet. Ansøger har anvendt *half-cycle correction*.

Ansøger modellerer tiden i de forskellige stadier for niraparib og olaparib ved at anvende ekstrapolerede Kaplan-Meier (KM)-data for PFS og OS. Dette er nødvendigt, da

opfølgningen i PRIMA-studiet er kortere end den anvendte tidshorisont. Ansøger har anvendt en log-logistisk funktion til at ekstrapolere PFS for både niraparib og olaparib, se Figur 2. For OS har ansøger valgt at ekstrapolere data med en log-logistisk funktion for både niraparib og olaparib, se Figur 3. Disse parametriske funktioner er valgt, da ekstrapoleringerne har det bedste statistiske fit på data.

Figur 2. PFS for niraparib og olaparib for patienter med BRCA-mutation

Figur 3. OS for niraparib og olaparib for patienter med BRCA-mutation

Ansøger har baseret behandlingsvarighed for niraparib og olaparib på den gennemsnitlige tid til behandlingsophør (TTD) fra PRIMA-studiet. Ansøger har anvendt en Gompertz funktion til at ekstrapolere behandlingsvarigheden for niraparib og olaparib, se Figur 4. Jf. produktresuméet (SPC) for olaparib må olaparib maksimalt anvendes i 2 år, og derfor antager ansøger, at alle patienter, der modtager olaparib, stoppes i behandling efter 2 år. For niraparib antager ansøger, at niraparib maksimalt må anvendes i 3 år i henhold til protokollen for PRIMA-studiet. På baggrund af studiedata og ekstrapoleringerne har ansøger estimeret den gennemsnitlige tid, patienten befinder sig i modellens stadier.

Figur 4. TTD for niraparib og olaparib for patienter med BRCA-mutation

HRD-positive patienter uden BRCA-mutation

Ansøger har indsendt en *partitioned survival model* til at estimere omkostningerne for sammenligningen mellem niraparib og ingen vedligeholdelsesbehandling for HRD-positive patienter uden BRCA-mutation. Ligesom modellen for patienter med BRCA-mutation, består modellen for HRD-positive patienter uden BRCA-mutation af tre stadier: PFS, PD og død, hvor patienternes bevægelse gennem modellen bestemmes ud fra ekstrapoleret time-to-event data.

Ansøger har anvendt en log-logistisk funktion til at ekstrapolere PFS for både niraparib og ingen vedligeholdelsesbehandling, se Figur 5 og Figur 6. For OS har ansøger også valgt at ekstrapolere data med en log-logistisk funktion for både niraparib og ingen vedligeholdelsesbehandling, se Figur 7 og Figur 8. Disse parametriske funktioner er valgt, da ekstrapoleringerne har det bedste statistiske fit.

Figur 5. PFS for niraparib for HRD-positive patienter uden BRCA-mutation

Figur 6. PFS for ingen vedligeholdelsesbehandling for HRD-positive patienter uden BRCA-mutation

Figur 7. OS for niraparib for HRD-positive patienter uden BRCA-mutation

Figur 8. OS for ingen vedligeholdelsesbehandling for HRD-positive patienter uden BRCA-mutation

Ansøger har baseret behandlingsvarigheden for niraparib på data for TTD fra PRIMA-studiet. Ansøger har anvendt en log-logistisk funktion til at ekstrapolere behandlingsvarigheden for niraparib, se Figur 9.

Figur 9. TTD for niraparib for HRD-positive patienter uden BRCA-mutation

HRD-negative patienter uden BRCA-mutation

Ansøger har ligeledes indsendt en *partitioned survival model* til at estimere omkostningerne for sammenligningen mellem niraparib og ingen vedligeholdelsesbehandling for HRD-negative patienter uden BRCA-mutation. Ligesom de to tidligere præsenterede modeller består modellen for HRD-negative patienter uden BRCA-mutation af tre stadier: PFS, PD og død, hvor patienternes bevægelse gennem modellen bestemmes ud fra ekstrapoleret time-to-event data.

Ansøger har anvendt en log-logistisk funktion til at ekstrapolere PFS for både niraparib og ingen vedligeholdelsesbehandling, se Figur 10 og Figur 11. For OS har ansøger også valgt at ekstrapolere data med en log-logistisk funktion for både niraparib og ingen vedligeholdelsesbehandling, se Figur 12 og Figur 13. Disse parametriske funktioner er valgt, da ekstrapoleringerne har det bedste statistiske fit.

Figur 10. PFS for niraparib for HRD-negative uden BRCA-mutation

Figur 11. PFS for ingen vedligeholdelsesbehandling for HRD-negative patienter uden BRCA-mutation

Figur 12. OS for niraparib for HRD-negative patienter uden BRCA-mutation

Figur 13. OS for ingen vedligeholdelsesbehandling for HRD-negative patienter uden BRCA-mutation

Ansøger har baseret behandlingsvarighed for niraparib på data for TTD fra PRIMA-studiet. Ansøger har anvendt en Weibull-funktion til at ekstrapolere behandlingsvarigheden for niraparib, se Figur 14.

Figur 14. TTD for niraparib for HRD-negative patienter uden BRCA-mutation

Medicinrådets vurdering af ansøgers modelantagelser

Patienter med BRCA-mutation

Fagudvalget vurderer, at overlevelsen for patienter med BRCA-mutation underestimeres ved anvendelse af ansøgers valgte ekstrapolering for OS, idet patienterne forventes at have en længere gennemsnitlig overlevelse end [redacted] år. Fagudvalget anser derimod en gennemsnitlig overlevelse på [redacted] år modelleret ved anvendelse af den log-normale funktion for mere klinisk plausibel. Derudover finder fagudvalget, at tid til progression på [redacted] år for samme patientpopulation er en smule overestimeret, da patienternes tid i post-progression-stadiet er for kort. Medicinrådet vælger derfor at ekstrapolere PFS ved anvendelse af Weibull-funktionen, der modellerer en gennemsnitlig tid til progression på

[redacted] år for både niraparib og olaparib. Disse ændringer vurderes at have lille betydning for analysens resultat for patienter med BRCA-mutation.

HRD-positive patienter uden BRCA-mutation

Ansøger estimerer, at HRD-positive patienter uden BRCA-mutation har en længere gennemsnitlig overlevelse end patienter med BRCA-mutation. Dette er fagudvalget ikke enige i, da intet data tyder på, at denne patientpopulation har bedre prognoser og derfor længere overlevelse. Desuden er KM-data for OS for HRD-positive patienter uden BRCA-mutation meget umodne, hvilket derfor giver usikre ekstrapoleringer af OS, hvilket ses i stor variation i den estimerede gennemsnitlige overlevelse ved anvendelse af de forskellige parametriske funktioner. Fagudvalget vurderer, at en gennemsnitlig overlevelse på [redacted] år for niraparib og [redacted] år for ingen vedligeholdelsesbehandling modelleret ved anvendelse af Weibull-funktionen er mere klinisk plausibel. Ligeledes vurderer fagudvalget, at den gennemsnitlige tid til progression for patienter, der behandles med niraparib, er overestimeret. Medicinrådet vælger derfor at ekstrapolere data for PFS ved anvendelse af Weibull-funktionen, der modellerer en gennemsnitlig tid til progression på [redacted] år for niraparib og [redacted] år for ingen vedligeholdelsesbehandling. Disse ændringer vurderes at have lille betydning for analysens resultat for HRD-positive patienter uden BRCA-mutation.

HRD-negative patienter uden BRCA-mutation

Ligeledes for HRD-negative patienter uden BRCA-mutation er KM-data for OS meget umodne, hvilket derfor giver usikre ekstrapoleringer af OS, hvilket også her ses i stor variation i den estimerede gennemsnitlige overlevelse ved anvendelse af de forskellige parametriske funktioner. Fagudvalget kan ikke vurdere, at der er forskel i overlevelsen mellem niraparib og ingen vedligeholdelsesbehandling. Medicinrådet vælger derfor at modellere overlevelsen for ingen vedligeholdelsesbehandling, således at den er lig overlevelsen for niraparib svarende til en gennemsnitlig overlevelse på [redacted] år.

Estimaterne for PFS, OS og TTD er præsenteret i Tabel 1 for patienter med BRCA-mutation, Tabel 2 for HRD-positive patienter uden BRCA-mutation og Tabel 3 for HRD-negative patienter uden BRCA-mutation.

Tabel 1. Gennemsnitlig tid i behandling og i stadierne PFS og PD for patienter med BRCA-mutation

Behandling	Behandlingsvarighed [år]	PFS [år]	OS [år]
Niraparib	[redacted]	[redacted]	[redacted]
Olaparib	[redacted]	[redacted]	[redacted]

Tabel 2. Gennemsnitlig tid i behandling og i stadierne PFS og PD for HRD-positive patienter uden BRCA-mutation

Behandling	Behandlingsvarighed [år]	PFS [år]	OS [år]
Niraparib	[redacted]	[redacted]	[redacted]
Ingen vedligeholdelsesbehandling	-	[redacted]	[redacted]

Tabel 3. Gennemsnitlig tid i behandling og i stadierne PFS og PD for HRD-negative patienter uden BRCA-mutation

Behandling	Behandlingsvarighed [år]	PFS [år]	OS [år]
Niraparib	[redacted]	[redacted]	[redacted]
Ingen vedligeholdelsesbehandling	-	[redacted]	[redacted]

Medicinrådet accepterer ansøgers tilgang vedr. modelantagelser. Dog ændrer Medicinrådet ekstrapoleringerne for OS og PFS for både patienter med BRCA-mutation og HRD-positive patienter uden BRCA-mutation samt ekstrapoleringen for OS for niraparib for HRD-negative patienter uden BRCA-mutation i Medicinrådets hovedanalyse.

4.1.2 Analyseperspektiv

I overensstemmelse med metoderne har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en tidshorisont på 30 år.

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

Medicinrådets vurdering af ansøgers analyseperspektiv
Medicinrådet accepterer ansøgers valgte tidshorisont. Tidshorisonten på 30 år er valgt, da ansøger argumenterer for, at den gennemsnitlige behandlingslængde (af både vedligeholdelsesfasen og efterfølgende behandlingslinjer) ligger inden for denne tidshorisont. Det betyder ikke, at patienterne modtager behandling med niraparib i hele tidshorisonten, men at analysen opfanger alle direkte og afledte økonomiske forskelle mellem niraparib og komparatorer set over en tidshorisont på 30 år.

Medicinrådet accepterer ansøgers valg vedr. analyseperspektiv.

4.2 Omkostninger

I det følgende er ansøgers antagelser for omkostningerne i de sundhedsøkonomiske analyser af niraparib præsenteret. Ansøger har inkluderet lægemiddelomkostninger, hospitalsomkostninger, bivirkningsomkostninger, omkostninger til efterfølgende behandling og patientomkostninger.

Omkostningerne er cyklusbestemt, hvilket betyder, at omkostningerne påregnes for hver cyklus, patienten befinder sig i et stadie.

4.2.1 Lægemiddelomkostninger

Ansøger har jf. *Metodevejledning for omkostningsanalyser af nye lægemidler og indikationer i hospitalssektoren* estimeret lægemiddelomkostninger på baggrund af apotekets indkøbspris (AIP). For ingen vedligeholdelsesbehandling har ansøger ikke inkluderet nogen aktiv behandling.

Niraparib gives som daglig oral dosering af 200 mg. Ansøger har på baggrund af PRIMA-studiet antaget en gennemsnitlig dosis på [redacted] mg for niraparib.

Olaparib gives som oral dosering af 300 mg to gange dagligt.

Medicinrådets vurdering af ansøgers antagelser vedr. lægemiddelomkostninger
Medicinrådet har udskiftet AIP med sygehusapotekets indkøbspris (SAIP), se Tabel 4.

Tabel 4. Anvendte lægemiddelpriser, SAIP (maj 2021)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Betingede pris* [DKK]	Kilde
Niraparib	100 mg	56 stk.	[redacted]	[redacted]	Amgros
	100 mg	84 stk.	[redacted]	[redacted]	Amgros
Olaparib	50 mg	448 stk.	[redacted]		Amgros
	100 mg	56 stk.	[redacted]		Amgros
	150 mg	56 stk.	[redacted]		Amgros

*GlaxoSmithKline har tilbudt en pris betinget af at niraparib bliver anbefalet til både patienter med BRCA-mutation og HRD-positive patienter uden BRCA-mutation.

Fagudvalget vurderer, at ikke alle patienter i dansk klinisk praksis modtager fuld dosis af olaparib. Medicinrådet ændrer derfor den gennemsnitlig dosis for olaparib til 575 mg dagligt de første tre måneder efterfulgt af 530 mg dagligt, jf. Medicinrådets behandlingsvejledning vedrørende lægemidler til BRCA-muteret kræft i æggestokkene, æggelederne eller primær kræft i bughinden [15]. Denne ændring vurderes at have lille betydning for analysens resultat, når spild er inkluderet.

Medicinrådet accepterer ansøgers valg vedr. lægemiddelomkostninger. Dog ændrer Medicinrådet doseringen af olaparib til 575 mg de første tre måneder efterfulgt af 530 mg.

4.2.2 Hospitalsomkostninger

Ansøger har ikke inkluderet omkostninger til administration af lægemidlerne, da niraparib og olaparib er orale behandlingsregimer.

Monitoreringsomkostninger

Ansøger har inkluderet monitoreringsomkostninger for niraparib, olaparib og ingen vedligeholdelsesbehandling i form af timeomkostninger for sundhedspersonale, DRG-takster og omkostninger til Rigshospitalets Labportal.

Ansøger antager, at patienter i behandling med niraparib vil have ét kontrolbesøg på 30 min ved en læge pr. måned for at overvåge behandlingseffekt og bivirkninger. Patienten vil derudover få udført en blodprøve hver uge i den første måned, hvorefter frekvensen reduceres til én gang pr. måned i de efterfølgende måneder. Det forventes, at niraparib-patienter vil være forpligtet til at foretage yderligere blodtryks- og pulsovervågning på 15 min udført af en sygeplejerske ugentligt i de første to måneder af behandlingen og derefter hver måned, indtil patienten afbryder behandlingen. Patienterne vil derudover få én CT-scanning hver 3. måned.

For patienter, der behandles med olaparib, antager ansøger, at patienterne vil have ét kontrolbesøg på 30 min ved en læge samt én blodprøvetagning pr. måned. Patienterne vil derudover have én CT-scanning hver 3. måned.

Hvis patienterne stopper behandling med enten niraparib eller olaparib, inden de er progredieret, vil de have ét kontrolbesøg på 30 min ved en læge, én blodprøvetagning samt én CT-scanning hver 3. måned.

For ingen vedligeholdelsesbehandling antager ansøger, at patienter på ingen vedligeholdelsesbehandling vil have ét kontrolbesøg på 30 min ved en læge, én blodprøvetagning samt én CT-scanning hver 3. måned. Dette ressourceforbrug er ligeledes gældende for patienter, som er progredieret.

Medicinrådets vurdering af ansøgers antagelser vedr. monitoreringsomkostninger

Medicinrådet accepterer ansøgers tilgang til estimering af monitoreringsomkostninger. Dog har fagudvalget enkelte justeringer i estimeringen af ressourceforbruget for niraparib og olaparib i den første måned i behandling: Patienter, der behandles med niraparib, vil have et ambulant besøg hver 14. dag i den første måned, mens patienter, der behandles med olaparib, vil have en blodprøvetagning hver 14. dag i den første måned. Disse ændringer vurderes at have minimal betydning for analysens resultat.

Til at estimere omkostningerne for monitorering har ansøger valgt at anvende timeomkostninger for sundhedspersonale fra *Medicinrådets værdisætning af enhedsomkostninger* som enhedsomkostninger. Dette betyder, at der er risiko for, at afledte omkostninger i forbindelse med besøgene på hospitalet ikke er inkluderet. Medicinrådet vælger derfor at udskifte enhedsomkostningerne for ambulant besøg til 1.636 DKK.

Anvendte ressourceforbrug for PFS og PD kan ses i hhv. Tabel 5 og Tabel 6, og enhedsomkostningerne kan ses i Tabel 7.

Tabel 5. Ressourceforbrug til monitorering i PFS pr. måned

	Stadie	Ambulant besøg	CT-scanning	Blodprøve	Blodtryks- og pulsmåling
Niraparib	PFS (1. måned)	2,0	0,3	4,0	4,0
	PFS (2. måned)	1,0	0,3	1,0	4,0
	PFS (efter 2. måned)	1,0	0,3	1,0	1,0
	PFS (ikke på behandling)	0,3	0,3	0,3	0,0
Olaparib	PFS (1. måned)	1,0	0,3	2,0	0,0
	PFS (efter 2. måned)	1,0	0,3	1,0	0,0
	PFS (ikke på behandling)	0,3	0,3	0,3	0,0
Ingen vedlige-holdelses-behandling	PFS	0,3	0,3	0,3	0,0

Tabel 6. Ressourceforbrug til monitorering i PD pr. måned

	Stadie	Ambulant besøg	CT-scanning	Blodprøve	Blodtryks- og pulsmåling
Niraparib	PD	1,0	0,3	0,3	0,0
Olaparib	PD	1,0	0,3	0,3	0,0
Ingen vedlige-holdelses-behandling	PD	1,0	0,3	0,3	0,0

Tabel 7. Enhedsomkostninger til monitorering

	Enhedsomkostning pr. time/test [DKK]	Kilde
Ambulant besøg	1.636	2021 DRG: 13MA98
CT-scanning	2.007	2021 DRG: 30PR06
Blodprøve	382	Rigshospital Labportal

	Enhedsomkostning pr. time/test [DKK]	Kilde
Blodtryks- og pulsmåling	138,50	Medicinrådets værdisætning af enhedsomkostninger

Medicinrådet accepterer ansøgers tilgang vedr. monitoreringsomkostninger, men retter enkelte estimater af ressourceforbruget for niraparib og olaparib i den første måned i behandling i Medicinrådets egen hovedanalyse.

Bivirkningsomkostninger

Ansøger har inkluderet omkostninger forbundet med bivirkninger og anvender grad 3-4 bivirkningshyppigheden med en frekvens på mindst 5 % i en af behandlingsarmene som mål for bivirkningerne. For niraparib og ingen vedligeholdelsesbehandling har ansøger anvendt de rapporterede bivirkningsrater i PRIMA-studiet, mens de rapporterede bivirkningsrater i SOLO-1-studiet er anvendt for olaparib. Ressourcerne brugt i forbindelse med de forskellige bivirkninger har ansøger baseret på 2021 DRG-takster.

I sin model har ansøger inkluderet bivirkningerne anæmi, trombocytopeni, fald i trombocytter, neutropeni, fald i neutrofile granulocytter, hypertension, træthed og lymfopeni. Ansøger antager, at ikke alle bivirkninger kræver behandling at de fleste alene kræver en telefonkonsultation. Specifikt for anæmi antager ansøger, at patienterne modtager blodtransfusion én gang hver måned.

Medicinrådets vurdering af ansøgers antagelser vedr. bivirkningsomkostninger

Medicinrådet accepterer ikke ansøgers tilgang til estimering af bivirkningsomkostninger for anæmi. Det er sjældent, at episoder med anæmi kræver månedlige blodtransfusioner. Medicinrådet vælger derfor at udskifte behandlingen for anæmi til et ambulant besøg, hvor 2021 DRG-taksten 13MA98 (MDC13 1-dagsgruppe, pat. mindst 7 år) anvendes som enhedsomkostning svarende til 1.636 DKK. Ligeledes for de resterende behandlingskrævende bivirkninger vurderer fagudvalget, at disse bivirkninger kræver ambulant besøg. Disse ændringer vurderes at have minimal betydning for analysens resultat.

I ansøgers bivirkningsfrekvenser er både fald i trombocytter og trombocytopeni inkluderet. Fagudvalget vurderer, at fald i trombocytter indgår i bivirkningen trombocytopeni, hvorfor fald i trombocytter ekskluderes fra Medicinrådets hovedanalyse. Det samme gør sig gældende for fald i neutrofile granulocytter og neutropeni, som begge er inkluderet i ansøgers inkluderede bivirkningsfrekvenser. Medicinrådet vælger kun at inkludere omkostninger til neutropeni. Disse ændringer vurderes at have minimal betydning for analysens resultat.

Bivirkningsfrekvenser og anvendte takster kan ses i Tabel 8.

Tabel 8. Rapporterede bivirkningsfrekvenser ved behandling med niraparib, olaparib og ingen vedligeholdelsesbehandling samt enhedsomkostninger for bivirkningerne

	Niraparib [%]	Olaparib [%]	Ingen vedligehol-delsesbe-handling [%]	Enhedsom kostning [DKK]	Kilde
Anæmi	31 %	22 %	2 %	1.636	2021 DRG: 13MA98
Trombocytopeni	29 %	0 %	0 %	1.636	2021 DRG: 13MA98
Neutropeni	13 %	9 %	1 %	1.636	2021 DRG: 13MA98
Hypertension	0 %	0 %	0 %	-	Ikke behandlingskrævende
Træthed	6 %	0 %	1 %	-	Ikke behandlingskrævende
Lymfopeni	0 %	0 %	0 %	-	Ikke behandlingskrævende

Medicinrådet accepterer ansøgers tilgang vedr. bivirkningsomkostninger, men ændrer behandlingen for anæmi, trombocytopeni og neutropeni til et ambulant besøg. Derudover ekskluderes bivirkningerne fald i trombocytter og fald i neutrofile granulocytter.

Testomkostninger

Ansøger har valgt ikke at inkludere omkostninger forbundet med HRD-testning i deres analyse. Testomkostninger er derimod undersøgt i en følsomhedsanalyse, hvor alle patienter uden BRCA-mutation får foretaget en HRD-test. Ansøger anvender en enhedsomkostning på 24.711,47 DKK pr. test. Ansøger anvender listeprisen på HRD-testen, myChoice test, fra Myriad Genetics. Ansøger har omregnet estimatet fra dollars til danske kroner ved anvendelse af den gennemsnitlige valutakurs for 2021.

Medicinrådets vurdering af ansøgers antagelser vedr. testomkostninger

På nuværende tidspunkt testes der ikke rutinemæssigt for HRD hos patienter uden BRCA-mutation, men dette vil være en forudsætning for ibrugtagning af niraparib, hvis Medicinrådets i dets anbefaling af niraparib skelner mellem HRD-positive og HRD-negative patienter uden BRCA-mutation. Hvis Medicinrådet anbefaler niraparib til begge patientpopulationer, vil det derimod ikke være nødvendigt at teste for HRD.

Medicinrådet vælger derfor at undersøge betydningen af omkostninger til test i scenarierne, hvor niraparib anbefales til kun én af de to populationer i to følsomhedsanalyser. Én følsomhedsanalyse, hvor omkostninger til test tildeles HRD-positive patienter uden BRCA-mutation i det scenarie, hvor kun niraparib anbefales til HRD-positive patienter uden BRCA-mutation. Ligeledes én følsomhedsanalyse, hvor omkostninger til test tildeles HRD-negative patienter uden BRCA-mutation i det scenarie, hvor kun niraparib anbefales til HRD-negative patienter uden BRCA-mutation.

Medicinrådet vælger at anvende enhedsomkostningen på 24.711,47 DKK pr. test baseret på listeprisen på HRD-testen, myChoice test, fra Myriad Genetics. Fagudvalget vurderer, at der årligt er 240 patienter uden BRCA-mutation, der enten er HRD-positive eller HRD-negative. Det er således i ovenstående population, at man skal identificere de patienter, som kan være kandidater til behandling med niraparib i tilfælde af, at niraparib kun anbefales til en af populationerne. Hvis niraparib kun anbefales til HRD-positive patienter uden BRCA-mutation, da vil 240 patienter (både HRD-positive og HRD-negative patienter uden BRCA-mutation) skulle testes for at finde de 100 HRD-positive patienter uden BRCA-mutation, som vil være kandidater til niraparib. Dermed bliver de samlede årlige testomkostninger 5.930.753 DKK, hvilket betyder, at den gennemsnitlige testomkostning er 59.308 DKK pr. HRD-positiv patient uden BRCA-mutation. Hvis niraparib kun anbefales til HRD-negative patienter uden BRCA-mutation, da vil 240 patienter (både HRD-positive og HRD-negative patienter uden BRCA-mutation) skulle testes for at finde de 140 HRD-negative patienter uden BRCA-mutation, som vil være kandidater til niraparib. Dermed bliver de samlede årlige testomkostninger 5.930.753 DKK, hvilket betyder, at den gennemsnitlige testomkostning er 42.363 DKK pr. HRD-negativ patient uden BRCA-mutation.

Der er konkrete tiltag i gang på Rigshospitalet for at kunne udbyde testen lokalt, hvilket vil medføre en pris på ca. [redacted] DKK. Det forventes, at testen vil være implementeret på Rigshospitalet i løbet af 2021. Derfor vælger Medicinrådet også at udarbejde følsomhedsanalyser, hvor den forventerede danske pris anvendes. Dermed bliver den gennemsnitlige testomkostning ca. [redacted] DKK pr. HRD-positiv patient uden BRCA-mutation og ca. [redacted] DKK pr. HRD-negativ patient uden BRCA-mutation.

Medicinrådet accepterer ansøgers tilgang vedr. testomkostninger, men udarbejder følsomhedsanalyser, hvor testomkostninger inkluderes i tilfælde af, at Medicinrådet kun anbefaler niraparib til enten HRD-positive og HRD-negative patienter uden BRCA-mutation.

4.2.3 Efterfølgende behandling

Ansøger inkluderer omkostninger til efterfølgende behandling, da OS forventes at afspejle både effekten af 1. linjebehandling og effekten af de efterfølgende behandlinger. Ansøger har valgt kun at inkludere 2. linjebehandling og har dertil inkluderet en lang række forskellige regimer, hvor fordelingen af efterfølgende behandling er baseret på data fra PRIMA. Grundet manglende data på fordelingen af efterfølgende behandling i Danmark har ansøger valgt at validere data for fordelingen opgjort i PRIMA med data fra Edinburgh ovariekræft-databasen. Edinburgh-databasen indeholder opfølgningsdata om patienter diagnosticeret med ovariekræft i den sydøstlige region i Skotland (N > 4.000). Ansøger vurderer, at patientkarakteristika i Edinburgh-databasen er svarende til dem, der blev observeret i placeboarmen i PRIMA-studiet. Dosis og behandlingsvarigheder for de forskellige regimer er baseret på SPC'er, vejledninger fra *Danish Gynaecological Cancer Group* (DGCG) og Sjællands Universitetshospital og studieprotokoller.

Medicinrådets vurdering af ansøgers antagelser vedr. efterfølgende behandling
Medicinrådet accepterer ansøgers tilgang til estimering af omkostninger til efterfølgende behandling. Fagudvalget har dog enkelte korrigeringer i doseringen af niraparib, doxorubicin og bevacizumab. Denne ændring vurderes at have minimal betydning for analysens resultat.

Fordelingen af efterfølgende behandling for patienter progredieret på enten niraparib, olaparib eller ingen vedligeholdelsesbehandling kan ses i hhv. Tabel 9, Tabel 10 og Tabel 11.

Tabel 9. Fordelingen af efterfølgende behandling for patienter progredieret på niraparib

Efterfølgende behandling	BRCA-muterede	HRD-positive ikke-BRCA-muterede	HRD-negative ikke-BRCA-muterede
Gemcitabin	16 %	13 %	16 %
Paclitaxel/docetaxel	13 %	7 %	13 %
Doxorubicin	20 %	17 %	20 %
Cisplatin	3 %	2 %	3 %
Carboplatin	29 %	23 %	29 %
Bevacizumab	8 %	5 %	8 %
Cyclophosphamid	1 %	1 %	1 %
Niraparib/olaparib	0 %	0 %	0 %

Tabel 10. Fordelingen af efterfølgende behandling for patienter progredieret på olaparib

Efterfølgende behandling	BRCA-muterede
Gemcitabin	16 %
Paclitaxel/docetaxel	13 %
Doxorubicin	20 %
Cisplatin	3 %
Carboplatin	29 %
Bevacizumab	8 %
Cyclophosphamid	1 %
Niraparib/olaparib	0 %

Tabel 11. Fordelingen af efterfølgende behandling for patienter progredieret på ingen vedligeholdelsesbehandling

Efterfølgende behandling	HRD-positive ikke-BRCA-muterede	HRD-negative ikke-BRCA-muterede
Gemcitabin	14 %	18 %
Paclitaxel/docetaxel	5 %	12 %
Doxorubicin	21 %	27 %
Cisplatin	2 %	2 %
Carboplatin	33 %	36 %
Bevacizumab	7 %	9 %
Cyclophosphamid	1 %	1 %
Niraparib/olaparib	6 %	4 %

Medicinrådet har udskriftet AIP for lægemiddelpriser til efterfølgende behandling med SAIP, se Tabel 12. Lægemiddelpriserne for niraparib og olaparib kan ses i Tabel 4.

Tabel 12. Anvendte lægemiddelpriser for efterfølgende behandling, SAIP (maj 2021)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Gemcitabin	40 mg/ml	25 ml	[redacted]	Amgros
Paclitaxel	6 mg/ml	50 ml	[redacted]	Amgros
Docetaxel	20 mg/ml	4 ml	[redacted]	Amgros
Doxorubicin	2 mg/ml	25 ml	[redacted]	Amgros
	2 mg/ml	10 ml	[redacted]	Amgros
Cisplatin	1 mg/ml	50 ml	[redacted]	Amgros
Carboplatin	10 mg/ml	45 ml	[redacted]	Amgros
Bevacizumab	25 mg/ml	4 ml	[redacted]	Amgros
Cyclophosphamid	50 mg	100 stk.	[redacted]	Amgros

Anvendte doser og behandlingsvarigheder af efterfølgende behandling kan ses i Tabel 13.

Tabel 13. Anvendte doser og behandlingsvarigheder for efterfølgende behandling

Lægemiddel	Doser	Behandlingsvarighed	Kilde
Gemcitabin	1000 mg/m^2	6 cyklusser á 21 dage	SPC'et for gemcitabin DGCG
Paclitaxel	175 mg/m^2	6 cyklusser á 21 dage	SPC'et for paclitaxel DGCG
Docetaxel	100 mg/m^2	6 cyklusser V 21 dage	SPC'et for docetaxel DGCG
Doxorubicin	40 mg/m^2 (monoterapi) eller 30 mg/m^2 (kombinationsterapi)	6 cyklusser á 28 dage	SPC'et for doxorubicin DGCG
Cisplatin	100 mg/m^2	6 cyklusser á 21 dage	SPC'et for cisplatin DGCG
Carboplatin	AUC (5mg/mL/min)	6 cyklusser á 21 dage	SPC'et for carboplatin DGCG
Bevacizumab	15 mg/kg	12 cyklusser á 21 dage	ICON7 [12–14]
Cyclophosphamid	50 mg	6 cyklusser á 28 dage	SPC'et for cyclophosphamid Sjællands Universitetshospital
Niraparib	200 mg	[redacted]	*Real World Evidens data*
Olaparib	600 mg	[redacted]	*Real World Evidens data*

Medicinrådet accepterer ansøgers tilgang vedr. efterfølgende behandling, dog korrigerer Medicinrådets doseringen af niraparib, doxorubicin og bevacizumab i egen hovedanalyse.

4.2.4 Patientomkostninger

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

Ansøger anvender en enhedsomkostning for patienttid på 179 DKK pr. time og transportomkostninger på 99 DKK pr. besøg, jf. Medicinrådets værdisætning af enhedsomkostninger.

Medicinrådets vurdering af ansøgers antagelser vedr. patientomkostninger
Medicinrådet accepterer ansøgers estimerede patienttid og ansøgers tilgang til estimering af patientomkostninger. I Tabel 14 og Tabel 15 er estimater for patienternes ressourceforbrug vist for hhv. PFS-stadiet og PD-stadiet.

Tabel 14. Estimerede patientomkostninger pr. måned i PFS

	Stadie	Antal besøg pr. måned	Patienttid [timer]	Transport [antal]
Niraparib	PFS (1. måned)	4,0	4,0	4,0
	PFS (2. måned)	4,0	4,0	4,0
	PFS (efter 2. måned)	1,0	1,0	1,0
	PFS (ikke på behandling)	0,3	0,3	0,3
Olaparib	PFS (1. måned)	2,0	2,0	2,0
	PFS (efter 2. måned)	1,0	1,0	1,0
	PFS (ikke på behandling)	0,3	0,3	0,3
Ingen vedligeholdelses-behandling	PFS	0,3	0,3	0,3

Tabel 15. Estimerede patientomkostninger pr. måned i PD

	Stadie	Antal besøg pr. måned	Patienttid [timer]	Transport [antal]
Niraparib	PD	1,0	1,0	1,0
Olaparib	PD	1,0	1,0	1,0
Ingen vedligeholdelses-behandling	PD	1,0	1,0	1,0

Medicinrådet accepterer ansøgers tilgang vedr. patientomkostningerne.

4.3 Følsomhedsanalyser

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

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

Tabel 16. Ansøgers følsomhedsanalyser og beskrivelse

Følsomhedsanalyse	Beskrivelse
Patienter med BRCA-mutation	
Ekstrapolering af TTD – generalised gamma	Data for TTD ekstrapoleres ved anvendelse af den parametriske funktion generalised gamma
Ingen begrænsning på behandlingsvarighederne for niraparib og olaparib	Ingen begrænsning på behandlingsvarighederne for niraparib på 3 år og olaparib på 2 år
Fuld dosis af niraparib og olaparib	Anvendelse af fuld dosis for niraparib på 200 mg og olaparib på 600 mg
HRD-positive patienter uden BRCA-mutation	
Ekstrapolering af OS – eksponentiel	Data for OS ekstrapoleres ved anvendelse af den parametriske funktion eksponentiel
Ekstrapolering af OS – generalised gamma	Data for OS ekstrapoleres ved anvendelse af den parametriske funktion generalised gamma
Ingen begrænsning på behandlingsvarighederne for niraparib og olaparib	Ingen begrænsning på behandlingsvarighederne for niraparib på 3 år og olaparib på 2 år
Fuld dosis af niraparib	Anvendelse af fuld dosis for niraparib på 200 mg
HRD-negative patienter uden BRCA-mutation	
Ekstrapolering af OS – generalised gamma	Data for OS ekstrapoleres ved anvendelse af den parametriske funktion generalised gamma
Ekstrapolering af TTD – generalised gamma	Data for TTD ekstrapoleres ved anvendelse af den parametriske funktion generalised gamma
Ingen begrænsning på behandlingsvarighederne for niraparib og olaparib	Ingen begrænsning på behandlingsvarighederne for niraparib på 3 år og olaparib på 2 år
Fuld dosis af niraparib	Anvendelse af fuld dosis for niraparib på 200 mg

Medicinrådets vurdering af ansøgers valg af følsomhedsanalyser

Da ansøger har valgt at præsentere de følsomhedsanalyser, hvor analysens resultat er mest følsom overfor ændringer i specifikke parametre, vælger Medicinrådet ikke at præsentere følsomhedsanalyserne vedr. alternative ekstrapoleringer, da der er stor risiko for, at ekstrapoleringerne ikke er klinisk plausible. Ligeledes vil ingen begrænsning på behandlingsvarighederne for niraparib og olaparib ikke være klinisk plausible i dansk klinisk praksis, hvorfor Medicinrådet vælger ikke at præsentere disse analyser.

Medicinrådet vælger derimod at præsentere følsomhedsanalyserne, hvor der anvendes fuld dosis af niraparib og olaparib. Derudover vælger Medicinrådet at udarbejde følsomhedsanalyser, hvor testomkostninger inkluderes i tilfælde af, at Medicinrådet i dets anbefaling skelner mellem HRD-positive og HRD-negative patienter, hvilket vil indebære, at alle patienter, der ikke har en BRCA-mutation, bør udredes for HRD, som beskrevet i vurderingsrapporten. Slutteligt udføres følsomhedsanalyser af Medicinrådets hovedanalyser, hvor den betingede pris på niraparib anvendes.

Medicinrådet vælger at præsentere nogle af ansøgers følsomhedsanalyser samt Medicinrådets egne følsomhedsanalyser vedr. testomkostninger og anvendelse af den betingede pris på niraparib.

4.4 Opsummering af basisantagelser

I Tabel 17 opsummeres basisantagelserne i henholdsvis ansøgers og Medicinrådets hovedanalyse.

Tabel 17. Basisantagelser for ansøgers og Medicinrådets hovedanalyse

Basisantagelser	Ansøger	Medicinrådet
Tidshorisont	30 år	30 år
Diskonteringsrate	3,5 %	3,5 %
Inkluderede omkostninger	Lægemiddelomkostninger Hospitalsomkostninger Efterfølgende behandling Patientomkostninger	Lægemiddelomkostninger Hospitalsomkostninger Efterfølgende behandling Patientomkostninger
Dosering		
Niraparib	[redacted] mg	[redacted] mg
Olaparib	600 mg	575 mg de første tre måneder efterfulgt af 530 mg
Behandlingslinje	1. linjebehandling	1. linjebehandling
Parametriske funktioner for patienter med BRCA-mutation		
PFS:	Log-logistisk	Weibull
OS:	Log-logistisk	Log-normal

Basisantagelser	Ansøger	Medicinrådet
Parametriske funktioner for HRD-positive patienter uden BRCA-mutation		
PFS:	Log-logistisk	Weibull
OS:	Log-logistisk	Weibull
Parametriske funktioner for HRD-negative patienter uden BRCA-mutation		
PFS:	Log-logistisk	Log-logistisk
OS:	Log-logistisk	Log-logistisk
Inkludering af spild	Ja	Ja

5. Resultater

5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse med undtagelse af de ændringer, der fremgår af Tabel 17.

Patienter med BRCA-mutation

Den gennemsnitlige inkrementelle omkostning pr. patient bliver [redacted] DKK i Medicinrådets hovedanalyse, hvor niraparib sammenlignes med olaparib for patienter med BRCA-mutation. Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient 172.000 DKK.

HRD-positive patienter uden BRCA-mutation

Den gennemsnitlige inkrementelle omkostning pr. patient bliver [redacted] DKK i Medicinrådets hovedanalyse, hvor niraparib sammenlignes med ingen vedligeholdelsesbehandling for HRD-positive patienter uden BRCA-mutation. Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient 614.000 DKK.

HRD-negative patienter uden BRCA-mutation

Den gennemsnitlige inkrementelle omkostning pr. patient bliver [redacted] DKK i Medicinrådets hovedanalyse, hvor niraparib sammenlignes med ingen vedligeholdelsesbehandling for HRD-negative patienter uden BRCA-mutation. Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient 426.000 DKK.

For alle analyserne gælder det, at størstedelen af omkostningerne forekommer de første år af behandlingsforløbet.

Resultaterne fra Medicinrådets hovedanalyser er præsenteret i Tabel 18, Tabel 19 og Tabel 20 for hhv. patienter med BRCA-mutation, HRD-positive patienter uden BRCA-mutation og HRD-negative patienter uden BRCA-mutation.

Tabel 18. Resultatet af Medicinrådets hovedanalyse ved sammenligning med olaparib for patienter med BRCA-mutation, DKK, diskonterede tal

	Niraparib	Olaparib	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	128.677	117.095	11.582
Efterfølgende behandling	[redacted]	[redacted]	[redacted]
Patientomkostninger	22.064	10.616	11.448
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 19. Resultatet af Medicinrådets hovedanalyse ved sammenligning med ingen vedligeholdelsesbehandling for HRD-positive patienter uden BRCA-mutation, DKK, diskonterede tal

	Niraparib	Ingen vedligeholdelses-behandling	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	107.183	88.674	18.509
Efterfølgende behandling	[redacted]	[redacted]	[redacted]
Patientomkostninger	18.281	7.534	10.747
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 20. Resultatet af Medicinrådets hovedanalyse ved sammenligning med ingen vedligeholdelsesbehandling for HRD-negative patienter uden BRCA-mutation, DKK, diskonterede tal

	Niraparib	Ingen vedligeholdelses-behandling	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	112.744	94.362	18.382
Efterfølgende behandling	[redacted]	[redacted]	[redacted]

	Niraparib	Ingen vedligeholdelses-behandling	Inkrementelle omkostninger
Patientomkostninger	14.708	7.289	7.419
Totale omkostninger	[redacted]	[redacted]	[redacted]

5.1.1 Resultatet af Medicinrådets følsomhedsanalyser

Ved samme antagelser som i Medicinrådets hovedanalyse for meromkostninger har Medicinrådet udført en følsomhedsanalyse på parametrene listet i Tabel 21.

Tabel 21. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalysen, DKK

Scenarie	Inkrementelle omkostninger
Patienter med BRCA-mutation	
Resultatet af hovedanalysen	[redacted]
Fuld dosis af niraparib og olaparib	[redacted]
Anvendelse af den betingede pris på niraparib	[redacted]
HRD-positive patienter uden BRCA-mutation	
Resultatet af hovedanalysen	[redacted]
Fuld dosis af niraparib	[redacted]
Testomkostninger tildeles HRD-positive patienter uden BRCA-mutation – pris fra Myriad Genetics	[redacted]
Testomkostninger tildeles HRD-positive patienter uden BRCA-mutation – pris fra Rigshospitalet	[redacted]
Anvendelse af den betingede pris på niraparib	[redacted]
HRD-negative patienter uden BRCA-mutation	
Resultatet af hovedanalysen	[redacted]
Fuld dosis af niraparib	[redacted]
Testomkostninger tildeles HRD-negative patienter uden BRCA-mutation – pris fra Myriad Genetics	[redacted]
Testomkostninger tildeles HRD-positive patienter uden BRCA-mutation – pris fra Rigshospitalet	[redacted]

Scenarie	Inkrementelle omkostninger
Anvendelse af den betingede pris på niraparib	[redacted]

6. Budgetkonsekvenser

Budgetkonsekvenserne pr. år er baseret på antagelsen om, at niraparib vil blive anbefalet som mulig standardbehandling. Man ser derfor på to scenarier:

- Niraparib bliver anbefalet som mulig standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler.
- Niraparib bliver ikke anbefalet som mulig standardbehandling.

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

6.1 Ansøgers estimat af patientantal og markedsandel

Ansøger har antaget, at:

- Patienter med BRCA-mutation: 60 patienter er kandidater til behandling med niraparib, hvoraf ansøger antager, at niraparib vil have et stigende markedsoptag til 80 % i år 5.
- HRD-positive patienter uden BRCA-mutation (bevacizumabkandidater): 37 patienter er kandidater til behandling med niraparib, hvoraf ansøger antager, at niraparib vil have et stigende markedsoptag til 80 % i år 5, se Tabel 23.
- HRD-positive patienter uden BRCA-mutation (ikke-bevacizumabkandidater): 63 patienter er kandidater til behandling med niraparib, hvoraf ansøger antager, at niraparib vil have et stigende markedsoptag til 80 % i år 5, se Tabel 24.
- HRD-negative patienter uden BRCA-mutation (bevacizumabkandidater): 53 patienter er kandidater til behandling med niraparib, hvoraf ansøger antager, at niraparib vil have et stigende markedsoptag til 80 % i år 5, se Tabel 25.
- HRD-negative patienter uden BRCA-mutation (ikke-bevacizumabkandidater): 87 patienter er kandidater til behandling med niraparib, hvoraf ansøger antager, at niraparib vil have et stigende markedsoptag til 80 % i år 5, se Tabel 26.

Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse
Fagudvalget er konsulteret i forhold til patientantal og markedsoptag, hvis niraparib anbefales som mulig standardbehandling, og hvis ikke niraparib anbefales. For de HRD-positive patienter uden BRCA-mutation og HRD-negative patienter uden BRCA-mutation er fagudvalget enige i ansøgers antagelser. Fagudvalget vurderer, at kun en lille andel af patienter med BRCA-mutation modtager ingen vedligeholdelsesbehandling svarende til 10% af den samlede population. Derudover forventer fagudvalget ikke, at niraparibs

markedsoptag vil overstige olaparib til patienter med BRCA-mutation. Derimod forventer fagudvalget, at niraparib og olaparib vil have et markedsoptag på 45 % hver i år 5, se Tabel 22.

Tabel 22. Medicinrådets estimat af antal nye patienter pr. år for patienter med BRCA-mutation

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Niraparib	21	24	27	27	27
Olaparib	33	30	27	27	27
Ingen vedligeholdelses-behandling	6	6	6	6	6
			Anbefales ikke		
Niraparib	0	0	0	0	0
Olaparib	54	54	54	54	54
Ingen vedligeholdelses-behandling	6	6	6	6	6

Tabel 23. Medicinrådets estimat af antal nye patienter pr. år for HRD-positive patienter uden BRCA-mutation (bevacizumabkandidater)

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Niraparib	24	28	30	30	30
Ingen vedligeholdelses-behandling	13	9	7	7	7
			Anbefales ikke		
Niraparib	0	0	0	0	0
Ingen vedligeholdelses-behandling	37	37	37	37	37

Tabel 24. Medicinrådets estimat af antal nye patienter pr. år for HRD-positive patienter uden BRCA-mutation (ikke-bevacizumabkandidater)

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Niraparib	41	47	50	50	50
Ingen vedligeholdelses-behandling	22	16	13	13	13
			Anbefales ikke		
Niraparib	0	0	0	0	0
Ingen vedligeholdelses-behandling	63	63	63	63	63

Tabel 25. Medicinrådets estimat af antal nye patienter pr. år for HRD-negative patienter uden BRCA-mutation (bevacizumabkandidater)

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Niraparib	34	40	42	42	42
Ingen vedligeholdelses-behandling	19	13	11	11	11
			Anbefales ikke		
Niraparib	0	0	0	0	0
Ingen vedligeholdelses-behandling	53	53	53	53	53

Tabel 26. Medicinrådets estimat af antal nye patienter pr. år for HRD-negative patienter uden BRCA-mutation (ikke-bevacizumabkandidater)

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Niraparib	57	65	70	70	70

	År 1	År 2	År 3	År 4	År 5
Ingen vedligeholdelses-behandling	30	22	17	17	17
			Anbefales ikke		
Niraparib	0	0	0	0	0
Ingen vedligeholdelses-behandling	87	87	87	87	87

Medicinrådet udarbejder følsomhedsanalyser af budgetkonsekvenserne, hvor den betingede pris på niraparib anvendes.

Medicinrådet har udført sin egen budgetkonsekvensanalyse for patienter med BRCA-mutation, hvor markedsoptaget for niraparib og olaparib ændres til 45 % hver i år 5 samt følsomhedsanalyser af budgetkonsekvensanalyserne.

6.2 Medicinrådets budgetkonsekvensanalyse

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

- Patienter med BRCA-mutation: niraparib og olaparib vil have et markedsoptag på 45 % hver i år 5.

Patienter med BRCA-mutation

Medicinrådet estimerer, at anvendelse af niraparib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5 for patienter med BRCA-mutation. Resultatet er præsenteret i Tabel 27. Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 4,6 mio. DKK i år 5.

HRD-positive patienter uden BRCA-mutation (bevacizumabkandidater)

Medicinrådet estimerer, at anvendelse af niraparib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5 for HRD-positive patienter uden BRCA-mutation (bevacizumabkandidater). Resultatet er præsenteret i Tabel 28. Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 18,3 mio. DKK i år 5.

HRD-positive patienter uden BRCA-mutation (ikke-bevacizumabkandidater)

Medicinrådet estimerer, at anvendelse af niraparib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5 for HRD-positive patienter uden BRCA-mutation (ikke-bevacizumabkandidater). Resultatet er præsenteret i Tabel 29. Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 31,1 mio. DKK i år 5.

HRD-negative patienter uden BRCA-mutation (bevacizumabkandidater)

Medicinrådet estimerer, at anvendelse af niraparib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5 for HRD-negative patienter uden BRCA-mutation (bevacizumabkandidater). Resultatet er præsenteret i Tabel 30. Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 17,9 mio. DKK i år 5.

HRD-negative patienter uden BRCA-mutation (ikke-bevacizumabkandidater)

Medicinrådet estimerer, at anvendelse af niraparib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5 for HRD-negative patienter uden BRCA-mutation (ikke-bevacizumabkandidater). Resultatet er præsenteret i Tabel 31. Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 29,5 mio. DKK i år 5.

Tabel 27. Medicinrådets analyse af totale budgetkonsekvenser for patienter med BRCA-mutation, mio. DKK, ikke-diskonterede tal

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

Tabel 28. Medicinrådets analyse af totale budgetkonsekvenser for HRD-positive patienter uden BRCA-mutation (bevacizumabkandidater), mio. DKK, ikke-diskonterede tal

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

Tabel 29. Medicinrådets analyse af totale budgetkonsekvenser for HRD-positive patienter uden BRCA-mutation (ikke-bevacizumabkandidater), mio. DKK, ikke-diskonterede tal

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

Tabel 30. Medicinrådets analyse af totale budgetkonsekvenser for HRD-negative patienter uden BRCA-mutation (bevacizumabkandidater), mio. DKK, ikke-diskonterede tal

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

Tabel 31. Medicinrådets analyse af totale budgetkonsekvenser for HRD-negative patienter uden BRCA-mutation (ikke-bevacizumabkandidater), mio. DKK, ikke-diskonterede tal

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

6.2.1 Resultat af følsomhedsanalyser for budgetkonsekvensanalysen

Ved samme antagelser som i Medicinrådets hovedanalyse for budgetkonsekvenser men med anvendelse af den betingede pris på niraparib.

Patienter med BRCA-mutation

Medicinrådet estimerer, at anvendelse af niraparib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5 for patienter med BRCA-mutation. Resultatet er præsenteret i Tabel 27.

HRD-positive patienter uden BRCA-mutation (bevacizumabkandidater)

Medicinrådet estimerer, at anvendelse af niraparib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5 for HRD-positive patienter uden BRCA-mutation (bevacizumabkandidater). Resultatet er præsenteret i Tabel 28.

HRD-positive patienter uden BRCA-mutation (ikke-bevacizumabkandidater)

Medicinrådet estimerer, at anvendelse af niraparib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5 for HRD-positive patienter uden BRCA-mutation (ikke-bevacizumabkandidater). Resultatet er præsenteret i Tabel 29.

HRD-negative patienter uden BRCA-mutation (bevacizumabkandidater)

Medicinrådet estimerer, at anvendelse af niraparib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5 for HRD-negative patienter uden BRCA-mutation (bevacizumabkandidater). Resultatet er præsenteret i Tabel 30.

HRD-negative patienter uden BRCA-mutation (ikke-bevacizumabkandidater)

Medicinrådet estimerer, at anvendelse af niraparib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5 for HRD-negative patienter uden BRCA-mutation (ikke-bevacizumabkandidater). Resultatet er præsenteret i Tabel 31.

Tabel 32. Medicinrådets analyse af totale budgetkonsekvenser for patienter med BRCA-mutation med den betingede pris på niraparib, mio. DKK, ikke-diskonterede tal

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

Tabel 33. Medicinrådets analyse af totale budgetkonsekvenser for HRD-positive patienter uden BRCA-mutation (bevacizumabkandidater) med den betingede pris på niraparib, mio. DKK, ikke-diskonterede tal

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

Tabel 34. Medicinrådets analyse af totale budgetkonsekvenser for HRD-positive patienter uden BRCA-mutation (ikke-bevacizumabkandidater) med den betingede pris på niraparib, mio. DKK, ikke-diskonterede tal

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

Tabel 35. Medicinrådets analyse af totale budgetkonsekvenser for HRD-negative patienter uden BRCA-mutation (bevacizumabkandidater) med den betingede pris på niraparib, mio. DKK, ikke-diskonterede tal

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

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

Tabel 36. Medicinrådets analyse af totale budgetkonsekvenser for HRD-negative patienter uden BRCA-mutation (ikke-bevacizumabkandidater) med den betingede pris på niraparib, mio. DKK, ikke-diskonterede tal

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

7. Diskussion

Behandling med niraparib til patienter med BRCA-mutation er forbundet med inkrementelle omkostninger på ca. [redacted] DKK sammenlignet med behandling med olaparib. Behandling med niraparib til HRD-positive patienter uden BRCA-mutation er forbundet med inkrementelle omkostninger på ca. [redacted] DKK sammenlignet med behandling med ingen vedligeholdelsesbehandling. Behandling med niraparib til HRD-negative patienter uden BRCA-mutation er forbundet med inkrementelle omkostninger på ca. [redacted] DKK sammenlignet med behandling med ingen vedligeholdelsesbehandling.

De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne for niraparib. Hvis dosis for niraparib og olaparib sættes til fuld dosis, da stiger de inkrementelle omkostninger med ca. [redacted] DKK for alle populationer.

På nuværende tidspunkt testes der ikke rutinemæssigt for HRD hos patienter uden BRCA-mutation, men dette vil være en forudsætning for ibrugtagning af niraparib, hvis niraparib ikke anbefales af Medicinrådet til både HRD-positive og HRD-negative patienter uden BRCA-mutation. Hvis Medicinrådet vælger kun at anbefale niraparib til HRD-positive patienter uden BRCA-mutation, vil de inkrementelle omkostninger stige fra [redacted] DKK til [redacted] DKK, hvis prisen på HRD-test fra Rigshospitalet anvendes. Hvis Medicinrådet derimod vælger kun at anbefale niraparib til HRD-negative patienter uden BRCA-mutation, vil de inkrementelle omkostninger stige fra [redacted] DKK til [redacted] DKK. Hvis Medicinrådet derimod vælger at anbefale niraparib til begge

patientpopulationer eller kun patienter med BRCA-mutation, da vil det ikke være nødvendigt at teste for HRD, da begge populationer alligevel vil få niraparib tilbudt uanset HRD-status.

8. Referencer

1. Mosgaard BJ, Pedersen LK, Bjørn SF, Christiansen T, Markauskas A, Lund B, et al. Retningslinier for visitation, diagnostik, behandling og opfølgning af epitelial ovarie-, tuba- og primær peritonealcancer samt borderline tumorer. Kapitel 1: Introduktion. 2.

2. NORDCAN - Association of the Nordic Cancer Registries. Kræftstatistik: Nøgetal og figurer. 2017.

3. Bolton KL, Chenevix-Trench G, Goh C, Sadetzki S, Ramus SJ, Karlan BY, et al. Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer. JAMA. 2012;307(4):382–90.

4. Hoppe MM, Sundar R, Tan DSP, Jeyasekharan AD. Biomarkers for homologous recombination deficiency in cancer. J Natl Cancer Inst. 2018;110(7):704–13.

5. Pellegrino B, Mateo J, Serra V, Balmaña J. Controversies in oncology: are genomic tests quantifying homologous recombination repair deficiency (HRD) useful for treatment decision making? ESMO open. 2019;4(2):e000480.

6. Charlotte Lautrup, Uffe Birk Jensen, Anders Bojesen, Mads Thomassen, Thomas van Overeem Hansen, Anne-Marie Gerdes, Jan Blaakær, Henrik Roed, Ulla Peen, Karina Dahl Steffensen, Bente Lund, Lotte Nedergaard Thomsen EH. Forslag til national guideline for gen.

7. González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2019;381(25):2391–402.

8. Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2018;379(26):2495–505.

9. Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, et al. Incorporation of Bevacizumab in the Primary Treatment of Ovarian Cancer for the Gynecologic Oncology Group*. Seattle Cancer Care Alliance, Seattle (BEG Minneap (MB); Harvard Med Sch Mas.

10. Monk BJ, Huang HQ, Burger RA, Mannel RS, Homesley HD, Fowler J, et al. Patient reported outcomes of a randomized, placebo-controlled trial of bevacizumab in the front-line treatment of ovarian cancer: a Gynecologic Oncology Group Study. Gynecol Oncol. 201.

11. Tewari KS, Burger RA, Enserro D, Norquist BM, Swisher EM, Brady MF, et al. Final overall survival of a randomized trial of bevacizumab for primary treatment of ovarian cancer. J Clin Oncol. 2019;37(26):2317–28.

12. Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, et al. A Phase 3 Trial of Bevacizumab in Ovarian Cancer. N Engl J Med. 2011;365(26):2484–96.

13. Stark D, Nankivell M, Pujade-Lauraine E, Kristensen G, Elit L, Stockler M, et al. Standard chemotherapy with or without bevacizumab in advanced ovarian cancer: quality-of-life outcomes from the International Collaboration on Ovarian Neoplasms (ICON7) phas.

14. Oza AM, Cook AD, Pfisterer J, Embleton A, Ledermann JA, Pujade-Lauraine E, et al. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. Lancet Oncol.

15. Medicinrådet. Medicinrådets behandlingsvejledning vedrørende lægemidler til BRCA-muteret kræft i æggestokkene, ægge-lederne eller primær kræft i bughinden. 2020;1–10. Tilgængelig fra: https://medicinraadet.dk/media/ibkdjfqg/medicinrådets_behandlingsvejledning_vedr-_lægemidler_til_brca-mutereret_kræft_i_æggestokkene-vers-_1-0_adlegacy.pdf

9. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	23. juni 2021	Godkendt af Medicinrådet.

10. Bilag

10.1 Resultatet af ansøgers hovedanalyse

Patienter med BRCA-mutation

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient [redacted] DKK over en tidshorisont på 30 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 32.

HRD-positive patienter uden BRCA-mutation

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient [redacted] DKK over en tidshorisont på 30 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 33.

HRD-negative patienter uden BRCA-mutation

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient [redacted] DKK over en tidshorisont på 30 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 34.

Tabel 37. Resultatet af ansøgers hovedanalyse ved sammenligning med olaparib for patienter med BRCA-mutation, DKK, diskonterede tal

	Niraparib	Olaparib	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	55.852	48.421	7.431
Efterfølgende behandling	[redacted]	[redacted]	[redacted]
Patientomkostninger	20.058	8.431	11.627
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 38. Resultatet af ansøgers hovedanalyse ved sammenligning med ingen vedligeholdelsesbehandling for HRD-positive patienter uden BRCA-mutation, DKK, diskonterede tal

	Niraparib	Ingen vedligeholdelses-behandling	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	60.845	49.272	11.573
Efterfølgende behandling	[redacted]	[redacted]	[redacted]

	Niraparib	Ingen vedligeholdelses-behandling	Inkrementelle omkostninger
Patientomkostninger	18.529	7.330	11.199
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 39. Resultatet af ansøgers hovedanalyse ved sammenligning med ingen vedligeholdelsesbehandling for HRD-negative patienter uden BRCA-mutation, DKK, diskonterede tal

	Niraparib	Ingen vedligeholdelses-behandling	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	50.045	29.934	20.110
Efterfølgende behandling	[redacted]	[redacted]	[redacted]
Patientomkostninger	13.069	4.552	8.517
Totale omkostninger	[redacted]	[redacted]	[redacted]

10.2 Resultatet af ansøgers budgetkonsekvensanalyse

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

Patienter med BRCA-mutation

Ansøger estimerer, at anvendelse af niraparib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 35.

HRD-positive patienter uden BRCA-mutation (bevacizumabkandidater)

Ansøger estimerer, at anvendelse af niraparib vil resultere i budgetkonsekvenser på ca. [redacted]. DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 36.

HRD-positive patienter uden BRCA-mutation (ikke-bevacizumabkandidater)

Ansøger estimerer, at anvendelse af niraparib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 37.

HRD-negative patienter uden BRCA-mutation (bevacizumabkandidater)

Ansøger estimerer, at anvendelse af niraparib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 38.

HRD-negative patienter uden BRCA-mutation (ikke-bevacizumabkandidater)

Ansøger estimerer, at anvendelse af niraparib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 39.

Tabel 40. Ansøgers hovedanalyse for totale budgetkonsekvenser for patienter med BRCA-mutation, mio. DKK, ikke-diskonterede tal

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

Tabel 41. Ansøgers hovedanalyse for totale budgetkonsekvenser for HRD-positiv patienter uden BRCA-mutation (bevacizumab kandidater), mio. DKK, ikke-diskonterede tal

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

Tabel 42. Ansøgers hovedanalyse for totale budgetkonsekvenser for HRD-positiv patienter uden BRCA-mutation (ikke bevacizumab kandidater), mio. DKK, ikke-diskonterede tal

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

Tabel 43. Ansøgers hovedanalyse for totale budgetkonsekvenser for HRD-negative patienter uden BRCA-mutation (bevacizumab kandidater), mio. DKK, ikke-diskonterede tal

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

Tabel 44. Ansøgers hovedanalyse for totale budgetkonsekvenser for HRD-negative patienter uden BRCA-mutation (ikke bevacizumab kandidater), mio. DKK, ikke-diskonterede tal

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

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Forhandlingsnotat

Dato for behandling i Medicinrådet	23.06.2021
Leverandør	GSK
Lægemiddel	Zejula (niraparib)
Ansøgt indikation	Til behandling af patienter med avanceret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden.

Forhandlingsresultat

Amgros har opnået følgende pris på niraparib på betingelse af en godkendelse til standardbehandling af **klinisk spørgsmål 1, 2 og 4:**

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP (DKK)	Tidligere SAIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Niraparib	100 mg	56 stk.	41.340	[redacted]	[redacted]	[redacted]
Niraparib	100 mg	84 stk.	62.010	[redacted]	[redacted]	[redacted]

Der er allerede aftale på begge lægemidler (olaparib og niraparib) til dette terapiområde og aftalen løber indtil slutningen af 2021. Planen er at gennemføre et udbud med kontraktstart d. 01.01.2022.

Vurdering af forhandlingsresultatet

Det er Amgros' vurdering, at vi har opnået den bedst mulige pris på niraparib til denne patientpopulation. Denne vurdering baserer vi på følgende punkter:

- Det er leverandørens intention at få niraparib godkendt som standardbehandling til hele patientpopulationen og alle kliniske spørgsmål.

- Leverandøren mener at niraparib møder et unmet need og det er en patientpopulation, der ikke har andre behandlingsalternativer.

Konklusion

Det er Amgros vurdering at vi har opnået den bedst mulige pris på niraparib.

Relation til markedet

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

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

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

*Betinget pris tilbudt af AstraZeneca i forhandling med Amgros i maj 2021.

Andelen af patienter der får hhv. 100, 200 og 300 mg. Fremgår af Amgros' udvidet sammenligningsgrundlag fra 2020[1].

[1] Microsoft Word - Udvidet sammenligningsgrundlag Ovariecancer version 2 (medicinraadet.dk)

Status fra andre lande

I Norge er Niraparib godkendt til 2. linje behandling, til patienter uden BRCA1/2-mutation i maj 2020[2].

I Sverige er Niraparib godkendt til patienter med og uden forandring af BRCA-generne som 2. linje behandling i december 2019[3].

[2] Niraparib (Zejula) - Indikasjon III (nyemetoder.no)
[3] Zejula ingår i högkostnadsskyddet med begränsning - Tandvårds- och läkemedelsförmånsverket TLV

Til Medicinrådet

Høringssvar vedr. vurdering af niraparib til 1. linje vedligeholdelses-behandling af avanceret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden

4. maj 2021

GSK takker for modtagelsen af Medicinrådets udkast til vurdering af Zejula (niraparib) til 1. linje vedligeholdelses-behandling af avanceret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden.

GSK har følgende kommentarer til høringsudkastet:

Klinisk spørgsmål 1, 2 og 4

GSK har ingen yderligere kommentarer.

Klinisk spørgsmål 3: niraparib vs bevacizumab til HRD-negativ uden BRCA-mutation

GSK er enig i, at den samlede værdi af niraparib sammenlignet med bevacizumab til patienter med nydiagnosticeret, HRD-negativ kræft i æggestokkene ikke kan kategoriseres efter Medicinrådets metoder.

GSK er til gengæld uenig i, at niraparib, modsat bevacizumab, ikke har nogen klinisk relevant effekt på PFS i denne patientgruppe. GSK mener, at det ikke kan konkluderes, at bevacizumab har dokumenteret effekt specifikt på populationen med HRD-negativ sygdom, eftersom homolog rekombination-status ikke er opgjort i ICON7. High risk populationen i ICON7 er derfor sammenlignelig med PRIMA ITT-populationen og ikke alene med subpopulationen der er HRD-negativ.[1,2]

Vi henstiller derfor til, at formuleringen af konklusionen vedr. klinisk spørgsmål 3 genovervejes, og at følgende tekst fjernes i konklusionen ”Fagudvalget vurderer, at niraparib, modsat bevacizumab, ikke har nogen klinisk relevant effekt på PFS i denne patientgruppe”.

Klinisk spørgsmål 5: niraparib vs placebo til HRD-negativ uden BRCA-mutation

GSK undrer sig over at fagudvalgets samlede konklusion vedr. niraparib vs placebo til patienter med HRD-negativ sygdom.

For både OS og PFS indikerer de relative værdier en merværdi af ukendt størrelse, hvorved det ikke kan udelukkes, at niraparib kan have en lille effekt på denne patientgruppe. GSK anerkender, at data for populationen i PRIMA med HRD-negativ sygdom er umodne, dog finder vi det uhensigtsmæssigt at ignorere en HR på 0,51 for OS og en absolut forskel på 22,3 procentpoint for OS raten efter 24 måneder[1].

Niraparib er forbundet med flere bivirkninger end placebo, hvilket er forventeligt, når man sammenligner en aktiv behandling med placebo. Samtidig vurderer fagudvalget, at bivirkningerne ved niraparib generelt er kendte og håndterbare i klinikken, bl.a. ved hjælp af individualiseret startdosis og løbende dosisreduktioner.

Vi henstiller derfor til, at konklusionen vedr. klinisk spørgsmål 5 ændres til en **merværdi af ukendt størrelse** alternativt **kan ikke kategoriseres**.

GSK mener, at den kliniske vurdering for ovenstående kliniske spørgsmål ikke tilgodeser patienternes mulighed for at bevare platinsensitivitet (>6 måneders PFS) ved behandling med niraparib.

Internationale eksperter udtaler endvidere, at niraparib giver en klinisk fordel for alle patienter uafhængigt af subgrupperne i PRIMA, om end BRCAmut/HRD populationen har den største gevinst.[3,4,5]

Påvirkning af efterfølgende behandlingslinjer og vurderingens relation til eventuel 2. linjebehandling

Fagudvalget skriver, at det biologiske rationale for behandlingen med niraparib ikke afviger mellem 1. linje eller senere behandlingslinjer. I begge tilfælde forventes, at HRD-positive patienter vil respondere bedre på niraparib end patienter med intakt homolog rekombination (HRD-negative). Fagudvalget vurderer derfor, at HRD-positive patienter i senere behandlingslinjer også vil have en klinisk relevant merværdi ved behandling med niraparib, hvis patienterne lever op til de betingelser, Medicinrådet har opstillet i behandlingsvejledningen for BRCA-muteret kræft i æggestokkene.

Median PFS for niraparib i 2 linie behandling for populationen med HRD-negativ sygdom er 3,1 måneder (HR= 0.58), hvilket i henhold til vurderingen af 1. linje behandling ville have medført en klinisk relevant merværdi[6].

GSK mener derfor, at niraparib ifølge indikation og på baggrund af tilgængelige data bidrager med en klinisk relevant værdi for alle patienter, uanset homolog rekombinant status.

Status på godkendelser i andre lande

GSK bemærker, at NICE i England via Cancer Drug Fund allerede har godkendt niraparib til brug i 1. linje indenfor indikation, dækkende alle subpopulationer i PRIMA.
I Tyskland, Sverige, Norge og Finland har sundhedsmyndighederne godkendt niraparib som standardbehandling i 2. linje til alle ovariecancerpatienter med BRCAwt biomarkør.

Med venlig hilsen

Birgit Andersen
Market Access og Tender Manager

GSK

Referencer:

1. González-Martín A, Pothuri B, Vergote I, et al: Niraparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med 381:2391-2402, 2019.

2. Oza AM et al.; ICON7 trial investigators. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. Lancet Oncol. 2015 Aug;16(8):928-36. doi: 10.1016/S1470-2045(15)00086-8. Epub 2015 Jun 23. PMID: 26115797; PMCID: PMC4648090.

3. Antonio González-Martín, MD, PhD, of Español de Investigación en Cáncer de Ovario and Clinica Universidad de Navarra, Spain: ESMO 2019: PRIMA Trial Reports Benefit With Niraparib Across Ovarian Cancer Subsets

4. González-Martín A, Pothuri B, Vergote I, et al: Niraparib therapy in patients with newly diagnosed advanced ovarian cancer. ESMO Congress 2019. Abstract LBA1. Presented September 28, 2019.

5. Expert Point of View: Ana Oaknin, MD, PhD; By The ASCO Post Staff September 10, 2020 - Supplement: Gynecologic Cancers Almanac
6. Mirza MR, et Al; ENGOT-OV16/NOVA Investigators. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med. 2016 Dec 1;375(22):2154-2164. doi: 10.1056/NEJMoa1611310. Epub 2016 Oct 7. PMID: 27717299.

Fra: Hans Christian Cederberg Helms
Sendt: 6. maj 2021 11:10
Til: Birgit Andersen <birgit.x.andersen@gsk.com>; Nikoline.x.vestergaarddich@gsk.com
Emne: Kvittering for høringssvar

Kære Birgit og Nikoline

Tak for jeres høringssvar vedrørende udkast til Medicinrådets vurdering af lægemidlets værdi for niraparib til kræft i æggestokkene, modtaget den 4. maj 2021.
Vi har gennemgået jeres kommentarer til vurderingsrapporten sammen med fagudvalgsformanden og finder ikke anledning til at ændre den nuværende kategorisering.
Jeres høringssvar vil indgå i den videre sagsbehandling, og vil blive offentliggjort sammen med den endelige anbefaling

mvh

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Medicinrådet

Medicinrådet

Medicinrådets vurdering vedrørende niraparib til 1. linje vedligeholdelses-behandling af avanceret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

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

Om vurderingsrapporten

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

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

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

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1. Medicinrådets konklusion

Medicinrådet har vurderet niraparib i patientpopulationer opdelt efter BRCA-mutationsstatus og HRD-status.

For patienter med BRCA-mutation kan den samlede værdi af niraparib sammenlignet med olaparib ikke kategoriseres. Medicinrådet finder, at begge lægemidler er effektive i forhold til placebo og har en håndterbar bivirkningsprofil. Derfor vurderer Medicinrådet, at niraparib kan ligestilles med olaparib.

For patienter uden BRCA-mutation kan den samlede værdi af niraparib sammenlignet med bevacizumab ikke kategoriseres. Medicinrådet finder, at niraparib er mere effektivt end bevacizumab til HRD-positive patienter, mens det tilgængelige datagrundlag ikke indikerer, at niraparib er mere effektivt end bevacizumab til HRD-negative patienter. Bivirkningsprofilerne er forskellige, men håndterbare og velkendte ved begge lægemidler.

For HRD-positive patienter har niraparib en lille merværdi sammenlignet med placebo. Derimod har niraparib ingen dokumenteret merværdi sammenlignet med placebo til HRD-negative patienter. Medicinrådet vurderer, at effekten af niraparib ved 2. linjebehandling er sammenlignelig med effekten ved 1. linjebehandling, når patienterne inddeles efter HRD-status.

Vurderingerne er baseret på evidens af meget lav kvalitet. Medicinrådet bemærker, at der ikke foreligger modne data til at vurdere niraparibs effekt på overlevelsen.

MEDICINRÅDET KATEGORISERER LÆGEMIDLERS VÆRDI I EN AF FØLGENDE KATEGORIER:

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

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

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

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

2. Begreber og forkortelser

BRCA	To specifikke gener involveret i homolog rekombination *(Breast cancer gene*)
CI:	Konfidensinterval
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EPAR:	*European Public Assessment Report*
FDA	*U.S. Food and Drug Administration*
GRADE:	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HGSC	High-grade serøst karcinom *(High-grade serous carcinoma)*
HR:	*Hazard ratio*
HRD	Homolog rekombinations-defekt (*Homologues recombination deficiency)*
HRD-negativ	Patienter med intakt homolog rekombination I tumorvævet
HRD-positiv	Patienter med defekt homolog rekombination i tumorvævet
HRP	*Homologues recombination proficient.* Det samme som HRD-negativ
ITT:	*Intention to treat*
OR:	*Odds ratio*
OS	Samlet overlevelse (*Overall survival*)
PARP	Poly-ADP-ribose-polymerase
PARPi	Poly-ADP-ribose-polymerase hæmmer (*Poly-ADP-ribose-polymerase inhibitor*)
PFS	Progressionsfri overlevelse (*Progression free survival*)
PICO:	Population, intervention, komparator og effektmål (*Population, Intervention, Comparator and Outcome)*
PP:	*Per Protocol*
RCT:	Randomiseret kontrolleret studie *(Randomised Controlled Trial)*
RR:	Relativ risiko
SMD	*Standardized Mean Difference*

3. Introduktion

Formålet med Medicinrådets vurdering af niraparib til 1. linje vedligeholdelsesbehandling af avanceret epitelial high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra GlaxoSmithKline. Medicinrådet modtog ansøgningen den 25. februar 2021.

De kliniske spørgsmål er:

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

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

3.1 Kræft i æggestokkene, æggelederne eller primær bughulekræft

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

Kræft i æggestokkene er den fjerde hyppigste kræftdødsårsag hos kvinder i Danmark. Der diagnosticeres omkring 450-550 nye tilfælde om året, og ved udgangen af 2016 levede 4697 kvinder med sygdommen [1,2]. Kræft i æggestokkene udgør i alt 2,8 % af alle kræfttilfælde hos kvinder, og livstidsrisikoen for at udvikle sygdommen er ca. 2 %. Median alder for diagnosen er 63 år, og overlevelsen er afhængig af alder ved diagnosen samt sygdomsstadiet (FIGO-stadium, herfra blot benævnt stadium). 5-års overlevelsesrater for stadium I, II, III og IV er henholdsvis 93, 76, 41 og 23 % med faldende respektive værdier ved stigende alder på diagnosetidspunktet [3,4]. Tidlige stadier af sygdommen er ofte asymptomatiske på grund af æggestokkenes frie beliggenhed i det lille bækken. Således har ca. 70-80 % af patienter med kræft i æggestokkene på diagnosetidspunktet lokal spredning eller avanceret sygdom (stadium II-IV) [1], hvilket er kraftigt medvirkende til en samlet 5-års overlevelse på ca. 40-50 % [4].

Kræft i æggestokkene er overordnet set en heterogen gruppe. Dog er omkring 90 % af tilfældene af epitelial type (karcinomer), og ca. 55 % af disse er af typen high-grade serøst karcinom (HGSC) (omkring 300 patienter per år fra 2016-2019) [4].

Mutationer i *Breast Cancer* (BRCA) 1- eller 2-genet er en væsentlig arvelig risikofaktor for udviklingen af kræft i æggestokkene. Forekomsten er ca. 15-20 % med en højere forekomst hos patienter med HGSC [5-7]. BRCA-mutationer kan være både arvelige eller somatiske. I dansk klinisk praksis behandles arvelige og somatiske BRCA-mutationer på samme måde, hvorved BRCA-mutationer i denne protokol bruges som fællesbetegnelse. Patienter med BRCA-mutation har generelt en bedre prognose, da mutationerne medfører et signifikant bedre respons på platinbaseret kemoterapi og hæmmere af Poly-ADP-Ribose-Polymerase (PARPi) [8-11].

BRCA er involveret i homolog rekombination, som er en vital celleproces til reparation af DNA-skader [8,12]. Tumorer med BRCA-mutation vil oftest også have homolog rekombinationsdefekt (HRD), men HRD kan også forekomme i ikke-BRCA-muterede tumorer. Flere studier har dokumenteret HRD i op mod 40 % af tumorer i æggestokkene uden BRCA-mutation, der responderer på platinbaseret kemoterapi, hvorved den HRD-positive gruppe er op mod dobbelt så stor som i gruppen med BRCA-mutation [6,11,13-15]. I studierne var HRD-positiv defineret som enten BRCA-mutation eller en genomisk ustabilitetsscore over 42 målt vha. MYRIAD myChoice CDx. Dette er en kompleks molekylærbiologisk analyse, der kombinerer genomic scar assays, hhv. 'Telomeric Allelic Imbalance', 'Loss Of Heterozygosity' og 'Large Scale Transition' med en samlet tærskelværdi på 42 til bestemmelse af HRD-positivitet. I denne rapport bruges HRD-positive som betegnelse for gruppen med påvist homolog rekombinationsdefekt, mens HRD-negative bruges som betegnelse for gruppen med normalt fungerende homolog rekombination (somme tider også omtalt som *Homologues recombination proficient/*HRP).

Det anbefales i dag, at alle patienter med kræft i æggestokkene udredes i forhold til BRCA-mutationsstatus [16], men der findes ingen nationale guidelines i forbindelse med udredning af HRD-status. Derfor vil det forventes, at en væsentlig gruppe af danske patienter uden påvist BRCA-mutation har tumorer, der udviser HRD. *U.S. Food and Drug Administration* (FDA) har i 2020 godkendt MYRIAD myChoice CDx som 'companion

diagnostics' til at identificere HRD i high-grade kræft i æggestokkene [17]. Denne diagnostiske metode er anvendt i flere kliniske forsøg med PARPi i Danmark, heriblandt på Herlev Hospital, Odense Universitetshospital, Rigshospitalet og Aarhus Universitetshospital, hvor mere end 100 patienter er blevet testet [10,11,14,18].

Tilstedeværelsen af en HRD-positiv patientgruppe uden BRCA-mutation gør det relevant at formulere kliniske spørgsmål for tre subpopulationer af forskellig forventet størrelse, ud fra en antagelse om samlet 300 nydiagnosticerede patienter med HGSC om året:

- Patienter med BRCA-mutation: Ca. 60 patienter om året.
- HRD-positive patienter uden BRCA-mutation: Ca. 100 patienter om året.
- HRD-negative patienter: Ca. 140 patienter om året.

3.2 Niraparib

Niraparib blev den 29. oktober 2020 godkendt af Europakomissionen til 1. linje vedligeholdelsesbehandling af patienter med avanceret high-grade kræft i æggestokkene, æggelederne og primær kræft i bughinden, som responderer på platinbaseret kemoterapi (komplet eller partiel respons). Niraparib er desuden godkendt som monoterapi til 2. linje vedligeholdelsesbehandling af platinsensitiv high-grade serøst karcinom i æggestokkene [19]. I 2010 blev niraparib betegnet som *orphan drug* af EMA [19].

Medicinrådet anbefaler niraparib til 2. linje vedligeholdelsesbehandling af patienter med påvist BRCA-mutation under forudsætning af, at der ikke er behandlet med PARPi i 1. linje [20].

Standarddoseringen af niraparib er på 2 kapsler af 100 mg dagligt indtil sygdomsprogression eller 3 kapsler af 100 mg dagligt, hvis patienten vejer over 77 kg og har tilstrækkelige thrombocytter [21]. Fagudvalget estimerer, at ca 70 % af patienterne starter på en dosis på 200 mg, og ca 10 % starter på 100 mg.

Niraparib tilhører gruppen af selektive PARPi, der hæmmer aktivering af enzymerne, PARP-1, -2 og -3 [19]. PARP indgår i cellens DNA-reparationsrespons, hvor de faciliterer reparation af enkeltstrengsbrud på DNA'et. Hæmning af denne proces resulterer i yderligere brud på DNA'et kaldet DNA-dobbeltstrengsbrud. Disse brud repareres normalt via homolog rekombination, men i HRD-positive celler (som er tilfældet i BRCA-mutationer), vil dobbeltstrengsbrud akkumulere og medføre celledød i tumoren [22]. Niraparib udviser, ligesom andre PARPi, en større effekt i tumorer med enten påvist BRCA-mutation eller HRD. Dog er der også påvist en mindre men statistisk signifikant øgning af progressionsfri overlevelse (PFS) hos patienter uden hverken BRCA-mutation eller HRD ved vedligeholdelsesbehandling efter 2. eller senere behandlingslinjer af platinsensitive HGSC-tumorer i æggestokkene [11].

3.3 Nuværende behandling

Det overordnede mål for behandlingen af kræft i æggestokkene er helbredelse, alternativt at forlænge overlevelsen og/eller at øge livskvaliteten. Den primære behandling er kirurgisk, hvor målet er at fjerne alt synligt kræftvæv (makroradikal operation) samt korrekt stadieinddeling [1,23]. Dette opnås for ca. 70 % af patienterne med stadium III eller IV enten primært eller efter indledende kemoterapi [4]. Efterfølgende behandling afhænger af patientens sygdomsstadie, operationsresultat og sundhedsmæssige status. I klinisk praksis skelnes der mellem patienter, hvor der er efterladt mindre end eller mere end eller lig med 1 cm tumorvæv efter operation.

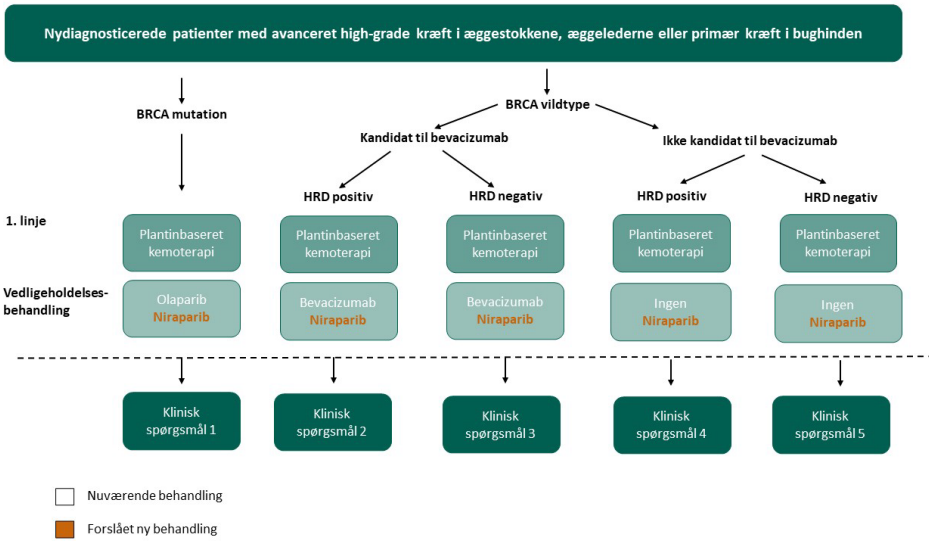
Patienter med avanceret kræft i æggestokkene uden makroskopisk tumorvæv efter operation (< 1 cm) behandles som standard med adjuverende platinbaseret kombinationskemoterapi bestående af carboplatin og paclitaxel. Behandlingen gives i 6 serier, med mindre der opstår progression eller uacceptabel toksicitet [24]. Patienter med BRCA-mutation, som responderer på kemoterapien, tilbydes vedligeholdelsesbehandling med olaparib i en standarddosering på 2 tabletter af 150 mg per styk 2 gange dagligt i 2 år eller indtil progression eller uacceptabel toksicitet [20]. Patienter uden BRCA-mutation tilbydes ikke yderligere vedligeholdelsesbehandling.

Patienter i stadium III med efterladt makroskopisk tumorvæv efter operation (≥ 1 cm) samt patienter i stadium IV og inoperable patienter behandles som standard også med carboplatin og paclitaxel. Patienter med BRCA-mutation tilbydes vedligeholdelsesbehandling med olaparib som beskrevet ovenfor, hvorimod patienter uden BRCA-mutation kan tilbydes behandling med bevacizumab i kombination med eller efter kemoterapien [24].

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

For en nærmere beskrivelse af efterfølgende behandling af platinsensitiv recidiverende kræft i æggestokkene henvises til Dansk Gynækologisk Cancer Gruppes retningslinjer [24].

Det nuværende behandlingsforløb, samt hvorledes niraparib placeres i forhold til dette i de fem kliniske spørgsmål er skitseret nedenfor.



Figur 3-1: Niraparibs indplacering som vedligeholdelsesbehandling efter den nuværende 1. linjebehandling med platinbaseret kemoterapi af kræft i æggestokkene. EMA-indikationen for niraparib dækker alle patienter med nydiagnosticeret kræft i æggestokkene, der responderer på platin, men den samlede patientpopulation er i denne vurderingsrapport opdelt for at belyse effekterne i de forskellige subgrupper.

4. Metode

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

5. Resultater

Niraparib er interventionen i alle 5 kliniske spørgsmål. Effekten af 1. linjebehandling med niraparib overfor placebo er undersøgt i et klinisk fase III-studie, PRIMA, som danner grundlag for effektestimaterne for interventionsarmen ved alle 5 kliniske spørgsmål. Intention to treat (ITT)-gruppen i PRIMA er inddelt i subpopulationer afhængig af BRCA- og HRD-status. Tabel 5-1 viser et overblik over subpopulationerne i PRIMA-studiet, og til hvilke kliniske spørgsmål de forskellige subpopulationer anvendes. Estimaterne for progressionsfri overlevelse (PFS) og samlet overlevelse (OS) fra de forskellige subpopulationer anvendes til de forskellige kliniske spørgsmål. ITT-populationen for interventionen anvendes i alle kliniske spørgsmål til besvarelse af effektmålene bivirkninger og livskvalitet.

Tabel 5-1. Oversigt over subpopulationerne i PRIMA-studiet, og hvilke kliniske spørgsmål de anvendes til besvarelse af

Klinisk studie	Subpopulation	Antal patienter (niraparib og placebo)	Relevant til klinisk spørgsmål
PRIMA [26]	Intention to treat	487 og 246	Bivirkninger og livskvalitet ved alle kliniske spørgsmål Grad 3/4 angives enten som uønskede hændelser (klinisk spørgsmål 1) eller bivirkninger (klinisk spørgsmål 2-5)
	BRCA-mutation	152 og 71	PFS ved klinisk spørgsmål 1
	BRCA-vildtype, HRD-positiv	95 og 55	PFS ved klinisk spørgsmål 2 og 4
	BRCA-vildtype, HRD-negativ	169 og 80	PFS og OS ved klinisk spørgsmål 3 og 5
	HRD-ukendt	71 og 40	Anvendes ikke

Komparatorerne er forskellige i de kliniske spørgsmål, og kun spørgsmål 4 og 5 angår en sammenligning med placebo, hvor PRIMA-studiet kan anvendes til en direkte sammenligning. Derfor anvendes andre studier til at estimere komparatorernes effekt ved klinisk spørgsmål 1-3. I de følgende afsnit gennemgås den samlede litteratur samt de relevante subpopulationer fra PRIMA-studiet for de kliniske spørgsmål enkeltvist.

5.1 Klinisk spørgsmål 1

Klinisk spørgsmål 1 er:

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

5.1.1 Litteratur

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

Ansøger har søgt litteratur med søgestrengen fra protokollen og har udvalgt 2 fuldtekstartikler og 1 konferenceabstract, fra 2 forskellige kliniske studier, som undersøger henholdsvis niraparib og olaparib overfor placebo. Desuden indgår data fra EMAs EPAR for niraparib og olaparib i ansøgningen. Sekretariatet har tilføjet en fuldtekstartikel og et konferenceabstract, der beskriver PFS-data fra SOLO-1 for en subpopulation med høj risiko for progression.

Tabel 5-2. Oversigt over studier vedr. klinisk spørgsmål 1

Publikationer	Klinisk forsøg	NCT-nummer	Population	Intervention overfor komparator	Median opfølgningstid for primært endepunkt
González-Martín et al. 2019 [26] EPAR – Zejula [27]	PRIMA	NCT02655016	Patienter med ny-diagnosticeret, platinsensitiv kræft i æggestokkene – kun patienter med stadium IV, stadium III og restsygdom efter operation, inoperable patienter eller patienter, der har gennemgået intervalkirurgi.	Niraparib overfor placebo	13,8 måneder
Moore et al. 2018 [28] EPAR - Lynparza [29] Banerjee et al. 2020 - konferenceabstract fra ESMO [30] DiSilvestro et al. 2020 [31] Colombo et al. 2020 – konferenceabstract fra ESGO 2020 [32]	SOLO-1	NCT01844986	BRCA-muterede patienter med ny-diagnosticeret, platinsensitiv kræft i æggestokkene. Patienter med stadie IV eller stadie III med og uden restsygdom efter operation.	Olaparib overfor placebo	41 måneder 5 års opfølgning for PFS i Banarjee et al. 2020, DiSilvestro et. al. 2020 og Colombo et al. 2020

PRIMA og SOLO-1 er to kliniske fase III-studier, der undersøger henholdsvis niraparib og olaparib overfor placebo som vedligeholdelsesbehandling til nydiagnosticeret kræft i æggestokkene efter behandling med platinbaseret kemoterapi. Begge er multicenter, randomiserede, dobbeltblindede kliniske undersøgelser, hvor patienterne er randomiseret 2:1 til hhv. interventionsarm og komparatorarm. Randomiseringerne var stratificerede for respons på platinbaseret kemoterapi og HRD-status (kun PRIMA). Begge studiepopulationer omfatter patienter med high-grade kræft i æggestokkene i stadium III og IV. Det primære endepunkt i begge studier var PFS defineret som tid fra randomisering indtil objektiv radiologisk progression ifølge RECIST-kriterierne eller død. I begge studier er kontrol- og interventionsarmene velbalancerede i forhold til baselinekarakteristika. PRIMA indeholder en subpopulation med BRCA-mutation, som kan anvendes sammen med data fra SOLO-1 til at besvare det kliniske spørgsmål (se Tabel 5-1).

Baselinekarakteristika for de relevante grupper i PRIMA og SOLO-1 er vist i tabellen nedenfor. For PRIMA er baselinekarakteristika for den samlede HRD-positive subpopulation vist, da baselinekarakteristika ikke er angivet for subpopulationen med BRCA-mutation. Ca. 60 % af den samlede HRD-positive population har BRCA-mutation.

Tabel 5-3. Baselinekarakteristika for den samlede HRD-positive population i PRIMA, og ITT-populationen i SOLO-1

		PRIMA – HRD-positiv* [26]		**SOLO-1** [28]	
		Niraparib	**Placebo**	**Olaparib**	**Placebo**
		N = 247	**N = 126**	**N = 260**	**N = 131**
Alder, median (rækkevidde)		58 (32-83)	58 (33-82)	53 (29-82)	53 (31-84)
ECOG PS **	0	182 (74 %)	97 (77 %)	200 (77 %)	105 (80 %)
	1	65 (26 %)	29 (23 %)	60 (23 %)	25 (19 %)
Primær tumorlokation ***	Æggestokkene	201 (81 %)	105 (83 %)	220 (85 %)	113 (86 %)
	Æggelederne	32 (13 %)	13 (10 %)	22 (8 %)	11 (8 %)
	Bughulen	14 (6 %)	8 (6 %)	15 (6 %)	7 (5 %)
Histologi	High-grade serøst karcinom	234 (95 %)	116 (92 %)	246 (95 %)	130 (99 %)
	Endometroid	5 (2 %)	6 (5 %)	9 (3 %)	0 (0 %)
	Anden	8 (3 %)	4 (3 %)	5 (2 %)	1 (1 %)
FIGO-stadium	III	161 (65 %)	78 (62 %)	220 (85 %)	105 (80 %)
	IV	86 (35 %)	48 (38 %)	40 (15 %)	26 (20 %)

Neoadjuverende kemoterapi	Nej	91 (37 %)	46 (37 %)	Ikke angivet	
	Ja	156 (63 %)	80 (63 %)	Ikke angivet	
Operationsstatus	Primært opereret – makroradikal operation	Ikke angivet		123 (47 %)	62 (47 %)
	Primært opereret – rest tumor	Ikke angivet		37 (14 %)	22 (17 %)
	Interval opereret – makroradikal operation	Ikke angivet		76 (29 %)	36 (27 %)
	Interval opereret – rest tumor	Ikke angivet		18 (7 %)	7 (5 %)
	Ukendt eller ikke opereret	Ikke angivet		5 (2 %)	4 (3 %)
Resultat af 1. linje kemoterapi	Komplet respons	185 (75 %)	93 (74 %)	213 (82 %)	107 (82 %)
	Partiel respons	62 (25 %)	33 (26 %)	47 (18 %)	24 (18 %)

* Baselinekarakteristika for PRIMA er vist for den samlede HRD-positive subpopulation, da de ikke er opgivet specifikt for subpopulationen med BRCA-mutation. Ca. 60 % af den HRD-positive subpopulation har BRCA-mutation. ** I SOLO-1-studiet angives 1 patient med manglende ECOG-status i placeboarmen. *** I SOLO-1-studiet angives primærlokation som ukendt i 3 tilfælde i olparibarmen.

Der er væsentlige forskelle mellem populationerne, hovedsageligt:

- PRIMA inkluderer kun patienter med kræft i enten stadium IV eller patienter med stadium III, der havde restsygdom efter operation eller var inoperable. SOLO-1 inkluderer også patienter med kræft i stadium III uanset operationsstatus, dvs. makroradikalt opererede patienter er inkluderede. Derfor har patienterne i PRIMA generelt dårligere prognose end i SOLO-1.
- PRIMA inkluderer en større andel af patienter med kræft i stadium IV end SOLO-1, hvilket påvirker prognosen i PRIMA negativt.
- Patienterne er generelt ældre i PRIMA (58 år overfor 53 år), hvilket kan påvirke prognosen i PRIMA negativt.
- Opfølgningstiderne er markant forskellige med median opfølgningstid på 13,8 måneder i PRIMA og 41 måneder i SOLO-1, hvilket kan give forskelle i uønskede hændelser og usikre estimater for OS og PFS i PRIMA.

For niraparib er alt anvendt data fra PRIMA-hovedpublikationen (González-Martín et al. 2019 [26]) eller EPAR [27]. Yderligere livskvalitetsdata er publiceret som poster ved ESMO 2020 [33], og figurer herfra er inkluderet i ansøgningen. For olaparib stammer

data vedr. OS, uønskede hændelser og livskvalitet fra SOLO-1-hovedpublikationen (Moore et al. 2018) og EPAR [29], mens opdaterede PFS-data efter 5 års opfølgning er publiceret i et konferenceabstract fra ESMO 2020 [30], og subgruppeanalyser af en høj-risiko population fra SOLO-1 er publiceret i et konferenceabstract fra ESGO 2020 [32] og i en fuldtekstartikel [31]. Høj-risiko populationen fra SOLO-1 indeholder 146 patienter behandlet med olaparib og 73 patienter behandlet med placebo og er karakteriseret ved, at patienterne havde stadium IV-sygdom, stadium III samt restsygdom efter primær operation, interval operation uanset resultat eller inoperabel sygdom.

Fagudvalget vurderer, at patientpopulationerne generelt stemmer overens med, hvad der observeres i klinisk praksis, bortset fra, at patienter med stadium III uden synlig restsygdom efter operation ikke er inkluderet i PRIMA. Dette medfører, at populationen i PRIMA overordnet set har dårligere prognose, end den samlede population i dansk klinisk praksis. Udover dette, er data fra studierne overførbare til dansk klinisk praksis.

5.1.2 Databehandling og analyse

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

Ansøger argumenterer for, at der ikke kan foretages en meningsfuld indirekte statistisk sammenligning mellem effekten af niraparib og olaparib baseret på PRIMA og SOLO-1 pga. de ovennævnte forskelle i prognostiske faktorer.

Medicinrådet er enig heri, grundet forskellene i patienternes generelle risiko for progression og forskellig opfølgningstid i studierne. Fagudvalget har i stedet udført en deskriptiv sammenligning mellem niraparib og olaparib. Heri sammenlignes effekterne af de respektive lægemidler med placebo, som er den interne kontrol i både PRIMA og SOLO-1, hvorefter de to lægemidlers effekt overfor placebo sammenlignes.

For effektmålet PFS har fagudvalget anvendt subgruppen af patienter i PRIMA med påvist BRCA-mutation. Disse blev sammenholdt med den samlede patientpopulation fra SOLO-1 samt subpopulationen fra SOLO-1 med høj risiko for progression, da denne formodes at have en mere sammenlignelig prognose med PRIMA-populationen.

For effektmålene, bivirkninger og livskvalitet, blev ITT-populationerne anvendt, da disse effektmål ikke er opgivet på subgruppeniveau. Fagudvalget har forudsat, at forekomsten af bivirkninger og ændringer i livskvalitet er uafhængige af BRCA- og HRD-status, hvorved ITT-populationen er anvendelig til at estimere disse effektmål. I protokollen efterspurgte fagudvalget effektmålet opgjort som andelen af patienter, der stopper behandlingen pga. bivirkninger (*adverse drug reactions*) samt andelen af patienter, der oplever minimum en bivirkning af grad 3-4. Disse data er dog kun tilgængelige i PRIMA, hvorimod de i stedet er opgjort ud fra uønskede hændelser (adverse events) i SOLO-1. Fagudvalget anvender derfor de kvantitative opgørelser af uønskede hændelser til at estimere effektmålene for både PRIMA og SOLO-1, for at tallene bliver sammenlignelige.

For OS har ansøger anvendt data fra den samlede HRD-positive population, hvoraf 60 % har BRCA-mutation. Fagudvalget bemærker, at patienter med BRCA-mutation generelt

har de bedste prognoser for overlevelse. Derfor bruges OS-data fra denne population kun perspektiverende.

5.1.3 Evidensens kvalitet

Da vurderingen af niraparib er baseret på en deskriptiv sammenligning med olaparib, kan Medicinrådet ikke anvende GRADE til at vurdere kvaliteten af evidensen. Medicinrådet har vurderet studierne ved Cochrane risk of bias tool 2.0. Overordnet er det vurderet, at PRIMA og SOLO-1 begge har lav risiko for bias. Den samlede evidenskvalitet er dog meget lav, da vurderingen beror på en deskriptiv sammenligning af resultaterne for niraparib og olaparib. Dette betyder, at nye studier eller en længere opfølgningstid med høj sandsynlighed kan ændre konklusionen.

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

5.1.4 Effektestimater og kategorier

I tabellen herunder fremgår de absolutte og relative effektforskelle mellem niraparib og placebo fra PRIMA og olaparib og placebo fra SOLO-1 samt de aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 1.

Tabel 5-4. Resultater for klinisk spørgsmål 1

Effektmål	Målenhed (MKRF)	Vigtighed	Niraparib overfor placebo (PRIMA – BRCA-mutation)		Olaparib overfor placebo (SOLO-1)		Aggregeret værdi for effektmålet
			Absolut forskel (95 % CI)	Relativ forskel (95 % CI)	Absolut forskel (95 % CI)	Relativ forskel (95 % CI)	
Samlet overlevelse (OS)	Median OS (3 måneder)	Kritisk	Ikke angivet*	Ikke angivet*	Ikke nået	HR = 0,95 (0,60; 1,53)	Kan ikke kategoriseres
	OS-rate ved 60 måneder (5 %-point)		Ikke angivet*		Ikke angivet		
Progressionsfri overlevelse (PFS)	Median PFS (6 måneder)	Kritisk	11,2 måneder	HR = 0,40 (0,27; 0,62)	42,2 måneder	HR = 0,33 (0,25; 0,43)	Kan ikke kategoriseres
	PFS-rate ved 24 måneder (10 %-point)		25 %-point		39,0 %-point		
Bivirkninger **	Andel af patienter, som ophører behandling pga. bivirkninger (5 %-point)***	Kritisk	9,5 %-point (6,0 ;13,0)	RR = 4,9 (2,1; 11,1)	9,2 %-point (4,6; 13,9)	RR = 5,0 (1,6; 16,1)	Kan ikke kategoriseres
	Andel af patienter, der oplever en eller flere bivirkninger af grad 3-4 (10 %-point)***		51,6 %-point (45,2; 58,0)	RR = 3,7 (2,9; 4,9)	20,8 %-point (11,8; 29,7)	RR = 2,1 (1,44; 3,14)	
	Kvalitativ gennemgang						
Livskvalitet **	Andel af patienter, der ikke viser statistisk signifikant	Vigtigt	Ikke angivet	Ikke angivet	Ikke angivet	Ikke angivet	Kan ikke kategoriseres

Effektmål	Målenhed (MKRF)	Vigtighed	Niraparib overfor placebo (PRIMA – BRCA-mutation)		Olaparib overfor placebo (SOLO-1)		Aggregeret værdi for effektmålet
			Absolut forskel (95 % CI)	Relativ forskel (95 % CI)	Absolut forskel (95 % CI)	Relativ forskel (95 % CI)	
	Forværring i livskvalitet (10 %-point)						

Konklusion	
Samlet kategori for lægemidlets værdi	Kan ikke kategoriseres. Fagudvalget finder, at der ikke er grundlag for at skelne imellem niraparib og olaparib på baggrund af data for effekt og bivirkninger og anser niraparib og olaparib som ligeværdige behandlingsalternativer.
Kvalitet af den samlede evidens	Meget lav.

* Der er ikke OS-data for niraparib i en ren BRCA-muteret population. I stedet bruges data fra den samlede HRD-positive-population, hvoraf ca. 60 % har BRCA-mutation, til perspektivering. ** Estimatet for niraparib overfor placebo stammer fra ITT-populationen. *** Effektmålet er opgjort på baggrund af uønskede hændelser i stedet for bivirkninger, da kvantitative opgørelser for bivirkninger kun var tilgængelige i PRIMA. CI = konfidensinterval, HR = Hazard Ratio, OR = Odds Ratio, RR = relativ risiko.

Samlet overlevelse (OS)
Som beskrevet i protokollen er effektmålet samlet overlevelse kritisk for vurderingen af lægemidlets værdi for patienterne. Data for samlet overlevelse er umodne i både PRIMA og SOLO-1 (henholdsvis 10,8 % og 21 % af patienterne er døde ved opfølgningstidspunktet). Overlevelsen for subpopulationen med BRCA-mutation er ikke angivet i PRIMA. I stedet anvendes OS-raten for den samlede HRD-positive population, hvoraf 60 % har BRCA-mutation til perspektivering.

Median OS er ikke nået, og opfølgningstiden er ikke tilstrækkelig til at rapportere 5-års OS-rate i hverken PRIMA eller SOLO-1. I stedet sammenlignes 2-års OS-rater samt hazard ratios (HR). I PRIMA var OS-raten ved 2 år 91,1 % (87,5-94,6 %) i niraparibarmen overfor 84,9 % (78,7-91.2 %) i placeboarmen. Dette giver en absolut forskel mellem grupperne på 6,2 %-point og en HR på 0,61 (0,27-1,39). I SOLO-1 var OS-raten ved 2 år 91,5 % i olaparibarmen overfor 87, 9 % i placeboarmen. Dette giver en absolut forskel mellem grupperne på 3,6 %-point. Ved længere opfølgning nærmede olaparib og placeboarmene sig hinanden, og ved 4 år var raterne henholdsvis 75,2 % og 74,8 %, og HR var 0,95 (0,60-1,53) [29].

Hverken niraparib eller olaparib giver en statistisk signifikant øget overlevelse sammenlignet med placebo, og effekten af niraparib i forhold til olaparib kan ikke kategoriseres efter Medicinrådets metoder. Fagudvalget kan ikke vurdere, om der kan forventes en forskel i samlet overlevelse på dette datagrundlag.

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

I PRIMA er PFS opgjort for populationen med påvist BRCA-mutation efter en median opfølgningstid på 13,8 måneder. Median PFS var henholdsvis 22,1 (19,3 ; ikke nået) måneder og 10,9 (8,0 ; 19,4) måneder i niraparib- og placebogruppen, hvilket giver en absolut forskel på 11,2 måneder. PFS-raten ved 2 år var henholdsvis 48 % og 23 % i niraparib- og placebogruppen, hvilket giver en absolut forskel på 25 %-point. PFS-raterne er dog meget usikre, da meget få patienter har tilstrækkelig opfølgningstid. HR var 0,40 (0,27 ; 0,62) (P < 0.001).

I SOLO-1 var median PFS efter 5-års opfølgning henholdsvis 56,0 måneder og 13,8 måneder i olaparib- og placebogruppen, hvilket giver en absolut forskel på 42,2 måneder. PFS-raten ved 2 år var henholdsvis 73,6 % og 34,6 % i olaparib- og placebogruppen, hvilket giver en absolut forskel på 39,0 %-point. HR var 0,33 (0,25 ; 0,43) (P < 0.001) [30]. I en subgruppeanalyse af populationen fra SOLO-1 med høj risiko for progression var median PFS henholdsvis 39 måneder og 11,1 måneder i olaparib- og placeboarmen (27,9 måneders forskel), mens PFS-raterne ved 2 år var 68 % og 26 % (38 %-points forskel). HR var 0,34 (0,24 ; 0,48).

Der kan ikke udføres en statistisk indirekte sammenligning mellem niraparibs og olaparibs effekt på effektmålet PFS, og derved kan værdien af niraparib ikke kategoriseres efter Medicinrådets metoder.

Fagudvalget vurderer, at både niraparib og olaparib er effektive behandlinger med stor effekt på PFS i patienter med BRCA-mutation, bedømt både ud fra absolutte forskelle i median PFS og PFS-rate og HR i forhold til placebo. Fagudvalget bemærker, at det ikke er muligt at sammenligne effektestimaterne for niraparib og olaparib pga. de store forskelle i median opfølgningstid og studiepopulationernes karakteristika. Det er fagudvalgets erfaring, at lægemidlerne har sammenlignelig effekt på PFS, når de anvendes til 2. linje vedligeholdelsesbehandling, og fagudvalget ser ingen grund til at antage, at dette ikke skulle gælde ved 1. linje vedligeholdelsesbehandling.

Bivirkninger
Forbedret OS med mindst mulig toksicitet er det optimale mål for kræftbehandling. Fagudvalget anser derfor bivirkninger som et kritisk effektmål. Effektmålet vurderes samlet ud fra behandlingsophør på grund af uønskede hændelser, andelen af patienter, der oplever minimum 1 uønsket hændelse af grad 3-4, samt en kvalitativ gennemgang af bivirkningerne (*adverse drug reactions*). Opgørelserne omkring uønskede hændelser og bivirkninger fra PRIMA er baseret på den samlede ITT-population, da BRCA-status ikke forventes at have indflydelse på profilen for uønskede hændelser.

Behandlingsophør grundet bivirkninger:
I PRIMA var andelen af behandlingsophør grundet uønskede hændelser 12,0 % i niraparibarmen og 2,5 % i placeboarmen, hvilket giver en absolut forskel på 9,5 (6,0 ; 13,0) %-point og en relativ risiko (RR) på 4,9 (2,1 ; 11,1).

I SOLO-1 var andelen af behandlingsophør grundet uønskede hændelser 11,5 % i olaparibarmen og 2,3 % i placeboarmen, hvilket giver en absolut forskel på 9,2 (4,6 ; 13,9) %-point og en RR på 5,0 (1,6 ; 16,1).

Effekten af niraparib overfor olaparib kan ikke kategoriseres. Fagudvalget bemærker, at data ikke indikerer nogen forskelle mellem behandlingerne for dette effektmål.

Bivirkninger af grad 3-4:
I PRIMA var andelen, der var udsat for en uønsket hændelse af grad 3-4 på 70,5 % i niraparibarmen og 18,9 % i placeboarmen, hvilket giver en absolut forskel på 51,6 (45,2 ; 58,0) %-point og en RR på 3,7 (2,9 ; 4,9). Andelen af grad 3-4-bivirkninger (*adverse drug reactions*) var 65,3 % I niraparibarmen og 6,6 % i placeboarmen, hvilket giver en absolut forskel på 58,7 (53,5 ; 64.0) %-point og en RR på 9,96 (6,2 ; 16,1).

I SOLO-1 var andelen, der oplevede en uønsket hændelse af grad 3-4 på 39,2 % i olaparibarmen og 18,5 % i placeboarmen, hvilket giver en absolut forskel på 20,8 (11,8 ; 29,7) %-point og en RR på 2,1 (1,44 ; 3,14). Andelen af grad 3-4-bivirkninger (*adverse drug reactions*) er ikke opgivet.

Effekten af niraparib overfor olaparib kan ikke kategoriseres. Fagudvalget bemærker, at forekomsten af grad 3-4 uønskede hændelser umiddelbart er større for niraparib end for

olaparib. Patienterne i PRIMA har dog generelt større sygdomsbyrde og højere alder, hvilket kan medføre, at disse mere skrøbelige patienter i højere grad udvikler uønskede hændelser.

Kvalitativ gennemgang af bivirkningerne
Størstedelen af bivirkningerne af grad 3-4 ved behandling med niraparib var hæmatologiske, særligt anæmi (31 %), thrombocytopeni (29 %) og neutropeni (13 %). Derudover var hypertension (6 %), træthed (2 %), mavesmerter (1 %) og kvalme (1 %) forekommende. De hæmatologiske bivirkninger er i høj grad dosisafhængige og kan håndteres ved pausering eller dosisjustering. Derudover medførte en individualiseret startdosis af niraparib baseret på patientens vægt og blodpladetal næsten en halvering af hyppigheden af de hæmatologiske bivirkninger. Den individualiserede dosis er standarddosering i det opdaterede produktresumé, hvorved der må forventes en lavere hyppighed af de hæmatologiske bivirkninger i klinisk praksis end i PRIMA.

Bivirkningerne forbundet med behandling med olaparib er for størstedelen af let eller moderat sværhedsgrad (grad 1-2) og kræver i en del tilfælde dosisreduktion men generelt ikke afbrydelse af behandling. De alvorligste bivirkninger (grad ≥ 3), som forekommer hos mindst 2 % af patienterne, er anæmi (16 %), neutropeni (6 %), træthed (13,9 %), leukopeni (3 %), trombocytopeni (2 %) og opkastning (2 %). De hyppigste bivirkninger, som ses hos mindst 10 % af patienterne, er kvalme, opkastning, diarré, dyspepsi, træthed, hovedpine, smagsforstyrrelser, nedsat appetit, svimmelhed, øvre abdominalsmerter, hoste, åndenød, anæmi, neutropeni, trombocytopeni og leukopeni.

Ved både niraparib og olaparib er der rapporteret om bivirkninger med dødelig udgang, bl.a. akut myeloid leukæmi. Dette er dog meget sjældent for begge lægemidler (< 1 %).

Samlet set kan effekten af niraparib overfor olaparib mht. bivirkninger ikke kategoriseres, da den er baseret på en kvalitativ sammenligning. Bivirkningerne er generelt velkendte og håndterbare i klinikken for begge lægemidler. Fagudvalget vurderer, at niraparib umiddelbart er forbundet med flere uønskede hændelser af grad 3-4 end olaparib. Fagudvalget bemærker dog, at patientpopulationen i PRIMA havde en større sygdomsbyrde og var ældre, hvilket kan medføre flere uønskede hændelser. Derudover modtog størstedelen af patienterne i PRIMA (315 ud af 484 patienter) en startdosis på 300 mg dagligt, hvorved forekomsten af hæmatologiske bivirkninger må forventes væsentlig lavere i dansk klinisk praksis, hvor størstedelen af patienterne vil modtage en startdosis på 200 mg.

I Medicinrådets behandlingsvejledning vedrørende lægemidler til BRCA-muteret kræft i æggestokkene, æggelederne eller primær kræft i bughinden vurderede fagudvalget, at der ikke er klinisk betydende forskelle mellem olaparib og niraparib, hvad angår sikkerhed ved behandling i 2. linje. Fagudvalget vurderer, at det samme gør sig gældende ved 1. linjebehandling.

Livskvalitet
Ændring i livskvalitet er et patientrelevant effektmål, som kan give indblik i lægemidlernes fordele og ulemper set fra patientens perspektiv. På denne baggrund betragter fagudvalget livskvalitet som et vigtigt effektmål. I protokollen efterspurgte fagudvalget en opgørelse af andelen af patienter, der ikke viser en statistisk signifikant forværring i livskvalitet ift. baseline. Dette er ikke opgivet. I stedet har ansøger opgivet ændringer i den samlede middelværdi i forhold til baselinemålingen over hele opfølgningstiden for PRIMA og over 24 måneder for SOLO-1.

Livskvalitet er undersøgt både ved hjælp af det ovariecancerspecifikke spørgeskema EORTC QLQ-OV28 og det generelle spørgeskema EORTC QLQ-C30. Fagudvalget definerede i protokollen, at data fra -OV28 prioriteres højest. Der er dog kun opgivet data for enkelte delmål ved -OV28 (’mave-tarm symptomer’ og ’andre kemoterapirelaterede bivirkninger’), hvorimod der findes data fra den samlende ’*global health score*’ fra EORTC QLQ-C30. Ansøger har ikke indsendt specifikke datapunkter men i stedet figurer, der viser middelværdi og spredninger i niraparibarmen og placeboarmen over tid. Ud fra disse kurver ses en tendens til en svag stigning i livskvalitet ved niraparibarmen overfor placeboarmen. Baseret på en visuel vurdering repræsenterer eventuelle ændringer dog ikke signifikante forskelle. Fagudvalget vurderer derfor, at behandling med niraparib ikke medfører ændringer i livskvalitet overfor placebo ud fra de tilgængelige målesystemer.

Data fra SOLO-1 er opgjort ved hjælp af det ovariecancerspecifikke FACT-O-spørgeskema, hvilket resulterer i en samlet TOI-score som mål for den samlede livskvalitet. Her sås en gennemsnitsændring på 0,30 (−0.717 ; 1.318) ud fra en baselinescore på 73,6 for olaparib og 3,3 (1,8 ; 4,8) ud fra en baselinescore på 75,0 for placebo. Derved var der en absolut forskel i udviklingen af TOI-scoren på -3,0 (-4,8 ; -1,2) ved behandling med olaparib, hvilket repræsenterer et lille fald i livskvalitet, der dog ikke betragtes som klinisk relevant.

Samlet kan effekten af niraparib overfor olaparib på livskvalitet ikke kategoriseres. De tilgængelige data indikerer ikke, at hverken behandling med niraparib eller olaparib medfører ændringer i patienternes livskvalitet.

5.1.5 Fagudvalgets konklusion

Den samlede værdi af niraparib sammenlignet med olaparib til patienter med nydiagnosticeret BRCA-muteret kræft i æggestokkene kan ikke kategoriseres. Fagudvalget vurderer, at begge lægemidler udgør en god behandlingsmulighed til patientgruppen. Fagudvalget bemærker, at den umiddelbart kortere forlængelse af PFS med niraparib kan forklares med forskelle i studiernes opfølgningstid (kortere opfølgning med niraparib) og forskelle i studiepopulationerne. Derfor finder fagudvalget ingen grund til at differentiere imellem lægemidlerne og anser dem som ligeværdige.

5.2 Klinisk spørgsmål 2

Klinisk spørgsmål 2 er:

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

5.2.1 Litteratur

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

Ansøger anvender PRIMA til at estimere effekten af niraparib, som beskrevet i Tabel 5-1 og Tabel 5-2. Ansøger har søgt litteratur med søgestrengen fra protokollen og har udvalgt 6 yderligere fuldtekstartikler, der beskriver 2 kliniske studier omhandlende bevacizumab. Desuden har sekretariatet tilføjet 1 fuldtekstartikel, der beskriver resultaterne af bevacizumabbehandling i GOG-0218 opdelt efter mutationsstatus [34]. Disse studier vises sammen med PRIMA i Tabel 5-5. EMAs EPAR for niraparib [27] og bevacizumab [35] indgår også i vurderingen.

Tabel 5-5 Oversigt over studier vedr. klinisk spørgsmål 2

Publikationer	Klinisk forsøg	NCT-nummer	Population	Intervention overfor komparator	Median opfølgningstid for primært endepunkt
González-Martín et al. 2019 [26] EPAR – Zejula [27]	PRIMA	NCT02655016	Patienter med ny-diagnosticeret, platinsensitiv kræft i æggestokkene – kun patienter med stadium IV, stadium III og restsygdom efter operation, inoperable patienter eller patienter, der har gennemgået intervalkirurgi.	Niraparib overfor placebo	13,8 måneder
Burger et al. 2011 [36] Monk et al. 2013 [37] Tewari et al. 2019 [38] Nordquist et al. 2018 [34] (tilføjet af sekretariatet)	GOG-0218	NCT00262847	Patienter med nydiagnosticeret kræft i æggestokkene, ikke opdelt efter BRCA-status eller HRD. Størstedelen af patienterne havde enten stadie IV eller stadie III med resttumor > 1 cm efter operation. BRCA-mutationsstatus blev undersøgt retrospektivt.	Platinbaseret kemoterapi + bevacizumab overfor platinbaseret kemoterapi	17,4 måneder (PFS) Endelig OS-analyse efter 102,9 måneder i Tewari et al. 2019
Perren et al. 2011 [39] Stark et al. 2013 [40] Oza et al. 2015 [41] EPAR – Avastin [35]	ICON7	ISRCTN91273375	Patienter med nydiagnosticeret kræft i æggestokkene, ikke opdelt efter BRCA-status eller HRD. Studiet inkluderede en prædefineret subgruppe med høj risiko for progression defineret som enten stadie III med restsygdom efter primær operation eller stadie IV.	Platinbaseret kemoterapi + bevacizumab overfor platinbaseret kemoterapi	48,9 måneder (OS) 10-15 måneder (PFS)

GOG-0218 er et multicenter, dobbeltblindet, placebokontrolleret fase 3-forsøg, hvor 1873 kvinder med kræft i æggestokkene i stadie III/IV, som havde gennemgået kirurgi, blev randomiseret til platinbaseret kemoterapi alene, sammen med bevacizumab efterfulgt af placebo vedligeholdelsesbehandling eller sammen med bevacizumab og efterfulgt af bevacizumab vedligeholdelsesbehandling.

Studiets primære effektmål er PFS. Fagudvalget vurderer, at studiet ikke kan anvendes til kategorisering af effekten af niraparib overfor bevacizumab pga. væsentlige forskelle mellem populationerne.

- GOG-0218 indeholder en stor gruppe af patienter med kræft i stadie III uden synlig restsygdom efter primær operation, hvorved populationen som helhed har en grundlæggende lavere risiko for progression end populationen i PRIMA.
- BRCA-mutation og HRD-status var ikke kendt ved randomisering. Mutationsstatus blev undersøgt retrospektivt, hvilket viste en ubalance mellem forekomst af BRCA-mutation samt en generel prognostisk effekt af begge [34].

Sammenligninger mellem subgruppen af patienter med BRCA-mutation eller anden mutation relateret til homolog rekombination viste dog, at bevacizumabs effekt på PFS og OS ikke var bedre i gruppen med mutationer end i gruppen uden, selvom de overordnede prognoser var bedre for patienter med BRCA-mutation [34,38].

ICON7 er et multicenter, open-label, randomiseret, kontrolleret forsøg, hvor 1528 kvinder med nydiagnosticeret kræft i æggestokkene i stadium I-IV med resttumor efter kirurgi blev randomiseret til at få platinbaseret kemoterapi alene eller i kombination med bevacizumab. Studiet inkluderede en præ-defineret subgruppe med høj risiko for progression defineret som enten stadie III med > 1 cm restsygdom efter primær operation eller stadie IV. Denne subgruppe er mere sammenlignelig med populationen i PRIMA-studiet og med populationen i det kliniske spørgsmål end den overordnede ITT-population.

Tabellen nedenfor viser baselinekarakteristika for PRIMA og højrisikogruppen i ICON7. For PRIMA kendes ikke baselinekarakteristika for den HRD-positive gruppe uden BRCA-mutation. Derfor angives baselinekarakteristika for den samlede HRD-positive population inklusive BRCA-muterede. For ICON7 angives baselinekarakteristika for bevacizumab- og placeboarmen for patienter med høj risiko for progression.

Tabel 5-6. Baselinekarakteristika for den samlede HRD-positive population (60 % med BRCA-mutation) i PRIMA-studiet samt sub-populationen i ICON7 med høj risiko for progression

		PRIMA – HRD-positiv [26]		**ICON7 – høj risiko** [41]	
		Niraparib N = 247	**Placebo N = 126**	**Bevacizu-mab N = 248**	**Placebo N = 254**
Alder, median (rækkevidde)		58 (32-83)	58 (33-82)	60 (26-80)	60 (18-81)
ECOG PS	0	182 (74 %)	97 (77 %)	100 (41 %)	98 (39 %)
	1	65 (26 %)	29 (23 %)	123 (50 %)	135 (53 %)
	2	0	0	21 (9 %)	20 (8 %)
Primær tumorlokation	Æggestokkene	201 (81 %)	105 (83 %)	207 (83 %)	210 (83 %)
	Æggelederne	32 (13 %)	13 (10 %)	6 (2 %)	5 (2 %)
	Bughulen	14 (6 %)	8 (6 %)	28 (11 %)	32 (13 %)
	Ukendt/flere lokationer	0	0	7 (3 %)	7 (3 %)
Histologi	High-grade serøst karcinom	234 (95 %)	116 (92 %)	186 (75 %)	195 (77 %)
	Endometroid	5 (2 %)	6 (5 %)	17 (7 %)	14 (6 %)
	Anden	8 (3 %)	4 (3 %)	45 (18 %)	45 (17 %)
FIGO-stadium	III	161 (65 %)	78 (62 %)	144 (58 %)	157 (62 %)
	IV	86 (35 %)	48 (38 %)	104 (42 %)	97 (38 %)
Neoadjuverende kemoterapi	Nej	91 (37 %)	46 (37 %)	Ikke angivet	
	Ja	156 (63 %)	80 (63 %)	Ikke angivet	
Operationsstatus	Primært opereret, ≤ 1 cm resttumor	Ikke angivet		41 (17 %)	43 (17 %)
	Primært opereret, > 1 cm resttumor	Ikke angivet		194 (78 %)	194 (76 %)
	Ikke opereret	Ikke angivet		13 (5 %)	17 (7 %)

Resultat af 1. linje kemoterapi	Komplet respons	185 (75 %)	93 (74 %)	Ikke angivet
	Partiel respons	62 (25 %)	33 (26 %)	Ikke angivet
Mutationsstatus	BRCA-mutation	152 (62 %)	71 (56 %)	Ukendt
	BRCA-viltype med HRD	95 (38 %)	55 (44 %)	Ukendt

Baselinekarakteristika mellem interventions- og kontrolarm er velbalancerede i både PRIMA og ICON7-studiet. Der er dog væsentlige forskelle mellem studierne, der betyder, at der ikke kan foretages en statistisk indirekte sammenligning:

- BRCA- og HRD-status var ukendte i ICON7, hvilket kan have påvirket effekten af bevacizumab, hvis patienter med BRCA-mutation ikke var ligeligt fordelt mellem interventions- og komparatorarm.
- Næsten alle patienter i PRIMA-studiet havde high-grade serøst karcinom mod 76 % af patienterne i ICON7.
- Resultatet af 1. linje kemoterapi er ukendt i ICON7, da kemoterapiregimet var en del af studiebehandlingen og ikke et inklusionskriterie som i PRIMA.
- Bivirkningsopgørelserne i ICON7 indeholder bivirkningerne fra kemoterapi, hvorimod disse ikke er medtaget i PRIMA.
- Næsten dobbelt så mange patienter var i performance status 0 i PRIMA i forhold til ICON7 (ca. 75 % overfor ca. 40 %).

Fagudvalget vurderer, at patientpopulationerne er sammenlignelige med populationen i dansk klinisk praksis, hvorved data fra studierne er overførbare.

5.2.2 Databehandling og analyse

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

Ansøger foretager en deskriptiv sammenligning af HRD-positiv-subgruppen fra PRIMA-studiet med ITT-populationerne i GOG-0218 og ICON7 og subpopulationen i ICON7 med høj risiko for progression, da forskellene mellem de ovennævnte studier ville medføre meget usikre estimater.

Medicinrådet er enigt i, at en formel indirekte sammenligning ikke er mulig på det foreliggende datagrundlag. Medicinrådet vurderer dog, at det er mest hensigtsmæssigt at udføre en deskriptiv sammenligning med data kun fra høj-risiko subpopulationen i ICON7 og ikke fra GOG-0218, da denne stemmer bedst overens med populationen i PRIMA, og da effekten af bevacizumab er afhængig af patienternes risiko for progression. Fremgangsmåden for sammenligningen er som ved klinisk spørgsmål 1, hvor lægemidlerne sammenlignes med placebo, som var intern komparator i begge studier, hvorefter lægemidlernes effekt overfor placebo sammenlignes deskriptivt. Dette er dog

kun muligt for effektmålene, OS, PFS og livskvalitet. For effektmålet uønskede hændelser kan der ikke foretages en sammenligning med ICON7 ved de kvantitative opgørelser. Dette skyldes, at studiet inkluderer kemoterapien i behandlingstiden. GOG-0218 indeholder dog en opgørelse over bivirkninger opstået i vedligeholdelsesbehandlingsfasen. Fagudvalget anvender dette, EMAs EPAR [35] og produktresumé [42] for bevacizumab samt deres kliniske erfaring til at sammenligne bivirkningerne. I protokollen efterspurgte fagudvalget effektmålet opgjort som andelen af patienter, der stopper behandlingen pga. bivirkninger (*adverse drug reactions*) samt andelen af patienter, der oplever minimum en bivirkning af grad 3-4. Disse data er tilgængelige i PRIMA for grad 3-4-bivirkninger, mens behandlingsstop er opgjort på baggrund af uønskede hændelser.

Der er ikke angivet OS-data for niraparib for den HRD-positive population uden BRCA-mutation, men kun for den samlede HRD-positive population inklusive patienter med BRCA-mutation. Derfor anvender fagudvalget kun OS-data for niraparib perspektiverende, ligesom i klinisk spørgsmål 1.

5.2.3 Evidensens kvalitet

Da vurderingen af niraparib er baseret på en deskriptiv sammenligning med bevacizumab, kan Medicinrådet ikke anvende GRADE til at vurdere kvaliteten af evidensen. Medicinrådet har vurderet studierne ved Cochrane risk of bias tool 2.0. Overordnet er det vurderet, at risikoen for bias ved PRIMA er lav, mens der tages forbehold for risiko for bias ved ICON7. Dette skyldes, at hverken patienterne eller investigatorerne var blindende, hvilket giver risiko for bias ved både effekt ved tildeling til intervention og ved dataindsamlingen. Den samlede evidenskvalitet er meget lav, da vurderingen er foretaget vha. deskriptive sammenligninger. Dette betyder, at nye studier eller en længere opfølgningstid med høj sandsynlighed kan ændre konklusionen.

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

5.2.4 Effektestimater og kategorier

I tabellen herunder fremgår de absolutte og relative effektforskelle mellem niraparib og placebo fra PRIMA og bevacizumab og placebo fra højrisikogruppen i ICON7 samt de aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 2.

Tabel 5-7. Resultater for klinisk spørgsmål 2

Effektmål	Målenhed (MKRF)	Vigtighed	Niraparib overfor placebo (PRIMA- HRD-positive, BRCA-vildtype)		Bevacizumab overfor placebo (ICON7- høj-risiko subpopulation)		Aggregeret værdi for effektmålet
			Absolut forskel (95 % CI)	Relativ forskel	Absolut forskel (95 % CI)	Relativ forskel	
Samlet overlevelse (OS)	Median OS (6 måneder)	Kritisk	Ikke angivet*	Ikke angivet*	7,5 måneder	Ikke mulig (non-proportional hazards)****	Kan ikke kategoriseres
	OS-rate ved 60 måneder (5 %-point)		Ikke angivet*		Ca. 5 %-point		
Progressionsfri overlevelse (PFS)	Median PFS (6 måneder)	Kritisk	11,4 måneder	HR = 0,5 (0,31; 0,83)	5,5 måneder	Ikke mulig (non-proportional hazards)****	Kan ikke kategoriseres
	PFS-rate ved 24 måneder (10 %-point)		16 %-point		Ca. 0 %-point		
Bivirkninger**	Andel af patienter, som ophører behandling pga. bivirkninger (5 %-point)***	Kritisk	9,5 %-point (6,0 ; 13,0)	RR = 4,9 (2,1; 11,1)	Ikke relevant	Ikke relevant	Kan ikke kategoriseres
	Andel af patienter, der oplever en eller flere bivirkninger af grad 3-4 (10 %-point)		58,7 %-point (53,5 ; 64,0)	RR = 9,96 (6,2 ; 16,1)	Ikke relevant	Ikke relevant	
	Kvalitativ gennemgang						

Effektmål	Målenhed (MKRF)	Vigtighed	Niraparib overfor placebo (PRIMA- HRD-positive, BRCA-vildtype)		Bevacizumab overfor placebo (ICON7- høj-risiko subpopulation)		Aggregeret værdi for effektmålet
			Absolut forskel (95 % CI)	Relativ forskel	Absolut forskel (95 % CI)	Relativ forskel	
Livskvalitet**	Andel af patienter, der ikke viser statistisk signifikant forværring i livskvalitet (10 %-point)	Vigtigt	Ikke angivet	Ikke angivet	Ikke angivet	Ikke angivet	Kan ikke kategoriseres

Konklusion	
Samlet kategori for lægemidlets værdi	Kan ikke kategoriseres. Fagudvalget vurderer, at niraparib samlet set har en bedre effekt end bevacizumab. Den samlede bivirkningsprofil for niraparib er ikke dårligere end for bevacizumab.
Kvalitet af den samlede evidens	Meget lav.

* Der er ikke OS-data for niraparib fra den HRD-positive population uden BRCA-mutation. I stedet bruges data fra den samlede HRD-positive population, hvoraf ca. 60 % har BRCA-mutation, til perspektivering. ** Estimatet for niraparib overfor placebo stammer fra ITT-populationen. *** Effektmålet er opgjort på baggrund af uønskede hændelser i stedet for bivirkninger, da PRIMA kun indeholder oplysninger om bivirkningsstop som følge af uønskede hændelser. **** Antagelsen om proportional hazards er ikke opfyldt. Der er således ikke en konstant risiko for event igennem observationstiden, og derfor kan der ikke opgives en hazard ratio. CI = konfidensinterval, HR = Hazard Ratio, OR = Odds Ratio, RR = relativ risiko.

Samlet overlevelse (OS)
Niraparibs effekt på OS er ikke angivet specifikt for populationen uden BRCA-mutation med HRD men kun for den samlede HRD-population. Disse data kan ikke anvendes til en kategorisering, da de mange patienter i gruppen med BRCA-mutation kan have påvirket resultaterne. Data er beskrevet i afsnit 5.1.4.

Bevacizumabs effekt på OS fra ICON 7 er beskrevet i patientpopulationen med høj risiko for progression efter en median opfølgningstid på 38,9 måneder for bevacizumab og 29,2 måneder for placebo. Median OS var 39,7 måneder for bevacizumab og 30,2 måneder for placebo, hvilket medfører en absolut forskel i median OS på 7,5 måneder. Data viste signifikant afvigelse fra antagelsen om proportional hazards mellem kurverne, hvorved der ikke kan udregnes HR. OS-raten ved 5 år var ca. 30 % for bevacizumab og 25 % for placebo. Data er generelt meget usikre, da risikoen for død ændres over tid. Desuden er der kun få patienter med tilstrækkelig opfølgningstid til at estimere OS-raten ved 5 år. Data indikerer dog, at overlevelsen i nogen grad påvirkes positivt af bevacizumab i patientpopulationen med høj risiko for progression.

Niraparibs effekt på OS overfor bevacizumab kan ikke kategoriseres ved Medicinrådets metoder. Fagudvalget kan ikke vurdere, om der kan forventes en forskel i samlet overlevelse på dette datagrundlag, da overlevelsesdata stammer fra en population, hvor 40 % af patienterne ikke har BRCA-mutation.

Progressionsfri overlevelse (PFS)
I PRIMA er PFS opgjort for den HRD-positive populationen uden BRCA-mutation med en median opfølgningstid på 13,8 måneder. Median PFS var henholdsvis 19,6 (13,6 ; ikke nået) måneder og 8,2 (6,7 ; 16,8) måneder i niraparib- og placebogruppen, hvilket giver en absolut forskel på 11,4 måneder. PFS-raten ved 2 år var henholdsvis 47 % og 31 % i niraparib- og placebogruppen, hvilket giver en absolut forskel på 16 %-point. PFS-raterne er dog meget usikre, da meget få patienter har tilstrækkelig opfølgningstid. HR for PFS var 0,50 (0,31 ; 0,83) (P < 0.001).

Bevacizumabs effekt på PFS er beskrevet i patientpopulationen med høj risiko for progression fra ICON 7 efter en median opfølgningstid på 15,6 måneder for bevacizumab og 10,1 måneder for placebo. Ligesom ved OS er der signifikant afvigelse fra antagelsen om proportional hazards. Median PFS var 16,0 måneder for bevacizumab overfor 10,5 måneder for placebo, hvilket medfører en forskel på 5,5 måneder. PFS-raten ved 2 år var ca. 10 % for både bevacizumab og placebo, hvorved bevacizumab ikke havde nogen effekt på PFS-raten.

Niraparibs effekt på PFS overfor bevacizumab kan ikke kategoriseres. Fagudvalget vurderer, at niraparib er mere effektivt end bevacizumab, for så vidt angår PFS. Forbedringen i median PFS er væsentlig større ved niraparib end bevacizumab. Dertil kommer, at niraparib modsat bevacizumab tilsyneladende medfører en langsigtet gevinst ift. andelen af progressionsfrie patienter.

Bivirkninger
Bivirkninger og uønskede hændelser for niraparib er beskrevet for den samlede ITT-population i afsnit 5.1.4.

De nedenstående beskrivelser for bevacizumab bygger hovedsageligt på bivirkningsopgørelser i vedligeholdelsesbehandlingsfasen af GOG-0218 samt EMAs produktresumé [42] og EPAR for bevacizumab [35].

Behandlingsophør grundet bivirkninger
Dette er ikke angivet for bevacizumab på en måde, hvor der kan laves en meningsfuld sammenligning med niraparib, da bivirkningerne fra kemoterapien er medtaget i bivirkningsopgørelserne i ICON7 (se afsnit 5.2.2).

Bivirkninger af grad 3-4
Dette er ikke angivet for bevacizumab på en måde, hvor der kan laves en meningsfuld sammenligning med niraparib, da bivirkningerne fra kemoterapien er medtaget i bivirkningsopgørelserne i ICON7 (se afsnit 5.2.2).

Kvalitativ gennemgang af bivirkningerne
De hyppigste bivirkninger forbundet med behandling med bevacizumab er hypertension, træthed eller asteni, diarré og mavesmerter. De mest almindelige bivirkninger af grad 3-4 er hypertension (op til 20 %), proteinuri (2 %), gastrointestinale perforationer (op til 2 %) og sårhelingskomplikationer (2 %) [35,42]. Tromboembolier optræder i 3-10 % af patienterne og med sammenlignelig frekvens i induktionsfasen med kemoterapi og vedligeholdelsesfasen [36]. Størstedelen af disse er grad 1-2, men i tilfælde af grad-2-4 tromboembolier medfører det behandlingsstop.

Gastrointestinale perforationer varierer i type og intensitet fra normalisering uden behandling til perforation af kolon med abdominal absces og fatalt udfald. Overordnet set er dødsfald pga. bivirkninger dog sjældne (< 1 %) [35].

Bivirkningerne forbundet med behandling med bevacizumab er som oftest håndterbare. Det er dog ikke muligt at dosisreducere eller pausere behandlingen med bevacizumab for at afhjælpe bivirkningerne.

Niraparibs effekt på bivirkninger overfor bevacizumab kan ikke kategoriseres. Det er fagudvalgets erfaring, at behandlingerne har hver deres bivirkningsprofil, men at de begge er håndterbare i klinisk praksis.

Livskvalitet
Effekten på livskvalitet for niraparib er beskrevet for den samlede population i afsnit 5.1.4.

Livskvaliteten er målt vha. EORTC QLQ-C30 i ICON7 for ITT-populationen, hvor gennemsnitlig '*global health score*' er angivet ved baseline og efter 54 uger. Baselinescoren var henholdsvis 55,1 (53,5-56,7) og 58,6 (57,1-60,1) i bevacizumab og placeboarmen. Efter 54 uger var scoren henholdsvis 69,7 (68,0-71,4) og 76,1 (74,3-77,9). Derved observeredes en stigning af livskvaliteten gennem forløbet for både bevacizumab

og placebo. Stigningen var dog større i placebogruppen (14,6 point overfor 19,4 point), hvilket indikerer, at bevacizumab i sig selv ikke har nogen positiv effekt på livskvaliteten målt ved EORTC QLQ-C30.

Niraparibs effekt på livskvalitet overfor bevacizumab kan ikke kategoriseres. Fagudvalget vurderer, at der ikke er grund til at antage, at nogen af behandlingerne har klinisk relevant effekt på livskvaliteten ved de anvendte målemetoder.

5.2.5 Fagudvalgets konklusion

Den samlede værdi af niraparib sammenlignet med bevacizumab til patienter med nydiagnosticeret, HRD-positiv kræft i æggestokkene uden BRCA-mutation kan ikke kategoriseres. Fagudvalget vurderer, at niraparib er et bedre behandlingsalternativ end bevacizumab til denne patientgruppe. Dette er primært baseret på den bedre median progressionsfri overlevelse ved behandling med niraparib (11 måneder overfor 5,5 måneder ved behandling med bevacizumab). Derudover var langtidseffekten udtrykt som PFS-rate ved 2 år markant større ved niraparib end ved bevacizumab. Fagudvalget kan ikke vurdere, om behandlingen med niraparib er forbundet med flere eller færre bivirkninger end bevacizumab. Det er fagudvalgets erfaring, at behandlingerne har hver deres bivirkningsprofil, men at de begge er håndterbare i klinisk praksis. Ved niraparib kan dosisreduktion eller pausering afhjælpe bivirkningerne, hvorimod bevacizumabbehandling kan pauseres, men ikke dosisjusteres.

5.3 Klinisk spørgsmål 3

Klinisk spørgsmål 3 er:

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

5.3.1 Litteratur

Litteraturen til besvarelse af klinisk spørgsmål 3 er den samme som for klinisk spørgsmål 2 (se afsnit 5.2.1). Til besvarelse af dette kliniske spørgsmål anvendes dog OS og PFS-data for den HRD-negative subpopulation (Tabel 5-1). Baselinekarakteristika er ikke opgjort specifikt for denne subpopulation. I stedet angives baselinekarakteristika for populationen, der enten har ukendt HRD-status eller er HRD-negativ overfor højrisiko-subpopulationen fra ICON7. Bemærk dog, at patienterne med ukendt HRD-status ikke indgår i effektestimaterne. Ligesom ved klinisk spørgsmål 2 kan der ikke foretages en statistisk indirekte sammenligning mellem niraparib og bevacizumab, jf. de nævnte studieforskelle i afsnit 5.2.1.

Tabel 5-8. Baselinekarakteristika for populationen uden demonstreret HRD-positiv (HRD-negativ samt ukendt HRD-status) i PRIMA samt populationen med høj risiko for progression i ICON7

		PRIMA – HRD-negativ og HRD-ukendt [26]		**ICON7 – høj risiko** [41]	
		Niraparib N = 240	**Placebo N = 120**	**Bevacizu-mab N = 248**	**Placebo N = 254**
Alder, median (rækkevidde)*		58 - 62	58 - 62	60 (26-80)	60 (18-81)
ECOG PS	0	155 (65 %)	77 (64 %)	100 (41 %)	98 (39 %)
	1	85 (35 %)	43 (36 %)	123 (50 %)	135 (53 %)
	2	0	0	21 (9 %)	20 (8 %)
Primær tumorlokation	Æggestokkene	187 (78 %)	96 (80 %)	207 (83 %)	210 (83 %)
	Æggelederne	33 (14 %)	19 (16 %)	6 (2 %)	5 (2 %)
	Bughulen	20 (8 %)	5 (4 %)	28 (11 %)	32 (13 %)
	Ukendt/flere lokationer	0	0	7 (3 %)	7 (3 %)
Histologi	High-grade serøst karcinom	231 (96 %)	114 (95 %)	186 (75 %)	195 (77 %)
	Endometroid	6 (3 %)	3 (3 %)	17 (7 %)	14 (6 %)
	Anden	3 (1 %)	2 (2 %)	45 (18 %)	45 (17 %)
FIGO-stadium	III	157 (65 %)	80 (67 %)	144 (58 %)	157 (62 %)
	IV	83 (35 %)	40 (33 %)	104 (42 %)	97 (38 %)
Neoadjuverende kemoterapi	Nej	74 (31 %)	33 (28 %)	Ikke angivet	
	Ja	166 (69 %)	87 (72 %)	Ikke angivet	
Operationsstatus	Primært opereret, ≤ 1 cm resttumor	Ikke angivet		41 (17 %)	43 (17 %)
	Primært opereret, > 1 cm resttumor	Ikke angivet		194 (78 %)	194 (76 %)
	Ikke opereret	Ikke angivet		13 (5 %)	17 (7 %)

Resultat af 1. linje kemoterapi	Komplet respons	152 (63 %)	79 (66 %)	Ikke angivet
	Partiel respons	88 (37 %)	41 (34 %)	Ikke angivet
Mutationsstatus	HRD-negativ	169 (70 %)	80 (67 %)	Ukendt
	HRD-ukendt	71 (30 %)	40 (33 %)	Ukendt

* Median alder og range er ikke angivet for denne population. Baselinekarakteristika er angivet for ITT-populationen og HRD-populationen, hvorved data for populationen uden HRD/ukendt HRD er fundet ved at subtrahere tallene for HRD-populationen fra ITT-populationen. Dette kan dog ikke anvendes til at bestemme median alder. Median alder i ITT-populationen er 62 år, mens den er 58 år i HRD-positiv-populationen.

Forskelle mellem baselinekarakteristika og studiedesign er beskrevet i afsnit 5.2.1.

5.3.2 Databehandling og analyse

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

Medicinrådet vurderer, ligesom ved klinisk spørgsmål 2, at der ikke kan foretages en statistisk indirekte sammenligning mellem niraparib og bevacizumab. I stedet foretages en deskriptiv sammenligning, mellem den HRD-negative population i PRIMA og højrisikogruppen fra ICON7 for effektmålene, OS, PFS og livskvalitet, mens der foretages en sammenligning med bivirkningsprofilen for bevacizumab ud fra EMAs produktresumé og EPAR samt GOG-0218 (se endvidere afsnit 5.2.2 for argumentation).

5.3.3 Evidensens kvalitet

Se afsnit 5.2.3.

5.3.4 Effektestimater og kategorier

I tabellen herunder fremgår de absolutte og relative effektforskelle mellem niraparib og placebo fra PRIMA og bevacizumab og placebo fra højrisikogruppen i ICON7 samt de aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 3.

Tabel 5-9. Resultater for klinisk spørgsmål 3

Effektmål	Målenhed (MKRF)	Vigtighed	Niraparib overfor placebo (PRIMA- HRD-negativ)		Bevacizumab overfor placebo (ICON7- høj-risiko subpopulation)		Aggregeret værdi for effektmålet
			Absolut forskel (95 % CI)	Relativ forskel	Absolut forskel (95 % CI)	Relativ forskel	
Samlet overlevelse (OS)	Median OS (3 måneder)	Kritisk	Ikke nået	HR = 0,51 (0,27; 0,97)	7,5 måneder	Ikke mulig (non-proportional hazards)***	Kan ikke kategoriseres
	OS-rate ved 60 måneder (5 %-point)		Ikke angivet		Ca. 5 %-point		
Progressionsfri overlevelse (PFS)	Median PFS (3 måneder)	Kritisk	2,7 måneder	HR = 0,68 (0,49 ; 0,94)	5,5 måneder	Ikke mulig (non-proportional hazards)***	Kan ikke kategoriseres
	PFS rate ved 24 måneder (5 %-point)		Ingen data		Ca. 0 %-point		
Bivirkninger*	Andel af patienter, som ophører behandling pga. bivirkninger (5 %-point)**	Kritisk	9,5 %-point (6,0-13,0)	RR = 4,9 (2,1 ; 11,1)	Ikke relevant	Ikke relevant	Kan ikke kategoriseres
	Andel af patienter, der oplever en eller flere bivirkninger af grad 3-4 (10 %-point)		58,7 %-point (53,5 ; 64,0)	RR = 9,96 (6,2 ; 16,1)	Ikke relevant	Ikke relevant	
	Kvalitativ gennemgang						

Effektmål	Målenhed (MKRF)	Vigtighed	Niraparib overfor placebo (PRIMA- HRD-negativ)		Bevacizumab overfor placebo (ICON7- høj-risiko subpopulation)		Aggregeret værdi for effektmålet
			Absolut forskel (95 % CI)	Relativ forskel	Absolut forskel (95 % CI)	Relativ forskel	
Livskvalitet*	Andel af patienter, der ikke viser statistisk signifikant forværring i livskvalitet (10 %-point)	Vigtigt	Ikke angivet	Ikke angivet	Ikke angivet	Ikke angivet	Kan ikke kategoriseres

Konklusion	
Samlet kategori for lægemidlets værdi	Kan ikke kategoriseres. Fagudvalget vurderer, at niraparib, modsat bevacizumab, ikke har nogen klinisk relevant effekt på PFS i denne patientgruppe. Der er ikke noget i det tilgængelige datagrundlag, der indikerer, at niraparib er et bedre behandlingsalternativ end bevacizumab til denne patientgruppe.
Kvalitet af den samlede evidens	Meget lav.

* Estimatet for niraparib overfor placebo stammer fra ITT-populationen. ** Effektmålet er opgjort på baggrund af uønskede hændelser i stedet for bivirkninger, da PRIMA kun indeholder oplysninger om bivirkningsstop som følge af uønskede hændelser. *** Antagelsen om proportional hazards er ikke opfyldt. Der er således ikke en konstant risiko for event igennem observationstiden, og derfor kan der ikke opgives en hazard ratio. CI = konfidensinterval, HR = Hazard Ratio, OR = Odds Ratio, RR = relativ risiko.

Samlet overlevelse (OS)
Median OS er ikke nået i hverken niraparib- eller placeboarmen, og OS-raten ved 5 år er ikke angivet, da opfølgningstiden ikke er tilstrækkelig lang. OS-raten ved 2 år var 81,1 (75,2-87,0) % i niraparibarmen overfor 58,7 (48,0-69,5) % i placeboarmen. Dette giver en absolut forskel på 22,3 %-point og en HR på 0,51 (0,27-0,97). Der er dog en væsentlig usikkerhed om estimaterne, da mange patienter er censureret ved opgørelsen af OS-raten, og forskellen derfor kan skyldes relativt få dødsfald i placebogruppen.

Bevacizumabs effekt på OS er beskrevet i afsnit 5.2.4.

Niraparibs effekt på OS overfor bevacizumab kan ikke kategoriseres. Fagudvalget kan ikke vurdere, om der kan forventes en forskel i samlet overlevelse på dette datagrundlag, da overlevelsesdata for niraparib er umodne. Derudover er en eventuel overlevelsesgevinst ved bevacizumabbehandling meget usikker. De tilgængelige OS-data for niraparib indikerer dog, at effekten af niraparib ikke er dårligere end bevacizumab for så vidt angår OS.

Progressionsfri overlevelse (PFS)
Median PFS var henholdsvis 8,1 (5,7-9,4) måneder og 5,4 (4,0-7,3) måneder i niraparib- og placebogruppen, hvilket giver en absolut forskel på 2,7 måneder. PFS-raten ved 2 år kan ikke estimeres, da alle patienter er enten censurerede eller progredierede efter 2 år. HR for PFS var 0,68 (0,49-0,94) (P = 0,02).

Bevacizumabs effekt på PFS er beskrevet i afsnit 5.2.4.

Niraparibs effekt på PFS overfor bevacizumab kan ikke kategoriseres. Fagudvalget vurderer, at niraparib, modsat bevacizumab, ikke har nogen klinisk relevant effekt på PFS i denne patientgruppe.

Bivirkninger
Bivirkninger for niraparib er beskrevet for den samlede population i afsnit 5.1.4 og for bevacizumab i afsnit 5.2.4.

Niraparibs effekt på bivirkninger overfor bevacizumab kan ikke kategoriseres. Det er fagudvalgets erfaring, at behandlingerne har hver deres bivirkningsprofil, men at de begge er håndterbare i klinisk praksis.

Livskvalitet
Effekten af behandling med niraparib på livskvalitet er beskrevet for den samlede population i afsnit 5.1.4, og effekten af bevacizumab er beskrevet i afsnit 5.2.4.

Niraparibs effekt på livskvalitet overfor bevacizumab kan ikke kategoriseres. Fagudvalget vurderer, at der ikke er grund til at antage, at nogen af behandlingerne har klinisk relevant effekt på livskvaliteten ved de anvendte målemetoder.

5.3.5 Fagudvalgets konklusion

Den samlede værdi af niraparib sammenlignet med bevacizumab til patienter med nydiagnosticeret, HRD-negativ kræft i æggestokkene kan ikke kategoriseres efter Medicinrådets metoder. Fagudvalget vurderer, at niraparib, modsat bevacizumab, ikke har nogen klinisk relevant effekt på PFS i denne patientgruppe. Der er derfor ikke noget i det tilgængelige datagrundlag, der indikerer, at niraparib er et bedre behandlingsalternativ til denne patientgruppe.

5.4 Klinisk spørgsmål 4

Klinisk spørgsmål 4 er:

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

5.4.1 Litteratur

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

Ansøger anvender PRIMA til at estimere effekten af niraparib over for placebo, som beskrevet i Tabel 5-1 og Tabel 5-2.

Til at besvare klinisk spørgsmål 4 anvendes den samme subpopulation som ved klinisk spørgsmål 2, dvs. HRD-positive uden BRCA-mutation. Baselinekarakteristika er opgivet i Tabel 5-3.

PRIMA-studiet er beskrevet i afsnit 5.1.1. For dette kliniske spørgsmål er det relevant at bemærke, at populationen i PRIMA-studiet hovedsageligt består af patienter, der ville være kandidater til bevacizumab ifølge dansk klinisk praksis, dvs. patienter med stadie IV-sygdom eller stadie III og > 1 cm restsygdom efter operation. Derved forventes det, at den generelle progressionsrisiko er højere i PRIMA-studiet end for populationen defineret i det kliniske spørgsmål, da denne er defineret ved at have stadie III-sygdom og < 1 cm restsygdom efter operation. Subgruppeanalyser fra SOLO-1-studiet har vist, at olaparib giver en signifikant forlængelse af PFS i en population med høj risiko for progression (svarende til populationen ved klinisk spørgsmål 2 og 3, som kandiderer til bevacizumab), men at effekten umiddelbart er større i en population med lav risiko (svarende til populationen ved klinisk spørgsmål 4 og 5, som ikke kandiderer til bevacizumab) [32]. Derfor vurderer fagudvalget, at effektestimaterne vedr. overlevelse og PFS for niraparib overfor placebo vil være konservativt estimerede ved at anvende data fra PRIMA. Derved kan studiet lægges til grund for en direkte sammenligning mellem niraparib og placebo i klinisk spørgsmål 4.

Fagudvalget vurderer, at patientpopulationerne, udover den generelt dårligere prognose, er sammenlignelig med population i dansk klinisk praksis.

5.4.2 Databehandling og analyse

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

Ansøger anvender den HRD-positive subpopulation uden BRCA-mutation til at foretage en direkte sammenligning af niraparibs effekt på PFS overfor placebo, mens den samlede HRD-positive population (inklusive patienter med BRCA-mutation) anvendes ved OS. Data for OS anvendes dog kun perspektiverende, ligesom ved klinisk spørgsmål 1 og 2. Datamodenheden er lav for både OS (10,8 % af patienterne er døde) og PFS (34 % for niraparib- og 60 % for komparatorarmen er døde eller progredierede). Ansøger anvender den samlede ITT-population til besvarelse af effektmålene bivirkninger og livskvalitet, da der ikke findes data for disse specifikt for den relevante subpopulation. Medicinrådet anser dette for validt, da de ikke forventer, at BRCA- eller HRD-status påvirker vurderingen af disse effektmål.

5.4.3 Evidensens kvalitet

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

For alle effektmål er der nedgraderet for inkonsistens, da der kun er et studie. For OS er der desuden nedgraderet 2 niveauer for indirekthed, da data stammer fra en population, der inkluderer patienter med BRCA-mutation, og data er opgivet som 2-års OS-rate i stedet for 5-års rate. Derved er evidensens kvalitet for OS meget lav. Evidenskvaliteten for PFS, bivirkninger og livskvalitet er henholdsvis lav, middel og meget lav. Den samlede evidenskvalitet er derved bestemt af OS, som det kritiske effektmål med lavest evidenskvalitet.

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

Medicinrådet har vurderet studierne ved Cochrane risk of bias tool 2.0. Overordnet er det vurderet, at der er lav risiko for bias ved PRIMA.

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

5.4.4 Effektestimater og kategorier

I tabellen herunder fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 4.

Tabel 5-10. Resultater for klinisk spørgsmål 4

Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Samlet overlevelse (OS)*	Median OS (3 måneder)	Kritisk	Ikke angivet	Kan ikke kategoriseres	Ikke angivet	Kan ikke kategoriseres	Kan ikke kategoriseres
	OS-rate ved 60 måneder (5 %-point)		Ikke angivet	Kan ikke kategoriseres			
Progressionsfri overlevelse (PFS)	Median PFS (6 måneder)	Kritisk	11,4 måneder	Kan ikke kategoriseres	HR = 0,50 (0,31 ; 0,83)	Moderat merværdi	Moderat merværdi
	PFS-rate ved 24 måneder (10 %-point)		16 %-point	Kan ikke kategoriseres			
Bivirkninger**	Andel af patienter, som ophører behandling pga. bivirkninger (5 %-point) ***	Kritisk	9,5 %-point (6,0 ; 13,0)	Negativ værdi	RR = 4,9 (2,1 ; 11,1)	Negativ værdi	Negativ værdi
	Andel af patienter, der oplever en eller flere bivirkninger af grad 3-4 (10 %-point)		58,7 %-point (53,5 ; 64.0)	Negativ værdi	RR = 9,96 (6,2 ; 16,1)	Negativ værdi	
	Kvalitativ gennemgang						

Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Livskvalitet**	Andel af patienter, der ikke viser statistisk signifikant forværring i livskvalitet (10 %-point)	Vigtigt	Ikke angivet	Kan ikke kategoriseres	Ikke angivet	Kan ikke kategoriseres	Kan ikke kategoriseres

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

* Der er ikke OS-data for niraparib fra den HRD-positive population uden BRCA-mutation. I stedet bruges data fra den samlede HRD-positive population, hvoraf ca. 60 % har BRCA-mutation, til perspektivering. ** Estimatet for niraparib overfor placebo stammer fra ITT-populationen. *** Effektmålet er opgjort på baggrund af uønskede hændelser i stedet for bivirkninger, da PRIMA kun indeholder oplysninger om bivirkningsstop som følge af uønskede hændelser. CI = konfidensinterval, HR = Hazard Ratio, RR = relativ risiko.

Samlet overlevelse (OS)
OS er ikke opgivet for populationen uden BRCA-mutation med HRD. Effekten kan derved ikke kategoriseres. OS for den samlede HRD-positive population inklusive BRCA-mutation er beskrevet i afsnit 5.1.4.

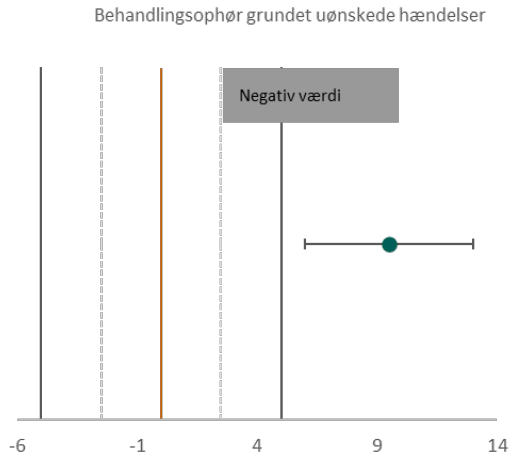
Progressionsfri overlevelse (PFS)
Median PFS var henholdsvis 19,6 (13,6 ; ikke nået) måneder og 8,2 (6,7 ; 16,8) måneder i niraparib- og placebogruppen, hvilket giver en absolut forskel på 11,4 måneder. PFS-raten ved 2 år var henholdsvis 47 % og 31 % i niraparib- og placebogruppen, hvilket giver en absolut forskel på 16 %-point. For begge effektmål gælder, at punkestimatet er højere end de fastsatte mindste klinisk relevante forskelle (hhv. 6 måneder og 10 %-point). Den foreløbige værdi for den absolutte effekt kan dog ikke kategoriseres, da der ikke kan udregnes konfidensintervaller for estimaterne.

HR for PFS var 0,50 (0,31 ; 0,83) (P < 0.001). Derved er den foreløbige værdi for den relative effekt en moderat merværdi.

Fagudvalget vurderer, at den aggregerede værdi af niraparib overfor placebo for effektmålet PFS er moderat merværdi. Dette er hovedsageligt baseret på den relative effektforskel. Fagudvalget bemærker, at de absolutte effektestimater for både PFS-raten og median PFS er væsentligt større end de mindste klinisk relevante forskelle. Fagudvalget bemærker desuden, at der er en vis usikkerhed i effektestimatet, grundet umodenhed af data i niraparibarmen.

Bivirkninger

Behandlingsophør grundet bivirkninger:
I PRIMA var andelen af behandlingsophør grundet uønskede hændelser 12,0 % i niraparibarmen og 2,5 % i placeboarmen, hvilket giver en absolut forskel på 9,5 (6,0-13,0) %-point.



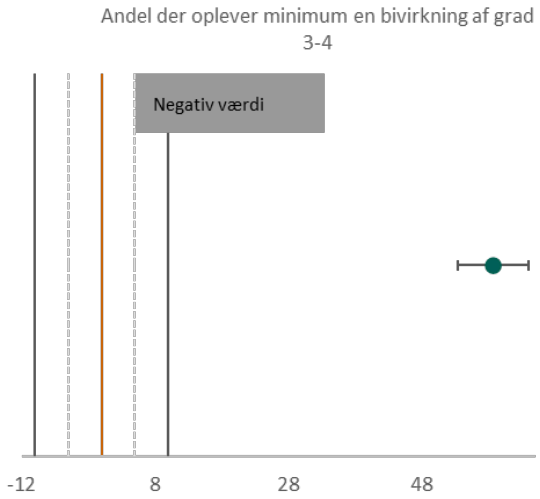
Figur 5-1. Punktestimat og 95 % konfidensinterval for den absolutte forskel for behandlingsophør grundet uønskede hændelser. De optrukne linjer indikerer den mindste klinisk

relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF

Den foreløbige værdi for det absolutte estimat er negativ værdi.

RR for behandlingsstop var 4,9 (2,1 ; 11,1), hvorved det foreløbige relative effektestimat er negativ værdi. Den samlede værdi for niraparib overfor placebo for så vidt angår behandlingsophør grundet uønskede hændelser er negativ værdi.

Bivirkninger af grad 3-4:
I PRIMA var andelen, der oplevede en grad 3-4-bivirkning (*adverse drug reactions*) 65,3 % i niraparibarmen og 6,6 % i placeboarmen, hvilket giver en absolut forskel på 58,7 (53,5 ; 64,0) %-point.



Figur 5-2. Punktestimat og 95 % konfidensinterval for den absolutte forskel for andelen af patienter, der oplever minimum en grad 3-4-bivirkning. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF

RR for at opleve minimum en grad 3-4-bivirkning var 9,96 (6,2-16,1), hvorved det foreløbige relative effektestimat er negativ værdi. Den samlede værdi for niraparib overfor placebo, for så vidt angår andelen af patienter, der oplever minimum en grad 3-4-bivirkning, er negativ værdi.

Fagudvalget bemærker, at den individualiserede dosis, der nu udgør standarddoseringen, kan medføre en lavere bivirkningsfrekvens i klinisk praksis end rapporteret i studiet (se endvidere afsnit 5.1.4.), men at dette ikke vil ændre kategoriseringen.

Kvalitativ gennemgang af bivirkningerne
Se afsnit 5.1.4 for en kvalitativ gennemgang af bivirkningerne ved niraparib.

Samlet vurderer fagudvalget, at niraparib giver en negativ værdi sammenlignet med placebo for effektmålet bivirkninger. Dette er dog forventeligt, når man sammenligner en aktiv behandling med placebo. Samtidig vurderer fagudvalget, at bivirkningerne ved niraparib generelt er velkendte og håndterbare i klinikken.

Livskvalitet
Livskvalitetsdata er ikke opgjort, som beskrevet i protokollen, og der er ikke indsendt datamateriale, som gør det muligt at udregne absolutte eller relative effektestimater. Se en beskrivelse af data for livskvalitet i afsnit 5.1.4.

Samlet kan effekten af niraparib overfor placebo på livskvalitet ikke kategoriseres. Fagudvalget vurderer, at hverken niraparib eller placebo medfører ændringer af patienternes livskvalitet i behandlingsforløbet ud fra de anvendte målemetoder.

5.4.5 Fagudvalgets konklusion

Fagudvalget vurderer, at niraparib til patienter med nydiagnosticeret HRD-positiv kræft i æggestokkene uden BRCA-mutation giver en lille merværdi sammenlignet med placebo.

Fagudvalget lægger til grund, at niraparib giver en moderat merværdi for det kritiske effektmål, PFS, og at de absolutte forbedringer af både median PFS og PFS-raten er væsentlig større end de fastsatte mindste klinisk relevante forskelle. Niraparib er forbundet med flere bivirkninger end placebo. Disse vurderes generelt at være håndterbare i klinikken, bl.a. ved hjælp af individualiseret startdosis og løbende dosisreduktioner. Bivirkningerne afspejler dog en negativ værdi, hvorved den samlede merværdi bliver lille.

5.5 Klinisk spørgsmål 5

Klinisk spørgsmål 5 er:

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

5.5.1 Litteratur

Litteraturen til besvarelse af klinisk spørgsmål 5 er den samme som for klinisk spørgsmål 4 (se afsnit 5.4.1). Til besvarelse af dette kliniske spørgsmål anvendes dog den HRD-negative subpopulationen (se Tabel 5-1). Se baselinekarakteristika for populationen i Tabel 5-8 i afsnit 5.3.1. Der gælder de samme overvejelser vedr. den grundlæggende progressionsrisiko i populationen i PRIMA-studiet overfor den definerede population i det kliniske spørgsmål, som i klinisk spørgsmål 4.

5.5.2 Databehandling og analyse

Ansøger anvender den HRD-negative subpopulation til at foretage en direkte sammenligning af niraparibs effekt overfor placebo. Datamodenheden er lav for OS (10,8 %), hvorimod modenheden for PFS er 66 % for niraparib- og 70 % for komparatorarmen. Ansøger anvender den samlede ITT-population til besvarelse af effektmålene bivirkninger og livskvalitet, som beskrevet i afsnit 5.4.2. Medicinrådet anser dette for validt, da de ikke forventer, at BRCA- eller HRD-status påvirker vurderingen af disse effektmål.

5.5.3 Evidensens kvalitet

Evidensens kvalitet er den samme som vurderet for klinisk spørgsmål 4 (afsnit 5.4.3). Der er dog nedgraderet forskelligt for OS, da populationen i klinisk spørgsmål 5 er korrekt. Evidensens kvalitet er alligevel meget lav, hvilket betyder, at nye studier eller en længere opfølgningstid med høj sandsynlighed kan ændre konklusionen. Se GRADE-skemaet i bilag 2.

5.5.4 Effektestimater og kategorier

I tabellen herunder fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 5.

Tabel 5-11. Resultater for klinisk spørgsmål 5

Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Samlet overlevelse (OS)	Median OS	Kritisk	Ikke nået	Kan ikke kategoriseres	HR = 0,51 (0,27 ; 0,97)	Merværdi af ukendt størrelse	Kan ikke kategoriseres
	OS rate ved 60 måneder		Ikke angivet	Kan ikke kategoriseres			
Progressionsfri overlevelse (PFS)	Median PFS	Kritisk	2,7 måneder	Kan ikke kategoriseres	HR = 0,68 (0,49 ; 0,94)	Merværdi af ukendt størrelse	Ingen merværdi
	PFS-rate ved 24 måneder		Ikke angivet	Kan ikke kategoriseres			
Bivirkninger*	Andel af patienter, som ophører behandling pga. bivirkninger**	Kritisk	9,5 %-point (6,0 ; 13,0)	Negativ værdi	RR = 4,9 (2,1 ; 11,1)	Negativ værdi	Negativ værdi
	Andel af patienter, der oplever en eller flere bivirkninger af grad 3-4		58,7 %-point (53,5 ; 64,0)	Negativ værdi	RR = 9,96 (6,2 ; 16,1)	Negativ værdi	
	Kvalitativ gennemgang						

Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Livskvalitet*	Andel af patienter, der ikke viser statistisk signifikant forværring i livskvalitet	Vigtigt	Ikke angivet	Kan ikke kategoriseres	Ikke angivet	Kan ikke kategoriseres	Kan ikke kategoriseres

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

* Estimatet for niraparib overfor placebo stammer fra ITT-populationen. ** Effektmålet er opgjort på baggrund af uønskede hændelser i stedet for bivirkninger, da PRIMA kun indeholder oplysninger om bivirkningsstop som følge af uønskede hændelser. CI = konfidensinterval, HR = Hazard Ratio, RR = relativ risiko.

Samlet overlevelse (OS)
Median OS er ikke nået i hverken niraparib- eller placeboarmen, og OS-raten ved 5 år er ikke angivet, da opfølgningstiden ikke er tilstrækkelig lang til at rapportere denne. OS-raten ved 2 år var 81,1 (75,2 ; 87,0) % i niraparibarmen overfor 58,7 (48,0 ; 69,5) % i placeboarmen. Dette giver en absolut forskel på 22,3 %-point og en HR på 0,51 (0,27 ; 0,97).

Da de specificerede effektmål var median OS og OS-raten, kan den absolutte værdi ikke kategoriseres. HR kan dog anvendes til en foreløbig kategorisering af den relative effekt ud fra antagelsen om '*proportional hazards*'. Det foreløbige relative effektestimat er en merværdi af ukendt størrelse for niraparib overfor placebo.

Fagudvalget vurderer, at den aggregerede værdi af niraparib overfor placebo, for så vidt angår OS, ikke kan kategoriseres. Selvom den relative værdi indikerer en merværdi af ukendt størrelse, er data overordnet set for umodne til at kunne fastslå en eventuel værdi.

Progressionsfri overlevelse (PFS)
Median PFS var henholdsvis 8,1 (5,7- 9,4) måneder og 5,4 (4,0-7,3) måneder i niraparib- og placebogruppen, hvilket giver en absolut forskel på 2,7 måneder. PFS-raten ved 2 år kan ikke estimeres, da alle patienter er enten censurerede eller progredierede efter 2 år. Punktestimatet for den absolutte forskel i median PFS er lavere end den fastsatte mindste klinisk relevante forskel (3 måneder). Den foreløbige værdi for den absolutte effekt kan ikke kategoriseres, da der ikke kan udregnes konfidensintervaller for estimaterne.

HR for PFS var 0,68 (0,49-0,94) (P = 0,02). Derved er den foreløbige værdi for den relative effekt en merværdi af ukendt størrelse.

Fagudvalget vurderer, at den aggregerede værdi af niraparib overfor placebo for effektmålet PFS er ingen merværdi, da de mindste klinisk relevante forskelle ikke er nået for median PFS, og PFS-raten ikke kan vurderes på det foreliggende datagrundlag.

Bivirkninger
Uønskede hændelser og bivirkninger er beskrevet under klinisk spørgsmål 4 (afsnit 5.4.4) (kvantitative opgørelser) og 1 (afsnit 5.1.4) (kvalitativ gennemgang).

Samlet vurderer fagudvalget, at niraparib giver en negativ værdi sammenlignet med placebo for effektmålet bivirkninger. Dette er dog forventeligt, når man sammenligner en aktiv behandling med placebo. Samtidig vurderer fagudvalget, at bivirkningerne ved niraparib generelt er velkendte og håndterbare i klinikken.

Livskvalitet
Livskvalitetsdata er ikke opgjort, som beskrevet i protokollen, og der er ikke indsendt datamateriale, som gør det muligt at udregne absolutte eller relative effektestimater. Se en beskrivelse af data for livskvalitet i afsnit 5.1.4.

Effekten af niraparib overfor placebo på livskvalitet kan ikke kategoriseres. Fagudvalget vurderer, at hverken niraparib eller placebo medfører ændringer af patienternes livskvalitet i behandlingsforløbet ud fra de anvendte målemetoder.

5.5.5 Fagudvalgets konklusion

Fagudvalget vurderer, at niraparib til patienter med nydiagnosticeret HRD-negativ kræft i æggestokkene giver ingen merværdi sammenlignet med placebo.

Fagudvalget vurderer, at niraparib ikke medfører en dokumenteret klinisk relevant merværdi på hverken OS eller PFS ud fra det nuværende datagrundlag. For både OS og PFS indikerer de relative værdier dog en merværdi af ukendt størrelse, hvorved det ikke kan udelukkes, at niraparib kan have en lille effekt på denne patientgruppe. Niraparib er forbundet med flere bivirkninger end placebo, hvilket giver en negativ værdi. Bivirkningerne er dog velkendte og vurderes generelt at være håndterbare i klinikken, bl.a. ved hjælp af individualiseret startdosis og løbende dosisreduktioner.

Det har ikke været muligt at opnå konsensus i fagudvalget omkring vurderingen af niraparibs effekt overfor placebo til HRD-negative patienter. De to patientrepræsentanter i fagudvalget er uenige i konklusionerne i dette afsnit.

6. Andre overvejelser

PFS2
Fagudvalget efterspurgte i protokollen en opgørelse for PFS2, defineret som tid fra randomisering indtil anden objektiv radiologisk progression ifølge RECIST-kriterierne eller død. Formålet med dette effektmål er at vurdere effekten af 1. linje vedligeholdelsesbehandlingen på længere sigt i de tilfælde, hvor OS-data ikke er modne. Ansøger har indsendt en analyse, som er præsenteret på SGO 2020 [43]. Data for PFS2 var inddelt efter HRD (inklusive BRCA-mutation), HRD-negativ og ITT-population. Fagudvalget vurderer, at data for PFS2 er for umodne til at blive vurderet. Desuden har ansøger kun indsendt relative effektdata. Fagudvalget har således ikke mulighed for at vurdere eventuelle absolutte forskelle eller PFS2-kurvernes forløb.

Diagnose af HRD
En eventuel anbefaling af niraparib, der skelner mellem HRD-positive og negative patienter vil indebære, at alle patienter, der ikke har en BRCA-mutation, bør udredes for HRD. Definitionen af HRD er uklar, men i de fleste studier defineres dette ved hjælp af MYRIAD myChoice-testen (se endvidere afsnit 3.1). Denne test er endvidere godkendt af FDA som *companion diagnostic* til identifikation af HRD-positive patienter.

Diagnosen vha. MYRIAD myChoice vil for nuværende kræve, at en tumorprøve sendes til virksomheden i USA for analysen. Fagudvalget vurderer, at dette vil være praktisk muligt, men at det vil medføre omkostninger for diagnosen. Fagudvalget bemærker, at der er klinisk interesse omkring diagnosen og definitionen af HRD. Der er således konkrete tiltag

i gang på Rigshospitalet for at kunne udføre MYRIAD myChoice testen lokalt. Det forventes, at testen vil være implementeret på Rigshospitalet i løbet af 2021.

Påvirkning af efterfølgende behandlingslinjer og vurderingens relation til eventuel 2. linjebehandling.
En eventuel anbefaling af niraparib som vedligeholdelsesbehandling i 1. linje til alle patienter med BRCA-mutation med respons på platinbaseret kemoterapi vil ikke medføre ændringer i behandlingsmulighederne i 2. linje, da PARP-hæmmere ikke anvendes til sekventiel behandling, og disse patienter i dag modtager olaparib i 1. linje. For patienter uden BRCA-mutation kan indførslen af niraparib i 1. linje udskyde behandling med bevacizumab til 2. linje, hvorved disse patienter vil få muligheden for vedligeholdelsesbehandling i både 1. og 2. linje.

For patienter, der ikke har modtaget PARPi i 1. linje, vil niraparib være en mulighed i en senere behandlingslinje. Niraparib er tidligere undersøgt til vedligeholdelsesbehandling til recidiverende kræft i æggestokkene, dvs. ved senere behandlingslinjer end 1. linje (NOVA) [11]. I NOVA modtog patienterne niraparib, enten efter 2. linje platinbaseret kemoterapi (ca. 50 % af patienterne) eller efter en senere platinbaseret behandlingslinje. NOVA dannede baggrund for Medicinrådets tidligere vurdering af niraparib som vedligeholdelsesbehandling til patienter med recidiverende kræft i æggestokkene. I denne vurdering var patienterne inddelt i subgrupper, afhængig af om de havde BRCA-mutation eller ej men uden hensyntagen til HRD-status. Niraparib blev anbefalet til patienter med BRCA-mutation men ikke til patienter uden BRCA-mutation [44].

I tilfælde af at niraparib i den aktuelle vurdering bliver anbefalet til patienter uden BRCA-mutation (med eller uden HRD), vil der opstå situationer, hvor patienter med nydiagnosticeret kræft i æggestokkene vil kunne få tilbudt niraparib, mens patienter, der tidligere er progredieret efter 1. linjebehandling, ikke vil få tilbudt dette pga. Medicinrådets tidligere anbefaling, der er baseret på en bredere subpopulation (patienter uden BRCA-mutation uagtet HRD-status).

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

Fagudvalget vurderer, at der som udgangspunkt ikke er grund til at antage, at effekten af niraparib på PFS afviger betragteligt, alt efter om det bliver anvendt til nydiagnosticerede patienter eller patienter med recidiverende kræft i æggestokkene.

Nedenstående tabel viser PFS-medianer samt absolutte og relative forskelle mellem niraparib og placebo opdelt på subgruppeniveau i PRIMA og NOVA.

Tabel 6-1. Oversigt over PFS-medianer og hazard ratios fra forskellige subpopulationer i PRIMA og NOVA

Subpopulation	Nydiagnosticerede (PRIMA)			Recidiverende (NOVA)		
	PFS median (niraparib)	PFS median (placebo)	Absolut og relativ forskel	PFS median (niraparib)	PFS median (placebo)	Absolut og relativ forskel
BRCA-mutation	22,1 måneder	10,9 måneder	11,2 måneder, HR = 0,40 (0,27; 0,62)	21,0 måneder	5,5 måneder	15,5 måneder HR = 0,27 (0,17; 0,41)
BRCA-vildtype-HRD-positiv	19,6 måneder	8,2 måneder	11,4 måneder, HR = 0,50 (0,31; 0,83)	9,3 måneder	3,7 måneder	5,6 måneder, HR = 0,38 (0,23; 0,63)
HRD-negativ	8,1 måneder	5,4 måneder	2,7 måneder, HR = 0,68 (0,49; 0,94)	6,9 måneder	3,8 måneder	3,1 måneder, HR = 0,58 (0,36; 0,92)

De absolutte PFS-medianer kan ikke sammenlignes direkte, da der er forskel på patienternes overordnede prognose. Dette skyldes især, at populationen i PRIMA er nydiagnosticeret, mens populationen i NOVA har recidiverende sygdom. Det er velkendt, at PFS reduceres ved hvert tilbagefald for patienter med kræft i æggestokkene [25]. Fagudvalget kan dog se samme tendens i effekten af niraparib på PFS i PRIMA og NOVA, når subgrupperne inddeles på samme måde. For patienter med både nydiagnosticeret og recidiverende kræft i æggestokkene gælder, at PFS-gevinsten er større i den HRD-positive gruppe end i den HRD-negative. De absolutte forskelle i PFS-medianer mellem niraparib og placebo er mere udtalte i PRIMA end i NOVA, hvorimod de relative forskelle er sammenlignelige mellem studierne.

Det biologiske rationale for behandlingen med niraparib afviger ikke mellem 1. linje eller senere behandlingslinjer. I begge tilfælde forventer fagudvalget, at HRD-positive patienter, hvad end det skyldes BRCA-mutation eller en anden årsag, vil respondere bedre på niraparib end patienter med intakt homolog rekombination (HRD-negative). Fagudvalget vurderer derfor, at HRD-positive patienter i senere behandlingslinjer også vil have en klinisk relevant merværdi ved behandling med niraparib, hvis patienterne lever op til de betingelser, Medicinrådet har opstillet i behandlingsvejledningen for BRCA-muteret kræft i æggestokkene, som er:

- Platinfrit interval på > 6 måneder ved den forudgående behandlingslinje
- Komplet eller partielt respons på carboplatinbaseret kemoterapi
- Ikke tidligere behandlet med PARPi
- Vurderet i stand til at tage tabletter og gennemføre behandlingen.

Fagudvalget bemærker, at man ikke på sigt forventer flere patienter, der skal behandles med niraparib i senere behandlingslinjer. Størstedelen af patienterne vil, i tilfælde af at Rådet anbefaler niraparib, blive behandlet med PARPi i 1. linje. Dette vil derfor hovedsageligt være relevant for den patientgruppe, der allerede har fået recidiverende sygdom, og som ville have været kandidater til PARPi-behandling i 1. linje, hvis anbefalingen havde været gældende.

Det har ikke været muligt at opnå konsensus i fagudvalget omkring vurderingen af niraparibs effekt i 2. linje. De to patientrepræsentanter i fagudvalget er uenige i konklusionerne i dette afsnit.

7. Relation til behandlingsvejledning

Fagudvalget vurderer ud fra de tilgængelige data og klinisk erfaring fra 2. linjebehandling, at niraparib kan ligestilles med olaparib i Medicinrådets behandlingsvejledning vedrørende lægemidler til BRCA-muteret kræft i æggestokkene, æggelederne eller primær kræft i bughinden.

Der findes ikke en relevant behandlingsvejledning for kræft i æggestokkene uden BRCA-mutation.

8. Referencer

1. Mosgaard BJ, Pedersen LK, Bjørn SF, Christiansen T, Markauskas A, Lund B, et al. Retningslinier for visitation, diagnostik, behandling og opfølgning af epitelial ovarie-, tuba- og primær peritonealcancer samt borderline tumorer. Kapitel 1: Introduktion. 2016;(5):1–9.

2. NORDCAN - Association of the Nordic Cancer Registries. Kræftstatistik: Nøgletal og figurer Danmark – Æggestok, æggeleder mv. 2019.

3. NORDCAN - Association of the Nordic Cancer Registries. Æggestok, æggeleder mv. 5-års aldersspecifik relativ overlevelse, diagnoseår 2012-2016. 2017.

4. Dansk Gynækologisk Cancer Database. Landsdækkende klinisk database for gynækologisk kræft. National Årsrapport 2017/2018 og 2018/2019. 2019.

5. Bolton KL, Chenevix-Trench G, Goh C, Sadetzki S, Ramus SJ, Karlan BY, et al. Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer. JAMA. 2012;307(4):382–90.

6. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature. 2011;474(7353):609–15.

7. Zhang S, Royer R, Li S, McLaughlin JR, Rosen B, Risch HA, et al. Frequencies of BRCA1 and BRCA2 mutations among 1,342 unselected patients with invasive ovarian cancer. Gynecol Oncol. 2011;121(2):353–7.

8. Hoppe MM, Sundar R, Tan DSP, Jeyasekharan AD. Biomarkers for homologous recombination deficiency in cancer. J Natl Cancer Inst. 2018;110(7):704–13.

9. Huang Y. Association of BRCA1/2 mutations with ovarian cancer prognosis: An updated meta-analysis. Medicine (Baltimore). 2018;97(2):e9380.

10. Ray-Coquard I, Pautier P, Pignata S, Pérol D, González-Martín A, Berger R, et al. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. N Engl J Med. 2019;381(25):2416–28.

11. Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med. 2016;375(22):2154–64.

12. Pellegrino B, Mateo J, Serra V, Balmaña J. Controversies in oncology: are genomic tests quantifying homologous recombination repair deficiency (HRD) useful for treatment decision making? ESMO open. 2019;4(2):e000480.

13. Takaya H, Nakai H, Takamatsu S, Mandai M, Matsumura N. Homologous recombination deficiency status-based classification of high-grade serous ovarian carcinoma. Sci Rep. 2020;10(1):1–8.

14. Mirza MR, Åvall Lundqvist E, Birrer MJ, dePont Christensen R, Nyvang GB, Malander S, et al. Niraparib plus bevacizumab versus niraparib alone for platinum-sensitive recurrent ovarian cancer (NSGO-AVANOVA2/ENGOT-ov24): a randomised, phase 2, superiority trial. Lancet Oncol. 2019;20(10):1409–19.

15. Mirza MR, Coleman RL, González-Martín A, Moore KN, Colombo N, Ray-Coquard

I, et al. The forefront of ovarian cancer therapy: update on PARP inhibitors. Ann Oncol. 2020;31(9):1148–59.

16. Charlotte Lautrup, Uffe Birk Jensen, Anders Bojesen, Mads Thomassen, Thomas van Overeem Hansen, Anne-Marie Gerdes, Jan Blaakær, Henrik Roed, Ulla Peen, Karina Dahl Steffensen, Bente Lund, Lotte Nedergaard Thomsen EH. Forslag til national guideline for genetisk udredning af patienter med ovariecancer . 2018. 1–4 sider.

17. MYRIAD ONCOLOGY. MYRIAD myChoice CDx [internet]. [citeret 20. august 2020]. Tilgængelig fra: https://myriad-oncology.com/mychoice-cdx/

18. Coleman RL, Fleming GF, Brady MF, Swisher EM, Steffensen KD, Friedlander M, et al. Veliparib with first-line chemotherapy and as maintenance therapy in ovarian cancer. N Engl J Med. 2019;381(25):2403–15.

19. European Medicines Agency Committee for Medicinal Products For Human Use (CHMP). Assesment report Zejula - EMA/648982/2017. 2017.

20. Medicinrådet. Medicinrådets behandlingsvejledning vedrørende lægemidler til BRCA-muteret kræft i æggestokkene, ægge-lederne eller primær kræft i bughinden. 2020.

21. European Medicines Agency E. Zejula SmPC. 2020.

22. O'Connor MJ. Targeting the DNA Damage Response in Cancer. Mol Cell. 2015;60(4):547–60.

23. Mosgaard BJ, Pedersen LK, Bjørn SF, Christiansen T, Markauskas A, Lund B, et al. Retningslinier for visitation, diagnostik, behandling og opfølgning af epitelial ovarie-, tuba- og primær peritonealcancer samt borderline tumorer. Kapitel 3: Kirurgisk behandling af epitheliale ovarietumorer. 2019;(6):1–19.

24. Mosgaard BJ, Pedersen LK, Bjørn SF, Christiansen T, Markauskas A, Lund B, et al. Retningslinier for visitation, diagnostik, behandling og opfølgning af epitelial ovarie-, tuba- og primær peritonealcancer samt borderline tumorer. Kapitel 5: Ikke-kirurgisk behandling af epiteliale tumorer. 2019;(6):1–36.

25. Hanker LC, Loibl S, Burchardi N, Pfisterer J, Meier W, Pujade-Lauraine E, et al. The impact of second to sixth line therapy on survival of relapsed ovarian cancer after primary taxane/platinum-based therapy. Ann Oncol. 2012;23(10):2605–12.

26. González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2019;381(25):2391–402.

27. European Medicines Agency Committee for Medicinal Products For Human Use (CHMP). Assessment report Zejula - EMA/531223/2020. 2020;(September).

28. Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2018;379(26):2495–505.

29. European Medicines Agency EMA. EPAR - Assessment report - Lynparza. 2019.

30. Banerjee S, Moore K, Colombo3 N, Scambia G, Kim B, Oaknin A, et al. 811MO -

Maintenance olaparib for patients (pts) with newly diagnosed, advanced ovarian cancer (OC) and a BRCA mutation (BRCAm): 5-year (y) follow-up (f/u) from SOLO1. Ann Oncol. 2020;31(suppl 4):s551–89.

31. DiSilvestro P, Colombo N, Scambia G, Kim B-G, Oaknin A, Friedlander M, et al. Efficacy of Maintenance Olaparib for Patients With Newly Diagnosed Advanced Ovarian Cancer With a BRCA Mutation: Subgroup Analysis Findings From the SOLO1 Trial. J Clin Oncol. 2020;38(30):3528–37.

32. Colombo N, Bradley W, Moore K, González-Martin A, Scambia G, Oaknin A, et al. 392 Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer and a BRCA mutation: subgroup analysis by risk in the phase III solo1 study. Int J Gynecol Cancer. 2020;30(Suppl 4):A76--A77.

33. Pothuri B. 810MO - Patient-reported outcomes (PROs) in patients (pts) receiving niraparib in the PRIMA/ENGOT-OV26/GOG-3012 trial. Ann Oncol. 2020;31(suppl 4):S551–89.

34. Norquist BM, Brady MF, Harrell MI, Walsh T, Lee MK, Gulsuner S, et al. Mutations in Homologous Recombination Genes and Outcomes in Ovarian Carcinoma Patients in GOG 218 : An NRG Oncology / Gynecologic Oncology Group Study. Clin Cancer Res. 2018;777–84.

35. European Medicines Agency EMA. EPAR - Assessment report - Avastin. 2017.

36. Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, et al. Incorporation of Bevacizumab in the Primary Treatment of Ovarian Cancer for the Gynecologic Oncology Group*. Seattle Cancer Care Alliance, Seattle (BEG Minneap (MB); Harvard Med Sch Massachusetts Gen-eral Hosp Bost (MJB. 2011;26(29):2473–83.

37. Monk BJ, Huang HQ, Burger RA, Mannel RS, Homesley HD, Fowler J, et al. Patient reported outcomes of a randomized, placebo-controlled trial of bevacizumab in the front-line treatment of ovarian cancer: a Gynecologic Oncology Group Study. Gynecol Oncol. 2013;128(3):573–8.

38. Tewari KS, Burger RA, Enserro D, Norquist BM, Swisher EM, Brady MF, et al. Final overall survival of a randomized trial of bevacizumab for primary treatment of ovarian cancer. J Clin Oncol. 2019;37(26):2317–28.

39. Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, et al. A Phase 3 Trial of Bevacizumab in Ovarian Cancer. N Engl J Med. 2011;365(26):2484–96.

40. Stark D, Nankivell M, Pujade-Lauraine E, Kristensen G, Elit L, Stockler M, et al. Standard chemotherapy with or without bevacizumab in advanced ovarian cancer: quality-of-life outcomes from the International Collaboration on Ovarian Neoplasms (ICON7) phase 3 randomised trial. Lancet Oncol. 2013;14(3):236–43.

41. Oza AM, Cook AD, Pfisterer J, Embleton A, Ledermann JA, Pujade-Lauraine E, et al. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. Lancet Oncol. 2015;16(8):928–36.

42. European Medicines Agency. Avastin SmPC. 2021.

43. Han SN, Monk BJ, Gonzalez-Martin A. Time to first subsequent therapy (TFST) and progression-free survival 2 (PFS2) from the phase 3 randomized, double-blind PRIMA/ENGOT-OV26/GOG-3012 study in patients with newly diagnosed ovarian cancer. Gynecol Oncol. 2020;159:18–9.

44. Medicinrådet. Medicinrådets anbefaling vedrørende niraparib som mulig standardbehandling til kræft i æggestokkene, æggelederne eller primær kræft i bughinden. 2019.

9. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende kræft i æggestokkene og livmoderkræft

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

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10. Versionslog

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

11. Bilag

Bilag 1: Cochrane – risiko for bias

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

Tabel 11-1. Vurdering af risiko for bias. González-Martín et al., 2019, PRIMA, NCT02655016

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiseringsprocessen	**Lav**	Allokering til behandling eller placebo var randomiseret i en ratio 2:1. Randomiseringen blev udført centralt via et *interactive web response system.*
Effekt af tildeling til intervention	**Lav**	Allokering til behandling eller placebo var dobbeltblindet.
Manglende data for effektmål	**Lav**	Frafald transparent og begrænset. Analyser af alle effektmål er baseret på alle patienter, som har modtaget mindst én behandling.
Risiko for bias ved indsamlingen af data	**Lav**	Effektmålene vurderes ikke at være påvirket på grund af blinding.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Protokol er offentlig tilgængelig. De primære og sekundære effektmål, der beskrives i protokollen, er rapporteret i studiet.
Overordnet risiko for bias	**Lav**	

Tabel 11-2. Vurdering af risiko for bias - K. Moore, 2018, SOLO-1, NCT01844986

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

Tabel 11-3. Vurdering af risiko for bias Perren et al., 2011, ICON7, ISRCTN91273375

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiseringsprocessen	**Lav**	Allokering til behandling eller placebo var randomiseret i en ratio 1:1. Randomiseringen blev udført centralt via et *interactive web or voice response system.*
Effekt af tildeling til intervention	**Høj**	Hverken patienter eller personale var blindede.
Manglende data for effektmål	**Lav**	Effektivitetsanalyser er baseret på *intention-to-treat* data, mens sikkerhedsanalyser er baseret på alle patienter, som har modtaget mindst én behandling.
Risiko for bias ved indsamlingen af data	**Høj**	Hverken patienter eller personale var blindede.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Protokol er offentlig tilgængelig. De primære og sekundære effektmål, der beskrives i protokollen, er rapporteret i studiet.
Overordnet risiko for bias	**Forbehold**	Væsentligste bias i studiet er, at hverken patienter eller personale var blindede.

Bilag 2: GRADE

Klinisk spørgsmål 4 – niraparib sammenlignet med placebo til behandling af kræft i æggestokkene ved patienter uden BRCA-mutation, HRD-positiv.

Tabel 11-4. GRADE-evidensprofil for klinisk spørgsmål 4

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Niraparib	Placebo	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
Overlevelse (median), follow up: median 13,8 måneder												
1	RCT	Ikke alvorlig	Alvorlig[a]	Alvorlig[b]	Meget alvorlig[c,d]	Ingen	--/247	--/126	HR = 0,61 (0,27;1,39)	Ikke nået	⨁◯◯◯ MEGET LAV	Kritisk
Overlevelse (OS-rate ved 5 år), follow up: median 13,8 måneder												
1	RCT	Ikke alvorlig	Alvorlig[a]	Meget alvorlig[e]	Meget alvorlig[c,d]	Ingen	--/247	--/126	HR = 0,61 (0,27;1,39)	6,2 %-point	⨁◯◯◯ MEGET LAV	Kritisk
Progressionsfri overlevelse (median), follow up: median 13,8 måneder												
1	RCT	Ikke alvorlig	Alvorlig[a]	Ikke alvorlig	Alvorlig[d]	Ingen	32/95	33/55	HR = 0,50 (0,31;0,83)	11,4 måneder	⨁⨁◯◯ LAV	Kritisk
Progressionsfri overlevelse (PFS-rate ved 2 år), follow up: median 13,8 måneder												

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	**Studie-design**	**Risiko for bias**	**Inkonsistens**	**Indirekthed**	**Unøjagtighed**	**Andre overvejelser**	**Niraparib**	**Placebo**	**Relativ (95 % CI)**	**Absolut (95 % CI)**	**Sikkerhed**	**Vigtighed**
1	RCT	Ikke alvorlig	Alvorlig[a]	Ikke alvorlig	Alvorlig[d]	Ingen	32/95	33/55	HR = 0,50 (0,31;0,83)	26,3 %-point	⨁⨁◯◯ LAV	Kritisk
Uønskede hændelser, Behandlingsophør (%-point)												
1	RCT	Ikke alvorlig	Alvorlig [a]	Alvorlig [f]	Ikke alvorlig	Ingen	58/484	5/244	RR = 4,9 (2,1 ; 11,1)	9,5 %-point (6,0 ; 13,0)	⨁⨁◯◯ LAV	Kritisk
Uønskede hændelser, Andel der oplever grad 3-4-bivirkninger (%-point)												
1	RCT	Ikke alvorlig	Alvorlig [a]	Ikke alvorlig [g]	Ikke alvorlig	Ingen	316/484	16/244	RR = 9,96 (6,2 ; 16,1)	58,7 %-point (53,5 ; 64,0)	⨁⨁⨁◯ MODERAT	Kritisk
Livskvalitet, Andel der oplever signifikant forværring (%-point)												
1	RCT	Ikke alvorlig	Alvorlig [a]	Alvorlig [h]	Alvorlig [i]		Ikke angivet				⨁◯◯◯ MEGET LAV	Vigtigt
Kvalitet af den samlede evidens	MEGET LAV [j]											

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

[b] Der er nedgraderet ét niveaue, da data stammer fra en forkert subpopulation med bedre prognose (BRCA-mutation).

[c] Der er nedgraderet to niveauer, da konfidensintervallet er meget bredt og indeholder både positive og negative konklusioner.

[d] Der er nedgraderet ét niveau, da Optimal information size-kriteriet ikke er opfyldt (evt. da konfidensintervallet overlapper to kategoriseringer).

[e] Der er nedgraderet to niveauer, da data stammer fra en forkert subpopulation med bedre prognose (BRCA-mutation) og for et andet endemål (OS-rate ved 2 år).

[f] Der er nedgraderet ét niveau, da effektmålet er angivet som behandlingsophør grundet uønskede hændelser og ikke grundet bivirkninger, som efterspurgt i protokollen.

[g] Der er ikke nedgraderet, selvom analysen er foretaget i hele ITT-populationen i stedet for kun populationen uden BRCA-mutation, HRD-positiv. Dette skyldes, at den indirekte population ikke skønnes at påvirke effektestimatet.

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

[i] Der er nedgraderet ét niveau, da der ikke er angivet præcise datapunkter og usikkerhedsestimater for livskvalitetsdata.

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

Klinisk spørgsmål 5 – niraparib sammenlignet med placebo til behandling af kræft i æggestokkene ved patienter uden BRCA-mutation, HRD-negativ.

Tabel 11-5. GRADE-evidensprofil for klinisk spørgsmål 5

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Niraparib	Placebo	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
Overlevelse (median), follow up: median 13,8 måneder												
1	RCT	Ikke alvorlig	Alvorlig[a]	Ikke alvorlig	Alvorlig [b]	Ingen	--/169	--/80	HR = 0,51 (0,27;0,97)	Ikke nået	⨁⨁◯◯ LAV	Kritisk
Overlevelse (OS-rate ved 5 år), follow up: median 13,8 måneder												
1	RCT	Ikke alvorlig	Alvorlig[a]	Alvorlig [c]	Alvorlig [b]	Ingen	--/169	--/80	HR = 0,51 (0,27;0,97)	22 %-point	⨁◯◯◯ MEGET LAV	Kritisk
Progressionsfri overlevelse (median), follow up: median 13,8 måneder												
1	RCT	Ikke alvorlig	Alvorlig[a]	Ikke alvorlig	Alvorlig [d]	Ingen	111/169	56/80	HR = 0,68 (0,49 ; 0,94)	2,7 måneder	⨁⨁◯◯ LAV	Kritisk
Progressionsfri overlevelse (PFS-rate ved 2 år), follow up: median 13,8 måneder												
1	RCT	Ikke alvorlig	Alvorlig[a]	Ikke alvorlig	Alvorlig[d]	Ingen	111/169	56/80	HR = 0,68 (0,49 ; 0,94)	4,3 %-point	⨁⨁◯◯ LAV	Kritisk

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Niraparib	Placebo	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
Uønskede hændelser, Behandlingsophør(%-point)												
1	RCT	Ikke alvorlig	Alvorlig [a]	Alvorlig [e]	Ikke alvorlig	Ingen	58/484	5/244	RR = 4,9 (2,1 ; 11,1)	9,5 %-point (6,0 ; 13,0)	⨁⨁◯◯ LAV	Kritisk
Uønskede hændelser, Andel der oplever grad 3-4-bivirkninger (%-point)												
1	RCT	Ikke alvorlig	Alvorlig [a]	Ikke alvorlig [f]	Ikke alvorlig	Ingen	316/484	16/244	RR = 9,96 (6,2 ; 16,1)	58,7 %-point (53,5 ; 64,0)	⨁⨁⨁◯ MODERAT	Kritisk
Livskvalitet, Andel der oplever signifikant forværring (%-point)												
1	RCT	Ikke alvorlig	Alvorlig [a]	Alvorlig [g]	Alvorlig [h]		Ikke angivet				⨁◯◯◯ MEGET LAV	Vigtigt
Kvalitet af den samlede evidens MEGET LAV [i]												

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

[b] Der er nedgraderet ét niveau, da konfidensintervallet overlapper flere kategoriseringer.

[c] Der er nedgraderet ét niveau, da der er anvendt et andet endemål (OS-rate ved 2 år).

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

[e] Der er nedgraderet ét niveau, da effektmålet er angivet som behandlingsophør grundet uønskede hændelser og ikke grundet bivirkninger, som efterspurgt i protokollen.

[f] Der er ikke nedgraderet, selvom analysen er foretaget i hele ITT-populationen i stedet for kun populationen uden BRCA-mutation, HRD-positiv. Dette skyldes, at den indirekte population ikke skønnes at påvirke effektestimatet.

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

[h] Der er nedgraderet ét niveau, da der ikke er angivet præcise datapunkter og usikkerhedsestimater for livskvalitetsdata.

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

Dissens vedrørende overførsel af resultater fra patientpopulationen i PRIMA-studiet til også at skulle gælde for patientpopulationen i NOVA-studiet samt konklusion på klinisk spørgsmål 5 i PRIMA-studiet

Dissens bedes vedlægges vurderingsrapporten

Patientpopulationen i PRIMA-studiet og NOVA-studiet var meget forskellig. Patientpopulationen i PRIMA-studiet bestod af inoperable patienter eller patienter, der havde fået NACT, eller som havde resttumor efter operation på < 1 cm. Patienter, som kunne opereres straks efter diagnosen og med > 1 cm tumor efter operation, var ikke inkluderet i studiet. Det vil sige studiet indeholdt patienter med den værst tænkeligt prognose. Populationen i NOVA-studiet var patienter med tilbagefald af æggestokkræft. Ca. 50 % havde tilbagefald i 2. linje. Resten havde tilbagefald i senere linjer. Man sammenligner nu de to populationer, men kun meget få patienter fra populationen i PRIMA-studiet vil overhovedet nå til carboplatin-behandling i 2. linje, og da slet ikke i efterfølgende behandlingslinjer. Derfor er det efter patienternes mening forkert, at overføre resultater fra patientpopulationen i PRIMA-studiet til også at gælde for patienter med tilbagefald i efterfølgende behandlinger.

Spørgsmål 4 og 5 i vurderingsrapporten indeholder patienter, der ikke kandiderer til behandling med bevacizumab (patienter med mindre end 1 cm resttumor), men da denne patientgruppe ikke findes i PRIMA-studiet, anvender man OS og PFS fra kliniske spørgsmål 2 og 3 på denne population, og overfører så disse resultater direkte til patientpopulationen i NOVA-studiet.

Konklusion på klinisk spørgsmål 5 i PRIMA-studiet

PFS for HRD-negative i PRIMA-studiet var 2,7 måneder (angivet median PSF = 3 måneder) – ifølge klinisk spørgsmål 5 – hvilket vurderes til en samlet konklusion på ingen merværdi sammenlignet med placebo (PFS overført fra kliniske spørgsmål 3). Dette er uforståeligt, da kommentarer under konklusionen også er, at "for både OS og PFS indikerer de relative værdier dog en merværdi af ukendt størrelse". Patienterne anmoder om at få den samlede konklusion ændret til merværdi 'kan ikke kategoriseres', da man jo ikke har de nødvendige data.

Patientpopulationen HRD-negativ i NOVA-studiet

PFS for HRD-negative i NOVA-studiet var 3,1 måneder (angivet median PFS = 3 måneder)

I NOVA-studiet var placebo 3,8 måneder + de 3,1 måneder på niraparib = 6,9 måneder – nok til fornyet behandling med carboplatin, men fordi man overfører resultatet af PRIMA-studiet med en helt anden patientpopulation, får patienter med tilbagefald ikke mulighed for vedligeholdelsesbehandling med PARP-hæmmeren niraparib, selv om median PFS er opfyldt.

Patienterne skal anmode om, at Rådet ved vurderingen tager højde for ovennævnte, og giver de få overlevende patienter med tilbagefald, som befinder sig i 2. linje og efterfølgende linjer, mulighed for vedligeholdelsesbehandling med PARP-hæmmeren niraparib, så disse patienter ikke er nødt til at have styrke og penge nok til at søge den livsforlængende behandling i et af Danmarks nabolande, hvor behandlingen længe har været godkendt til hele patientgruppen med high grade serøs æggestokkræft – uanset mutationsstatus.
Danmark sparer penge til HRD-test i USA. Patienterne scannes efter 3 måneders vedligeholdelsesbehandling, som først påbegyndes 8-12 uger efter behandling med carboplatin; så på scanningstidspunktet ved man, hvem behandlingen virker på.
Mvh
Birthe Lemley og Dorte Blou

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12. maj 2021

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Kære Birthe Lemley og Dorte Blou

Rådet fik forelagt jeres dissens på rådsmødet den 28. april 2021, hvor Rådet behandlede sagen vedrørende niraparib til vedligeholdelsesbehandling af kræft i æggestokkene.

I er uenige i dele af vurderingsrapporten, specifikt:

- vurderingen af, at niraparib ikke har en dokumenteret merværdi sammenlignet med placebo for HRD-negative patienter med BRCA-mutation (klinisk spørgsmål 5), samt
- vurderingen af, at effekten af niraparib ved 2. linjebehandling er sammenlignelig med effekten ved 1. linjebehandling, når patienterne inddeles efter HRD-status.

I stiller også spørgsmålstegn ved validiteten af HRD-testen, som er baggrunden for opdelingen af patienterne i subgrupper.

Dissensen blev drøftet af Rådets medlemmer. Fagudvalgsformanden deltog i Rådets drøftelse og redegjorde blandt andet for de studier, der ligger til grund for vurderingsrapportens konklusioner samt for fagudvalgets metodiske tilgang, herunder det valg at opdele patienter uden BRCA-mutation efter HRD-status.

Rådet drøftede også HRD-testens sensitivitet og lagde vægt på, at de studier der er til grund for vurderingen, baserer sig på en opdeling af patienterne efter samme test.

Et samlet Råd var enige i konklusionerne i vurderingsrapporten. Rådet har lagt vægt på, at den påviste progressionsfrie overlevelse hos HRD-negative patienter uden BRCA-mutation, som behandles med niraparib, kun er 2,7 måneder. Dertil får patienterne bivirkninger, som i nogle tilfælde kan være alvorlige. Til sammenligning er den progressionsfrie overlevelse i de andre subgrupper omkring 11 måneder, når de får samme behandling.

Afslutningsvis kan vi også fortælle, at kun data fra NOVA-studiet er brugt i vurderingen af effekten ved 2. linjebehandling. Vi har ikke overført data fra PRIMA-studiet.

Vi takker jer for jeres engagement i fagudvalget og jeres grundige arbejde i forbindelse med vurderingsrapporten for niraparib, som har bidraget til en nuanceret diskussion af sagen.

Med venlig hilsen

Steen Werner Hansen og Jørgen Schøler Kristensen

Formænd for Medicinrådet

Application for the assessment of niraparib (Zejula®) for maintenance treatment of adult patients with advanced high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy

Contents

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Statistical and medical writing assistance for this application was provided by Larix A/S, Lyskær 8b, DK-2730 Herlev	

Overview of the pharmaceutical	
Proprietary name	Zejula®
Generic name	niraparib
Marketing authorization holder in Denmark	GlaxoSmithKline (Ireland) Limited
ATC code	L01XX54
Pharmacotherapeutic group	Other antineoplastic agents
Active substance	Niraparib (tosylate monohydrate)
Pharmaceutical form	Hard capsules
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.

Overview of the pharmaceutical	
Dosage regimen	The recommended starting dose of niraparib 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 niraparib is 300 mg (three 100-mg capsules), taken once daily.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Niraparib 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.
Other approved therapeutic indications	Niraparib is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	No
Packaging – types, sizes/number of units, and concentrations	Aclar/PVC/aluminium foil perforated unit dose blisters in cartons of 84 × 1 and 56 × 1 hard capsules.
Orphan drug designation	Yes

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2. Abbreviations and definition of terms

AE	adverse events
ADR	adverse drug reaction
AUC	area under the curve
BICR	blinded, independent central review
BRCA	BReast CAncer
BRCAm	BRCA mutated
BRCAwt	BRCA wildtype
CA125	cancer antigen 125
CI	confidence interval
CNS	central nervous system
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DNA	deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
ENGOT	The European Network for Gynaecological Oncological Trial groups is a research network of the European Society of Gynaecological Oncology
EORTC	The European Organisation for Research and Treatment of Cancer
EORTC-QLQ-C30	EORTC Quality of Life Questionnaire; a validated, 30-item, health-related quality-of-life instrument developed to assess health outcomes from a wide variety of interventions on a common scale.
EORTC-QLQ-OV28	The EORTC Quality of Life Questionnaire Ovarian Cancer module; a scale which assesses ovarian cancer patients' abdominal/gastrointestinal symptoms, other chemotherapy side effects, hormonal/menopausal symptoms, body image, attitude to disease/treatment and sexual functioning.
EPAR	European public assessment report
EQ-5D-5L	European Quality of Life 5-dimension, 5-level questionnaire; a generic quality of life scale which measures the patient's perceived health state in the following 5 domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each domain has 5 possible levels: no problems (level 1), slight problems (level 2), moderate problems (level 3), severe problems (level 4), and extreme problems (level 5).
FACT-O	Functional Assessment of Cancer Therapy - Ovarian Cancer
FACT-O TOI	Functional Assessment of Cancer Therapy - Ovarian Trial Outcome Index
FIGO	International Federation of Gynecology and Obstetrics
FOSI	Functional Assessment of Cancer Therapy–Ovarian Symptom Index; a validated 8-item measure of symptom response to treatment for ovarian cancer based on a subset of questions from the Functional Assessment of Cancer Therapy - Ovarian Cancer questionnaire. For each question, patients responded to their symptom experience over the previous 7 days using a 5-point Likert scale of 'not at all' (0) to 'very much' (4). The FOSI score range is 0 (severely symptomatic) to 32 (asymptomatic).
GI	gastrointestinal
GOG	Gynecologic Oncology Group
HR	hazard ratio
HRD	homologous recombination deficient
HRP	homologous recombination proficient
HRQoL	health-related quality of life;
ITC	indirect treatment comparison
ITT	intention-to-treat

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IV	intravenous
MCID	minimal clinically important difference
MRI	magnetic resonance imaging
NACT	neoadjuvant chemotherapy
NE	not estimable
NR	not reported
NVRD	no visible residual disease
OS	overall survival
PARP	poly(ADP ribose) polymerase
PDX	patient-derived xenograft tumours
PFS	progression-free survival
PFS2	progression-free survival 2. The time from randomisation to the earlier date of assessment of progression on the next anticancer therapy following trial treatment or death from any cause
PRO	patient-reported outcome(s)
PVC	polyvinyl chloride
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumours
RR	relative risk
SPC	summary of product characteristics
TOI	Trial Outcome Index

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3. Summary

Niraparib is a poly(ADP ribose) polymerase (PARP) inhibitor indicated as monotherapy for the maintenance treatment of adult patients with advanced epithelial (International Federation of Gynecology and Obstetrics [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. Niraparib is administered as two or three 100-mg capsules taken once daily.

Systematic literature searches for this application were performed in MEDLINE via PubMed and CENTRAL via Cochrane Library on 27-Nov-2020 and resulted in 8 publications covering 4 phase 3 clinical trials: PRIMA (niraparib), SOLO1 (olaparib), GOG-0218 and ICON7 (both bevacizumab). All trials were randomised, controlled, parallel-group trials in patients with newly diagnosed ovarian, fallopian tube or primary peritoneal cancer.

Patients in PRIMA were enrolled regardless of BReast CAncer (BRCA) mutations and homologous recombination status, while all patients in SOLO1 had a BRCA mutation (BRCAm). BRCA or homologous recombination status were unknown in the bevacizumab trials. In addition, the trial populations in the SOLO1, GOG-0218 and ICON7 trials generally had a better prognosis than the PRIMA trial population due to differences in important prognostic factors. The PRIMA population had a more severe disease stage, and a larger proportion of patients received neoadjuvant chemotherapy (NACT) and/or had visible residual disease. Niraparib and olaparib treatments were initiated after response to platinum-based chemotherapy, while bevacizumab treatment was initiated with chemotherapy. Consequently, due to significant differences, only narrative comparisons were performed between niraparib and olaparib, while neither indirect nor narrative comparisons of niraparib versus bevacizumab were considered meaningful.

The protocol for this application included 5 clinical questions related to different (sub)populations and comparators. The questions and main findings are briefly summarised below.

1. **What is the added clinical value of niraparib compared with olaparib as maintenance treatment for newly diagnosed patients with advanced BRCA-mutated high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response following platinum-based chemotherapy (complete or partial response)?**
   This clinical question concerned niraparib in stage III-IV with BRCAm. In the homologous recombination deficient (HRD) population of PRIMA (of which 60% had BRCAm), the hazard ratio for death was 0.61 (0.27; 1.39). In the BRCAm subgroup, the hazard ratio for progression-free survival (PFS) was 0.40 (0.27; 0.62), and the absolute difference in PFS rate (by blinded independent central review) between niraparib and placebo was 24.1 (10.38; 37.82)%-points. The survival data are immature in both trials. Even though the PRIMA population had a worse prognosis than the SOLO1 population, the hazard ratios for PFS within trials were relatively similar.

2. **What is the added clinical value of niraparib compared with bevacizumab as maintenance treatment for newly diagnosed patients with advanced not BRCA-mutated, HRD, high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response following platinum-based chemotherapy (complete or partial response) and are candidates for bevacizumab?**
   This clinical question concerned niraparib in a stage III-IV, BRCA wildtype (BRCAwt) and HRD subgroup. In this subgroup, a clinically relevant absolute difference between niraparib and placebo in median PFS of 11.4 months was shown; confidence intervals could not be estimated. The hazard ratio for PFS in the niraparib group was 0.50 (0.31; 0.83), P=0.006. The PFS rate showed a clinically relevant and statistically significant benefit of niraparib over placebo with an absolute difference of 26.3 (10.25; 42.38)%-points, P=0.0017. Overall survival was not reported for this specific subgroup. Generally, bevacizumab resulted in small benefits in median PFS and no survival benefit.

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3. **What is the added clinical value of niraparib compared with bevacizumab as maintenance treatment for newly diagnosed patients with advanced not BRCA mutated, HRP, high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response following platinum-based chemotherapy (complete or partial response) and are candidates for bevacizumab?**
   This clinical question concerned niraparib in a stage III-IV, BRCAwt and homologous recombination proficient (HRP) subgroup. In this subgroup, niraparib resulted in a clinically relevant and statistically significant benefit over placebo in survival rate with an absolute difference of 22.3 (10.0; 34.6)%-points, P=0.0002. Furthermore, a small but statistically significant benefit in median PFS was shown in this subgroup with an absolute difference in PFS of 2.7 (0.2; 5.2) months, P=0.0328.

4. **What is the added clinical value of niraparib compared with placebo as maintenance treatment for newly diagnosed patients with advanced not BRCA-mutated, HRD, high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response following platinum-based chemotherapy (complete or partial response) and who are not candidates for bevacizumab?**
   This clinical question concerned niraparib in a stage III, BRCAwt, HRD population with <1 cm residual tumour after surgery (i.e., not candidates for bevacizumab). The results for the BRCAwt, HRD population in question 2 were used as an alternative, since the efficacy estimates from the PRIMA trial are expected to be conservative estimates for the efficacy in a population with less severe disease as the PRIMA trial did not include stage III patients with NVRD after primary debulking surgery. This was supported by a new analysis of real-world data showing that a simulated cohort with stage III disease and no visible residual disease (NVRD) had significantly longer PFS with a hazard ratio of 0.43 (0.32; 0.58) and significantly longer overall survival with a hazard ratio of 0.43 (0.32; 0.60) versus a simulated PRIMA cohort.

5. **What is the added clinical value of niraparib compared with placebo as maintenance treatment for newly diagnosed patients with advanced not BRCA-mutated, HRP, high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response following platinum-based chemotherapy (complete or partial response) and who are not candidates for bevacizumab?**
   This clinical question concerned niraparib in a stage III, BRCAwt, HRP population with <1 cm residual tumour after surgery (i.e., not candidates for bevacizumab). The results for the BRCAwt, HRP population in question 3 were used as an alternative with the same rationale as described above.

Class effects of PARP inhibitors are well-known; these include myelosuppression. However, the implementation of an individualised starting dose of niraparib and the possibility to reduce or interrupt the treatment dose helps to mitigate and manage the experienced adverse events (AEs) and adverse drug reactions. In the PRIMA trial, the absolute differences between niraparib and placebo in proportion of patients discontinued due to AE was 9.5 (6.04; 13.01)%-points, and in proportion of patients with grade 3–4 adverse drug reactions 58.7 (53.48; 63.99)%-points. This is as expected for a trial comparing active treatment with placebo.

Based on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 and -OV28 tools, niraparib treatment for up to approximately 30 months had a slightly positive effect or no effect on the overall health-related quality of life (HRQoL) and specific symptoms.

The preliminary results on progression-free survival 2 (PFS2) favour niraparib maintenance treatment with point estimates <1 in all population groups analysed (HRD, HRP and overall population) which support the clinical benefit of niraparib.

In conclusion, niraparib is an effective and relevant first-line treatment in a broad population of newly diagnosed patients, regardless of biomarker status, with advanced, high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response following platinum-based chemotherapy. An individualised dosing regimen for niraparib has been shown to have a positive impact on safety outcomes.

4. Literature search

4.1 Databases and search strategy

Systematic literature searches were performed in MEDLINE via PubMed and CENTRAL via Cochrane Library on 27-Nov-2020 according to the search strategies provided by the Medicines Council [1]. No language or date limits were applied. The complete search strategies are provided in Figure 8 and Figure 9, respectively.

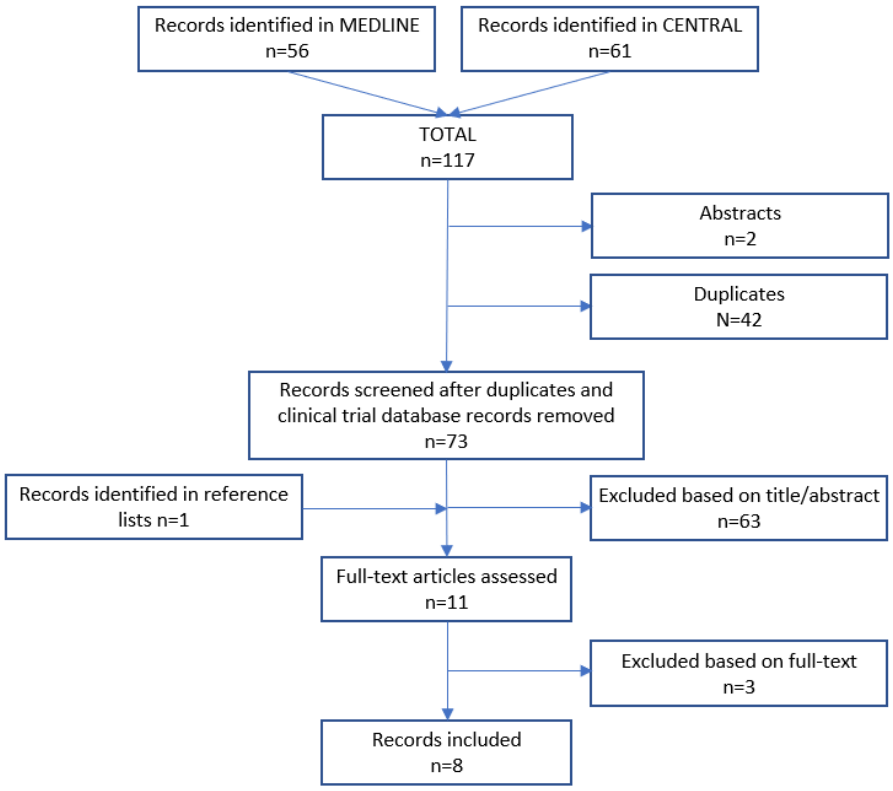
A total of 117 records were retrieved, 56 in MEDLINE and 61 in CENTRAL. After removal of duplicates and abstracts/posters, 73 records were left for screening. The records were screened and assessed by 2 researchers independently based on the PICOs (patients, intervention, comparator, outcomes) and inclusion and exclusion criteria as described in the protocol [1]. The inclusion and exclusion criteria are summarised in Table A1a.

Based on screening at the title and abstract level, 63 references were excluded. During the selection process, 1 additional reference was found based on the reference lists of the publications assessed. Full-text screening was performed for 11 publications, of which 3 were excluded based on full-text read. These are included in the list of excluded references in Table A1b. Any disagreements during the selection process were resolved by discussion between the 2 reviewers. A PRISMA flow diagram of the selection process is provided in Figure 1.

The 8 publications included covered 4 clinical trials: 1 publication of 1 niraparib trial, 1 publication of 1 olaparib trial, and 3 publications of each of 2 bevacizumab trials (see Table 1).

After selection of relevant articles, data were extracted into a project-specific Microsoft Excel table by one researcher and a second researcher independently checked the data extraction for accuracy and completeness. Any disagreements were resolved by discussion between the 2 reviewers.

Figure 1 PRISMA flow chart for literature search



4.2 Relevant studies

Table 1 Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question[1]
Niraparib trials				
Niraparib in patients with newly diagnosed advanced ovarian cancer. González-Martín A et al; for the PRIMA/ENGOT-OV26/GOG-3012 Investigators. N Engl J Med. 2019 [2]	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/ENGOT-OV26/GOG-3012). **PRIMA**	NCT02655016	Start of trial Jul-2016 Primary completion date[2] 17-May-2019 Estimated trial completion Mar-2024	1, 2, 3, 4, 5
Olaparib trials				
Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. Moore K, et al. N Engl J Med. 2018 [3]	A phase III, randomised, double blind, placebo controlled, multicentre study of olaparib maintenance monotherapy in patients with BRCA mutated advanced (FIGO stage III-IV) ovarian cancer following first line platinum-based chemotherapy. **SOLO1**	NCT01844986	Start of trial Aug-2013 Primary completion date[2] May-2018 Estimated trial completion Jan-2024	1

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question[1]
Bevacizumab trials				
Incorporation of bevacizumab in the primary treatment of ovarian cancer. Burger RA et al; for the Gynecologic Oncology Group. N Engl J Med. 2011 [4] Patient reported outcomes of a randomized, placebo-controlled trial of bevacizumab in the front-line treatment of ovarian cancer: A Gynecologic Oncology Group Study. Monk BJ et al. Gynecol Oncol. 2013 [5] Final Overall Survival of a Randomized Trial of Bevacizumab for Primary Treatment of Ovarian Cancer. Tewari KS, et al. J Clin Oncol. 2019 [6]	A phase III trial of carboplatin and paclitaxel plus placebo versus carboplatin and paclitaxel plus concurrent bevacizumab (NSC # 704865) followed by placebo, versus carboplatin and paclitaxel plus concurrent and extended bevacizumab, in women with newly diagnosed, previously untreated, stage III or IV epithelial ovarian, primary peritoneal or fallopian tube cancer. **GOG-0218**	NCT00262847	Start of trial Sep-2005 Primary completion date[2] Nov-2010 Trial completion Apr-2015	2, 3
A phase 3 trial of bevacizumab in ovarian cancer. Perren TJ, et al. N Engl J Med. 2011 [7] 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, et al. Lancet Oncol. 2015 [8] Standard chemotherapy with or without bevacizumab in advanced ovarian cancer: quality-of-life outcomes from the International Collaboration on Ovarian Neoplasms (ICON7) phase 3 randomised trial. Stark D, et al. Lancet Oncol. 2013 [9]	A randomised, two-arm, multi-centre Gynaecologic Cancer InterGroup trial of adding bevacizumab to standard chemotherapy (carboplatin and paclitaxel) in patients with epithelial ovarian cancer. **ICON7**	NCT00483782	Trial start Apr-2006 Trial end date Mar-2013	2, 3

[1] Multiple clinical questions are defined in the protocol

[2] Final collection of data for primary outcome measure

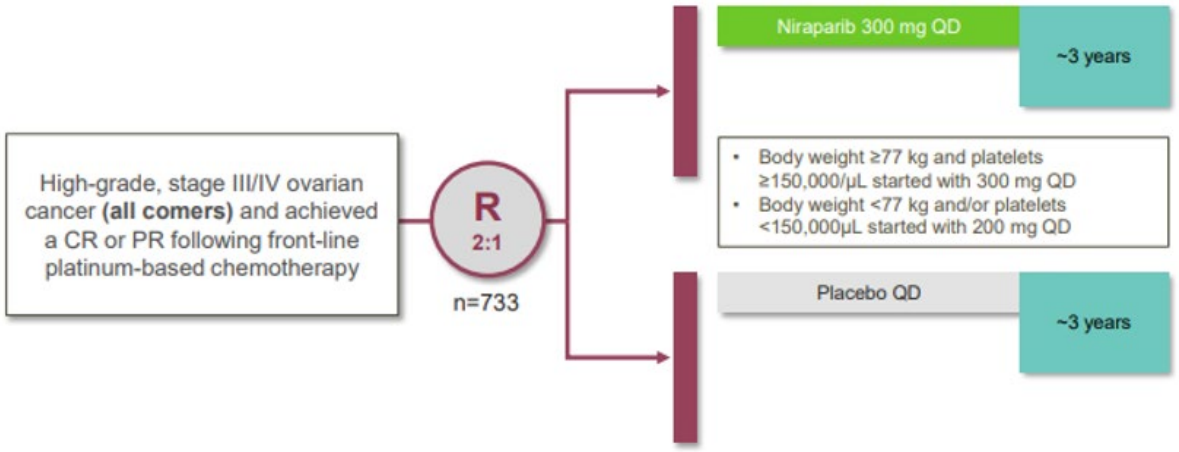
4.3 Main characteristics of included studies

The main characteristics of the included studies are summarised in the tables in Section 10.2 and described briefly below.

4.3.1 PRIMA trial (niraparib)

PRIMA was a randomised, double-blind, placebo-controlled, parallel-group, phase 3 trial conducted in 20 countries, including Denmark (Figure 2). The trial included patients with newly diagnosed, histologically confirmed, advanced (the International Federation of Gynecology and Obstetrics (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) with clinical complete or partial response. All stage IV patients were eligible, irrespective of residual disease, after primary or interval debulking surgery. Stage III patients were required to have visible residual disease after primary surgery. Patients with inoperable stage III and IV disease were eligible.

Figure 2 PRIMA trial design



Source: Figure developed based on Gonzalez-Martin A, et al. N Engl J Med 2019 [2].

Abbreviations: CR, complete response; PR, partial response; QD, once daily; R, ratio.

Within 12 weeks after completion of the last dose of platinum-based chemotherapy, the patients were randomly assigned in a 2:1 ratio to receive oral niraparib or placebo once daily in 28-day cycles for 36 months or until the objective identification of disease progression on imaging, provided that the patient was receiving benefit and did not meet any other criteria for discontinuation, as defined in the protocol. Patients receiving placebo were not allowed to cross over to receive niraparib treatment during the trial.

Tumour assessment was performed via a computed tomography (CT) or magnetic resonance imaging (MRI) scan at screening and then every 12 weeks until treatment discontinuation. Blinded, independent central review (BICR) was used to define the date of disease progression according to RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1, and an identical schedule of assessments was used for the two study groups. Clinical progression was reviewed if an increased cancer antigen 125 (CA125) level was accompanied by histologic proof or clinical symptoms, as specified in the protocol.

Homologous-recombination deficiency (HRD) was defined as the presence of a Breast Cancer (BRCA) deleterious mutation and/or a test result indicating other genomic abnormalities.

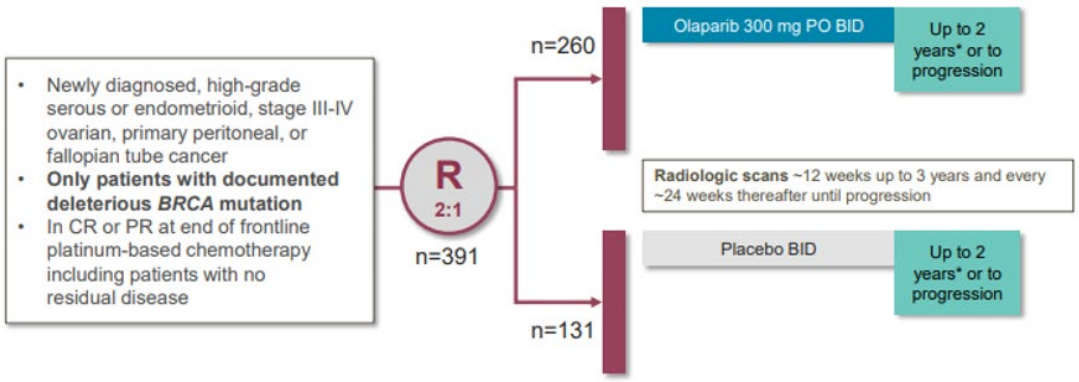
Patient-reported outcomes (PRO) were collected regularly from the screening visit until 24 weeks after the last dose of niraparib or placebo. Adverse events (AEs), laboratory testing, measurement of vital signs and physical examinations were monitored throughout the treatment period.

Additional details of the trial and baseline characteristics of the enrolled patients are provided in Table A2a.

4.3.2 SOLO1 trial (olaparib)

SOLO1 was a randomised, double-blind, placebo-controlled, phase 3 trial conducted in 15 countries not including Denmark (Figure 3). The trial included 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 had completed first-line platinum-based chemotherapy (intravenous (IV) or intraperitoneal) with clinical complete or partial response, in the opinion of the investigator, and no clinical evidence of disease progression on the post treatment scan or rising CA125 level. Stage III patients had to have one attempt at optimal debulking surgery (upfront or interval debulking). Stage IV patients had to have either a biopsy and/or upfront or interval debulking surgery.

Figure 3 SOLO1 trial design



Source: Figure developed based on Moore K, et al. N Engl J Med 2018 [3].

Abbreviations: BID, twice daily; BRCA, breast cancer gene; CR, complete response; PO, to be taken orally; PR, partial response; R, ratio.

After completion of platinum-based chemotherapy, patients were randomly assigned, in a 2:1 ratio, to receive olaparib or placebo. Treatment continued up to 3 years or until objective disease progression on imaging (according to modified RECIST version 1.1), provided that the patient was having a benefit and did not meet any discontinuation criteria. Patients with no evidence of disease terminated treatment after 2 years, while those still in partial response after 2 years were permitted to continue treatment in a blinded manner. Crossover between trial groups was not specified in the protocol. After discontinuation of the trial intervention, patients could receive treatments at the investigators' discretion.

Progression free survival (PFS) was defined as the time from randomisation to investigator-assessed objective disease progression on imaging or death from any cause (primary endpoint). Objective disease progression on imaging was assessed using CT or MRI scans performed at baseline and every 12 weeks for up to 3 years and then every 24 weeks until objective disease progression. A sensitivity analysis of PFS as assessed by BICR was performed.

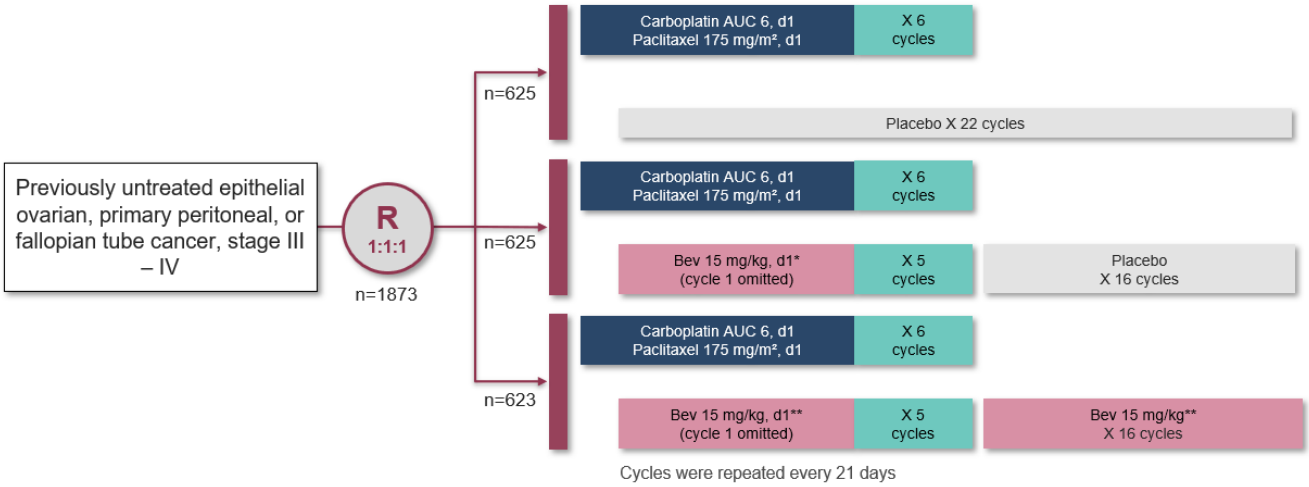
PROs were collected regularly during the entire trial and until the time of data cut off for the primary efficacy analysis. Safety parameters, including AEs and laboratory assessments were monitored throughout the treatment period.

Additional details of the trial and baseline characteristics of the enrolled patients are provided in Table A2b.

4.3.3 GOG-0218 trial (bevacizumab)

GOG-0218 was a double-blind, placebo-controlled phase 3 trial investigating the integration of bevacizumab into front-line ovarian cancer therapy (Figure 4). The trial was conducted in 4 countries, not including Denmark. The trial included patients with previously untreated, stage III or IV epithelial ovarian, primary peritoneal, or fallopian-tube cancer histologically confirmed by the Gynecologic Oncology Group (GOG) Pathology Committee after standard abdominal surgery with maximal debulking effort within 12 weeks before study entry. Patients with stage III disease and no residual lesions >1 cm in maximal diameter were initially excluded but were permitted after a protocol modification.

Figure 4 GOG-0218 trial design



Source: Figure developed based on Burger RA, et al. N Engl J Med 2011 [4]. * Bev initiation. ** Bev throughout.

Abbreviations: AUC, area under the curve; Bev, bevacizumab; R, ratio.

Patients were randomised in a 1:1:1 ratio. Each of the 3 trial regimens comprised 22 3-week cycles with IV infusions on day 1, with the first 6 cycles consisting of standard chemotherapy (carboplatin and paclitaxel) (Figure 4). Bevacizumab (15 mg per kilogram of body weight) or placebo was initiated at cycle 2, rather than cycle 1, to reduce the risk of wound-healing complications. Treatment was discontinued at the onset of disease progression, unacceptable toxic effects, completion of all 22 cycles, or withdrawal, whichever came first.

Disease was assessed before cycle 1 by means of CT or MRI scan of at least the abdomen and pelvis, measurement of the CA125 level and physical examination. In patients without progression, imaging was repeated after treatment cycles 3, 6, 10, 14, 18 and 22 (i.e., every 12 weeks). After completing study treatment, disease assessments were repeated every 3 months for 2 years, then every 6 months for 3 years, and then annually.

The primary endpoint was initially specified as overall survival (OS) but was changed to PFS during the trial. PFS and OS were calculated from the date of enrolment. PFS was considered to have ended at the time of cancer progression as shown on imaging, an increase in the CA125 level according to Gynecologic Cancer InterGroup criteria, global deterioration of health, or death from any cause.

Quality of life (QoL) was assessed by use of the Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy–Ovary (FACT-O) survey regularly throughout the trial.

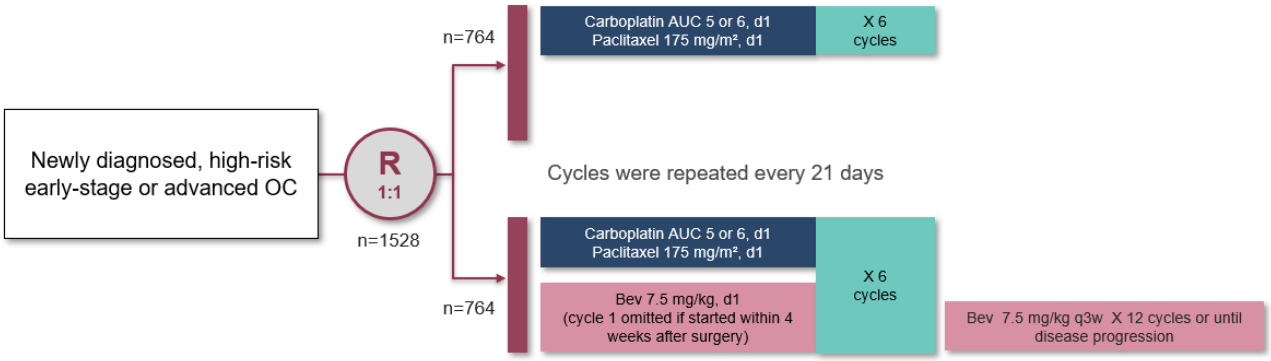
Safety was monitored during each treatment cycle.

Additional details of the trial and baseline characteristics of the enrolled patients are provided in Table A2c.

4.3.4 ICON7 trial (bevacizumab)

ICON7 was a multicentre, open-label, randomised, controlled phase 3 study (Figure 5). The trial included patients with histologically confirmed, high-risk, early-stage disease (FIGO stage I or IIA and clear-call or grade 3 tumours) or advanced (FIGO stage IIB to IV) epithelial ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer (based on local histopathological findings). Patients were required to have undergone initial surgery (e.g., debulking cytoreductive surgery or a biopsy if the patient had stage IV disease) within the past 6 weeks.

Figure 5 ICON7 trial design



Source: Figure developed based on Perren TJ, et al. N Engl J Med 2011 [7].

Abbreviations: AUC, area under the curve; Bev, bevacizumab; R, ratio.

Patients were randomised in a 1:1 ratio to 6 standard chemotherapy (IV carboplatin and paclitaxel) 3-week cycles or to the same chemotherapy regimen plus bevacizumab IV every 3 weeks (bevacizumab 7.5 mg per kilogram of body weight), given concurrently and continued for 12 additional 3-weekly cycles of maintenance therapy or until progression of disease. Bevacizumab was omitted at cycle 1 to avoid delayed wound healing if chemotherapy was started within 4 weeks of surgery.

CT or MRI scans were performed at baseline, after treatment cycles 3 and 6 (i.e., weeks 9 and 18), at 9 and 12 months after randomisation, and following treatment every 6 months until the end of year 3 and then as clinically indicated until disease progression. All tumour assessments were reviewed by the principal investigator who was unaware of treatment assignments. Clinical assessments and CA125 measurements were performed before each cycle of chemotherapy, then every 6 weeks in year 1, every 3 months during years 2 and 3, every 6 months during years 4 and 5, and then yearly. Assessments were performed at the same time points in the two treatment groups.

Disease progression was defined according to RECIST based on radiologic, clinical, or symptomatic indicators of progression and did not include isolated asymptomatic progression based on CA125 levels. PFS was calculated from the date of randomisation to the date of the first CA125-based progression or first RECIST-based progression, whichever occurred first. OS was calculated from the date of randomisation to the date of death from any cause.

QoL was assessed by use of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 and OV28 questionnaires regularly during the entire trial.

Additional details of the trial and baseline characteristics of the enrolled patients are provided in Table A2d.

4.3.5 Comparability of data across included trials

In the protocol for this application, comparisons between niraparib and olaparib (clinical question 1), between niraparib and bevacizumab (clinical questions 2 and 3) and between niraparib and placebo (clinical questions 4 and 5) in different (sub)populations have been requested.

The feasibility of indirect treatment comparisons (ITCs) between these 3 first-line treatments for ovarian cancer has previously been investigated, and it was concluded that several confounding factors preclude an objective systematic comparison between the randomised controlled trials included in this application [10]. This feasibility analysis found that neither a network meta-analysis nor an ITC would meet current guidelines for objective comparative clinical effectiveness analyses, due to the uncontrolled heterogeneity to which they are subject, as outlined below. It was concluded that such ITCs should not be considered appropriate evidence for use in clinical decision making or reimbursement decisions.

Due to the heterogeneity in the clinical trial designs and populations, summarised below, a reliable evaluation of the comparative efficacy of niraparib versus olaparib and niraparib versus bevacizumab using ITCs was deemed invalid:

a. The PRIMA trial enrolled patients with a high risk of disease recurrence and as such the study population differed markedly from the population enrolled in the other first-line maintenance trials.
b. There were significant differences between the studies in the primary endpoints, biomarker subgroups, the percentage of patients with NVRD/no evidence of disease and the frequency of outcome assessments.
c. In the GOG-0218 and ICON7 trials, bevacizumab was co-administered with chemotherapy and continued into the maintenance phase of the first-line regimen. Currently no methods are available that can accurately adjust the data to isolate the treatment effect of bevacizumab in the maintenance phase and thus permit a reliable comparison with niraparib.

Additional details on the confounding factors for each of the comparisons are included in Sections 4.3.5.1 and 4.3.5.2.

4.3.5.1 Differences between the PRIMA trial (niraparib) and the SOLO1 trial (olaparib)

Due to the heterogeneity in the clinical trial designs and the resulting confounding factors, it has been concluded that indirect comparisons will not yield reliable results on the comparative efficacy of niraparib versus olaparib. Narrative comparisons have been performed (see Section 5.1.3) which should, however, be interpreted with caution. The key differences in the PRIMA [2] and SOLO1 [3] clinical trials are summarised below:

- A higher percentage of patients in SOLO1 (olaparib intention-to-treat [ITT] population 77%, placebo 80%) had an Eastern Cooperative Oncology Group (ECOG) performance score of 0 compared to those in PRIMA (niraparib ITT population 69%, placebo 71%).
- Patients with FIGO stage IV disease have a poor prognosis compared to those with stage III ovarian cancer [11]. In the PRIMA ITT population 35% of patients in the niraparib arm had stage IV disease whereas in the SOLO1 ITT population, 15% of patients in the olaparib arm had stage IV disease. Patients in PRIMA therefore had a worse prognosis.
- Patients in receipt of neoadjuvant chemotherapy (NACT) usually have high volume tumours and hence high-risk disease. NACT is a prognostic factor and is associated with interval cytoreductive surgery. In PRIMA 67% of the patients in the niraparib arm had received NACT whereas in SOLO1 the corresponding proportion was 35% [2, 12].
- The SOLO1 trial only recruited ovarian cancer patients with a BRCA mutation (BRCAm). Furthermore, the ITT population included stage III patients with NVRD following primary debulking surgery (44% of the ITT population), a patient subgroup which was not included in the PRIMA trial [3]. Retrospective studies have shown that patients with NVRD after primary debulking surgery have a better prognosis compared to those with visible residual

disease, especially patients with stage III disease [13, 14]. This suggests that the SOLO1 ITT population had a better prognosis than the PRIMA BRCAm population. The presence of residual disease following debulking surgery (cytoreduction) is a treatment effect modifier, thus an indirect comparison between the PRIMA BRCAm subgroup and the ITT population in SOLO1 is likely to be biased.

- In SOLO1 [3] the median follow-up duration was reported as 40.7 and 41.2 months in the olaparib and placebo arms, respectively, while in PRIMA [2], the median follow-up was reported as 13.8 months across both treatment arms. This could bias the comparison of outcomes, such as proportion of patients discontinued due to AE or proportion of patients with Common Terminology Criteria for Adverse Events (CTCAE) grade 3-4 AE, which are highly dependent on the duration of follow-up and therefore not appropriate to compare across trials with different duration of follow-up. However, previous trials with niraparib have shown that many types of AEs, including those leading to discontinuation, are transient and remain low after the first months of treatment [15, 16].
- A subgroup analysis of the SOLO1 trial in which patients with NVRD have been removed has been recently published [17]. This post-hoc analysis included patients with visible residual disease after primary debulking surgery or interval debulking surgery. This population is still not comparable with that of PRIMA as the inclusion criteria in PRIMA meant that stage III interval debulking surgery with NVRD and Stage IV patients with NVRD were eligible for enrolment. Based on currently published data, it is unclear whether the joint distribution of patients by type of debulking surgery (primary debulking surgery or interval debulking surgery) plus stage of disease and residual disease status combined, are balanced between the PRIMA BRCAm and SOLO1 populations. Disease prognosis (and potentially treatment effect) varies between primary and interval debulking surgery and by stage of disease [18] and therefore an indirect comparison between the PRIMA BRCAm and SOLO1 visible residual disease subgroups would be potentially biased. Furthermore, a comparative efficacy analysis based on the NVRD subgroups may not be generalisable to the whole BRCAm population. Due to these concerns, the publication was excluded from the literature selection (see Table A1b).

Despite improved prognosis in patients that achieve complete surgical cytoreduction, even those with NVRD are at risk of recurrence. Studies of second-look surgery (now an outdated procedure) have shown residual disease following complete cytoreduction is present in 30-50% of ovarian cancer patients across all stages; this proportion is even higher for stage III patients [19]. NVRD does not imply no microscopic residual disease. Microscopic disease present after complete cytoreduction, is a potential risk factor for recurrence [20] and as such, a critical therapeutic target for systemic treatments though not explicitly assessed in clinical trials. This and other unobserved/unknown prognostic factors would confound an indirect comparison of maintenance treatments for ovarian cancer.

In clinical practice there is no standard methodology for surgeons to report residual disease following cytoreductive surgery. Discordance of up to 48% between a surgeon's operative assessment and pre-treatment imaging has been reported even in surgeries deemed to be complete cytoreduction [21, 22]. Most patients do not undergo imaging after primary debulking surgery to identify areas of residual disease in clinical practice. Therefore, accuracy in determining the presence or absence of visible residual disease remains dependent on the individual surgeon and the extent of her/his experience in treating advanced ovarian cancer.

Based on the above, it is unlikely that indirect comparisons between populations from these 2 trials will give reliable input to clinical decision making in the treatment of ovarian cancer.

4.3.5.2 Differences between the PRIMA trial (niraparib) and GOG-0218 and ICON7 trials (bevacizumab)

Due to important differences in the clinical trial designs and confounding factors, it has been concluded that neither indirect nor narrative comparisons on the comparative efficacy of niraparib versus bevacizumab are meaningful. This has also previously been confirmed by the Danish Medicines Council [23]. Thus, the individual study results have been

described (see Section 5.2.2 and 5.4.2), but no attempt to compare the data has been made. The differences are summarised below:

- Bevacizumab was administered with chemotherapy and then continued in the maintenance phase, in the GOG-0218 and ICON7 studies. The eligibility criteria for the PRIMA trial were such that few patients received bevacizumab, prior to commencing niraparib maintenance therapy. The potential unaccounted-for imbalance caused by prior exposure to bevacizumab is a source of bias and uncertainty. There are no data or analytical methods currently available that will allow the treatment effect of bevacizumab in the maintenance phase to be isolated from its effect in the chemotherapy phase.
- The timepoint from which PFS and OS were measured differed between studies due to differences in the study designs. In GOG-0218 and ICON7, PFS and OS outcomes were measured from randomisation i.e., prior to administration of platinum-based chemotherapy while in PRIMA, PFS and OS were measured from completion of platinum-based chemotherapy. The PFS and OS estimates in GOG-0218 and ICON7 thus include the chemotherapy period plus the maintenance phase, and therefore comparisons of these time-to-event endpoints are not meaningful.
- Differences in the patient populations.
    - The GOG-0218 ITT population included stage III patients with NVRD following primary debulking surgery, a patient subgroup not included in the PRIMA trial. As stated above, patients with NVRD after primary debulking surgery have a better prognosis compared to those with visible residual disease, especially patients with stage III disease [13, 14].
    - PRIMA enrolled patients with stage III or IV ovarian cancer at high risk of disease recurrence including patients who received NACT. NACT is usually administered to patients with high-volume tumours and hence high-risk disease to reduce the tumour before surgery; receipt of NACT is therefore a prognostic factor. GOG-0218 enrolled patients with stage III or IV ovarian cancer, all had primary debulking surgery and patients administered NACT were excluded from the study. ICON7, enrolled patients with stage I-IV ovarian cancer and patients administered NACT were excluded. In PRIMA, 67% of the patients in the niraparib arm had received NACT [2, 12]. Therefore, the study populations of GOG-0218 and ICON7 had a better prognosis than the PRIMA population.
    - BRCA and homologous recombination status were not analysed in GOG-0218 and ICON7; therefore, the proportion of patients with deleterious mutations or other genomic instability is unknown. Patients with BRCAm and/or homologous recombination deficiency (HRD) generally have a better prognosis compared to patients with BRCA wildtype (BRCAwt) and homologous recombination proficiency (HRP) [1, 24]. In PRIMA, the patient population was presented by homologous recombination status (HRD/HRP) and within HRD by BRCA status (BRCAm/BRCAwt). This results in an unknown difference in important prognostic factors, which are considered to make any comparisons between the data invalid.
    - Although the 'high-risk' subgroup of ICON7 is more comparable to the PRIMA ITT population, differences in the patient characteristics and study designs remain a source of heterogeneity that would impact the validity of the results from any ITC.
- Scanning intervals differed across studies. In PRIMA, scans were performed every 12 weeks; in GOG-0218, scans were completed every 12 weeks for 2 years, then every 24 weeks; and in ICON7, scans were completed every 6 weeks in year 1, every 12 weeks in years 2 and 3, every 24 weeks in years 4 and 5, and then every 52 weeks. More frequent scanning interval may potentially have led to shorter median PFS estimates which is therefore a source of bias.

5. Clinical questions – efficacy results

In this section, efficacy data are provided for the 5 clinical questions raised by the Danish Medicines Council in the protocol [1]. The 5 questions differ by the defined patient populations/subgroups and the comparator.

The efficacy outcomes requested in the protocol are OS (median OS and 5-year OS rate) and PFS (median PFS and 2-year PFS rate). These outcomes are included in this application to the extent that they have been reported in full publications, the European public assessment report (EPAR)/Summary of product characteristics (SPC), or in abstracts based on data from clinical trials where the main results are published. If the outcome is not reported in the desired unit or in the defined subpopulation, relevant alternative data have been included to the extent possible. All data below are presented with 95% confidence intervals (CIs), where possible.

Since safety data for niraparib are only available for the full safety population in the PRIMA trial, and since BRCA mutation status and homologous recombination status are not expected to impact safety, the safety results are presented separately for each medicine in Section 6. For similar reasons, health-related quality of life (HRQoL) data are presented separately for each medicine in Section 7.

5.1 Clinical question 1

What is the added clinical value of niraparib compared with olaparib as maintenance treatment for newly diagnosed patients with advanced BRCA-mutated high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response following platinum-based chemotherapy (complete or partial response)?

Population:	Newly diagnosed patients with advanced (stage III-IV) BRCAm high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response following platinum-based chemotherapy (complete or partial response).
Intervention:	niraparib, 2 x 100 mg capsules once daily or 3x 100 mg capsules once daily for patients who weigh ≥77 kg and have baseline platelet count ≥150,000/µL.
Comparator:	olaparib, 2 x 150 mg tablets twice daily for 2 years, or until progression of disease or unacceptable toxicity.

5.1.1 Presentation of relevant studies

The studies used in the assessment of this clinical question are PRIMA (niraparib) [2] and SOLO1 (olaparib) [3, 25]. The main study characteristics are described in Section 4.3.1 and 4.3.2, respectively, and differences between the studies are described in Section 4.3.5.1.

Baseline demographics for the study populations are presented in Table A2a and Table A2b, and results per study are tabulated in Table A3a and Table A3b.

5.1.2 Results per study

5.1.2.1 Overall survival

PRIMA was an event-driven trial, and the primary efficacy analysis was performed after disease progression or death had occurred in 154 HRD patients and in 386 patients in the overall population. The median duration of follow-up at the time of the data cut-off was 13.8 months [2]. Overall survival for the BRCAm subgroup has not been reported for the PRIMA trial. However, results for the HRD subgroup (N=373), where 60% of the patients had BCRAm (N=223) are reported instead [2]; this is considered a relevant alternative subgroup since patients with HRD are expected to have a prognosis comparable to BRCAm patients [1].

In the HRD subgroup, the estimated probability of survival at 2 years numerically favoured niraparib over placebo with 91.1 (87.5; 94.6)% in the niraparib group versus 84.9 (78.7; 91.2)% in the placebo group; the absolute difference between groups was 6.2 (-1.01; 13.36)%-points, P=0.0774. Hazard ratio for death was 0.61 (0.27; 1.39), P=0.237 (Table A3a). The data maturity in this planned interim analysis of OS was 10.8% in the overall population. The median OS was not reported due to low event rate and insufficient follow-up time [2].

In SOLO1, the estimated 3-year survival rate was 83.8 (79.4; 88.3)% in the olaparib group and 80.2 (73.3; 87.0)% in the placebo group with an absolute difference of 3.7 (-4.47; 11.86)%-points, P=0.3671. Hazard ratio for death was 0.95 (0.60; 1.53), P=0.83 (Table A3b). The data maturity for OS was 21%. The median OS was not reported [3].

5.1.2.2 Progression-free survival

PFS as assessed by blinded independent central review (BICR) was the primary endpoint in the PRIMA trial. The median PFS (BICR) in the BRCAm subgroup was 22.1 (19.3; NE[1]) months in the niraparib group and 10.9 (8.0; 19.4) months in the placebo group with an absolute difference in PFS of 11.2 months (CI not estimable). Hazard ratio for PFS was 0.40 (0.27; 0.62), P<0.001 (Table A3a).

The estimated PFS rate (BICR) for the BRCAm subgroup in PRIMA was 67.8 (60.3; 75.2)% in the niraparib group and 43.7 (32.1; 55.2)% in the placebo group, an absolute difference of 24.1 (10.38; 37.82)%-points, P=0.0007 (Table A3a).

In SOLO1, investigator-assessed PFS was the primary endpoint; PFS assessed by BICR was analysed in a sensitivity analysis. At the time of the primary analysis, a median investigator-assessed PFS of 13.8 months was reported for the placebo group, while median PFS was not reached in the olaparib group [3]. The estimated 2-year PFS rate (BICR) at the time of the primary analysis was 78.1 (73.0; 83.1)% in the olaparib group and 40.5 (32.1; 48.9)% in the placebo group with an absolute difference of 37.6 (27.8; 47.4)%-points, P<0.0001 (Table A3b). At the time of the primary analysis, hazard ratio for PFS was reported as 0.28 (0.20; 0.39), P<0.001 [3].

Analysis based on data from the 5-year follow-up reported a median investigator-assessed PFS of 56.0 months in the olaparib group and 13.8 months in the placebo group; the absolute difference in PFS was 42.2 months (CI not estimable). Based on the 5-year data, hazard ratio for investigator-assessed PFS was 0.33 (0.25; 0.43), P<0.001, comparable to the hazard ratio for PFS (BICR) reported at the time of the primary analysis (Table A3b).

5.1.3 Comparative analyses

The PRIMA trial demonstrated efficacy of niraparib as first-line treatment of advanced ovarian cancer after response to platinum-based chemotherapy in a subgroup of patients with BRCAm. In the HRD population (of which 60% had BRCAm), hazard ratio for death was 0.61 (0.27; 1.39) (data maturity 10.8%). In the BRCAm subgroup, hazard ratio for PFS was 0.40 (0.27; 0.62), and the absolute difference in PFS rate (BICR) between niraparib and placebo was 24.1 (10.38; 37.82)%-points (Table A3a).

In the SOLO1 trial, hazard ratio for death was 0.95 (0.60; 1.53). The hazard ratio for PFS (BICR) was 0.28 (0.20; 0.39), and the absolute difference in estimated PFS rate (BICR) was 37.6 (27.8; 47.4).

For the reasons outlined in Section 4.3.5.1, a formal ITC is unlikely to generate reliable estimates of relative clinical efficacy for niraparib and olaparib. It is however noticeable that, although data are immature, hazard ratio for death is numerically lower after niraparib treatment than olaparib treatment. Furthermore, despite that the PRIMA population had a worse prognosis than the SOLO1 population (see Section 4.3.5.1 for details), the hazard ratios for PFS within trials are relatively similar. Thus, niraparib is a highly relevant treatment option, which seems to be equally efficient to

[1] Not estimable

olaparib, in patients with advanced, high-grade BRCAm ovarian, fallopian tube or primary peritoneal cancer who are in response following platinum-based chemotherapy.

5.2 Clinical question 2

What is the added clinical value of niraparib compared with bevacizumab as maintenance treatment for newly diagnosed patients with advanced not BRCA-mutated, HRD, high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response following platinum-based chemotherapy (complete or partial response) and are candidates for bevacizumab?

Population:	Newly diagnosed patients with advanced (stage III-IV) BRCAwt, HRD, high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response following platinum-based chemotherapy (complete or partial response) and who are candidates for bevacizumab treatment (i.e., patients with ≥1 cm residual tumour, patients with tumour spread outside the abdominal cavity (stage IV), and patients who are inoperable (primary or interval debulking surgery)).
Intervention:	niraparib, 2 x 100 mg capsules once daily or 3x 100 mg capsules once daily for patients who weigh ≥77 kg and have baseline platelet count ≥150,000/µL.
Comparator:	Bevacizumab, every 3 weeks for a total of 15 months first-line treatment.

5.2.1 Presentation of relevant studies

The studies used in the assessment of this clinical question are PRIMA (niraparib) [2], and GOG-0218 and ICON7 (bevacizumab) [4, 6-8]. The main study characteristics are described in Section 4.3.1, 4.3.3 and 4.3.4, respectively, and differences between the studies are described in Section 4.3.5.2.

Baseline demographics for the study populations are presented in Table A2a, Table A2c and Table A2d. Results per study are tabulated in Table A3a ,Table A3c and Table A3d.

5.2.2 Results per study

5.2.2.1 Overall survival

Overall survival for the BRCAwt, HRD subgroup has not been reported. The results for overall survival in the HRD subgroup (N=373), where 40% of the patients had BCRAwt (N=150) [2] are described in Section 5.1.2.1.

In GOG-0218, at the time of the primary analysis after a median follow-up of 17.4 months, the estimated median OS was 39.7 months in the bevacizumab group and 39.3 months in the placebo group (CIs not reported) and hazard ratio for death was 0.92 (0.73; 1.15), P=0.45. The estimated survival rate was 77.8 (74.6; 81.1)% in the bevacizumab group and 75.0 (71.6; 78.4)% in the placebo group; the absolute difference was not statistically significant (2.8 [-1.90; 7.51]%-points, P=0.2422) (Table A3c). After a median follow-up of 102.9 months, the median OS was 43.4 months in the bevacizumab group and 41.1 months in the placebo group (CIs not reported) and hazard ratio for death was 0.96 (0.85; 1.09), P=0.53. The estimated survival rate was 21.0 (17.8; 24.2)% in the bevacizumab group and 21.1 (17.9; 24.3)% in the placebo group, i.e., no absolute difference between treatment groups in survival rate (-0.1 [-4.62; 4.43]%-points, P=0.9680) (Table A3c).

In ICON7, at the time of the planned mature analysis after a median follow-up of 48.9 months, the estimated median OS was 58.0 (52.4; 66.9) months in the bevacizumab group and 58.6 (53.5; 67.5) months in the control group, i.e., no noticeable difference between treatment groups (-0.6 [-10.7; 9.5] months, P=0.9071). Hazard ratio for death was 0.99 (0.85; 1.14), P=0.85. The estimated survival rate was 52.6 (49.1; 56.2)% in the bevacizumab group and

53.9 (50.4; 57.5)% in the control group, i.e., no noticeable difference between treatment groups (-1.3 [-6.31; 3.69]%-points, P=0.6081) (Table A3d).

In the high-risk group, the estimated median OS was 39.7 (36.0; 44.2) months in the bevacizumab group and 30.2 (27.0; 34.3) months in the control group; with an absolute difference between treatment groups of 9.5 (4.0; 15.0) months, P=0.0007. Hazard ratio for death was 0.78 (0.63; 0.97), P=0.03. The estimated survival rate was 36.3 (30.3; 42.3)% in the bevacizumab group and 31.5 (25.8; 37.2)% in the control group; the difference between treatment groups was not statistically significant (4.8 [-3.48; 13.07]%-points, P=0.2564) (Table A3d).

5.2.2.2 Progression-free survival

PRIMA was an event-driven trial, and median duration of follow-up at the data cut-off for the primary efficacy analysis was 13.8 months [2]. PFS as assessed by BICR was the primary endpoint in PRIMA. The median PFS (BICR) in the BRCAwt, HRD subgroup was 19.6 (13.6; NE) months in the niraparib group and 8.2 (6.7; 16.8) months in the placebo group with an absolute difference in PFS of 11.4 months (CI not estimable). Hazard ratio for PFS was 0.50 (0.31; 0.83), P=0.006 (Table A3a).

The estimated PFS rate (BICR) in the BRCAwt, HRD subgroup in PRIMA was 66.3 (56.8; 75.8)% in the niraparib group and 40.0 (27.1; 52.9)% in the placebo group with an absolute difference of 26.3 (10.25; 42.38)%-points, P=0.0017 (Table A3a).

In GOG-0218, the median investigator-assessed PFS was 14.1 months in the bevacizumab group and 10.3 months in the placebo group (CIs not reported) with an absolute difference of 3.8 months (CI not estimable). Hazard ratio for PFS was 0.72 (0.63; 0.82), P<0.001 (Table A3c). The PFS rate was not reported [4, 6].

In ICON7, at the time of the primary analysis of OS and a median follow-up in the total population of 48.9 months, the median investigator-assessed PFS was 19.9 (19.1; 22.0) months in the bevacizumab group and 17.5 (15.7; 18.7) months in the control group; an absolute difference of 2.4 (0.3; 4.5) months, P=0.0241. Hazard ratio for PFS was 0.93 (0.83; 1.05), P=0.25. PFS rates were 27.5 (24.3; 30.7)% in the bevacizumab group and 31.2 (27.9; 34.4)% in the control group, the absolute difference between treatment groups was not statistically significant (-3.7 [-8.23; 0.90]%-points, p=0.1155) (Table A3d).

In the high-risk subgroup in ICON7, the median investigator-assessed PFS was 16.0 (14.2; 17.8) months in the bevacizumab group and 10.5 (9.3; 12.0) months in the control group; an absolute difference of 5.5 (3.3; 7.8) months, P<0.0001. Hazard ratio for PFS was 0.73 (0.61; 0.88), P=0.001. PFS rates in the high-risk group were 10.1 (6.3; 13.8)% in the bevacizumab group and 10.2 (6.5; 14.0)% in the control group, i.e., no noticeable difference between groups (absolute difference -0.2 [-5.44; 5.13]%-points, P=0.9540) (Table A3d).

5.2.3 Comparative analyses

For the reasons described in Section 4.3.5.2, neither indirect nor narrative comparison of niraparib and bevacizumab are considered meaningful.

In the BRCAwt, HRD subgroup, a clinically relevant absolute difference between niraparib and placebo in median PFS of 11.4 months was shown; CIs could not be estimated since the upper end of the median PFS in the niraparib group could not be estimated at the time of analysis. The hazard ratio for PFS in the niraparib group was 0.50 (0.31; 0.83), P=0.006. The PFS rate showed a clinically relevant and statistically significant benefit of niraparib over placebo with an absolute difference of 26.3 (10.25; 42.38)%-points, P=0.0017. OS was not reported for this specific subgroup (Table A3a).

In the full study populations in GOG-2018 and ICON7, bevacizumab showed small benefits over control treatment in median PFS, which was statistically significant in the ICON7 trial (absolute differences 3.8 months and 2.4 months in

the GOG-0218 and ICON7 trials, respectively). In the high-risk subgroup in ICON7, hazard ratio for PFS was 0.73 (0.61; 0.88), and the absolute difference in median PFS between treatments was 5.5 (3.3; 7.8) months. No significant differences were shown in PFS rates. No survival benefit was shown for bevacizumab in the final analyses of OS in the full populations in the GOG-0218 and ICON7 trials. However, in the high-risk subgroup in ICON7, a survival benefit was shown with a hazard ratio for death of 0.78 (0.63; 0.97) and an absolute difference in median OS between treatments of 9.5 (4.0; 15.0) months.

It is estimated that 10-15% of patients are treated with bevacizumab in the chemotherapy and maintenance phases. This is in accordance with clinical insights and real-world evidence [26].

5.3 Clinical question 3

What is the added clinical value of niraparib compared with bevacizumab as maintenance treatment for newly diagnosed patients with advanced not BRCA mutated, HRP, high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response following platinum-based chemotherapy (complete or partial response) and are candidates for bevacizumab?

Population:	Newly diagnosed patients with advanced (stage III-IV) BRCAwt, HRP, high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response following platinum-based chemotherapy (complete or partial response) and who are candidates for bevacizumab treatment (i.e., patients with ≥1 cm residual tumour, patients with tumour spread outside the abdominal cavity (stage IV), and patients who are inoperable (primary or interval debulking surgery)).
Intervention:	niraparib, 2 x 100 mg capsules once daily or 3x 100 mg capsules once daily for patients who weigh ≥77 kg and have baseline platelet count ≥150,000/µL.
Comparator:	Bevacizumab, every 3 weeks for a total of 15 months first-line treatment.

5.3.1 Presentation of relevant studies

The studies used in the assessment of this clinical question are PRIMA (niraparib) [2], and GOG-0218 and ICON7 (bevacizumab) [4, 6-8]. The main study characteristics are described in Section 4.3.1, 4.3.3 and 4.3.4, respectively, and differences between the studies are described in Section 4.3.5.2.

Baseline demographics for the study populations are presented in Table A2a, Table A2c and Table A2d. Results per study are tabulated in Table A3a ,Table A3c and Table A3d.

5.3.2 Results per study

5.3.2.1 Overall survival

The median duration of follow-up at the data cut-off for the primary efficacy analysis in PRIMA was 13.8 months [2]. The OS rate in the BRCAwt, HRP subgroup favoured niraparib over placebo with a survival rate of 81.1 (75.2; 87.0)% in the niraparib group versus 58.7 (48.0; 69.5)% in the placebo group and an absolute difference of 22.3 (10.0; 34.6)%-points, P=0.0002. Hazard ratio for death was 0.51 (0.27; 0.97), P=0.039 (Table A3a). The data maturity in this planned interim analysis was 10.8% in the overall population. The median OS were not reported due to low event rate and insufficient follow-up time [2].

The OS results for bevacizumab are described in Section 5.2.2.1.

5.3.2.2 Progression-free survival

PFS as assessed by BICR was the primary endpoint in PRIMA. The median PFS (BICR) in the BRCAwt, HRP subgroup was 8.1 (5.7; 9.4) months in the niraparib group and 5.4 (4.0; 7.3) months in the placebo group; an absolute difference in PFS of 2.7 (0.2; 5.2) months, P=0.0328. Hazard ratio for PFS in the BRCAwt HRP subgroup was 0.68 (0.49; 0.94), P=0.020 (Table A3a).

The estimated PFS rate (BICR) in the BRCAwt HRP subgroup in PRIMA was 34.3 (27.2; 41.5)% in the niraparib group and 30.0 (20.0; 40.0)% in the placebo group, the absolute difference between treatment groups was not statistically significant (4.3 [-8.01; 16.65]%-points, P=0.4964) (Table A3a).

The PFS results for bevacizumab are described in Section 5.2.2.2.

5.3.3 Comparative analyses

For the reasons described in Section 4.3.5.2, neither indirect nor narrative comparison of niraparib and bevacizumab are considered meaningful.

In the BRCAwt HRP subgroup, niraparib resulted in a clinically relevant and statistically significant benefit over placebo in survival rate with an absolute difference of 22.3 (10.0; 34.6)%-points, P=0.0002. Furthermore, a small but statistically significant benefit in median PFS was shown in the subgroup with an absolute difference in PFS of 2.7 (0.2; 5.2) months, P=0.0328, and the hazard ratio for PFS was 0.68 (0.49; 0.94), P=0.020 (Table A3a).

Bevacizumab showed small benefits over control treatment in median PFS, which was statistically significant in the ICON7 trial (absolute differences 3.8 months and 2.4 months in the GOG-0218 and ICON7 trials, respectively), but no significant differences in PFS rates. No survival benefit has been shown for bevacizumab in the final analyses of OS in the GOG-0218 and ICON7 trials.

It is estimated that 10-15% of patients are treated with bevacizumab in the chemotherapy and maintenance phases. This is in accordance with clinical insights and real-world evidence [26].

5.4 Clinical question 4

What is the added clinical value of niraparib compared with placebo as maintenance treatment for newly diagnosed patients with advanced not BRCA-mutated, HRD, high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response following platinum-based chemotherapy (complete or partial response) and who are not candidates for bevacizumab?

Population:	Newly diagnosed patients with stage III, BRCAwt, HRD, high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response following platinum-based chemotherapy (complete or partial response) and with <1 cm residual tumour after surgery.
Intervention:	niraparib, 3 x 100 mg capsules once daily or 2x 100 mg capsules once daily for patients who weigh <77 kg and have baseline platelet count <150,000/µL.
Comparator:	Placebo.

Comment on the population

As already noted in the protocol section 4 [1], stage III patients with NVRD after primary debulking surgery were not enrolled in the PRIMA trial. The literature search retrieved no additional trials that have investigated niraparib in a

patient population with stage III cancer and NVRD. Thus, no data are available for the specific population defined in the protocol.

As a relevant alternative, data from the BRCAwt, HRD subgroup in the PRIMA trial are presented. The trial included patients with stage III disease with visible residual disease after primary surgery, all stage IV patients irrespective of residual disease after primary or interval debulking, and patients with inoperable stage III and IV disease. Thus, these patients have more severe disease than the patient population defined in the protocol. Since a higher FIGO disease stage and visible residual disease are associated with a worse prognosis [13, 14], the efficacy estimates from the PRIMA trial are expected to be conservative estimates for the efficacy in a population with less severe disease (i.e. stage III patients with <1 cm residual tumour after surgery who are not candidates for bevacizumab).

The above assessment is supported by a new analysis of real-world data that explored the data gap in PRIMA for stage III patients with not visible residual disease after primary debulking surgery [27]. Based on data from the Edinburgh Ovarian Cancer Database, differences in OS and PFS were explored in a retrospective observational study that examined characteristics and long-term outcomes for patients diagnosed with advanced ovarian cancer from 2000–2015 and followed until January 2019. Analyses were performed for a 'simulated PRIMA cohort', a 'simulated not visible residual disease after primary debulking surgery cohort', and a 'simulated broader cohort' (including the previous 2 cohorts plus stage III patients with non-evaluable debulking status). The baseline patient characteristics matched the PRIMA population in most categories. The results for the simulated PRIMA cohort and the simulated cohort with not visible residual disease are shown in Table 2. When compared with the simulated PRIMA cohort, the cohort with stage III disease and not visible residual disease had significantly longer PFS with a hazard ratio of 0.43 (0.32; 0.58) and significantly longer OS with a hazard ratio of 0.43 (0.32; 0.60).

Table 2 OS and PFS in a simulated cohort with stage III disease with NVRD

Population/subgroup	Statistic	Median PFS (years)	Median OS (years)
Simulated PRIMA (N=472)		1.20 years	2.71 years
Simulated stage III with not visible residual disease after primary debulking surgery (N=69)	Hazard ratio (95% CI) P-value	2.45 years 0.43 (0.32; 0.58) P<0.0001	6.84 years 0.43 (0.32; 0.60) P<0.0001

Source: Hollis et al [27].

Abbreviations: CI, confidence interval; N, total number of patients in the specific (sub)population; NVRD, no visible residual disease; OS, overall survival; PFS, progression-free survival.

5.4.1 Presentation of relevant studies

The trial used in the assessment of this clinical question is PRIMA (niraparib) [2]. The main characteristics of the clinical trial are described in Section 4.3.1 . Baseline demographics for the study population are presented in Table A2a and study results are tabulated in Table A3a.

5.4.2 Results per study

5.4.2.1 Overall survival

Overall survival for the BRCAwt, HRD subgroup has not been reported .The results for overall survival in the HRD subgroup (N=373), where 40% of the patients had BCRAwt (N=150) [2] are described in Section 5.1.2.1.

5.4.2.2 Progression-free survival

PFS results in the BRCAwt HRD subgroup are described in Section 5.2.2.2.

5.4.3 Comparative analyses

Results are tabulated in Table A4. In the BRCAwt, HRD subgroup, a clinically relevant absolute difference between niraparib and placebo in median PFS of 11.4 months was shown; CIs could not be estimated since the upper end of the median PFS in the niraparib group could not be estimated at the time of analysis. The hazard ratio for PFS in the niraparib group was 0.50 (0.31; 0.83), P=0.006. The PFS rate showed a clinically relevant and statistically significant benefit of niraparib over placebo with an absolute difference of 26.3 (10.25; 42.38)%-points, P=0.0017. OS was not reported for this specific subgroup.

5.5 Clinical question 5

What is the added clinical value of niraparib compared with placebo as maintenance treatment for newly diagnosed patients with advanced not BRCA-mutated, HRP, high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response following platinum-based chemotherapy (complete or partial response) and who are not candidates for bevacizumab?

Population:	Newly diagnosed patients with stage III, BRCAwt, HRP, high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response following platinum-based chemotherapy (complete or partial response) and with <1 cm residual tumour after surgery.
Intervention:	niraparib, 2 x 100 mg capsules once daily or 3x 100 mg capsules once daily for patients who weigh ≥77 kg and have baseline platelet count ≥150,000/µL.
Comparator:	Placebo.

Comment on the population

As already noted in the protocol section 4 [1], stage III patients with NVRD after primary debulking surgery were not enrolled in the PRIMA trial. The literature search retrieved no additional trials that have investigated niraparib in a patient population with stage III cancer and NVRD. Thus, no data are available for the specific population defined in the protocol.

As a relevant alternative, data from the BRCAwt, HRP subgroup in the PRIMA trial are presented. The efficacy estimates from this population are expected to be conservative estimates for the efficacy in a population with less severe disease, which is supported by new real-world data, see details in Section 5.4.

5.5.1 Presentation of relevant studies

The trial used in the assessment of this clinical question is PRIMA (niraparib) [2]. Baseline demographics for the study population are presented in Table A2a and study results are tabulated in Table A3a.

5.5.2 Results per study

5.5.2.1 Overall survival

The OS results for the BRCAwt, HRP subgroup are described in Section 5.3.2.1.

5.5.2.2 Progression-free survival

The PFS results in the BRCAwt, HRP subgroup are described in Section 5.3.2.2.

5.5.3 Comparative analyses

Results are tabulated in Table A4. In the BRCAwt HRP subgroup, niraparib resulted in a clinically relevant and statistically significant benefit over placebo in survival rate with an absolute difference of 22.3 (10.0; 34.6)%-points, P=0.0002. Furthermore, a small but statistically significant benefit in median PFS was shown in the subgroup with an absolute difference in PFS of 2.7 (0.2; 5.2) months, P=0.0328. The hazard ratio for PFS in the niraparib group was 0.68 (0.49; 0.94), P=0.020.

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6. Safety results

6.1 Niraparib (relevant for clinical questions 1–5)

In the present application, safety endpoints for niraparib are described for the full patient population in the PRIMA trial. BRCA mutation status and homologous recombination status are not expected to influence safety, which has previously been confirmed by the Danish Medicines Council [23].

6.1.1 Proportion of patients who discontinued treatment due to adverse events

The frequency of different types of AEs and adverse drug reactions (treatment-related AEs) reported in the PRIMA trial is shown in Table 3. Adverse drug reactions leading to treatment discontinuation were not reported. AEs leading to treatment discontinuation were of greater frequency in the niraparib group (12.0 [9.1; 14.9]% of patients) than the placebo group (2.5 [0.5; 4.4]%); an absolute difference of 9.5 (6.04; 13.01)%-points. The relative risk of discontinuation due to AE was 4.87 (2.13; 11.14) in the niraparib group (Table A3a). This is as expected for a comparison of active treatment versus placebo. Myelosuppressive AEs were the main reason for discontinuation but were infrequent (Table 4); the highest frequency was 4.3% of patients experiencing thrombocytopenia in the niraparib group. AEs leading to dose reduction or dose interruption were also greater in the niraparib group than the placebo group (Table 3).

Table 3 Frequency of adverse events in the PRIMA trial

Type of adverse event	Niraparib (N=484) Number of patients (%)	Placebo (N=244) Number of patients (%)
Any AE	478 (98.8%)	224 (91.8%)
Any AE of grade 3 or 4	341 (70.5%)	46 (18.9%)
Any ADR	466 (96.3%)	168 (68.9%)
Any ADR of grade 3 or 4[1]	316 (65.3%)	16 (6.6%)
Any SAE	156 (32.2%)	32 (13.1%)
Any serious ADR	118 (24.4%)	6 (2.5%)
AEs leading to treatment discontinuation	58 (12.0%)	6 (2.5%)
AEs leading to dose reduction	343 (70.9%)	20 (8.2%)
AEs leading to dose interruption	385 (79.5%)	44 (18.0%)
AEs leading to an outcome of death[2]	2 (0.4%)	1 (0.4%)

Source: PRIMA publication Table 2 [2].

[1] presented as ADR grade ≥3 in the publication but corresponding to grade 3-4 events since no treatment-emergent deaths were reported during this trial.

[2] Not treatment-emergent deaths. There were no treatment-emergent deaths in the trial.

Abbreviations: ADR, adverse drug reaction (treatment-related AE); AE, adverse event; N, total number of patients in the safety population; SAE, serious AE.

Table 4 Treatment discontinuations due to myelosuppressive adverse events in the PRIMA trial

Adverse event	Niraparib (N=484) Number of patients (%)	Placebo (N=244) Number of patients (%)
Thrombocytopenia*	21 (4.3%)	0
Neutropenia*	9 (1.9%)	0
Leukopenia*	10 (2.1%)	0
Anaemia	9 (1.9%)	0
Pancytopenia	0	0

Source: PRIMA publication, appendix Table S8 [2].

*Grouped terms

Abbreviations: N, total number of patients in the safety population.

6.1.2 Proportion of patients who experienced grade 3 and 4 adverse reactions and events

No treatment-related deaths (grade 5 AEs) occurred in either treatment group. As expected for an active treatment versus placebo, the frequency of adverse drug reactions of grade 3 and 4 was greater in the niraparib group (65.3 [61.0; 69.5]% of patients) than the placebo group (6.6 [3.5; 9.7]%); a difference of 58.7 (53.48; 63.99)%-points. The relative risk of experiencing an adverse drug reaction of grade 3 or 4 was 9.96 (6.17; 16.06) (Table A3a).

A greater frequency of patients in the niraparib group (70.5 [66.4; 74.5]%) than the placebo group (18.9 [13.9; 23.8]%) experienced any AE of grade 3 and 4; a difference of 51.6 (45.23; 57.97)%-points (P<0.0001). The relative risk of experiencing any AE of grade 3 or 4 was 3.73 (2.86; 4.88) with niraparib (Table A3a). The most common AEs in the niraparib group were anaemia, thrombocytopenia, platelet count decreased and neutropenia (Table 5).

Two patients treated with niraparib experienced events of intestinal perforation and pleural effusion that led to death [28]. Neither of these deaths were considered as related to treatment with niraparib.

Table 5 Most common adverse events of grade 3 and 4 in the PRIMA trial

MedDRA preferred term	Niraparib (N=484) Number of patients (%)	Placebo (N=244) Number of patients (%)
Anaemia	150 (31.0%)	4 (1.6%)
Thrombocytopenia	139 (28.7%)	1 (0.4%)
Platelet count decreased	63 (13.0%)	0
Neutropenia	62 (12.8%)	3 (1.2%)
Fatigue	9 (1.9%)	1 (0.4%)
Abdominal pain	7 (1.4%)	1 (0.4%)
Nausea	6 (1.2%)	2 (0.8%)
Insomnia	4 (0.8%)	1 (0.4%)
Vomiting	4 (0.8%)	2 (0.8%)
Headache	2 (0.4%)	0
Constipation	1 (0.2%)	0

Source: PRIMA publication Table 2 [2].

The most common reported AEs are listed in descending order of frequency.

Abbreviations: AE, adverse event; N, total number of patients in the safety population; MedDRA, Medical Dictionary for Regulatory Activities.

In the PRIMA trial, 31% of niraparib-treated patients experienced grade 3-4 anaemia compared to 2% of placebo-treated patients with a median time from first dose to first onset of 80 days (range: 15 to 533 days) and with a median duration of 7 days (range: 1 to 119 days) [2, 28]. Moreover, 29% of niraparib-treated patients experienced grade 3-4 thrombocytopenia compared to 0.4% of placebo-treated patients with a median time from first dose to first onset of

22 days (range: 15 to 335 days) and with a median duration of 6 days (range: 1 to 374 days). Also, 13% of niraparib-treated patients experienced grade 3-4 neutropenia compared to 1% of placebo-treated patients with a median time from first dose to first onset of 29 days (range: 15 to 421 days) and with a median duration of 8 days (range: 1 to 42 days).

The percentages of grade 3-4 thrombocytopenia and neutropenia reported in the SPC were slightly higher than those reported above, as each included additional preferred terms [28].

6.1.3 Qualitative description of adverse events

While the overall frequency of AEs of any type was greater in the niraparib than the placebo group, safety was generally improved with the implementation of an individualised dosing regimen, as shown in Table 6 for the total safety population of 728 patients.

In patients in the PRIMA trial who were administered a starting dose of niraparib based on baseline weight or platelet count, the frequencies of grade ≥3 thrombocytopenia, anaemia and neutropenia were reduced compared to the group administered a fixed starting dose of 300 mg [2, 28].

Table 6 Grade ≥3 haematologic AEs in patients receiving a fixed versus individualised dose of niraparib in the PRIMA trial

MedDRA preferred term	Niraparib (N=484)		Placebo (N=244)	
	Fixed dose (n=315)	Individualised dose (n=169)	Fixed dose (n=158)	Individualised dose (n=86)
Thrombocytopenia	114 (36.2%)	25 (14.8%)	0	1 (1.2%)
Anaemia	112 (35.6%)	38 (22.5%)	3 (1.9%)	1 (1.2%)
Platelet count decreased	51 (16.2%)	12 (7.1%)	0	0
Neutropenia	46 (14.6%)	16 (9.5%)	2 (1.3%)	1 (1.2%)
Neutrophil count decreased	28 (8.9%)	9 (5.3%)	0	0
Febrile neutropenia	3 (1.0%)	1 (0.6%)	0	0
Myelodysplastic syndrome	1 (0.3%)	0	0	0
Pancytopenia	1 (0.3%)	0	0	0
Neutropenic sepsis	0	1 (0.6%)	0	0

Source: PRIMA publication, appendix Table S11 [2].

Abbreviations: N, total number of patients in the safety population; n, number of patients with fixed or individualised niraparib dose; MedDRA, Medical Dictionary for Regulatory Activities.

Recommended dose modifications of niraparib in case of adverse reactions are described in the SPC, Tables 1, 2 and 3 [29]. In general, it is recommended to first interrupt the treatment (but no longer than 28 consecutive days) to allow the patient to recover from the adverse reaction and then restart at the same dose. In the case that the adverse reaction recurs, it is recommended to interrupt the treatment and then resume at the lower dose. If adverse reactions persist beyond a 28-day dose interruption, it is recommended that niraparib be discontinued. If adverse reactions are not manageable with this strategy of dose interruption and reduction, it is recommended that niraparib be discontinued.

Haematologic adverse reactions were observed during the treatment with niraparib especially during the initial phase of the treatment. It is therefore recommended to monitor complete blood counts weekly during the first month of treatment and modify the dose as needed. After the first month, it is recommended to monitor complete blood

counts monthly and periodically after this time. Based on individual laboratory values, weekly monitoring for the second month may be warranted [29].

Cases of **myelodysplastic syndrome/acute myeloid leukaemia** have been observed in patients treated with niraparib monotherapy or combination therapy in clinical trials and post-marketing surveillance. If such cases are confirmed while on treatment with niraparib, treatment should be discontinued and the patient treated appropriately [29]. In the PRIMA trial, one case of myelodysplastic syndrome was identified in a patient in the niraparib group [2].

A total of 5 patients (1%) treated with niraparib in the PRIMA trial experienced **pneumonitis** events compared to no patients who received placebo. All events were grade 1 or 2 in intensity and reported as serious as instructed per trial protocol. Events led to dose interruption/reduction in 1 patient, drug withdrawal in 1 patient, and no change in 2 patients. Three patients experienced grade 2 events that were assessed as related or possibly related to trial treatment [28].

6.1.4 Summary

In the PRIMA trial, a greater proportion of patients discontinued the trial due to AEs in the niraparib group compared to the placebo group, as expected for a trial comparing active treatment with placebo. The absolute difference between niraparib and placebo in proportion of patients discontinued due to AE was 9.5 (6.04; 13.01)%-points, thus the target minimal clinically important difference (MCID) of 5%-points difference, as set by the Medicine's Council, was not met. Furthermore, a greater proportion of patients in the niraparib group than the placebo group experienced adverse drug reactions of grade 3–4. The absolute difference between niraparib and placebo in proportion of patients with grade 3–4 adverse drug reactions was 58.7 (53.48; 63.99)%-points; thus, the target MCID of 10%-points difference, as set by the Medicine's Council, was not met. However, the implementation of an individualised dosing regimen for niraparib and the possibility to reduce or interrupt the treatment dose helps to mitigate the experienced AEs and adverse drug reactions.

Niraparib is associated with myelosuppression, which is a class effect of poly(ADP ribose) polymerase (PARP) inhibitors [30]. Anaemia is the most common haematological toxicity among PARP inhibitors, occurring in 31.0% of patients with niraparib (PRIMA trial). As the primary mechanism of PARP inhibition involves interference with deoxyribonucleic acid (DNA) repair pathways, secondary malignancies, such as myelodysplastic syndrome and acute myeloid leukaemia, may be observed with niraparib. Such events can have a substantial impact as they increase the burden of the patient's condition, require discontinuation of a treatment that might be sustaining their lives, and complicates any further treatment. Respiratory side-effects are not commonly associated with PARP inhibition, but they do occur [30]. Cases of pneumonitis, albeit of low frequency, were observed with niraparib (PRIMA trial)

In summary, while PARP inhibitors have a common class effect toxicity profile, individual PARP inhibitors have unique side-effects that require a thorough understanding of the specific toxicities and knowledge regarding monitoring and dose regime customisation [30]. Typically, toxicity is manageable with supportive care and dose reduction.

6.2 Olaparib (relevant for clinical question 1)

6.2.1 Proportion of patients who discontinued treatment due to adverse events

The frequency of different types of AEs reported in the SOLO1 trial is shown in Table 7. Adverse drug reactions leading to treatment discontinuation were not reported. As expected for a comparison of active treatment versus placebo, AEs leading to treatment discontinuation were of greater frequency in the olaparib group (11.5 [7.7; 15.4]% of patients) than the placebo group (2.3 [0.0; 4.9]%); a difference of 9.2 (4.57; 13.89)%-points (P=0.0007). The relative risk of discontinuation due to AE was 5.00 (1.56; 16.08) in the olaparib group (Table A3b). The most common AEs that led to discontinuation were nausea and anaemia; each led to 2.3% of the olaparib discontinuations ([3], Table S6). AEs

leading to dose reduction or dose interruption were also greater in the olaparib group than the placebo group (Table 7).

Table 7 Frequency of adverse events in the SOLO1 trial

Type of adverse event	Olaparib (N=260) Number of patients (%)	Placebo (N=130) Number of patients (%)
Any AE	256 (98.5%)	120 (92.3%)
Any AE of grade 3 or 4	102 (39.2%)	24 (18.5%)
Any SAE	54 (20.8%)	16 (12.3%)
AEs leading to treatment discontinuation	30 (11.5%)	3 (2.3%)
AEs leading to dose reduction	74 (28.5%)	4 (3.1%)
AEs leading to dose interruption	135 (51.9%)	22 (16.9%)
AEs leading to an outcome of death	0	0

Source: SOLO publication Table 2 [3] and EPAR Table 43 [31].

Abbreviations: AE, adverse event; N, total number of patients in the safety population; SAE, serious AE.

6.2.2 Proportion of patients who experienced grade 3 and 4 adverse events

There were no AEs with an outcome of death (grade 5). AEs of grade 3 and 4 were reported in 39.2 (33.3; 45.2)% of patients receiving olaparib and 18.5 (11.8; 25.1)% of patients receiving placebo; a difference of 20.8 (11.84; 29.70)%-points (P<0.0001). The relative risk of experiencing an AE of grade 3 or 4 in the olaparib group was 2.13 (1.44; 3.14) (Table A3b). Of these AEs, the most commonly observed were blood and lymphatic system disorders, gastrointestinal disorders, investigations and general disorders and administration-site conditions [31]. Anaemia and neutropenia were the only AEs of grade 3 and 4 reported in ≥5% of patients (Table 8). Adverse drug reactions of grade 3–4 were not reported.

Table 8 Most common adverse events of grade 3 and 4 in the SOLO1 trial

MedDRA preferred term	Olaparib (N=260) Number of patients (%)	Placebo (N=130) Number of patients (%)
Anaemia	56 (22%)	2 (2%)
Neutropenia	22 (9%)	6 (5%)
Fatigue or asthenia	10 (4%)	2 (2%)
Diarrhoea	8 (3%)	0
Abdominal pain	4 (2%)	1 (1%)
Thrombocytopenia	2 (1%)	2 (2%)
Nausea	2 (1%)	0
Headache	1 (<1%)	3 (2%)
Vomiting	1 (<1%)	1 (1%)
Dizziness	0	1 (<1%)

Source: SOLO publication Table 2 [3] and EPAR Table 46 [31].

The most common reported AEs are listed in descending order of frequency.

Anaemia data include patients with anaemia, a decreased haemoglobin level, a decreased haematocrit, a decreased red-cell count, erythropenia, macrocytic anaemia, normochromic anaemia, normochromic normocytic anaemia, or normocytic anaemia.

Neutropenia data include patients with neutropenia, febrile neutropenia, neutropenic sepsis, neutropenic infection, a decreased neutrophil count, idiopathic neutropenia, granulocytopenia, a decreased granulocyte count, or agranulocytosis.

Thrombocytopenia data include patients with thrombocytopenia, decreased platelet production, decreased platelet count, or decreased plateletcrit.

Abbreviations: AE, adverse event; N, total number of patients in the safety population; MedDRA, Medical Dictionary for Regulatory Activities.

AEs of grade ≥3 were typically known adverse drug reactions for olaparib [32]. In total, 9 patients in the olaparib arm had grade 4 AEs. These included anaemia (n=6), neutrophil count decreased, platelet count decreased, sepsis and white blood cell count decreased (n=1 each). In the placebo arm, 3 patients experienced grade 4 AEs (platelet count decreased n=2 patients) and neutrophil count decreased and small intestinal obstruction (n=1 each).

6.2.3 Qualitative description of adverse reactions

In the SOLO1 trial, AEs were usually managed by dose interruption or dose reduction, rather than by discontinuation.

Treatment of olaparib may be interrupted or dose may be reduced to manage adverse reactions such as nausea, vomiting, diarrhoea and anaemia and dose reduction can be considered. The incidence and severity of anaemia events following olaparib treatment in SOLO1 were consistent with the known safety profile of olaparib. Anaemia remained manageable by interrupting or reducing the olaparib dose or giving blood transfusions, when indicated and treatment discontinuation was rarely required [31].

Haematological toxicity has been reported in patients treated with olaparib, including clinical diagnoses and/or laboratory findings of generally mild or moderate (CTCAE grade 1 or 2) anaemia, neutropenia, thrombocytopenia and lymphopenia. Patients should not start treatment with olaparib until they have recovered from haematological toxicity caused by previous anticancer therapy. Baseline testing, followed by monthly monitoring, of complete blood counts is recommended for the first 12 months of treatment and periodically after this time to monitor for clinically significant changes in any parameter during treatment [33].

Acute myeloid leukaemia occurred in 3 of 260 patients (1.2%) in the olaparib group and in none of 130 patients in the placebo group in the SOLO1 trial. All three cases of acute myeloid leukaemia were fatal. Because the deaths due to acute myeloid leukaemia occurred more than 30 days after treatment discontinuation they were not classified as treatment-emergent AEs with an outcome of death. New primary cancers occurred in 5 (2%) and 3 (2%) of patients, respectively, and pneumonitis or interstitial lung disease occurred in 5 (2%) patients in the olaparib group and no patients in the placebo group [3].

Four cases of **pneumonitis** and one case of **interstitial lung disease** were reported in the olaparib group; three of these cases were non-serious. Two cases resolved after treatment interruption and two cases resolved after treatment discontinuation. The final patient continued olaparib treatment; pneumonitis did not resolve or worsen in this patient [3].

6.2.4 Conclusion on safety and comparison of olaparib with niraparib

Niraparib and olaparib are both PARP inhibitors with a similar mechanism of action. In both the PRIMA trial with niraparib and the SOLO1 trial with olaparib, a greater proportion of patients discontinued the trial due to AEs in the active treatment group compared to the placebo group. The relative risk of discontinuation due to AEs was similar in the two trials. In the PRIMA trial, the relative risk of discontinuation with niraparib versus placebo was 4.87 (2.13; 11.14) and in the SOLO1 trial, the relative risk was 5.00 (1.56; 16.08) with olaparib versus placebo. It should be noted that the duration of follow-up was different in the two trials, therefore comparison of the discontinuation rates should be interpreted with caution (median duration in SOLO1 was 40.7 months in the olaparib group and 41.2 months in the placebo group [3], and median duration of follow-up in PRIMA was 13.8 months [2]). However, previous trials with niraparib have shown that many types of AEs, including those leading to discontinuation, are transient and remain low after the first months of treatment [15, 16].

In terms of AEs of grade 3 and 4, a greater proportion of patients in the active treatment group than the placebo group experienced such events in both trials. The relative risk of experiencing an AE of grade 3 or 4 was

3.73 (2.86; 4.88) with niraparib and 2.13 (1.44; 3.14) with olaparib. Comparison of these relative risks should be interpreted with caution due to differences in duration of follow-up between the 2 trials.

Both niraparib and olaparib are associated with myelosuppression, which is a class effect of PARP inhibitors [30]. However, the introduction of an individualised dosing regimen had a positive impact on safety outcomes for niraparib, as also recognised by the Danish Medicine's Council [1]. Anaemia is the most common haematological toxicity among PARP inhibitors, occurring in 31.0% of patients with niraparib in the PRIMA trial [2] and in 22% of patients with olaparib in the SOLO1 trial [3]. The implementation of individualised dosing regimens for niraparib helps to mitigate the experienced AEs and adverse drug reactions. As the primary mechanism of PARP inhibition involves interference with DNA repair pathways, secondary malignancies, such as myelodysplastic syndrome and acute myeloid leukaemia, may be observed with both niraparib and olaparib treatment. Such events can have a substantial impact as they increase the burden of the patient's condition, require discontinuation of a treatment that might be sustaining their lives, and complicates any further treatment. Respiratory side-effects are not commonly associated with PARP inhibition, but they do occur. Cases of pneumonitis, albeit of low frequency, were observed with both niraparib [2] and olaparib [3]. In summary, while PARP inhibitors have a common class effect toxicity profile, individual PARP inhibitors have unique side-effects that require a thorough understanding of the specific toxicities and knowledge regarding monitoring and dose regime customisation [30]. Typically, toxicity is manageable with supportive care and dose reduction. Previous studies have revealed a higher tumour and tissue exposure as unique features of niraparib in comparison to other PARP inhibitors, including olaparib [34], which may explain some of the differences in the AE profiles between the two drugs.

6.3 Bevacizumab (relevant for clinical questions 2 and 3)

It should be noted that due to the fact that bevacizumab was administered together with standard chemotherapy in the GOG 0218 and ICON7 trials, the contribution made by bevacizumab alone cannot be assessed and the data are therefore subject to bias.

6.3.1 Proportion of patients who discontinued treatment due to adverse events

The frequency of different types of AEs reported in the GOG-0218 trial is shown in Table 9 and those from the ICON7 trial are shown in Table 10. Adverse drug reactions leading to treatment discontinuation were not reported.

In the GOG-0218 trial, the proportion of patients who discontinued due to AEs was greater in the bevacizumab group (17.8 [14.7; 20.8]%) than in the placebo group (10.3 [7.9; 12.7]%); an absolute difference of 7.4 (3.56; 11.34)%-points, P=0.0002. The relative risk of discontinuation due to AE in the bevacizumab group was 1.7 (1.29; 2.30), P=0.0002 (Table A3c).

Also, in the ICON7 trial, a greater proportion of patients discontinued due to AEs in the bevacizumab group (21.8 [18.9; 24.8]%) than in the control group (8.9 [6.9; 10.9]%); an absolute difference of 12.9 (9.35; 16.53)%-points, P<0.0001. The relative risk of discontinuation due to AE in the bevacizumab group was 2.45 (1.88; 3.19), P<0.0001 (Table A3d).

No dose reductions of bevacizumab or placebo occurred in the GOG-0218 trial [6].

Table 9 Frequency of adverse events in the GOG-0218 trial

Type of adverse event	Bevacizumab maintenance (N=608) Number of patients (%)	Placebo (N=601) Number of patients (%)
Any AE	607 (99.8%)	601 (100%)
Any AE of grade 3 or 4	561 (92.3%)	557 (92.7%)
Any SAE	157 (25.8%)	128 (21.3%)
AEs leading to treatment discontinuation	108 (17.8%)	62 (10.3%)
AEs leading to an outcome of death	15 (2.5%)	4 (0.7%)

Source: EPAR Variation Report 2011 Table 28 [35] and Variation Report 2017 Table 44 (SAEs) [36].Due to inconsistencies between the publications and the EPAR, the above data are included from the EPAR.

Bevacizumab maintenance group (15 mg/kg): Five cycles of bevacizumab in combination with carboplatin and paclitaxel for 6 cycles followed by continued use of bevacizumab as single agent for a total of up to 15 months of therapy.

Placebo group: Five cycles of placebo (started cycle 2) in combination with carboplatin and paclitaxel for 6 cycles followed by placebo alone, for a total of up to 15 months of therapy.

Abbreviations: AE, adverse event; N, total number of patients in the safety population; SAE, serious AE.

Table 10 Frequency of adverse events in the ICON7 trial

Type of adverse event	Bevacizumab maintenance (N=746) Number of patients (%)	Control (N=763) Number of patients (%)
Any AE	746 (100%)	756 (99.1%)
Any AE of grade 3 or 4	481 (64.5%)	410 (53.7%)
Any SAE	281 (37.7%)	181 (23.7%)
AEs leading to treatment discontinuation	163 (21.8%)	68 (8.9%)
AEs leading to an outcome of death	4 (0.5%)	6 (0.8%)

Source: EPAR Variation Report 2017 Table 44 [36]. Due to inconsistencies between the publications and the EPAR, the above data are included from the EPAR.

Bevacizumab maintenance group (7,5 mg/kg): Six cycles of bevacizumab in combination with carboplatin and paclitaxel for 18 weeks followed by continued use of bevacizumab as single agent for a total of up to 54 weeks of therapy.

Control group: Six cycles of standard chemotherapy (carboplatin and paclitaxel) for a total of up to 18 weeks of therapy.

Abbreviations: AE, adverse event; N, total number of patients in the safety population; SAE, serious AE.

6.3.2 Proportion of patients who experienced grade 3 and 4 adverse events

In the GOG-0218 trial, AEs of grade 3 and 4 were reported in a similar proportion of patients (approximately 92%) receiving either bevacizumab or placebo (Table 9). The relative risk of an AE of grade 3 or 4 in the bevacizumab group was 0.996 (0.96; 1.03), P=0.7874 (Table A3c). Adverse drug reactions of grade 3–4 were not reported.

In the ICON7 trial, the frequency of AEs of grade 3 and 4 was greater in the bevacizumab group (64.5 [61.0; 67.9]% of patients) than in the control group (53.7[50.2; 57.3]% of patients); an absolute difference between treatment groups of 10.7 (5.81; 15.67)%-points, P<0.0001. The relative risk of an AE of grade 3 or 4 in the bevacizumab group was 1.20 (1.10; 1.31), P<0.0001 (Table A3d). Adverse drug reactions of grade 3–4 were not reported.

For bevacizumab compared with placebo, there were 15 versus 4 deaths due to AEs in the GOG-0218 trial and 4 versus 6 deaths due to AEs in the ICON7 trial (Table 9 and Table 10, respectively).

In the GOG-0218 trial, AEs of interest were updated with long-term toxicity data in the final analysis of OS [6]. Those AEs of ≥grade 3 are shown in Table 11.

Table 11 Adverse events of special interest of ≥ grade 3 in the GOG-0218 trial

Type of adverse event	Bevacizumab maintenance (N=608) Number of patients (%)	Placebo (N=601) Number of patients (%)
Neutropenia (grade ≥4)	386 (63.5%)	347 (57.7%)
Proteinuria	12 (2.0%)	4 (0.7%)
Non-CNS bleeding	13 (2.1%)	5 (0.8%)

The above long-term safety data are included from Tewari et al [6].

Abbreviations: N, total number of patients in the safety population.

In the ICON7 trial, bevacizumab treatment was associated with an increase in grade 3 or worse thromboembolic events (51 [7%] patients in the bevacizumab group versus 23 [3%] patients in the standard chemotherapy group) and grade 3 or worse gastrointestinal (GI) perforations (10 [1%] versus 3 [<1%]), as well as in grade 1–2 mucocutaneous bleeding (271 [36%] versus 55 [7%]) and grade 2 or worse hypertension (136 [18%] versus 16 [2%]) [8].

The most common AEs in both trials occurred in the system organ classes gastrointestinal disorders (abdominal pain, constipation, diarrhoea, nausea, vomiting), nervous system disorders (headache, peripheral sensory neuropathy), general disorders and administration site conditions (fatigue), skin and subcutaneous tissue disorders (alopecia), and musculoskeletal and connective tissue disorders (myalgia) [35].

6.3.3 Qualitative description of adverse reactions

In the GOG-0218 trial, treatment dose was to be modified only when weight changed by more than 10% and no dose modification was needed [6].

Dose reduction of bevacizumab for adverse reactions is not recommended. If indicated, therapy should either be permanently discontinued or temporarily suspended [37].

In both GOG-0218 and ICON7 trials, the incidence of **arterial thromboembolic events** was higher in the bevacizumab-containing treatment groups than in the respective control groups. The incidence of events was higher after the chemotherapy treatment than during chemotherapy. Most events were grade ≥3 in severity. In the GOG-0218 trial, the 2 grade 5 events (deaths) were in the bevacizumab treatment groups. In the ICON7 trial, 2 grade 5 events (death) occurred in the bevacizumab group and 1 grade 5 event occurred in the control group [35].

The incidence of all **bleeding events** in both trials was higher in the bevacizumab groups compared with the respective control groups. Most bleeding events in both trials were non-central nervous system (CNS) bleeding events (in particular, epistaxis), and most of those events were grade 1 or 2 in severity. CNS bleeding events were reported for 3 patients in each trial and most events were reported during the chemotherapy treatment phase [35].

In the GOG-0218 trial, **congestive heart failure** events were reported only in the bevacizumab maintenance group (3 patients, 0.5%), all of whom experienced grade 3 left ventricular systolic dysfunction during the period from cycle 2 to the start of cycle 7. One of these patients also reported grade 3 cardiomyopathy. In the ICON7 trial, 3 patients in each group experienced congestive heart failure events [35].

In the GOG-0218 trial, the incidence of **febrile neutropenia** in the bevacizumab treatment groups was higher than that in the placebo group. All events were either grade 3 or 4 in severity. All events were reported prior to cycle 7. In the ICON7 trial, the incidence of febrile neutropenia was higher in the bevacizumab group than the control group. Most events were grade 3 or 4 in severity [35].

Overall incidence rates of **fistulae** and **abscesses** were similar across both trials, with a higher incidence of events recorded in the bevacizumab treatment groups. There were no grade 5 fistulae or abscesses in either trial [35].

The incidence rates of **GI perforations** were higher in all bevacizumab treatment groups compared to the control groups across both trials. Most GI perforations were grade ≥3 events. Only patients in the bevacizumab treatment groups had GI perforations leading to death [35].

In both trials, a higher incidence of **hypertension** was observed in the bevacizumab treatment groups compared with the control groups. Most events were grade 1 or 2 events. There were no grade 5 hypertension events in either trial [35].

The rate of **neutropenia** was higher in the GOG-0218 trial compared to the ICON7 trial due to the data collection methods; therefore, the results from the 2 trials cannot be compared. In the GOG-0218 trial, grade ≥3 laboratory values were recorded as AEs regardless of whether the investigator considered them clinically relevant. Therefore, most patients experienced an AE of decreased neutrophil count and the incidence rate was similar across the treatment groups. Most were grade ≥3 events. Three patients in the bevacizumab maintenance group had AEs of neutropenia leading to death which occurred during the period from cycle 2 to the start of cycle 7. There were no grade 5 neutropenia events in the placebo group. In the ICON7 trial, the overall incidence of AEs reported as neutropenia was similar in both groups (bevacizumab 28.3% and control 28.7%), consistent with that seen in other trials with bevacizumab across indications. Most events occurred during the chemotherapy phase and there were no grade 5 neutropenia events in either group [35].

In the GOG-0218 trial, the highest incidence of **proteinuria** was observed in the bevacizumab treatment group (8.4% versus 6.5% in the placebo group). Most events were either grade 1 or 2. There were no grade 5 proteinuria events. In the ICON7 trial, the incidence of proteinuria was higher in the bevacizumab group than in the control group (4.4% versus 2.2%). Most events of proteinuria were grade 1 or 2 in severity [35].

In the GOG-0218 trial, the incidence of **venous thromboembolic events** was similar across the treatment groups (around 4%). Most events occurred during the chemotherapy period. Most of these events were grade 3. In the ICON7 trial, 6.8% of patients in the bevacizumab maintenance group experienced a venous thromboembolic event compared with 4.5% in the control group. Most events occurred during the chemotherapy phase. Grade ≥3 venous thromboembolic events were reported in 30 patients (4.0%) in the bevacizumab group and 12 patients (1.6%) in the control group. Eleven patients (1.5%) in the bevacizumab group had a grade 4 event compared with 2 patients (0.3%) in the control group. There were no grade 5 venous thromboembolic events in either trial [35].

In the GOG-0218 trial, the incidence of **wound-healing complications/dehiscence events** was similar across the treatment groups (around 4%). One patient in the bevacizumab maintenance group experienced grade 4 wound complications. There were no wound-healing complications leading to death. In the ICON7 trial, wound-healing complications were reported in 4.6% of patients in the bevacizumab group compared with 1.6% in the control group. Most wound-healing complications were grade 1 or 2 events. Grade 3 wound-healing complications were recorded for 9 patients (1.2%) in the bevacizumab group and 1 patient (0.1%) in the control group. No grade 4 or 5 wound-healing complications were reported in either treatment group [35].

6.3.4 Conclusion on safety of bevacizumab

For the reasons described in Section 4.3.5.2, neither indirect nor narrative comparison of niraparib and bevacizumab are considered meaningful.

With regard to bevacizumab, a greater proportion of patients discontinued the trial due to AEs in the active treatment group compared to the placebo group in both the GOG-0218 and ICON7 trials. The relative risks of discontinuation due to AE were 1.7 (1.29; 2.30) and 2.45 (1.88; 3.19), respectively.

In terms of AEs of grade 3 and 4, a greater proportion of patients in the active treatment group than the control group experienced such events in the ICON7 trial, with a relative risk of grade 3–4 events of 1.20 (1.10; 1.31). In the

GOG-0218 trial, more than 90% of patients experienced grade 3–4 events in both the active group and the placebo group.

Patients treated with bevacizumab do not have the possibility to reduce their treatment dose, therefore adverse reactions cannot be mitigated by dose reduction.

Bevacizumab binds and inactivates vascular endothelial growth factor, thereby inhibiting endothelia cell activation and possibly tumour proliferation. Extensive experience with bevacizumab has proven it to be generally well tolerated. The most common AE associated with bevacizumab treatment, hypertension, can be medically managed, but more serious AEs, such as bowel perforation, require drug discontinuation [38]. Most AEs are mild in severity and manageable, but some do result in significant morbidity and even mortality, as observed in the GOG-0218 and ICON7 trials. In addition, some toxicities, such as bowel perforation, are seemingly disease site-dependent. Others, such as mucosal bleeding, hypertension, and proteinuria, are more nonspecific. Regardless, most AEs likely result from the loss of vascular endothelial growth factor activity that normally promotes physiologic, adaptive stabilisation of malignant and non-malignant blood flow [38].

In summary, while bevacizumab tends to be generally well tolerated, the AEs events associated with treatment are specific to its biologic effects and can be potentially serious, even fatal [38].

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7. Health-related quality of life

In the protocol, the EORTC QLQ-OV28 questionnaire is defined as the preferred tool for assessment of HRQoL, which should be presented as the proportion of patients who did not show significant deterioration in HRQoL during the trial. If not available, other quality of life (QoL) tools can be used.

In the PRIMA trial, HRQoL was assessed by use of the tools: Functional Assessment of Cancer Therapy–Ovarian Symptom Index (FOSI), European Quality of Life 5-dimension, 5-level questionnaire (EQ-5D-5L), EORTC QLQ-C30, and EORTC QLQ-OV28. EORTC QLQ-C30 and -OV28 questionnaires were also used in the ICON7 trial.

In SOLO1 and GOG-0218, the FACT-O tool was used for assessment of HRQoL. The FACT-O questionnaire is a reliable and validated instrument to assess HRQoL in women with ovarian cancer. The TOI is a summary index of physical and functional wellbeing and key ovarian cancer symptoms derived from the FACT-O questionnaire. FACT-O TOI scores range from 0 to 100, with higher scores indicating better HRQoL, and a difference of 10 points indicating a clinically meaningful difference.

Since the proportion of patients with deterioration in HRQoL was not reported in any of the trials, changes from baseline were reported, where possible, to provide an indication of the mean deterioration or improvement in HRQoL during the trials.

7.1 Niraparib (relevant for clinical questions 1–5)

Data from EORTC-QLQ-OV28 was requested in the protocol as the main outcome for assessment of impact on HRQoL [1]. However, since only the abdominal/GI symptoms and other chemotherapy side effects have been published for EORTC QLQ-OV28, the results for global health/overall QoL as well as the results for physical function, fatigue and pain from EORTC QLQ-C30 have been included to support the assessment of the impact of niraparib on HRQoL. Furthermore, the data were not reported as proportion of patients with deterioration in HRQoL but as mean scores and standard deviations.

Data presented recently showed that there was no difference in HRQoL outcomes between the HRD and HRP subgroups [39], thus only results for the full PRIMA ITT population are presented here.

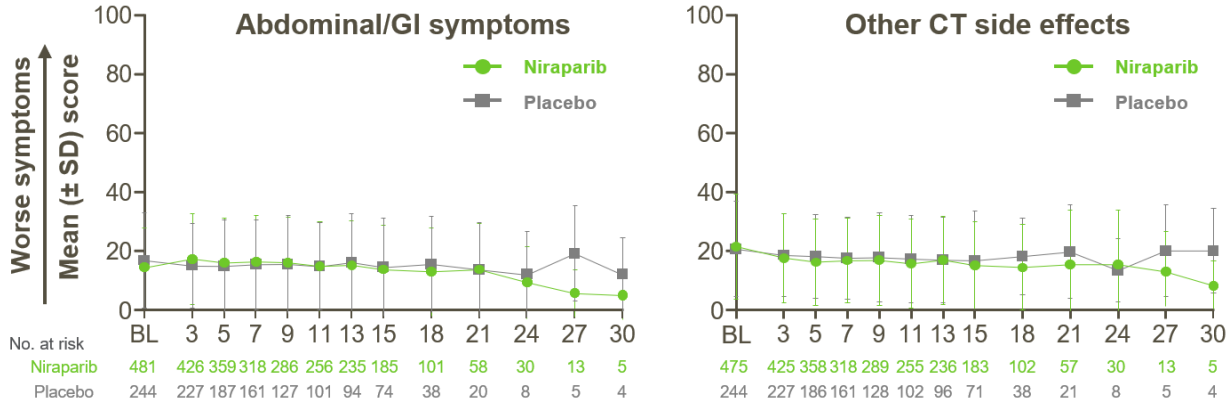
Patient compliance rates for the HRQoL questionnaires were generally high for all HRQoL tools and remained consistently >80% throughout the trial.

Figure 6 shows the results of EORTC QLQ-OV28. 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.

Figure 7 shows the results of the 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.

Thus, based on the EORTC QLQ-C30 and -OV28, niraparib treatment for up to approximately 30 months had a slightly positive effect or no effect on the overall HRQoL and specific symptoms.

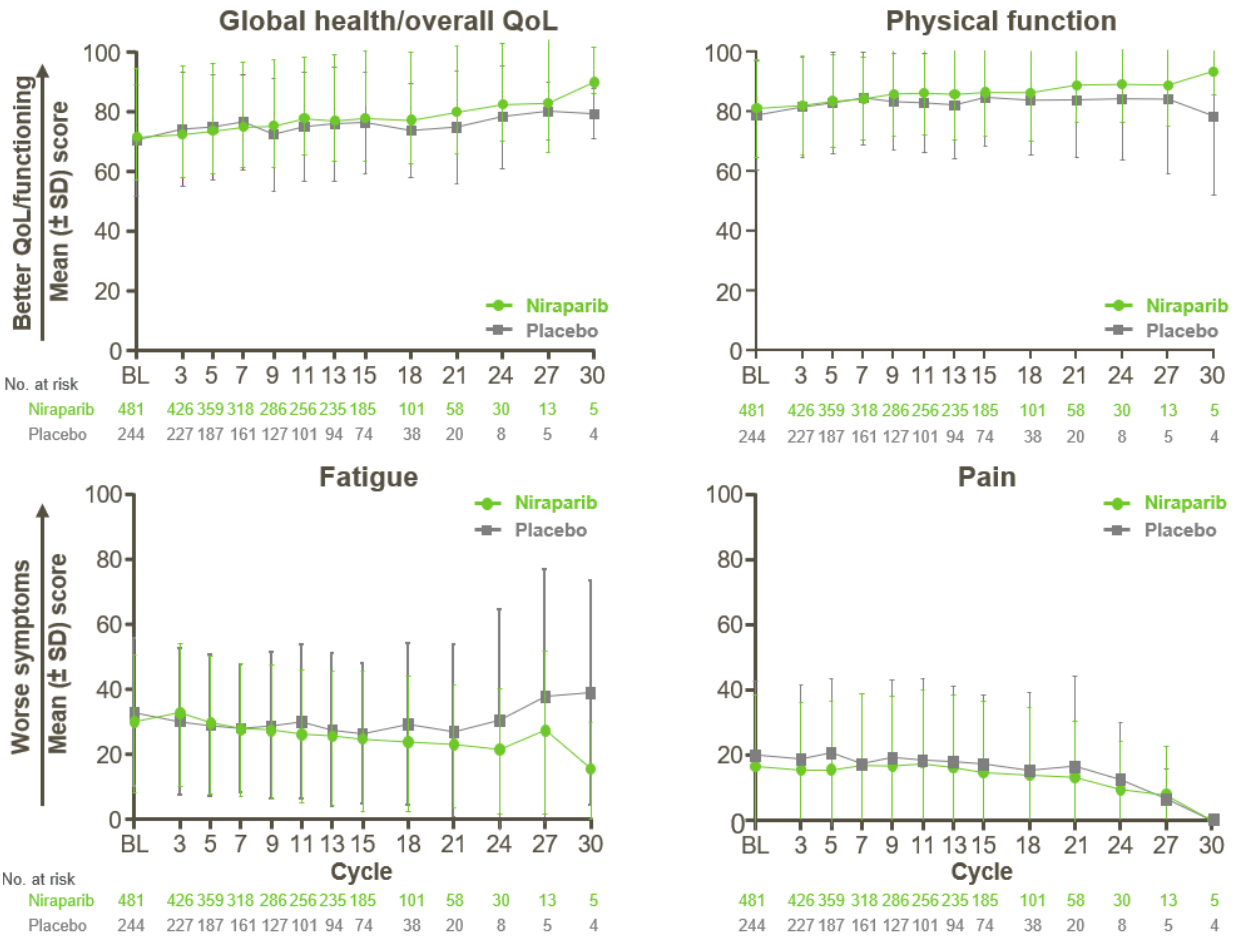
Figure 6 Results of the EORTC QLQ-OV28 in the full ITT population in PRIMA



Source: Pothuri B, et al 2020. Presented at ESMO 2020 [40]. Other CT side effects included: Hair loss, upset regarding hair loss, taste changes, muscle aches/pains, hearing and skin problems, and urinary frequency.

Abbreviations: BL, baseline; CT, chemotherapy; EORTC QLQ-OV28, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Ovarian Cancer Module; GI, gastrointestinal; ITT, intention-to-treat; SD, standard deviation.

Figure 7 Results of the EORTC QLQ-C30 in the full ITT population in PRIMA



Source: Pothuri B, et al 2020. Presented at ESMO 2020 [40].

Abbreviations: BL, baseline; CT, chemotherapy; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; ITT, intention-to-treat; QoL, quality of life; SD, standard deviation.

7.2 Olaparib (relevant for clinical question 1)

In the SOLO1 trial, HRQoL was assessed by use of the FACT-O TOI.

The adjusted mean change in the FACT-O TOI score from baseline to 2 years was 0.3 (-0.72; 1.32) in the olaparib group and 3.3 (1.84; 4.76) in the placebo group. The estimated difference in change from baseline of -3.00 (-4.78; -1.22) was not considered to be clinically meaningful (Table A3b).

Thus, based on the available data from the SOLO1 trial, olaparib treatment for 2 years does not seem to be associated with any change in HRQoL.

7.3 Bevacizumab (relevant for clinical questions 2 and 3)

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 (Table A3c). 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. By week 54 (i.e., at the end of bevacizumab maintenance treatment), the global HRQoL scores were increased to 69.7 (68.0; 71.4) in the bevacizumab group and 76.1 (74.3; 77.9) in the control group (Table A3d); thus, in both treatment groups, HRQoL improved 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 (Table A3d).

In summary, based on available data from the GOG-0218 and ICON7 trials, bevacizumab treatment was associated with a small improvement in HRQoL, although lower than the improvement in the control group.

7.4 Comparative analyses

For the reasons described in Section 4.3.5.1 and 4.3.5.2, indirect or narrative comparisons of niraparib, olaparib and bevacizumab are not considered meaningful.

However, based on the clinical trial data described above, 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.

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8. Other considerations

8.1 Suggested strategy for HRD testing in clinical practice in Denmark

Niraparib has demonstrated that it can be used across all advanced ovarian cancer patients as a first-line maintenance treatment option, regardless of biomarker status. However, GSK recognise HRD as an evolving biomarker and continues to recognise the value of platinum response, BRCA and HRD status by including the myChoice HRD/ CDx to evaluate subpopulations of ovarian cancer patients across the clinical programme for niraparib (NOVA, QUADRA and PRIMA trials).

HRD status in ovarian cancer patients may stratify patients for treatment and inform aspects of clinical efficacy such as PFS, but a restriction of treatment to HRD patients would require a diagnostic test to identify patients. Currently, there is no validated, broadly accessible test available in Denmark.

Since no test is available and relevant for niraparib, GSK cannot currently suggest a strategy for HRD testing in Denmark.

8.2 Progression-free survival 2 for niraparib

The results of a prespecified interim analysis of progression-free survival 2 (PFS2), which was a secondary endpoint in PRIMA, have recently been presented at the Society of Gynecologic Oncology Annual meeting on women's cancer (SGO 2020) [41]. Results for the HRD and HRP populations are presented in Table 12 together with the result for the overall population regardless of biomarker status. The data are immature, therefore definitive conclusions cannot be drawn at present; however, the preliminary data numerically favour niraparib maintenance treatment with point estimates <1 in all population groups analysed.

Thus, the preliminary data on PFS2 are supportive of a clinical benefit of niraparib therapy in a broad population of patients with newly-diagnosed advanced high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response following platinum-based chemotherapy.

Table 12 Analysis of PFS2 in the PRIMA trial

Population/subgroup	Treatment group	Hazard ratio (95% CI)	Data maturity
HRD	Niraparib (N=247) Placebo (N=126)	0.84 (0.49; 1.45)	15%
HRP	Niraparib (N=169) Placebo (N=80)	0.56 (0.34; 0.91)	27%
Overall	Niraparib (N=487) Placebo (N=246)	0.81 (0.58; 1.14)	20%

Source: Han et al [41].

Abbreviations: CI, confidence interval; HRD, homologous recombination deficient; HRP, homologous recombination proficient; N, total number of patients in the specific (sub)population; PFS2, progression-free survival 2.

8.3 Impact of niraparib on subsequent line of therapies

Patients with recurrent disease after primary treatment generally have a bad prognosis and the treatment goal is no longer cure in intent, but life prolongation and palliation. The prognosis is very variable; some patients can live for a long time and benefit from different subsequent treatment options. In recurrent ovarian cancer, one of the most important prognostic factors is the platinum-free interval, which describes the time from completion of platinum-based chemotherapy to recurrence. The platinum-free interval is also an important predictive factor, as it is closely

correlated with not only the probability of, but also the duration of, a possible response to new platinum-based chemotherapy [42].

Recurrent ovarian cancer is considered to be platinum sensitive when the recurrence occurs ≥ 6 months after the end of platinum-based treatment and when the treatment has had a primary effect.

PARP inhibitors cannot be used sequentially as there is yet no evidence for this [43].

For patients with BRCAm, the introduction of niraparib as first-line treatment will not affect later treatment lines, as these patients are already being treated with a PARP inhibitor.

For patients without BRCAm, treatment with niraparib as maintenance treatment in the first-line setting is expected to increase the chemotherapy-free interval and thus the chance of having platinum sensitive disease in the second-line setting. For patients eligible for treatment with bevazicumab, this represents a further treatment option in the second-line setting. Studies have shown PFS and OS benefit for patients treated with bevacizumab as maintenance treatment in combination with chemotherapy (platinum as well as other combinations) [44-48]. Thus, this strategy gives these patients the option of receiving a maintenance therapy as first-line as well as second-line treatment, with the opportunity to have longer chemotherapy-free intervals.

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9. References

1. Danish Medicines Council. Medicinrådets protokol for vurdering af niraparib til 1. linje vedligeholdelsesbehandling af avanceret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden. Version 1.0, 26 Nov 2020. Available from: https://medicinraadet.dk/media/frzbgcod/medicinr%C3%A5dets-protokol-for-vurdering-af-niraparib-til-nydiagnosticeret-kr%C3%A6ft-i-%C3%A6ggestokkene-vers-1-0_adlegacy.pdf
2. González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, *et al.* Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med. 2019;381(25):2391-402.
3. Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, *et al.* Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med. 2018;379(26):2495-505.
4. Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, *et al.* Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med. 2011;365(26):2473-83.
5. Monk BJ, Huang HQ, Burger RA, Mannel RS, Homesley HD, Fowler J, *et al.* Patient reported outcomes of a randomized, placebo-controlled trial of bevacizumab in the front-line treatment of ovarian cancer: a Gynecologic Oncology Group Study. Gynecol Oncol. 2013;128(3):573-8.
6. Tewari KS, Burger RA, Enserro D, Norquist BM, Swisher EM, Brady MF, *et al.* Final Overall Survival of a Randomized Trial of Bevacizumab for Primary Treatment of Ovarian Cancer. J Clin Oncol. 2019;37(26):2317-28.
7. Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, *et al.* A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med. 2011;365(26):2484-96.
8. Oza AM, Cook AD, Pfisterer J, Embleton A, Ledermann JA, Pujade-Lauraine E, *et al.* Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. Lancet Oncol. 2015;16(8):928-36.
9. Stark D, Nankivell M, Pujade-Lauraine E, Kristensen G, Elit L, Stockler M, *et al.* Standard chemotherapy with or without bevacizumab in advanced ovarian cancer: quality-of-life outcomes from the International Collaboration on Ovarian Neoplasms (ICON7) phase 3 randomised trial. Lancet Oncol. 2013;14(3):236-43.
10. Lorusso D, Guy H, Hamilton J, Samyshkin Y, Travers K, Hawkes C, *et al.* 366 Feasibility study of a network meta-analysis and unanchored population-adjusted indirect treatment comparison of niraparib, olaparib, and bevacizumab as maintenance therapies in patients with newly diagnosed advanced ovarian cancer. International Journal of Gynecologic Cancer. 2020;30(Suppl 4):A71-A2.
11. Dansk Gynækologisk Cancer Gruppe (DGCG). Ovariecancer – epidemiologi, arvelige faktorer, screening, sygdomsforløb, stadieinddeling og overlevelse2020. Available from: http://www.dgcg.dk/images/retningslinier/Ovariecancer/DGCG_epidemiologi_c_ovarii_AdmGodk_1809202640%20ovariecancer.pdf
12. Mathews CA MK, Colombo N, et al.,. Maintenance olaparib after platinumbased chemotherapy in patients (pts) with newly diagnosed advanced ovarian cancer (OC) and a BRCA mutation (BRCAm): efficacy by surgical and tumor status in the Phase III SOLO1 trial. J Clin Oncol. 2019;37.
13. Hamilton CA, Miller A, Miller C, Krivak TC, Farley JH, Chernofsky MR, *et al.* The impact of disease distribution on survival in patients with stage III epithelial ovarian cancer cytoreduced to microscopic residual: a Gynecologic Oncology Group study. Gynecol Oncol. 2011;122(3):521-6.
14. Elattar A, Bryant A, Winter-Roach BA, Hatem M, Naik R. Optimal primary surgical treatment for advanced epithelial ovarian cancer. Cochrane Database Syst Rev. 2011;2011(8):Cd007565.
15. Berek JS, Matulonis UA, Peen U, Ghatage P, Mahner S, Redondo A, *et al.* Safety and dose modification for patients receiving niraparib. Ann Oncol. 2018;29(8):1784-92.
16. Mirza MR, Benigno B, Dorum A, Mahner S, Bessette P, Barcelo IB, *et al.* Long-term safety in patients with recurrent ovarian cancer treated with niraparib versus placebo: Results from the phase III ENGOT-OV16/NOVA trial. Gynecol Oncol. 2020;159(2):442-8.
17. DiSilvestro P, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, *et al.* Efficacy of Maintenance Olaparib for Patients With Newly Diagnosed Advanced Ovarian Cancer With a BRCA Mutation: Subgroup Analysis Findings From the SOLO1 Trial. J Clin Oncol. 2020;38(30):3528-37.
18. Vergote I, Tropé CG, Amant F, Kristensen GB, Ehlen T, Johnson N, *et al.* Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med. 2010;363(10):943-53.

19. Chu CS, Rubin SC. Second-look laparotomy for epithelial ovarian cancer: a reappraisal. Curr Oncol Rep. 2001;3(1):11-8.
20. Azaïs H, Estevez JP, Foucher P, Kerbage Y, Mordon S, Collinet P. Dealing with microscopic peritoneal metastases of epithelial ovarian cancer. A surgical challenge. Surg Oncol. 2017;26(1):46-52.
21. Eskander RN, Kauderer J, Tewari KS, Mannel RS, Bristow RE, O'Malley DM*, et al.* Correlation between Surgeon's assessment and radiographic evaluation of residual disease in women with advanced stage ovarian cancer reported to have undergone optimal surgical cytoreduction: An NRG Oncology/Gynecologic Oncology Group study. Gynecol Oncol. 2018;149(3):525-30.
22. Chi DS, Ramirez PT, Teitcher JB, Mironov S, Sarasohn DM, Iyer RB*, et al.* Prospective study of the correlation between postoperative computed tomography scan and primary surgeon assessment in patients with advanced ovarian, tubal, and peritoneal carcinoma reported to have undergone primary surgical cytoreduction to residual disease 1 cm or less. J Clin Oncol. 2007;25(31):4946-51.
23. Danish Medicines Council. Baggrund for Medicinrådets anbefaling vedrørende niraparib som mulig standardbehandling til kræft i æggestokkene, æggelederne eller primær kræft i bughinden. Version 1.0, 30 Jan 2019. Available from: https://medicinraadet.dk/media/ayefu1dv/baggrund-for-medicinraadets-anbefaling-vedr-niraparib-til-kraeft-i-aeggestokkene-aeggelederne-eller-primaer-kraeft-i-bughinden-vers-1-0-m-bilag_adlegacy.pdf
24. Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A*, et al.* Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med. 2016;375(22):2154-64.
25. Banerjee S, Moore KN, Colombo N, Scambia G, Kim B, Oaknin A*, et al.* Maintenance olaparib for patients (pts) with newly diagnosed, advanced ovarian cancer (OC) and a BRCA mutation (BRCAm): 5-year (y) follow-up (f/u) from SOLO1. 811MO. Annals of Oncology [Internet]. 2020; 31(suppl 4):[S551-S89 pp.]. Available from: https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020/maintenance-olaparib-for-patients-pts-with-newly-diagnosed-advanced-ovarian-cancer-oc-and-a-brca-mutation-brcam-5-year-y-follow-up-f-u
26. Monberg MJ, Hall JP, Moon R, Higson O, McLaurin K, Dalvi T. Real-world bevacizumab utilization and outcomes in first-line ovarian cancer. Journal of Clinical Oncology. 2019;37(15_suppl):5578.
27. Hollis RL, Kiss Z, Roebuck N, Starkie-Camejo H, Heffernan K, Gourley C. 367 The use of real-world evidence from the Edinburgh Ovarian Cancer Database to explore a data gap in the PRIMA trial. Int J Gynecol Cancer [Internet]. 2020; 30(Suppl 4):[A72-3 pp.].
28. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). EPAR. Assessment report variation. Zejula (niraparib). 2020. Available from: https://www.ema.europa.eu/documents/variation-report/zejula-h-c-003943-ii-0019-epar-assessment-report-variation_en.pdf
29. Zejula: EPAR - Product information Annex 1. Summary of product characteristics. Available from: https://www.ema.europa.eu/documents/product-information/zejula-epar-product-information_en.pdf
30. LaFargue CJ, Dal Molin GZ, Sood AK, Coleman RL. Exploring and comparing adverse events between PARP inhibitors. Lancet Oncol. 2019;20(1):e15-e28.
31. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). EPAR. Assessment report variation. Lynparza (olaparib). 2019. Available from: https://www.ema.europa.eu/documents/variation-report/lynparza-h-c-003726-ii-0023-epar-assessment-report-variation_en.pdf
32. Danish Medicines Council. Baggrund for Medicinrådets anbefaling vedrørende olaparib til behandling af nydiagnosticeret avanceret high-grade BRCA-muteret kræft i æggestokkene, æggelederne eller primær kræft i bughinden. Version 1.0, 23 Oct 2019. Available from: https://medicinraadet.dk/media/l3tmaarp/baggrund-for-medicinraadets-anbefaling-vedr-olaparib-til-nydiagnosticeret-kraeft-i-aeggestokkene-vers-1-0-med-bilag_adlegacy.pdf
33. Lynparza: EPAR - Product information Annex 1. Summary of product characteristics. Available from: https://www.ema.europa.eu/documents/product-information/lynparza-epar-product-information_en.pdf
34. Sun K, Mikule K, Wang Z, Poon G, Vaidyanathan A, Smith G*, et al.* A comparative pharmacokinetic study of PARP inhibitors demonstrates favorable properties for niraparib efficacy in preclinical tumor models. Oncotarget. 2018;9(98):37080-96.
35. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). EPAR. Assessment report variation. Avastin (bevacizumab). 2011. Available from:

https://www.ema.europa.eu/documents/variation-report/avastin-h-c-582-ii-0041-epar-assessment-report-variation_en.pdf
36. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). EPAR. Assessment report variation. Avastin (bevacizumab).2017. Available from: https://www.ema.europa.eu/en/documents/variation-report/avastin-h-c-582-ii-0092-epar-assessment-report-variation_en.pdf
37. Avastin: EPAR - Product information Annex 1. Summary of product characteristics. Available from: https://www.ema.europa.eu/documents/product-information/avastin-epar-product-information_en.pdf
38. Randall LM, Monk BJ. Bevacizumab toxicities and their management in ovarian cancer. Gynecol Oncol. 2010;117(3):497-504.
39. Freyer G, Pothuri B, Han S, Chase D, Monk B, Heitz F*, et al.* 17 Safety and patient-reported outcomes in patients receiving niraparib in the PRIMA/ENGOT-OV26/GOG-3012 trial. Int J Gynecol Cancer. 2020;30(Suppl 3):A12-A3.
40. Pothuri B, Han S, Chase D, Heitz F, Burger R, Gaba L*, et al.* Patient-reported outcomes (PROs) in patients (pts) receiving niraparib in the PRIMA/ENGOT-OV26/GOG-3012 trial. Annals of oncology. 2020;31:S612-S3.
41. Han SN, Monk BJ, Gonzalez-Martin A. Time to first subsequent therapy (TFST) and progression-free survival 2 (PFS2) from the phase 3 randomized, double-blind PRIMA/ENGOT-OV26/GOG-3012 study in patients with newly diagnosed ovarian cancer. Gynecologic Oncology. 2020;159:18-9.
42. Dansk Gynækologisk Cancer Gruppe (DGCG). Retningslinier for visitation, diagnostik, behandling og opfølgning af epitelial ovarie-, tuba- og primær peritonealcancer samt borderline tumorer. 5. udgave 2016.2016. Available from: http://www.dgcg.dk/images/Grupper/Ovariecancergruppen/Retningslinier2016/nye_filer/Kap_5.pdf
43. Danish Medicines Council. Baggrund for Medicinrådets behandlingsvejledning vedrørende lægemidler til BRCA-muteret kræft i æggestokkene, æggelederne eller primær kræft i bughinden. Version 1.0, 24 april 2020.2020. Available from: https://medicinraadet.dk/media/pbccncwr/baggrund_for_medicinr%C3%A5dets_behandlingsvejledning_vedr-_l%C3%A6gemidler_til_brca-muteret_kr%C3%A6ft_i_%C3%A6ggestokkene-vers-_1-0_adlegacy.pdf
44. Parmar MK, Ledermann JA, Colombo N, du Bois A, Delaloye JF, Kristensen GB*, et al.* Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. Lancet. 2003;361(9375):2099-106.
45. Aghajanian C, Blank SV, Goff BA, Judson PL, Teneriello MG, Husain A*, et al.* OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol. 2012;30(17):2039-45.
46. Aghajanian C, Goff B, Nycum LR, Wang YV, Husain A, Blank SV. Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. Gynecol Oncol. 2015;139(1):10-6.
47. Coleman RL, Brady MF, Herzog TJ, Sabbatini P, Armstrong DK, Walker JL*, et al.* Bevacizumab and paclitaxel-carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2017;18(6):779-91.
48. Pujade-Lauraine E, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G*, et al.* Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. J Clin Oncol. 2014;32(13):1302-8.

10. Appendices

10.1 Literature search

Table A1a Inclusion and exclusion criteria	
Inclusion criteria	**Population:** Newly diagnosed patients with advanced (stage III-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 **Interventions:** Niraparib **Comparators:** Olaparib, bevacizumab, or placebo **Outcomes:** OS, PFS, discontinuations due to ADRs (or AEs), proportion of patients with CTCAE grade 3-4 ADRs (or AEs), quality of life **Settings (if applicable):** No restrictions **Study design:** Randomised, controlled trial, open-label studies acceptable **Language restrictions:** English or Scandinavian languages **Other search limits or restrictions applied:** None
Exclusion criteria	**Population:** Other than defined in the inclusion criteria **Interventions:** Other than defined in the inclusion criteria **Comparators:** Other than those defined in the inclusion criteria **Outcomes:** Studies not reporting at least one of the critical or important outcomes **Settings (if applicable):** NA **Study design:** Non-randomised **Language restrictions:** Other languages than English or Scandinavian languages **Other search limits or restrictions applied:** None

Abbreviations: ADR, adverse drug reactions; AE, adverse events; CTCAE, Common Terminology Criteria for Adverse Events; NA, not applicable; OS, overall survival; PFS, progression free survival.

10.1.1 Literature searches performed

Both searches were performed on 27 November 2020. No date limit was applied. Pictures of the actual searches performed in MEDLINE and CENTRAL are included in Figure 8 and Figure 9, respectively.

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Figure 8 MEDLINE search

Search	Actions	Details	Query	Results
#19	•••	›	Search: **#14 NOT #18** Sort by: **Publication Date**	56
#18	•••	›	Search: **#15 OR #16 OR #17** Sort by: **Publication Date**	11,363,465
#17	•••	›	Search: **Review[pt] OR Systematic Review[pt] OR Meta-Analysis[pt] OR review[ti] OR meta-analys*[ti]** Sort by: **Publication Date**	3,002,469
#16	•••	›	Search: **Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR case report[ti]** Sort by: **Publication Date**	4,090,178
#15	•••	›	Search: **Animals[mh] NOT Humans[mh]** Sort by: **Publication Date**	4,760,687
#14	•••	›	Search: **#12 AND #13** Sort by: **Publication Date**	114
#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]** Sort by: **Publication Date**	1,378,180
#12	•••	›	Search: **#10 AND #11** Sort by: **Publication Date**	309
#11	•••	›	Search: **niraparib[nm] OR niraparib[tiab] OR Zejula*[tiab] OR 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]** Sort by: **Publication Date**	39,566
#10	•••	›	Search: **#7 AND (#8 OR #9)** Sort by: **Publication Date**	3,234
#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]** Sort by: **Publication Date**	118,560
#8	•••	›	Search: **newly diagnosed[tiab]** Sort by: **Publication Date**	50,352
#7	•••	›	Search: **#1 OR #2 OR #3 OR #4 OR #5 OR #6** Sort by: **Publication Date**	111,451
#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])** Sort by: **Publication Date**	6,438
#5	•••	›	Search: **Peritoneal Neoplasms[mh]** Sort by: **Publication Date**	16,097
#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])** Sort by: **Publication Date**	1,808
#3	•••	›	Search: **Fallopian Tube Neoplasms[mh]** Sort by: **Publication Date**	2,913
#2	•••	›	Search: **(ovary[ti] OR ovari*[ti]) AND (cancer[ti] OR carcinoma*[ti] OR neoplasm*[ti] OR tumor*[ti] OR tumour*[ti])** Sort by: **Publication Date**	58,029
#1	•••	›	Search: **Ovarian Neoplasms[mh]** Sort by: **Publication Date**	84,816

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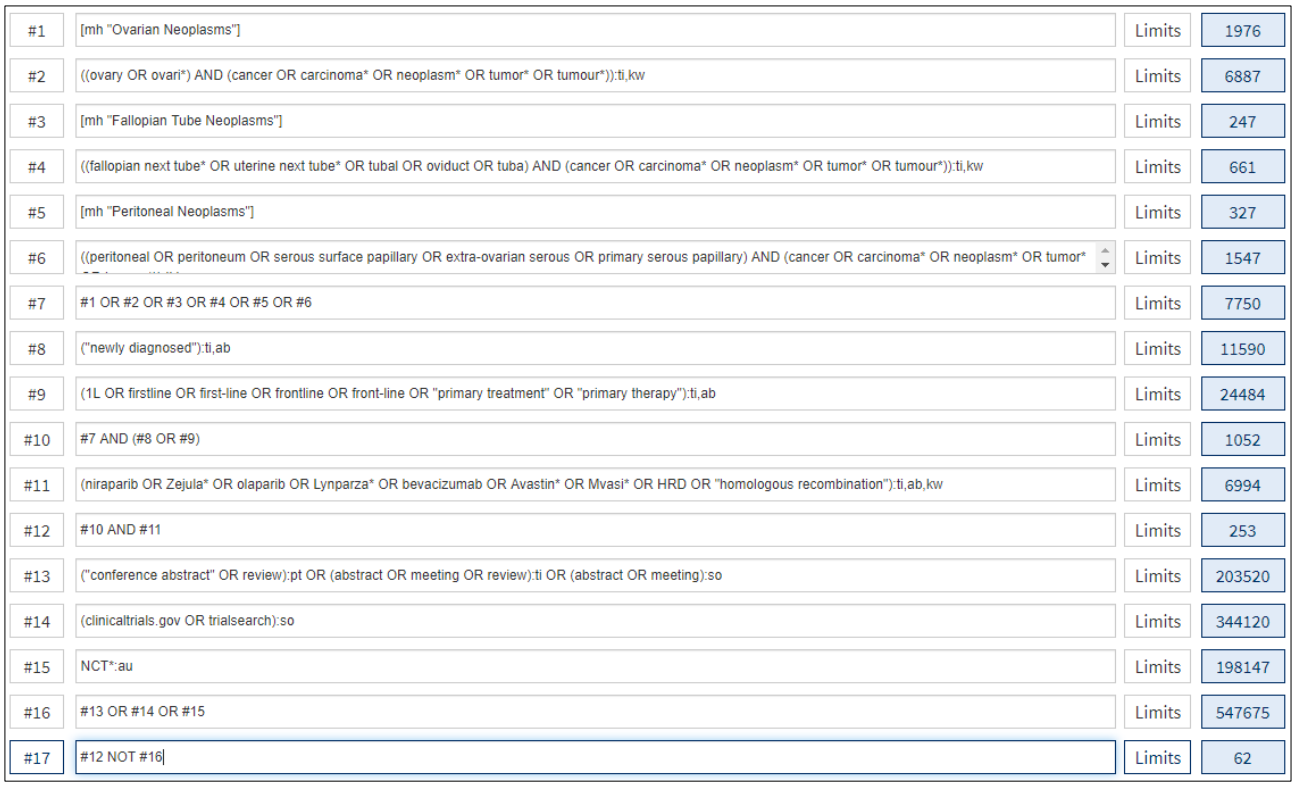
Figure 9 CENTRAL search



#1	[mh "Ovarian Neoplasms"]	Limits	1976
#2	((ovary OR ovari*) AND (cancer OR carcinoma* OR neoplasm* OR tumor* OR tumour*)):ti,kw	Limits	6887
#3	[mh "Fallopian Tube Neoplasms"]	Limits	247
#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	Limits	661
#5	[mh "Peritoneal Neoplasms"]	Limits	327
#6	((peritoneal OR peritoneum OR serous surface papillary OR extra-ovarian serous OR primary serous papillary) AND (cancer OR carcinoma* OR neoplasm* OR tumor*	Limits	1547
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	Limits	7750
#8	("newly diagnosed"):ti,ab	Limits	11590
#9	(1L OR firstline OR first-line OR frontline OR front-line OR "primary treatment" OR "primary therapy"):ti,ab	Limits	24484
#10	#7 AND (#8 OR #9)	Limits	1052
#11	(niraparib OR Zejula* OR olaparib OR Lynparza* OR bevacizumab OR Avastin* OR Mvasi* OR HRD OR "homologous recombination"):ti,ab,kw	Limits	6994
#12	#10 AND #11	Limits	253
#13	("conference abstract" OR review):pt OR (abstract OR meeting OR review):ti OR (abstract OR meeting):so	Limits	203520
#14	(clinicaltrials.gov OR trialsearch):so	Limits	344120
#15	NCT*:au	Limits	198147
#16	#13 OR #14 OR #15	Limits	547675
#17	#12 NOT #16	Limits	62

Of the 62 results, 61 were in "Trials" and screened.

Table A1b List of studies excluded based on full-text read

Reference	Reason for exclusion
DiSilvestro P, et al. Efficacy of maintenance olaparib for patients with newly diagnosed advanced ovarian cancer with a BRCA mutation: Subgroup analysis findings from the SOLO1 trial. J Clin Oncol. 2020;38(30):3528-37.	SOLO1, subgroup analysis of PFS, no relevant subgroups
Garcia K, et al. Addition of bevacizumab to paclitaxel/carboplatin in first-line management of advanced ovarian cancer: results of the GOG 0218 phase III study. Clinical ovarian cancer. 2010;3(2):E1-E5.	Meeting highlights with initial presentation of GOG-0218 data. No relevant data not included in primary publication (Burger 2011)
Miller RE, et al. Olaparib maintenance for first-line treatment of ovarian cancer: will SOLO1 reset the standard of care? Future Oncol. 2019;15(16):1845-53.	Clinical trial evaluation. SOLO1 results in the context of the current management of advanced ovarian cancer. No additional data.

10.2 Main characteristics of included studies

Table A2a Main study characteristics for the PRIMA trial	
Trial name	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).
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	PRIMA was a randomised, double-blind, placebo-controlled, parallel-group, phase 3 trial conducted at 181 clinical sites (4 in Denmark) in 20 countries. Within 12 weeks after completion of the last dose of platinum-based chemotherapy, the patients were randomly assigned in a 2:1 ratio to receive oral niraparib or placebo once daily in 28-day cycles for 36 months or until disease progression. Randomisation was performed in a double-blind manner with the use of an interactive web-response system and was stratified according to clinical response after first-line platinum-based chemotherapy (complete or partial response), receipt of neoadjuvant chemotherapy (yes or no) and status regarding tumour homologous recombination (deficient, proficient or not determined). Niraparib or placebo was administered continuously until the objective identification of disease progression on imaging, provided that the patient was receiving benefit and did not meet any other criteria for discontinuation, as defined in the protocol. Patients receiving placebo were not allowed to cross over to receive niraparib treatment during the trial. Tumour assessment was performed via a CT or MRI scan at screening and then every 12 weeks until treatment discontinuation. Blinded, independent central review (BICR) were used to define the date of disease progression according to RECIST version 1.1, and an identical schedule of assessments was used for the two study groups. Clinical progression was reviewed if an increased CA125 level was accompanied by histologic proof or clinical symptoms, as specified in the protocol. HRD was defined as the presence of a BRCA deleterious mutation and/or a test result indicating other genomic abnormalities. PROs were collected regularly from the screening visit until 24 weeks after the last dose of niraparib or placebo. AEs, laboratory testing, measurement of vital signs and physical examinations were monitored throughout the treatment period. The study is currently ongoing for follow up.

Table A2a Main study characteristics for the PRIMA trial	
Follow-up time	The patients were treated for 36 months or until disease progression. The trial is event-driven, and the primary efficacy analysis was performed after disease progression or death had occurred in 154 patients with HRD and in 386 patients in the overall population. As of the data cut off on 17 May 2019, a total of 246 patients (177 patients in the niraparib arm and 69 patients in the placebo arm) were still receiving study treatment. Patients are being followed for overall survival and other secondary objectives.
Population (inclusion and exclusion criteria) **(from clinicaltrials.gov)**	*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.
Intervention	• Niraparib 200/300 mg once daily (N=487) • Placebo once daily (N=246) 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. Therefore, the PRIMA protocol was amended on 27 November 2017, incorporating individualised dosing whereby patients with a baseline body weight of <77 kg, a platelet count of <150,000/µL or both, received a starting dose of 200 mg once daily. The dose could be reduced further if patients experienced toxicities.

Table A2a Main study characteristics for the PRIMA trial

Baseline characteristics[1]

	Niraparib		Placebo	
	HRD population (N=247)	Overall population (N=487)	HRD population (N=126)	Overall population (N=246)
Median age (range); years	58 (32-83)	62 (32-85)	58 (33-82)	62 (33-88)
ECOG score; n (%)[2]				
0	182 (73.7)	337 (69.2)	97 (77.0)	174 (70.7)
1	65 (26.3)	150 (30.8)	29 (23.0)	72 (29.3)
FIGO stage; n (%)				
III	161 (65.2)	318 (65.3)	78 (61.9)	158 (64.2)
A	4 (1.6)	7 (1.4)	1 (0.8)	4 (1.6)
B	10 (4.0)	16 (3.3)	9 (7.1)	12 (4.9)
C	140 (56.7)	285 (58.5)	67 (53.2)	138 (56.1)
Not specified	7 (2.8)	10 (2.1)	1 (0.8)	4 (1.6)
IV	86 (34.8)	169 (34.7)	48 (38.1)	88 (35.8)
Primary tumour location; n (%)				
Ovary	201 (81.4)	388 (79.7)	105 (83.3)	201 (81.7)
Fallopian tube	32 (13.0)	65 (13.3)	13 (10.3)	32 (13.0)
Peritoneum	14 (5.7)	34 (7.0)	8 (6.3)	13 (5.3)
Histologic type; n (%)[3]				
Serous	234 (94.7)	465 (95.5)	116 (92.1)	230 (93.5)
Endometroid	5 (2.0)	11 (2.3)	6 (4.8)	9 (3.7)
Other	8 (3.2)	11 (2.3)	4 (3.2)	6 (2.4)
Receipt of neoadjuvant therapy; n (%)				
Yes	156 (63.2)	322 (66.1)	80 (63.5)	167 (67.9)
No	91 (36.8)	165 (33.9)	46 (36.5)	79 (32.1)
Clinical response after platinum-based chemotherapy; n (%)				
Complete response	185 (74.9)	337 (69.2)	93 (73.8)	172 (70.0)
Partial response	62 (25.1)	150 (30.8)	33 (26.2)	74 (30.0)
CA125 level; n (%)				
≤ULN	236 (95.5)	450 (92.4)	120 (95.2)	226 (91.9)
>ULN	9 (3.6)	34 (7.0)	5 (4.0)	18 (7.3)
Missing data	2 (0.8)	3 (0.6)	1 (0.8)	2 (0.8)
No. of cycles of platinum-based chemotherapy; n (%)				
6	165 (66.8)	333 (68.4)	84 (66.7)	170 (69.1)
7-9	52 (21.1)	124 (25.5)	28 (22.2)	62 (25.2)
Missing data	30 (12.1)	30 (6.2)	14 (11.1)	14 (5.7)

[1] Percentages may not total 100 because of rounding.

[2] According to ECOG performance-status evaluation, a score of 0 indicates that the patient is fully active and able to carry on all predisease performance without restriction, and a score of 1 indicates that the patient is restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature.

[3] Histologic data for one patient were missing, but a serous tumour was identified on cytologic analysis.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HRD, homologous-recombination deficiency; n, number of subjects with characteristic; N, number of randomised subjects; ULN, upper limit of normal range

Table A2a Main study characteristics for the PRIMA trial	
Primary and secondary 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. ○ FOSI ○ EQ-5D-5L ○ EORTC-QLQ-C30 ○ EORTC-QLQ-OV28
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

Table A2a Main study characteristics for the PRIMA trial	
	were not adjusted for multiple comparisons. All P values are reported at a two-sided significance level of 0.05.
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 the 10% level (P<0.10), this may have been taken as evidence of heterogeneity of the treatment effect across the subgroup categories.

Table A2b Main study characteristics for the SOLO1 trial	
Trial name	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.
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 [3].
Study type and design	SOLO1 was a randomised, double-blind, placebo-controlled, phase 3 trial conducted in 15 countries. There were no sites in Denmark. After completion of platinum-based chemotherapy, patients were randomly assigned, in a 2:1 ratio, to receive olaparib tablets (300 mg twice daily) or placebo. Randomisation was performed centrally using a block design, with stratification according to clinical response after platinum-based chemotherapy (complete or partial). Patients were assigned to a trial group through an interactive Web-based or voice-response system. The trial intervention was continued until investigator-assessed objective disease progression on imaging (according to modified RECIST, version 1.1, provided that the patient was having a benefit and did not meet any discontinuation criteria. Patients who had no evidence of disease at 2 years stopped receiving the trial intervention, but patients who had a partial response at 2 years were permitted to continue receiving the trial intervention in a blinded manner. Crossover between trial groups was not specified in the protocol. After discontinuation of the trial intervention, patients could receive treatments at the investigators' discretion.
Follow-up time	The patients were treated for up to 3 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.
Population (inclusion and exclusion criteria) **(from clinicaltrials.gov)**	*Main 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).

Table A2b Main study characteristics for the SOLO1 trial	
	• 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 CA125 level, following completion of this chemotherapy course. Patients with stable disease on the post-treatment scan at completion of first-line platinum-containing therapy were not eligible for the trial. • Patients were to be randomised within 8 weeks of their last dose of chemotherapy. *Main exclusion criteria* • BRCA1 and/or BRCA2 mutations that were considered to be non-detrimental (e.g., "variants of uncertain clinical significance" or "variant of unknown significance" or "variant, favour 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 had been performed before randomisation to the trial. (Patients who, at the time of diagnosis, were deemed to be unresectable and underwent only a biopsy or oophorectomy but then went on to receive chemotherapy and interval debulking surgery were eligible). • Patients who had previously been diagnosed and treated for earlier stage ovarian, fallopian tube or primary peritoneal cancer. • Patients who had 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 had received prior adjuvant chemotherapy for localised breast cancer were eligible, provided that it was completed more than three years prior to registration, and that the patient remained free of recurrent or metastatic disease). • Patients with synchronous primary endometrial cancer unless both of the following criteria were 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 were not eligible.
Intervention	• Olaparib tablets 300 mg twice daily (N=260). • Placebo tablets twice daily (N=131). Dose reduction of olaparib to 250 mg and subsequently 200 mg was permitted following confirmation of toxicity.

Table A2b Main study characteristics for the SOLO1 trial

Baseline characteristics[1]

	Olaparib (N=260)	Placebo (N=131)
Median age (range); years	53.0 (29-82)	53.0 (31-84)
Response after platinum-based chemotherapy; n (%)[2]		
Clinical complete response	213 (81.9)	107 (81.7)
Partial response	47 (18.1)	24 (18.3)
No. of cycles of platinum-based chemotherapy; n (%)		
4	2 (0.8)	0
5	2 (0.8)	1 (0.8)
6	198 (76.2)	106 (80.9)
7	17 (6.5)	10 (7.6)
8	18 (6.9)	7 (5.3)
9	23 (8.8)	7 (5.3)
ECOG performance status; n (%)[3]		
0	200 (76.9)	105 (80.2)
1	60 (23.1)	25 (19.1)
Missing	0	1 (0.8)
Primary tumour location		
Ovary	220 (84.6)	113 (86.3)
Fallopian tubes	22 (8.5)	11 (8.4)
Primary peritoneal	15 (5.8)	7 (5.3)
Other[4]	3 (1.2)	0
FIGO stage; n (%)		
III	220 (84.6)	105 (80.2)
IV	40 (15.4)	26 (19.8)
CA125 level; n (%)		
≤ULN	247 (95.0)	123 (93.9)
>ULN	13 (5.0)	7 (5.3)
Missing data	0	1 (0.8)
Histology; n (%)		
Serous	246 (94.6)	130 (99.2)
Endometroid	9 (3.5)	0
Mixed serous/endometrioid	5 (1.9)	1 (0.8)
BRCA mutation; n (%)		
BRCA1	191 (73.5)	91 (69.5)
BRCA2	66 (25.4)	40 (30.5)
Both *BRCA1* and *BRCA2*	3 (1.2)	0
BRCA mutation status; n (%)		
Myriad/BGI-confirmed germline *BRCA* mutation[5]	257 (98.8)	131 (100.0)
FMI-confirmed somatic *BRCA* mutation	2 (0.8)	0
History of cytoreductive surgery; n (%)		
Upfront surgery	161 (61.9)	85 (64.9)
Residual macroscopic disease	37 (23.0)	22 (25.9)
No residual macroscopic disease	123 (76.4)	62 (72.9)
Unknown	1 (0.6)	1 (1.2)
Interval cytoreductive surgery	94 (36.2)	43 (32.8)
Residual macroscopic disease	18 (19.1)	7 (16.3)
No residual macroscopic disease	76 (80.9)	36 (83.7)
No surgery	4 (1.5)	3 (2.3)

Table A2b Main study characteristics for the SOLO1 trial

[1] Percentages may not total 100 because of rounding.
[2] Clinical complete response was defined as no evidence of (RECIST) measurable or non-measurable disease on the post-treatment scan and a normal CA125 level. Partial response was defined as ≥30% reduction in tumour volume from the start to the end of chemotherapy or no evidence of disease on the post-treatment scan, but with a CA125 level which had not decreased to within the normal range.
[3] According to ECOG performance-status evaluation, a score of 0 indicates that the patient is fully active and able to carry on all pre-disease performance without restriction, and a score of 1 indicates that the patient is restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature.
[4] Other includes ovary, fallopian tube, peritoneum, and omentum (n=1), ovary and peritoneum (n=1), and tubo-ovary (n=1).
[5] Myriad/BGI or locally reported; the five patients from China had germline BRCA mutation testing performed within China, using the BGI test.
Abbreviations: BGI, BGI Genomics; BRCA, BReast CAncer; CA125, cancer antigen 125; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; FMI, Foundation Medicine; n, number of subjects with characteristic; N, number of randomised subjects; RECIST, Response Evaluation Criteria in Solid Tumours; ULN, upper limit of normal range.

Primary and secondary 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.
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).

Table A2b Main study characteristics for the SOLO1 trial	
Subgroup analyses	Subgroup analyses of the PFS endpoint were performed in the following prespecified subgroups: • Clinical response after chemotherapy (complete or partial) • ECOG performance status (normal activity or restricted activity) • CA125 level (≤ULN or >ULN) • Germline BRCA mutation (BRCA1, BRCA2, BRCA1 and BRCA2, or none) • Age (<65 years or ≥65 years) • FIGO stage of disease at initial diagnosis (III or IV) • Presence of residual macroscopic disease after debulking surgery performed before trial entry • Neoadjuvant chemotherapy (yes or no) The subgroup analyses were performed to evaluate the HR with 95% CI for disease progression or death in patients treated with olaparib versus placebo.

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Table A2c Main study characteristics for the GOG218 study	
Trial name	A phase 3 trial of carboplatin and paclitaxel plus placebo versus carboplatin and paclitaxel plus concurrent bevacizumab (NSC # 704865) followed by placebo, versus carboplatin and paclitaxel plus concurrent and extended bevacizumab, in women with newly diagnosed, previously untreated, stage III or IV epithelial ovarian, primary peritoneal or fallopian tube cancer.
NCT number	NCT00262847
Objective	The primary objectives of the trial were: 1. To determine if the addition of 5 concurrent cycles of bevacizumab to 6 cycles of standard therapy (carboplatin and paclitaxel) increased the duration of PFS when compared to 6 cycles of standard therapy alone in women with newly diagnosed stage III (with any gross residual disease) and stage IV, epithelial ovarian, peritoneal primary or fallopian tube cancer. 2. To determine if the addition of 5 concurrent cycles of bevacizumab plus extended bevacizumab for 16 cycles beyond the 6 cycles of standard therapy (carboplatin and paclitaxel) increased PFS when compared to 6 cycles of standard therapy in the above women.
Publications – title, author, journal, year	Incorporation of bevacizumab in the primary treatment of ovarian cancer. Burger RA, et al; for the Gynecologic Oncology Group. N Engl J Med. 2011 [4]. Patient reported outcomes of a randomized, placebo-controlled trial of bevacizumab in the front-line treatment of ovarian cancer: A Gynecologic Oncology Group Study. Monk BJ, et al. Gynecol Oncol. 2013 [5]. Final Overall Survival of a Randomized Trial of Bevacizumab for Primary Treatment of Ovarian Cancer. Tewari KS, et al. J Clin Oncol. 2019 [6].
Study type and design	GOG-0218 was a double-blind, placebo-controlled phase 3 trial investigating the integration of bevacizumab into front-line ovarian cancer therapy. The trial was conducted in 4 countries not including Denmark (Canada, Japan, South Korea, USA). Patients were stratified on the basis of GOG performance-status score and cancer stage and debulking status (stage III cancer and maximal residual lesion diameter ≤1 cm versus stage III cancer and maximal residual lesion diameter >1 cm versus stage IV cancer) before being randomly assigned to a treatment group. Disease was assessed before cycle 1 by means of CT or MRI of at least the abdomen and pelvis, measurement of the serum CA125 level, and physical examination. Each of the three trial regimens comprised 22 3-week cycles with intravenous infusions on day 1, with the first 6 cycles consisting of standard chemotherapy with carboplatin at an area under the curve (AUC) of 6 and paclitaxel at a dose of 175 mg per square meter of body-surface area. Control treatment was chemotherapy with placebo added in cycles 2 through 22; bevacizumab-initiation treatment was chemotherapy with bevacizumab (15 mg per kilogram of body weight) added in cycles 2 through 6 and placebo added in cycles 7 through 22. Bevacizumab-throughout treatment was chemotherapy with bevacizumab added in cycles 2 through 22. Bevacizumab or placebo was initiated at cycle 2, rather than cycle 1, to reduce the risk of wound-healing complications. Treatment was discontinued at the onset of disease progression, unacceptable toxic effects, completion of all 22 cycles, or withdrawal — whichever came first. In patients without progression, imaging was repeated after treatment cycles 3, 6, 10, 14, 18, and 22. Serum CA125 levels were measured, and physical examinations were performed at the beginning of

Table A2c Main study characteristics for the GOG218 study	
	each cycle for cycles 1 through 6 (chemotherapy) and at the beginning of alternate cycles for cycles 7 through 22 (extended therapy). After completing trial treatment, disease assessments were repeated every 3 months for 2 years, then every 6 months for 3 years, and then annually. Safety was monitored during each cycle.
Follow-up time	Treatment was discontinued at the onset of disease progression, unacceptable toxic effects, completion of all 22 cycles, or withdrawal — whichever came first. After completing trial treatment, disease assessments were repeated every 3 months for 2 years, then every 6 months for 3 years, and then annually.
Population (inclusion and exclusion criteria) **(from clinicaltrials.gov)**	*Main inclusion criteria:* • Patients with a histologic diagnosis of epithelial ovarian cancer, peritoneal primary carcinoma or fallopian tube cancer; FIGO stage III with any gross (macroscopic or palpable) residual disease or FIGO stage IV, defined surgically at the completion of initial abdominal surgery and with appropriate tissue available for histologic evaluation; the minimum surgery required was an abdominal surgery providing tissue for histologic evaluation and establishing and documenting the primary site and stage, as well as a maximal effort at tumour debulking; if additional surgery was performed, it should have been in accordance with appropriate surgery for ovarian or peritoneal carcinoma described in the GOG Surgical Procedures Manual; however, the surgeon was not required to have performed all of the items contained in this section of the GOG Surgical Procedures Manual; those patients with stage III cancer in which the largest maximal diameter of any residual tumour implant at the completion of the initial surgery was no greater than 1 cm were to be defined as "optimal;" all others were to be defined as "suboptimal;" measurable disease on post-operative imaging studies was not required for eligibility. • Patients with the following histologic epithelial cell types were eligible: serous adenocarcinoma, endometrioid adenocarcinoma, mucinous adenocarcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, transitional cell carcinoma, malignant Brenner's Tumour, or adenocarcinoma not otherwise specified; however, the histologic features of the tumour were to be compatible with a primary Müllerian epithelial adenocarcinoma; if doubt existed, it was recommended that the investigator should have the slides reviewed by an independent pathologist or, if necessary, the Pathology Co-Chair, prior to entry; patients could have co-existing fallopian tube carcinoma in-situ so long as the primary origin of invasive tumour was ovarian, peritoneal or fallopian tube. • Patients with a GOG Performance Status of 0, 1, or 2. • Patients were to be entered between 1 and 12 weeks after initial surgery performed for the combined purpose of diagnosis, staging and cytoreduction. • Patients with measurable and non-measurable disease were eligible; patients may or may not have had cancer-related symptoms. • Patients who had met the pre-entry requirements. • Patients in this trial could receive ovarian oestrogen +/- progestin replacement therapy as indicated at the lowest effective dose(s) for control of menopausal symptoms at any time, but not progestins for management of anorexia while on protocol directed therapy or prior to disease progression.

Table A2c Main study characteristics for the GOG218 study

	Main exclusion criteria: • Patients with a current diagnosis of borderline epithelial ovarian tumour (formerly "tumours of low malignant potential") or recurrent invasive epithelial ovarian, primary peritoneal or fallopian tube cancer treated with surgery only (such as patients with stage IA or IB low grade epithelial ovarian or fallopian tube cancers) were not eligible; patients with a prior diagnosis of a borderline tumour that was surgically resected and who subsequently developed an unrelated, new invasive epithelial ovarian, peritoneal primary or fallopian tube cancer were eligible, provided that they had not received prior chemotherapy for any ovarian tumour. • Patients who had received prior radiotherapy to any portion of the abdominal cavity or pelvis were excluded; prior radiation for localised cancer of the breast, head and neck, or skin was permitted, provided that it was completed more than three years prior to registration, and the patient remained free of recurrent or metastatic disease. • Patients who had received prior chemotherapy for any abdominal or pelvic tumour including neo-adjuvant chemotherapy for their ovarian, primary peritoneal or fallopian tube cancer were excluded; patients may have received prior adjuvant chemotherapy for localised breast cancer, provided that it was completed more than three years prior to registration, and that the patient remained free of recurrent or metastatic disease. • Patients who had received any targeted therapy (including but not limited to vaccines, antibodies, tyrosine kinase inhibitors) or hormonal therapy for management of their epithelial ovarian or peritoneal primary cancer. • Patients with synchronous primary endometrial cancer, or a history of primary endometrial cancer, were excluded, unless all of the following conditions were met: stage not greater than IB; no more than superficial myometrial invasion, without vascular or lymphatic invasion; no poorly differentiated subtypes, including papillary serous, clear cell or other FIGO grade 3 lesions. • With the exception of non-melanoma skin cancer and other specific malignancies as noted above, patients with other invasive malignancies who had (or have) any evidence of the other cancer present within the last five years or whose previous cancer treatment contraindicates this protocol therapy were excluded. • Patients with GOG Performance Grade of 3 or 4. • Patients who had received prior therapy with any anti-vascular endothelial growth factor (VEGF) drug, including bevacizumab.
Intervention	• Bevacizumab maintenance group (paclitaxel, carboplatin, bevacizumab) (N=623): Paclitaxel and carboplatin as in the placebo group. Beginning in course 2, patients also received bevacizumab IV over 30-90 minutes on day 1. Treatment repeated every 21 days for 6 courses. Beginning in course 7, patients received bevacizumab alone IV over 30-90 minutes on day 1. Treatment with bevacizumab repeated every 21 days for up to 22 courses in the absence of disease progression or unacceptable toxicity. • Bevacizumab initiation group (placebo, paclitaxel, carboplatin, bevacizumab) (N=625): Paclitaxel and carboplatin as in the placebo group. Beginning in course 2, patients also received bevacizumab IV over 30-90 minutes on day 1. Treatment repeated every 21 days for 6 courses. Beginning in course 7, patients received placebo alone IV over 30-90 minutes on day 1. Treatment with placebo repeats every 21 days for up to 22 courses in the absence of disease progression or unacceptable toxicity. Note that the results for this groups are not included in this application, since it is not considered relevant for clinical practice in Denmark.

Table A2c Main study characteristics for the GOG218 study

- Placebo group (placebo, paclitaxel, carboplatin) (N=625):
  Paclitaxel IV over 3 hours and carboplatin IV over 30 minutes on day 1. Beginning in course 2, patients also received placebo IV over 30-90 minutes on day 1. Treatment repeats every 21 days for 6 courses. Beginning in course 7, patients received placebo alone IV over 30-90 minutes on day 1. Treatment with placebo repeated every 21 days for up to 22 courses in the absence of disease progression or unacceptable toxicity.

In patients with limiting peripheral neuropathy or hypersensitivity, paclitaxel was replaced with docetaxel (75 mg per square meter).

The bevacizumab (and placebo) dose was modified only in patients whose weight changed by more than 10% but could be delayed or discontinued depending on the occurrence, duration, and severity of uncontrolled hypertension (systolic blood pressure >150 mm Hg or diastolic blood pressure >90 mm Hg), proteinuria (urine protein to-creatinine ratio §3.5), wound or bowel-wall disruption (of any grade, during cycle 2 or later), reversible posterior leukoencephalopathy syndrome, arterial thrombosis (grade §3 at any time or grade 2 during cycle 2 or later), and venous thrombosis, coagulopathy, intestinal obstruction, or hypersensitivity of grade 3 or greater.

Baseline characteristics[1]

	Bevacizumab maintenance (N=623)	Bevacizumab initiation (N=625)	Placebo (N=625)
Median age (range); years	60 (22-89)	60 (24-88)	60 (25-86)
Race or ethnic group; n (%)[2]			
Non-Hispanic white	521 (83.6)	519 (83.0)	526 (84.2)
Asian	39 (6.3)	37 (5.9)	41 (6.6)
Non-Hispanic black	27 (4.3)	28 (4.5)	25 (4.0)
Hispanic	25 (4.0)	28 (4.5)	21 (3.4)
Other or unspecified	11 (1.8)	13 (2.1)	12 (1.9)
GOG performance status; n (%)[3]			
0	305 (49.0)	315 (50.4)	311 (49.8)
1	267 (42.9)	270 (43.2)	272 (43.5)
2	51 (8.2)	40 (6.4)	42 (6.7)
Stage/debulking status; n (%)			
III (Macroscopic, ≤ 1cm)	216 (34.7)	205 (32.8)	218 (34.9)
III (>1 cm)	242 (38.8)	256 (41.0)	254 (40.6)
IV	165 (26.5)	164 (26.2)	153 (24.5)
Histologic type; n (%)[4]			
Serous adenocarcinoma	524 (84.1)	519 (83.0)	541 (86.6)
Endometroid	24 (3.9)	14 (2.2)	21 (3.4)
Clear cell	20 (3.2)	23 (3.7)	12 (1.9)
Mucinous	8 (1.3)	5 (0.8)	6 (1.0)
Other or not specified	47 (7.5)	64 (10.2)	45 (7.2)
Tumour grade; n (%)			
3	460 (73.8)	465 (74.4)	445 (71.2)
2	97 (15.6)	86 (13.8)	102 (16.3)
1	18 (2.9)	28 (4.5)	36 (5.8)
Not graded	48 (7.7)	46 (7.4)	42 (6.7)

[1] Percentages may not total 100 because of rounding.

[2] Race or ethnic group was self-reported.

[3] A Gynecologic Oncology Group (GOG) performance status score of 0 indicates that the patient is fully active, 1 that the patient is restricted in physically strenuous activities but ambulatory, and 2 that the patient is ambulatory and capable of self-care but unable to work.

[4] Histologic type and tumour grade were obtained from the central GOG Pathology Committee review updated in September 2010. All clear-cell

Table A2c Main study characteristics for the GOG218 study

tumours were classified as grade 3.

Abbreviations: GOG, Gynecologic Oncology Group; n, number of subjects with characteristic; N, number of randomised subjects.

Primary and secondary endpoints	*Primary endpoint* The primary endpoint was initially specified as OS but was changed to PFS during the trial. Thereafter, treatment assignments could be revealed to the trial investigators and patients if documented progression occurred. PFS was from trial entry until first disease progression, death, or date of last contact, up to 6 years. PFS and OS were calculated from the date of enrollment. PFS was considered to have ended at the time of cancer progression as shown on radiography, according to the RECIST; an increase in the CA125 level according to Gynecologic Cancer InterGroup criteria; global deterioration of health; or death from any cause. Progression defined solely based on increased CA125 level was permitted only if the patient had completed chemotherapy. If patients remained free of progression at their last follow-up visit, data on duration of PFS were censored at the time of the last radiographic assessment. Median PFS onset of progression could be based on radiographic (RECIST) criteria or rising CA125 (GCIG criteria). *Secondary endpoints included* • OS counted from trial entry to death or last contact, up to 6 years. • AEs, graded with the use of CTCAE (version 3), were reported until 30 days after the last trial treatment had been administered and were summarised for patients who received at least one cycle of bevacizumab or placebo. • Impact on quality of life measured by the FACT-O TOI administered at baseline, 9, 18, 36, 60, and 84 weeks.
Method of analysis	Differences in PFS among the three groups were assessed by means of the log-rank test. A sample size of 1800 was estimated to provide 90% statistical power to detect a 23% reduction in the hazard for progression with either of the two bevacizumab-containing regimens versus the control regimen while limiting the overall one-sided type I error for both comparisons to 2.5%. The final analysis was planned to be conducted after at least 375 patients in the control group died or had disease progression. Relative hazard ratios were estimated with the use of a proportional-hazards model. The PFS and OS analyses included all enrolled patients. All reported P values were two-sided. Differences in FACT-O TOI scores among the three groups were assessed by means of a linear mixed model with adjustment for baseline score and age. Assessment time points were treated as categorical. Hypotheses were tested at a 1.67% significance level to account for multiple comparisons. Differences among the groups in the severity of AEs were examined by means of Fisher's exact test.
Subgroup analyses	Subgroup analyses of the PFS endpoint were performed in the following prespecified subgroups: • Age (<60 years, 60-69 years or ≥70 years) • EGOG performance status score (0 or 1-2) • Cancer stage and residual lesion size (III macroscopic ≤1 cm, III >1 cm, or IV) • Histologic type (serous, non-serous)

Table A2c Main study characteristics for the GOG218 study	
	• Tumour grade (1–2 or 3) • GOG performance status score (0 or 1–2)

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Table A2d Main study characteristics for the ICON7 trial	
Trial name	ICON7 - A randomised, two-arm, multi-centre Gynaecologic Cancer InterGroup trial of adding bevacizumab to standard chemotherapy (carboplatin and paclitaxel) in patients with epithelial ovarian cancer.
NCT number	NCT00483782
Objective	The primary objective of the trial was to compare the PFS and OS of patients with newly diagnosed ovarian epithelial, fallopian tube, or primary peritoneal cavity cancer treated with carboplatin and paclitaxel with or without bevacizumab.
Publications – title, author, journal, year	A phase 3 trial of bevacizumab in ovarian cancer. Perren TJ, et al. N Engl J Med. 2011 [7]. 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, et al. Lancet Oncol. 2015 [8]. Standard chemotherapy with or without bevacizumab in advanced ovarian cancer: quality-of-life outcomes from the International Collaboration on Ovarian Neoplasms (ICON7) phase 3 randomised trial. Stark D, et al. Lancet Oncol. 2013 [9]
Study type and design	This was a multicentre, randomised, controlled, open label trial of adding bevacizumab to standard chemotherapy (carboplatin and paclitaxel) in patients with epithelial ovarian cancer. The trial was conducted in 5 countries (Australia, France, Germany, Norway, United Kingdom). Patients were randomised to bevacizumab or control group and were stratified according to FIGO stage (stage I-III with residual disease ≤1 cm versus stage I-III with residual disease >1 cm versus stage IV disease), intended time to start chemotherapy after surgery (≤4 weeks versus >4 weeks), and participating centre.
Follow-up time	After completion of trial treatment, patients were followed every 3–6 months for 5 years and then annually thereafter.
Population (inclusion and exclusion criteria) **(from clinicaltrials.gov)**	*Main inclusion criteria* • Histologically confirmed ovarian epithelial, fallopian tube, or primary peritoneal cavity cancer, newly diagnosed disease. • Met 1 of the following staging criteria: ◦High-risk stage I or IIA disease (grade 3 disease or clear cell carcinoma only) ◦Stage IIB-IV disease (all grades and all histological types) • Must have undergone initial surgery (e.g., debulking cytoreductive surgery or a biopsy if the patient had stage IV disease) within the past 6 weeks. Patients with stage IV disease for which initial surgical debulking was not appropriate were eligible provided the following criteria were met: Stage IV disease diagnosed by histology, and no planned surgery prior to disease progression, including interval debulking surgery. • Patients with prior early-stage ovarian epithelial or fallopian tube carcinoma treated with surgery alone were eligible at the time of diagnosis of abdominopelvic recurrence provided no further interval cytoreductive therapy was planned prior to disease progression. • Synchronous primary endometrial carcinoma or a history of primary endometrial carcinoma was allowed provided the following criteria were met: Disease ≤ stage IB, no more than superficial

Table A2d Main study characteristics for the ICON7 trial	
	myometrial invasion, no lymphovascular invasion, and not poorly differentiated (i.e., no grade 3, papillary serous, or clear cell disease). • Measurable or non-measurable disease • ECOG performance status 0-2 • Life expectancy > 12 weeks • Prior adjuvant chemotherapy allowed for other malignancies (e.g., breast or colorectal carcinoma) if malignancy was diagnosed over 5 years ago with no evidence of subsequent recurrence. *Main exclusion criteria* • History or clinical suspicion of brain metastases or spinal cord compression. CT scan or MRI of the brain was mandatory (within 4 weeks prior to randomisation) in case of suspected brain metastases, and spinal MRI was mandatory (within 4 weeks prior to randomisation) in case of suspected spinal cord compression. • Other malignancies within the past 5 years except for adequately treated carcinoma in situ of the cervix, and/or basal cell skin cancer, and/or early endometrial carcinoma. • Known hypersensitivity to bevacizumab and its excipients, chemotherapy, or Cremophor EL • Evidence of other disease or condition, metabolic dysfunction, physical examination findings, or laboratory findings that would contraindicate the use of an investigational drug or put the patient at high-risk for treatment-related complications. • Prior systemic therapy for ovarian cancer (e.g., chemotherapy, monoclonal antibody therapy, tyrosine kinase inhibitor therapy, or hormonal therapy). • Prior mouse CA125 antibody. • Prior radiotherapy to the abdomen or pelvis. • Other concurrent systemic antitumour agents. • Concurrent surgery. • Concurrent maintenance chemotherapy or intraperitoneal chemotherapy (including cytotoxic chemotherapy). • Less than 4 weeks since other prior surgery or open biopsy.
Intervention	• Bevacizumab (N=764) Bevacizumab IV (7.5 mg per kilogram of body weight) over 30-90 minutes followed by paclitaxel IV (175 mg per square meter of body-surface area) over 3 hours and carboplatin IV (AUC, 5 or 6) over 30-60 minutes on day 1. Treatment was repeated every 3 weeks for up to 6 courses in the absence of disease progression or unacceptable toxicity. Patients then continued to receive bevacizumab alone every 3 weeks for 12 courses. • Control (N=764) Paclitaxel (175 mg per square meter of body-surface area) over 3 hours followed by carboplatin IV (AUC, 5 or 6) over 30-60 minutes on day 1. Treatment was repeated every 3 weeks for up to 6 courses in the absence of disease progression or unacceptable toxicity.

Table A2d Main study characteristics for the ICON7 trial

Baseline characteristics[1,2]

	Bevacizumab (N=764)	Control (N=764)
Median age (range); years	57 (24-82)	57 (18-81)
Race; n (%)		
White	730 (96)	737 (96)
Asian/Black/Other	34 (4)	27 (4)
ECOG PS; n (%)		
0	334 (45)	358 (47)
1	366 (49)	354 (47)
2	45 (6)	43 (6)
Origin of cancer; n (%)		
Ovary (epithelial)	673 (88)	667 (87)
Fallopian tube	27 (4)	29 (4)
Primary peritoneal	50 (6)	56 (7)
Multiple sites	14 (2)	12 (2)
Histology; n (%)		
Serous	525 (69)	529 (69)
Mucinous	19 (2)	15 (2)
Endometroid	60 (8)	57 (7)
Clear cell	67 (9)	60 (8)
Mixed	40 (5)	48 (6)
Other	53 (7)	55 (7)
FIGO stage; n (%)		
I/IIA	67 (9)	75 (10)
IIB/IIC	70 (9)	70 (9)
III	18 (2)	14 (2)
IIIA	22 (3)	32 (4)
IIIB	45 (6)	44 (6)
IIIC	438 (57)	432 (57)
IV	104 (13)	97 (12)
Grade; n (%)		
Grade 1 - well	41 (5)	56 (7)
Grade 2 - moderately	175 (23)	142 (19)
Grade 3 - poorly	538 (71)	556 (74)
Unknown	10	10
Debulking surgery; n (%)		
No (inoperable)	13 (2)	17 (2)
Yes	751 (98)	747 (98)
>1 cm residual disease	192 (26)	195 (26)
≤1 cm residual disease	559 (74)	552 (74)
High-risk of progression (FIGO III>1cm/ IV debulking); n (%)		
Yes	533 (70)	530 (69)
No	231 (30)	234 (31)
GCIG group; n (%)		
ANZGOG (Australia & New Zealand)	39 (5)	37 (5)
AGO-OVAR (Germany)	267 (35)	266 (35)
GEICO (Spain)	22 (3)	19 (3)
GINECO (France)	98 (13)	98 (13)
MRC/NCRI (UK)	188 (25)	187 (24)
NCIC CTG (Canada)	57 (7)	61 (8)
NSGO (Denmark/Finland/Norway/Sweden)	93 (12)	96 (12)

FIGO stage and surgery; n (%)		
I-III and residual disease ≤1 cm	518 (68)	508 (66)
I-III and residual disease >1 cm	140 (18)	150 (20)
III inoperable or IV	106 (14)	106 (14)
Intent to start chemotherapy following surgery; n (%)		
≤4 weeks	326 (43)	328 (43)
>4 weeks	438 (57)	436 (57)

[1] Percentages may not total 100 because of rounding.

[2] A phase 3 trial of bevacizumab in ovarian cancer. Perren TJ et al., N Engl J Med. 2011 [7].

Abbreviations: AGO-OVAR, Arbeitsgemeinschaft Gynäkologische Onkologie - Ovarialkarzinom; ANZGOG, Australia New Zealand Gynaecological Oncology Group; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FIGO, International Federation of Gynecology and Obstetrics; GCIG, Gynecologic Cancer InterGroup; GEICO, The Spanish Ovarian Cancer Research Group; GINECO, Groupe d'Investigateurs National des Etudes des Cancers Ovariens et du sein; MRC/NCRI, Medical Research Council/National Cancer research Institute; n, number of subjects with characteristic; N, number of randomised subjects; NCIC CTG, National Cancer Institute of Canada – Clinical Trials Group; NSGO, Nordic Society of Gynaecological Oncology.

Baseline characteristics, high-risk subgroup[1,2,3]

	High-risk	
	Bevacizumab (N=248)	**Control (N=254)**
Median age (range); years	60 (26-80)	60 (18-81)
Race; n (%)		
White	237 (96)	242 (95)
Asian/Black/Other	11 (4)	12 (5)
ECOG PS; n (%)		
0	100 (41)	98 (39)
1	123 (50)	135 (53)
2	21 (9)	20 (8)
Unknown	4	1
Origin of cancer; n (%)		
Ovary (epithelial)	207 (83)	210 (83)
Fallopian tube	6 (2)	5 (2)
Primary peritoneal	28 (11)	32 (13)
Multiple sites	7 (3)	7 (3)
Histology; n (%)		
Serous	186 (75)	195 (77)
Mucinous	6 (2)	4 (2)
Endometroid	17 (7)	14 (6)
Clear cell	6 (2)	6 (2)
Mixed	14 (6)	14 (6)
Other	19 (8)	21 (8)
FIGO stage; n (%)		
I/IIA		
IIB/IIC		
III	6 (2)	6 (2)
IIIA	2 (0.8)	2 (0.8)
IIIB	6 (2)	8 (3)
IIIC	130 (52)	141 (56)
IV	104 (42)	97 (38)
Grade; n (%)		
Grade 1 - well	5 (2)	10 (4)
Grade 2 - moderately	70 (29)	45 (18)
Grade 3 - poorly	169 (69)	195 (78)
Unknown	4	4
Debulking surgery; n (%)		

Table A2d Main study characteristics for the ICON7 trial		
Inoperable	13 (2)	17 (7)
>1 cm residual	194 (78)	194 (76)
≤1 cm residual	20 (8)	19 (7)
0 cm residual[4]	21 (8)	24 (9)

[1] Percentages may not total 100 because of rounding.

[2] High-risk sub-group: High risk of progression was defined as stage IV disease, inoperable stage III disease, or sub-optimally debulked (>1 cm) stage III disease.

[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 et al., Lancet Oncol. 2015; 16: 928-936.

[4] Includes 2 patients in the bevacizumab group and 2 patients in the placebo group with residual ≤1cm, exact size unknown.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; FIGO, International Federation of Gynecology and Obstetrics; GCIG, Gynecologic Cancer InterGroup; n, number of subjects with characteristic; N, number of randomised subjects.

Primary and secondary endpoints	*Primary endpoint* PFS, the primary endpoint, was calculated from the date of randomisation to the date of the first indication of disease progression or death, whichever occurred first. Disease progression was defined according to the (RECIST) guidelines on the basis of radiologic, clinical, or symptomatic indicators of progression and did not include isolated asymptomatic progression on the basis of CA125 levels. *Secondary endpoints included* • Duration of OS, which was calculated from the date of randomisation to the date of death from any cause; data for patients still alive were censored at the date the patient was last known to be alive. • Biological progression-free interval, as measured by increasing CA125 levels, which was calculated from the date of randomisation to the date of the first CA125–based progression or first RECIST–based progression, whichever occurred first. • Safety as measured by CTCAE version 3.0. • Health-related quality of life, which was reported by patients using the EORTC QLQ-C30 and -OV28 questionnaires. Quality of life was assessed at baseline, before every course, every 6 weeks for 1 year, every 3 months until disease progression or for up to 2 years, and then at 3 years.
Method of analysis	The primary analysis was carried out with the use of an unstratified log-rank test for the difference in the distribution of PFS between the two groups. Other planned analyses included a log-rank test that stratified for factors used for randomisation (excluding GCIG groups to limit the number of categories being tested); Cox regression analyses that adjusted for baseline covariates to assess the robustness of the result if the proportional-hazards assumption held; flexible parametric survival models to smooth survival curves and estimate survival differences with the use of all survival data collected; and interaction analyses to explore the difference in the relative size of treatment effects in subgroups classified according to baseline characteristics, high risk for progression (i.e., FIGO stage IV disease or FIGO stage III disease and >1.0 cm of residual disease after debulking surgery), and stratification factors. All efficacy analyses for PFS included all patients who had been randomly assigned to treatment (i.e., the intention-to-treat population). Safety analyses included patients who had received at least one cycle of the assigned protocol treatment. All reported P values were two-sided.

Table A2d Main study characteristics for the ICON7 trial	
	The magnitude and timing of treatment effects were explored with the use of hazard functions, including a formal test of the proportional-hazards assumption. With 1520 women randomly assigned to treatment over a period of 2 years, the required PFS and OS events were expected to occur 1 and 3 years, respectively, after entry of the last patient. After submission of the primary analysis of the protocol defined PFS, regulatory authorities requested an OS analysis with at least 365 deaths (50% of the required total number of deaths) and an update on PFS with the use of the same data set.
Subgroup analyses	Subgroup analyses of the PFS endpoint were performed in the following subgroups: • Age (<60 years, 60-69 years or ≥70 years) • ECOG PS (0, 1 or 2) • Origin of cancer (ovary, fallopian tube, primary peritoneal or multiple sites) • Grade (1, 2 or 3) • FIGO stage (I, II, III or IV) • Outcome of surgery (>1 cm residual disease or ≤1 cm residual disease) • High-risk of progression (FIGO III >1 cm residual/IV debulking) • Baseline CA125 • FIGO stage and outcome of surgery (I-III ≤1 cm, I-III >1 cm or inoperable III or IV) • Intent to start chemotherapy within 28 days (No or Yes)

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10.3 Results per study

Table A3a Results of the PRIMA trial											
Trial name:	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).										
NCT number:	NCT02655016										
Outcome (subgroup)	**Study arm**	**N**	**Result (CI)**	**Estimated absolute difference in effect**			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
				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. In addition, see appendix 10.5.	González-Martin 2019, Table S5 [2]
	Placebo	126	84.9 (78.7; 91.2)								
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		González-Martin 2019, Table S5 [2]
	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		González-Martin 2019, Fig3 and Table S6 [2]
	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		González-Martin 2019, Fig3 and Table S6 [2]
	Placebo	71	43.7 (32.1; 55.2)								
Median 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, Fig3 and Table S6 [2]
	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, Fig3 and Table S6 [2]
	Placebo	55	40.0 (27.1; 52.9)								

Table A3a Results of the PRIMA trial											
Median PFS[2], 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	0.020	Same as described above for all time-to-event endpoints.	González-Martin 2019, Fig3 and Table S6 [2]
	Placebo	80	5.4 (4.0; 7.3)								
PFS rate[2], 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, Fig3 and Table S6 [2]
	Placebo	80	30.0 (20.0; 40.0)								
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	See appendix 10.5	González-Martin 2019, Table 2 [2]
	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	RR: 9.96	6.17; 16.06	<0.0001	See appendix 10.5	González-Martin 2019, Table 2 [2]
	Placebo	244[3]	6.6 (3.5; 9.7)								
Proportion with CTCAE AE ≥grade 3[5]	Niraparib	484[3]	70.5 (66.4; 74.5)	51.6	45.23; 57.97	<0.0001	RR: 3.73	2.86; 4.88	<0.0001	See appendix 10.5	González-Martin 2019, Table 2 [2]
	Placebo	244[3]	18.9 (13.9; 23.8)								

Numbers not shaded are extracted from the publication. Grey shaded numbers are calculated by the applicant, see details on the statistical methods in appendix 10.5.

[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.

Abbreviations: ADR, adverse drug reaction; AE, adverse event; BICR, blinded independent central review; BRCA, BReast CAncer; BRCAm, BRCA mutated; BRCAwt, BRCA wildtype; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; HR, hazard ratio; HRD, homologous recombination deficient; HRP, homologous recombination proficient; N, number of patients in study arm and (sub)population; NE, not estimable; OS, overall survival; PFS, progression free survival; RR, relative risk.

Table A3b Results of the SOLO1 trial											
Trial name:	A phase III, randomised, double blind, placebo controlled, multicentre study of olaparib maintenance monotherapy in patients with BRCA mutated advanced (FIGO stage III-IV) ovarian cancer following first line platinum-based chemotherapy.										
NCT number:	NCT01844986										
Outcome (subgroup)				**Estimated absolute difference in effect**			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
	Study arm	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Estimated 3-year OS rate[1] (%)	Olaparib	260	83.8 (79.4; 88.3)	3.7	-4.47; 11.86	0.3671	HR: 0.95	0.60; 1.53	0.830	Stratified log-rank test with calculation of HR, 95% CI and P value. The assumption of proportionality was assessed by producing plots of complementary log-log (event times) versus log (time) and, if these raised concerns, a time-dependent covariate would be fitted to assess the extent to which this represents random variation.	Moore 2018, p2499 [3]
	Placebo	131	80.2 (73.3; 87.0)								
2-year PFS rate[2], BICR (%) (Primary analysis)	Olaparib	260	78.1 (73.0; 83.1)	37.6	27.8; 47.4	<0.0001	HR[3]: 0.28	0.20; 0.39	<0.001		Moore 2018, Fig2B [3]
	Placebo	131	40.5 (32.1; 48.9)								
Median PFS, INV[4] (months) (5-year results)	Olaparib	260	56.0 (NR; NR)	42.2	NE	NE	HR: 0.33	0.25; 0.43	<0.001		ESMO 2020 abstract #811MO [25]
	Placebo	131	13.8 (NR; NR)								
Proportion discontinued due to AE[5]	Olaparib	260[6]	11.5 (7.7; 15.4)	9.2	4.57; 13.89	0.0007	RR: 5.00	1.56; 16.08	0.0007	See appendix 10.5	Moore 2018, Fig1 and Table 2 [3]
	Placebo	130[6]	2.3 (0.0; 4.9)								
Proportion with AE CTCAE grade 3-4[7]	Olaparib	260[6]	39.2 (33.3; 45.2)	20.8	11.84; 29.70	<0.0001	RR: 2.13	1.44; 3.14	<0.0001	See appendix 10.5	Moore 2018, Table 2 [3]
	Placebo	130[6]	18.5 (11.8; 25.1)								
FACT-O TOI, change from baseline at 2 years[8]	Olaparib	237	0.3 (-0.72; 1.32)	-3.00	-4.78; -1.22	NR	-	-	-	Mixed effects model for repeated measures.	Moore 2018, p2503 [3]
	Placebo	125	3.3 (1.84; 4.76)								

Numbers not shaded are extracted from the publication. Grey shaded numbers are calculated by the applicant, see details on the statistical methods in appendix 10.5

[1] OS data maturity 21% data maturity. Median estimates were not reported.

[2] PFS as assessed by BICR was analysed as a sensitivity analysis. PFS rates were read from the Kaplan-Meier curve.

[3] Estimated HR for PFS (BICR) at the time of the primary analysis, reported in Moore 2018.

[4] PFS as assessed by investigators was the primary endpoint in the SOLO1 trial.

[5] Proportions of patients who discontinued treatment due to ADRs are not reported; instead, proportions who discontinued due to AE are provided.

[6] Proportions are calculated based on the number of patients treated (safety population).

[7] Proportions of patients with CTCAE grade 3-4 ADR are not reported; instead, proportions with CTCAE grade 3-4 AE are provided.

[8] HRQoL was assessed by the FACT-O TOI score. Higher scores indicate better HRQoL.

Abbreviations: -, not applicable; ADR, adverse drug reaction; AE, adverse event; BICR, blinded independent central review; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; FACT-O TOI, Functional Assessment of Cancer Therapy-Ovarian Trial Outcome Index; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; HRQoL, health-related quality of life; INV, investigator assessed; N, number of patients in study arm and (sub)population; NE, not estimable; NR, not reported; OS, overall survival; PFS, progression free survival; RR, relative risk

Table A3c Results of the GOG-0218 trial											
Trial name:	A phase III trial of carboplatin and paclitaxel plus placebo versus carboplatin and paclitaxel plus concurrent bevacizumab (NSC # 704865) followed by placebo, versus carboplatin and paclitaxel plus concurrent and extended bevacizumab, in women with newly diagnosed, previously untreated, stage III or IV epithelial ovarian, primary peritoneal or fallopian tube cancer.										
NCT number:	NCT00262847										
Outcome (subgroup)	**Study arm[1]**	**N**	**Result (CI)**	**Estimated absolute difference in effect**			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
				Difference	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median OS[2,3] (months)	Bevacizumab maintenance	623	39.7 (NR; NR)	0.4	NE	NE	HR: 0.92	0.73; 1.15	0.45	Differences between the 3 treatment groups were assessed by means of the log-rank test. Relative HRs were estimated with the use of a proportional-hazards model.	Burger 2011, p2478 [4]
	Placebo	625	39.3 (NR; NR)								
OS rate[2,3] (%)	Bevacizumab maintenance	623	77.8 (74.6; 81.1)	2.8	-1.90; 7.51	0.2422	HR: 0.92	0.73; 1.15	0.45	See appendix 10.5	Burger 2011, Fig3A [4]
	Placebo	625	75.0 (71.6; 78.4)								
Median OS[3,4] (months)	Bevacizumab maintenance	623	43.4 (NR; NR)	2.3	NE	NE	HR: 0.96	0.85; 1.09	0.53	As described above for median OS.	Tewari 2019, p2319 [6]
	Placebo	625	41.1 (NR; NR)								
OS rate[3,4] (%)	Bevacizumab maintenance	623	21.0 (17.8; 24.2)	-0.1	-4.62; 4.43	0.9680	HR: 0.96	0.85; 1.09	0.53	See appendix 10.5	Tewari 2019, Fig1 [6]
	Placebo	625	21.1 (17.9; 24.3)								

Table A3c Results of the GOG-0218 trial											
Median PFS[2], (INV) (months)	Bevacizumab maintenance	623	14.1 (NR; NR)	3.8	NE	NE	HR: 0.72	0.63; 0.82	<0.001	As described above for median OS.	Burger 2011, p2476-77 [4]
	Placebo	625	10.3 (NR; NR)								
Proportion discontinued due to AE[5] (%)	Bevacizumab maintenance	608[6]	17.8 (14.7; 20.8)	7.4	3.56; 11.34	0.0002	RR: 1.7	1.29; 2.30	0.0002	See appendix 10.5	EPAR Table 44, p61 [36]
	Placebo	601[6]	10.3 (7.9; 12.7)								
Proportion with AE CTCAE grade 3-4[7]	Bevacizumab maintenance	608[5]	92.3 (90.1; 94.4)	-0.4	-3.38; 2.56	0.7874	RR: 0.996	0.96; 1.03	0.7874	See appendix 10.5	EPAR Table 44, p61 [36]
	Placebo	601[5]	92.7 (90.6; 94.8)								
LS means FACT-O TOI score before treatment[8]	Bevacizumab maintenance	564[9]	67.4 (66.1; 68.7)	-0.8	-2.6; 1.0	NR	-	-	-	See appendix 10.5	Monk 2013, Table 3 [5]
	Placebo	556[9]	68.2 (66.9; 69.5)								
LS means FACT-O TOI score before cycle 21[8]	Bevacizumab maintenance	427[9]	78.6 (77.3; 79.9)	1.0	-0.9; 2.9	NR	-	-	-	See appendix 10.5	Monk 2013, Table 3 [5]
	Placebo	407[9]	77.6 (76.2; 79.0)								

Numbers not shaded are extracted from the publications. Grey shaded numbers are calculated by the applicant, see details on the statistical methods in appendix 10.5

[1] 3 treatment groups were included in the trial: bevacizumab maintenance (during chemotherapy and up to cycle 22), bevacizumab initiation (only during chemotherapy), and placebo. Only the bevacizumab maintenance and placebo groups are included in this application, since the bevacizumab initiation is not assessed as relevant for Danish clinical practice.

[2] At the time of the primary analysis; median follow-up 17.4 months.

[3] The HRs for OS are provided from the publication and there is only one HR per population.

[4] At the time of the final analysis; median follow-up 102.9 months.

[5] Proportions of patients who discontinued treatment due to ADRs are not reported; instead, proportions who discontinued due to AE are provided. The numbers in the EPAR are different from those reported in Burger 2011 p2476 [4], but the reason for the discrepancy is not clear. For consistency with the number for proportion of patients with CTCAE grade 3-4 AEs and with the data from the ICON7 trial, the numbers from the EPAR were used for these 2 safety outcomes.

[6] Proportions are calculated based on the safety set (N = 1816), which comprised all randomised patients who received at least one full or partial dose of any study treatment during cycle 2 or later.

[7] Proportions of patients with CTCAE grade 3-4 ADR are not reported; instead, proportions with CTCAE grade 3-4 AE are provided.

[8] HRQoL was assessed by the FACT-O TOI score. Higher scores indicate better HRQoL.

[9] Number of patients with data.

Abbreviations: -, not applicable; ADR, adverse drug reaction; AE, adverse event; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; FACT-O TOI, Functional Assessment of Cancer Therapy-Ovarian Trial Outcome Index; HR, hazard ratio; HRQoL, health-related quality of life; INV, investigator assessed; N, number of patients in study arm and (sub)population; NE, not estimable; NR, not reported; OS, overall survival; PFS, progression free survival; RR, relative risk

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Table A3d Results of the ICON7 trial											
Trial name:	A randomised, two-arm, multicentre Gynaecologic Cancer InterGroup trial of adding bevacizumab to standard chemotherapy (carboplatin and paclitaxel) in patients with epithelial ovarian cancer.										
NCT number:	NCT00483782										
Outcome (subgroup)	**Study arm**	**N**	**Result (CI)**	**Estimated absolute difference in effect**			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
				Difference	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median OS[1,2] (months) All patients	Bevacizumab	764	58.0 (52.4; 66.9)	-0.6	-10.7; 9.5	0.9071	HR: 0.99	0.85; 1.14	0.85	Unstratified log-rank test and Cox regression[8]. Appendix 10.5.	Oza 2015, Table1 [8]
	Control	764	58.6 (53.5; 67.5)								
OS rate[1,2] (%) All patients	Bevacizumab	764	52.6 (49.1; 56.2)	-1.3	-6.31; 3.69	0.6081	HR: 0.99	0.85; 1.14	0.85	See Appendix 10.5	Oza 2015, Table1 [8]
	Control	764	53.9 (50.4; 57.5)								
Median OS[1,2] (months) High-risk group[2]	Bevacizumab	248	39.7 (36.0; 44.2)	9.5	4.0; 15.0	0.0007	HR: 0.78	0.63; 0.97	0.03	Unstratified log-rank test and Cox regression.	Oza 2015, Table1 [8]
	Control	254	30.2 (27.0; 34.3)								
OS rate[1,2] (%) High-risk group[3]	Bevacizumab	248	36.3 (30.3; 42.3)	4.8	-3.48; 13.07	0.2564	HR: 0.78	0.63; 0.97	0.03	See Appendix 10.5	Oza 2015, Table1 [8]
	Control	254	31.5 (25.8; 37.2)								
Median PFS[1,2] (months) All patients	Bevacizumab	764	19.9 (19.1; 22.0)	2.4	0.3; 4.5	0.0241	HR: 0.93	0.83; 1.05	0.25	Unstratified log-rank test and Cox regression.	Oza 2015, Table1 [8]
	Control	764	17.5 (15.7; 18.7)								

Table A3d Results of the ICON7 trial											
PFS rate[1,2], INV (%) All patients	Bevacizumab	764	27.5 (24.3; 30.7)	-3.7	-8.23; 0.90	0.1155	HR: 0.93	0.83; 1.05	0.25	See Appendix 10.5	Oza 2015, Table1 [8]
	Control	764	31.2 (27.9; 34.4)								
Median PFS[1,2], INV (months) High-risk group[3]	Bevacizumab	248	16.0 (14.2; 17.8)	5.5	3.3; 7.8	<0.0001	HR: 0.73	0.61; 0.88	0.001	Unstratified log-rank test and Cox regression.	Oza 2015, Table1 [8]
	Control	254	10.5 (9.3; 12.0)								
PFS rate[1,2], INV (%) High-risk group[3]	Bevacizumab	248	10.1 (6.3; 13.8)	-0.2	-5.44; 5.13	0.9540	HR: 0.73	0.61; 0.88	0.001	See Appendix 10.5	Oza 2015, Table1 [8]
	Control	254	10.2 (6.5; 14.0)								
Proportion discontinued due to AE[4] (%)	Bevacizumab	746[5]	21.8 (18.9; 24.8)	12.9	9.35; 16.53	<0.0001	RR: 2.45	1.88; 3.19	<0.0001	See Appendix 10.5	EPAR Table 44, p61 [36]
	Control	763[5]	8.9 (6.9; 10.9)								
Proportion with AE CTCAE grade 3-4[6] (%)	Bevacizumab	746[5]	64.5 (61.0; 67.9)	10.7	5.81 15.67	<0.0001	RR: 1.20	1.10; 1.31	<0.0001	See Appendix 10.5	EPAR Table 44, p61 [36]
	Control	763[5]	53.7 (50.2; 57.3)								
EORTC QLQ-C30 global HRQoL baseline[7]	Bevacizumab	691[8]	55.1 (53.5; 56.7)	-3,5	-5.7; -1.3	-	-	-	-	See Appendix 10.5	Stark 2013 Table 1 and 2 [9]
	Control	684[8]	58.6 (57.1; 60.1)								
EORTC QLQ-C30 global HRQoL week 54 (end of treatment)[7]	Bevacizumab	502[8]	69.7 (68.0; 71.4)	-6.4	-9.0; -3.7	<0.0001	-	-	-	Difference and 95% CI adjusted for baseline score. See Appendix 10.5	Stark 2013 Table 1 and 2 [9]
	Control	388[8]	76.1 (74.3; 77.9)								

Numbers not shaded are extracted from the publications. Grey shaded numbers are calculated by the applicant, see details on the statistical methods in appendix 10.5

[1] At the time of primary analysis of OS; median follow-up in the total population 48.9 months.

[2] The HRs for OS and PFS are provided from the publication and there is only one HR per population.

[3] High-risk groups were defined at the time of the primary PFS analysis and refined before database lock for the primary OS analysis. Baseline characteristics for the high-risk groups are included in Table A2d

[4] Proportions of patients who discontinued treatment due to ADRs are not reported; instead, proportions who discontinued due to AE are provided. The numbers as well as the size of the safety population in the EPAR are different from those reported in Perren 2011 Table 1 [7]. For consistency with the GOG-0218 trial, numbers from the EPAR have been used.

[5] Proportions are calculated based on the safety set, which comprised all randomised patients who received at least one full or partial dose of any study treatment during cycle 2 or later.

[6] Proportions of patients with CTCAE grade 3-4 ADR are not reported; instead, proportions with CTCAE grade 3-4 AE are provided. The numbers as well as the size of the safety population in the EPAR are different from those reported in Perren 2011 Table 1 [7]. For consistency with the GOG-0218 trial, numbers from the EPAR have been used.

[7] HRQoL was assessed by EORTC QLQ C-30. The global HRQoL was on a translated scale from 0 (worst) to 100 (best).

[8] Number of patients with data.

[9] Proportional hazards assumption questionable.

Abbreviations: -, not applicable; ADR, adverse drug reaction; AE, adverse event; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; EORTC QLQ C-30, EORTC Quality of Life Questionnaire Cancer 30 item; HR, hazard ratio; HRQoL, health-related quality of life; INV, investigator assessed; N, number of patients in study arm and (sub)population; NE, not estimable; NR, not reported; OS, overall survival; PFS, progression free survival; RR, relative risk

10.4 Results per PICO (clinical question)

Not applicable for questions 1-3 since no indirect comparisons have been performed (see Section 4.3.5).

Table A4 Results referring to clinical questions 4 and 5

Trial name:	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).									
NCT number:	NCT02655016									
Outcome (subgroup)	**Study arm**	**N**	**Result (CI)**	**Estimated absolute difference in effect**			**Estimated relative difference in effect**			**References**
				Difference	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**	
Question 4: BRCAwt, HRD subgroup										
OS rate[1] (%)	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	González-Martin 2019, Table S5 [2]
	Placebo	126	84.9 (78.7; 91.2)							
Median PFS[2], BICR (months)	Niraparib	95	19.6 (13.6; NE)	11.4	NE	NE	HR: 0.50	0.31; 0.83	0.006	González-Martin 2019, Fig3 and Table S6 [2]
	Placebo	55	8.2 (6.7; 16.8)							
PFS rate[2], BICR (%)	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, Fig3 and Table S6 [2]
	Placebo	55	40.0 (27.1; 52.9)							
Question 5: BRCAwt, HRP subgroup										
OS rate[1] (%)	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	González-Martin 2019, Table S5 [2]
	Placebo	80	58.7 (48.0; 69.5)							

Table A4 Results referring to clinical questions 4 and 5										
Median PFS[2], BICR (months)	Niraparib	169	8.1 (5.7; 9.4)	2.7	0.2; 5.2	0.0328	HR: 0.68	0.49; 0.94	0.020	González-Martin 2019, Fig3 and Table S6 [2]
	Placebo	80	5.4 (4.0; 7.3)							
PFS rate[2], BICR (%)	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, Fig3 and Table S6 [2]
	Placebo	80	30.0 (20.0; 40.0)							

Numbers not shaded are extracted from the publication(s). Grey shaded numbers are calculated by the applicant, see details on the statistical methods in appendix 10.5.

[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.

Abbreviations: BICR, blinded independent central review; BRCA, BReast CAncer; BRCAwt, BRCA wildtype; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficient; HRP, homologous recombination proficient; N, number of patients in study arm and (sub)population; NE, not estimable; OS, overall survival; PFS, progression free survival.

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10.5 Statistical methods

The statistical principles used for analysis followed specifications in the Danish Medicines Council's protocol [1].

The endpoints requested by the protocol were of 3 types:

- binary (fractions)
- continuous outcomes
- time to event endpoints

The 4 treatments involved (niraparib, olaparib, bevacizumab, placebo) were reported in 4 phase 3 trials (PRIMA, SOLO1, GOG-0218, ICON7) comparing the treatments pairwise.

In general, some simple pre-processing imputations were performed on published data in cases where no doubt existed as to the relevant procedure, e.g., missing proportions (including 95% CI) were derived from the number of events and patients and missing P-values were derived from the corresponding 95% CIs, if available.

For binary outcomes, risk-ratios and differences could be derived in every case, including 95% CI and a P-value. The incidences and 95% CIs were found as exact Clopper-Pearson intervals, whereas risk differences were derived directly as Newcombe intervals. The P-value derived from the likelihood ratio test was taken as a common P-value for relative risk and risk difference.

No imputation was done for subjects with missing endpoint(s).

For a few time-to-event outcomes, the corresponding (adjusted) hazard ratio from a proportional hazards regression was reported, but the P-value corresponding to the statistical test of HR=1 was missing. In this case, an approximative P-value was derived from the 95% CI for the HR.

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Brøndby d. 9.3.2021

GSK's besvarelse af spørgsmål fra Medicinrådet modtaget d. 5.3.2021

I forbindelse med ansøgning for niraparib til 1L ovariecancer – har GSK anført PFS-rater baseret på PRIMA-publikationen, figur 3 i ansøgningen.

Medicinrådet ønsker oplyst PFS-rater for 2 år baseret på Kaplan Meyer kurver for populationerne: BRCAm; BRCAwt,HRd og BRCAwt, HRp.

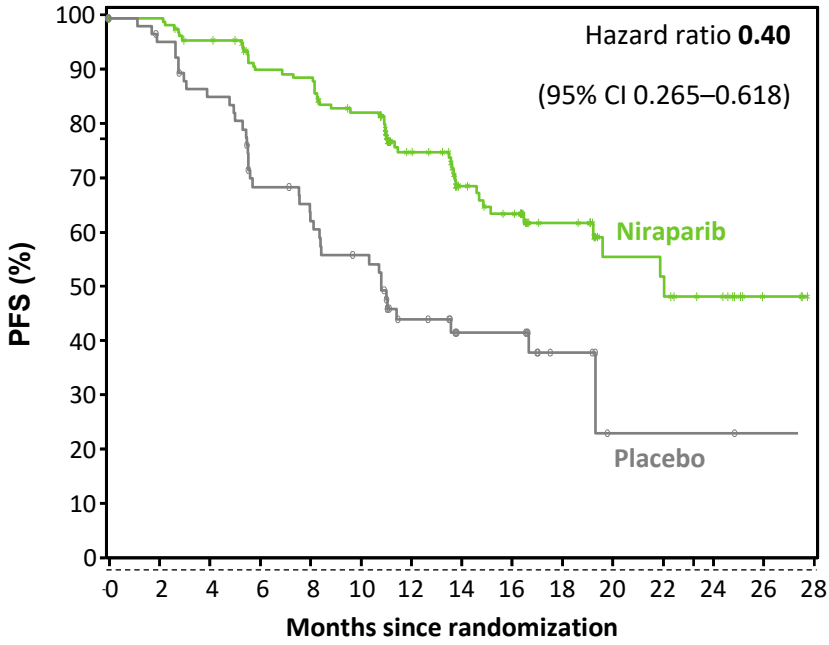
I forbindelse med virtuel ESGO-kongres 14.- 16. december 2020 blev der præsenteret data på diverse sekundære endepunkter i PRIMA studiet, herunder Kaplan Meyer kurverne i relation til ovenstående populationer i forbindelse med mundtlige præsentationer.

På baggrund af disse kurver har vi aflæst PFS-rater ved 24 måneder, hvor muligt. Det skal understreges, at disse data er behæftet med stor usikkerhed – set i lyset af **n** i både niraparib og placebo-grupperne.

BRCAm

Kilde: Niraparib in Patients With Newly Diagnosed Advanced Ovarian *BRCA*m Cancer: A Post Hoc Analysis of the PRIMA/ENGOT-OV26/GOG-3012 Trial. Datacut off May 2019. Presented by Dr. Korach.

Visuel aflæsning af PFS-rate ved 24 måneder: Niraparib 48% vs placebo: 23%

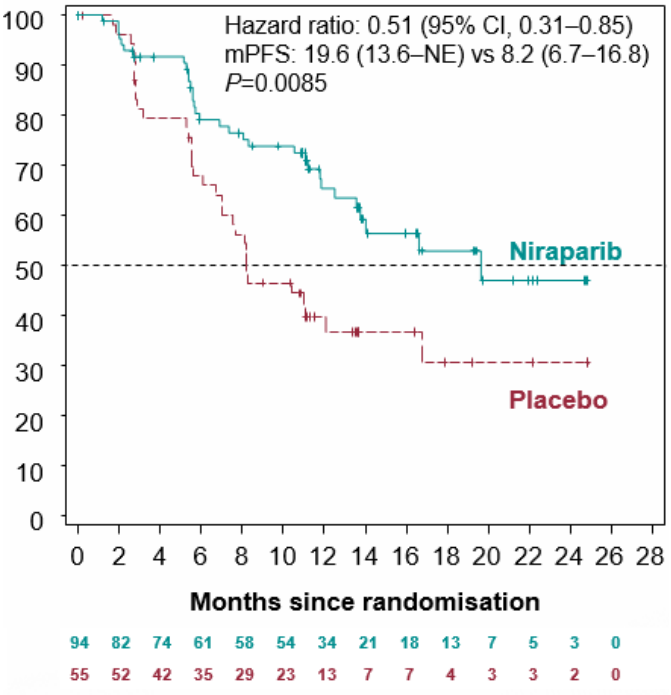


Niraparib	152	148	140	127	125	113	77	55	48	29	15	14	10	4	0
Placebo	71	65	57	44	41	34	21	14	14	7	2	2	2	1	0

BRCAwt, HRd

Kilde: Efficacy of Niraparib Therapy in Patients With Newly Diagnosed Advanced Ovarian Cancer by *BRCA*wt Status: PRIMA/ENGOT-OV26/GOG-3012 Study. Datacut off May 2019. Presented by Dr. Braicu.

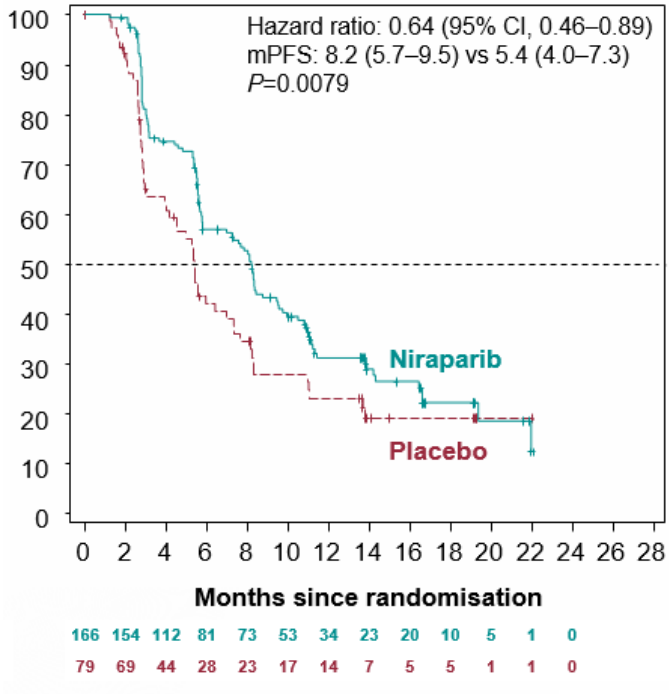
Visuel aflæsning af PFS-rater ved 24 måneder: Niraparib 47% vs placebo 31%



BRCAwt, HRp

Kilde: Efficacy of Niraparib Therapy in Patients With Newly Diagnosed Advanced Ovarian Cancer by *BRCA*wt Status: PRIMA/ENGOT-OV26/GOG-3012 Study. Datacut off May 2019. Presented by Dr. Braicu.

Visuel aflæsning af PFS-rater ved 24 måneder: Ingen data.



Cost and budget impact analysis of Zejula (niraparib) first line maintenance treatment for ovarian cancer patients in Denmark

Technical document - Application to the Danish Medicines Council

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4 ABBREVIATIONS

AE	Adverse event
AIC	Akaike information criterion
AUC	Area under the curve
BER	Base excision repair
BIC	Bayesian information criterion
BICR	Blinded independent central review
BRCA	Breast susceptibility cancer gene
BRCAm	Breast susceptibility cancer gene mutation
BRCAwt	Breast cancer susceptibility gene wild type
CDF	Cancer Drug Fond
CI	Confidence interval
CSR	Clinical study report
DGCG	Danish Gynacological Cancer Group
DK	Denmark
DMC	Danish Medicines Council
DNA	Deoxyribonucleic acid
DSU	Decision Support Unit
EMA	European Medicines Agency
ESGO	European Society of Gynaecological Oncology
FIGO	International Federation of Gynecology and Obstetrics
FOSI	Functional Assessment of Cancer Therapy–Ovarian Symptoms Index
HR	Hazard ratio
HRD	Homologous recombination deficiency
HR-d	Homologous recombination deficient
HR-p	Homologous recombination proficient
HTA	Health technology assessment
ITC	Indirect treatment comparison
ITT	Intention-to-treat
KM	Kaplan-Meier
MA	Marketing Authorisation
NACT	Neoadjuvant chemotherapy
NICE	National Institute for Health and Clinical Excellence
NVRD	No visible residual disease

OC	Ovarian Cancer
OS	Overall survival
PARP	Poly(ADP-ribose) polymerase
PARPi	PARP inhibitor
PBC	Platinum-based chemotherapy
PD	Progressed disease
PFD	Progression-free disease
PFS	Progression-free survival
PFS-2	Progression-free survival on subsequent treatment
PLD	Patient level data
PSM	Partitioned survival model
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RS	Routine surveillance
RWE	Real world evidence
SLR	Systematic literature review
SmPC	Summary of product characteristics
TEAE	Treatment-emergent adverse event
TFST	Time to first subsequent treatment
TTD	Time to treatment discontinuation

5 SUMMARY

5.1 BAGGRUND

Den 26. November 2020 offentliggjordes Medicinrådets protokol for vurdering af niraparib til 1. linje vedligeholdelsesbehandling af avanceret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden. Protokollen omfattede fem kliniske spørgsmål.

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

For klinisk spørgsmål 1 er olaparib indkluderet som komparator for den HRD positiv BRCA-muteret population. For klinisk spørgsmål 2 og 4 er standard behandling valgt som relevant komparator for HRD positiv non-BRCA populationerne. For klinisk spørgsmål 3 og 5 er standard behandling indkluderet som komparator for HRD negativ non-BRCA populationerne.

5.2 METODE

Der er udarbejdet en partitioned survival model (PSM). Modellen indbefatter tre sundhedstilstande, progressionsfri (PF), progredieret sygdom (PD) og død. Modellen blev udviklet for at estimere de

inkrementelle omkostninger per patient i behandling med niraparib, sammenlignet med de relevante komparatorer. Omkostningsanalysen er delvist indlejret i budgetkonsekvensanalysen. Modellen er primært baseret på resultater fra PRIMA studiet (1). PRIMA studiet var et randomiseret, dobbelt-blindet, multicenter, placebo-kontrolleret fase 3 studie, som havde til formål at vurdere effekten og sikkerheden af niraparib hos patienter med nydiagnosticeret, avanceret stadie III-IV, serøs endometriod ovarie kræft, som er i fuldstændig eller delvis repsons på platin-baseret-kemoterapi.

Tre patient populationer er analyseret i modellen på baggrund af Medicinrådets protokol. Grundet heterogenitet i studie design og i populationerne, var det ikke muligt at udføre indirekte sammenligning mellem niraparib, olaparib og bevacizumab. Der er for klinisk spørgsmål 1 lavet en omkostningsminimerings-analyse der sammenligner niraparib med olaparib.

Modellen anvender en tidshorisont på 30 år. Omkostninger er diskonteret med 3,5% per år i overenstemmelse med Medicinrådets metodevejledning (2). Modellen tager et begrænset samfundsperspektiv og indkluderer lægemiddelomkostninger, administrationsomkostninger, monitoreringsomkostninger, omkostninger til uønskede hændelser, patientomkostninger og transportomkostninger.

5.3 RESULTATER

Base-case analysen viser inkrementelle diskonterede omkostninger for niraparib på [redacted]. sammenlignet med olaparib for HRD positiv BRCAm populationen, [redacted]. sammenlignet med standard behandling for HRD positiv non-BRCA og [redacted]. sammenlignet med standard behandling for HRD negativ non-BRCA.

Budgetkonsekvenserne estimeres i år 5 til at være [redacted] (klinisk spørgsmål 2), [redacted] (klinisk spørgsmål 3), [redacted] (klinisk spørgsmål 5).

5.4 DISKUSSION

Resultatet for klinisk spørgsmål 1 viser, at der er meromkostninger forbundet med behandling af niraparib sammenlignet med olaparib. Dette skyldes primært, at TTD kurven for niraparib er brugt for olaparib i omkostningsminimeringsanalysen, da effekten af disse er antaget at kunne sidestilles. Der er indkluderet forskellig stopping rules for olaparib og niraparib på henholdsvis 2 år og 3 år. Dette resulterer i, at der tillægges ét års omkostninger mere til behandling med niraparib sammenlignet med olaparib. For klinisk spørgsmål 2 til 5 er der betydelige meromkostninger forbundet med behandling med niraparib sammenlignet med standard behandling. Dette ses for populationerne HRD positiv non-BRCA og HRD negativ non-BRCA. Disse omkostninger er primært drevet af lægemiddelomkostninger.

6 INTRODUCTION

6.1 OVARIAN, FALLOPIAN OR PRIMARY PERITONEAL CANCER

Ovarian cancer is a rare disease with around 450 to 550 new cases each year. OC is the 4th deadliest cancer among woman and at the end of 2016, 4697 women lived with the diagnosis (3,4). Ovarian cancer accounts for 2.8% of all cancers in woman and the lifetime risk of developing OC is approximately 2%. The median age at diagnosis is 63 years, the survival rate largely depends on the age at diagnosis and the stage of the disease. The 5-year survival rate for stage I, II, III and IV is 93, 76, 41, and 25% respectively (4,5). In 70-80% of cases OC are diagnosed at an advanced stage (III-IV) leaving the patients with a poor prognosis (5,6). There are different groups of ovarian cancer, however, 90% of the cases are epithelial carcinoma and 55% of these are high grade serous carcinomas (HGSC)(5).

Patients with a mutation in Breast Cancer (BRCA) 1 or 2-gene are at increased risk of developing ovarian cancer. An estimated 15-20% of the HGSC OC patients has a BRCA mutation, which can either be hereditary or somatic (7–9). BRCA is involved in the homologous recombination, which is a vital cell process for repairing DNA damage. In BRCA mutated tumors homologous recombination deficiency HRD will be present, but HRD may also occur in non-BRCA mutated tumors. Several studies have documented HRD in up to 40% of platinum-sensitive tumors without a BRCA mutation. The group of patients with HRD are considered twice as large as the group of BRCA mutated patients (7,10–13). It is recommended that all patients with ovarian cancer is screened to identify their BRCA mutation status (14). Currently, no national guidelines for assessing HRD status is available. It is therefore expected that a large group of the OC patients without a detective BRCA mutation will have tumors that show HRD (3).

6.1.1 Niraparib

Niraparib (Zejula®) is a potent and selective Poly (ADP-ribose) Polymerase-1 and -2 inhibitor (PARPi), indicated in the European Medicines Agency (EMA) marketing authorisation (MA) as a 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 (PBC) (15). Niraparib was the first PARPi monotherapy to show significant clinical efficacy in the first-line maintenance setting of OC, irrespective of biomarker mutation status (1). Niraparib is currently approved only for second-line maintenance treatment in Denmark for patients with a BRCA mutation, that has not been treated with a PARPi in first-line.(16)

The recommended starting dose of niraparib 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(17).

6.1.2 Current treatment

Treatment of OC aims to cure in intent, alternative prolong patients' lives, without impacting their quality of life (QoL). The primary treatment option is surgical removal of all visible tumor tissue (radical surgery), as well as correct staging of the disease(4). This is achieved in 70% of patients with stage III-IV disease either primarily or after initial neoadjuvant chemotherapy (NACT) (5). Stage IIB-IV patients without macroscopic tumor tissue after debulking surgery (<1 cm) is treated with adjuvant platinum-based chemotherapy agents, carboplatin and paclitaxel. Stage III patients with macroscopic tumor tissue (≥ 1 cm) left after surgery and patients with stage IV and inoperable patients are treated with carboplatin and paclitaxel as standard (4). Patients with a BRCA mutation are offered maintenance treatment with olaparib, whereas patients without a BRCA mutation may be offered bevacizumab in combination with or after chemotherapy (16). Clinicians estimate that around 10%-15% of patients are treated with bevacizumab in the chemotherapy and maintenance phase. This is also in accordance with new real world evidence data(18).

Most patients (60-80%) respond to first line treatment, however 80% will have relapse within the first 2-3 years after chemotherapy (4). These patients generally have a poor prognosis compared to newly diagnosed patients and will experience shorter progression free periods after repeated chemotherapy regimens (19). Niraparib has indication for maintenance treatment of all OC patients that are in complete or partial response to PBC regardless of their biomarker status (17).

6.1.3 Clinical evidence: PRIMA

PRIMA(1) is a randomised, double-blind, multicentre, placebo-controlled, phase 3 trial which aimed to assess the efficacy and safety of niraparib in patients with newly diagnosed, advanced (Stage III or IV), high-grade serous or endometrioid OC who had a complete or partial response to first-line PBC.

Patients were eligible for inclusion in the PRIMA trial if they had newly diagnosed, advanced, high-grade serous or endometrioid ovarian, fallopian tube or primary peritoneal cancer, and were in complete or partial response to first-line PBC. All patients had high-grade serous or endometrioid tumours that were classified as FIGO stage III or IV. Stage III patients who had complete cytoreduction (i.e. NVRD) after primary cytoreductive surgery were excluded from the PRIMA trial. Patients with NVRD following surgery have an improved survival prognosis, compared to patients with visible residual disease. (20,21)

6.1.3.1 *Outcomes*

The primary efficacy endpoint of PRIMA was PFS as assessed by blinded, independent, central review (BICR), and defined as time from treatment randomisation to progression or death due to any cause in the absence of documented progression, whichever occurred first. The following secondary endpoints were assessed:

- Overall survival (OS), defined as the time from the date of randomisation to the date of death by any cause; OS data are immature, with 48 (9.9%) and 31 (12.6%) events occurring in the niraparib and routine surveillance (RS) groups, respectively. Data for median OS are currently immature but demonstrate numerical benefit for niraparib (HR 0.70; 95% CI 0.44, 1.11; [redacted]). Interpretation of OS can be difficult, due to the effect of subsequent treatment.
- Time to first subsequent treatment (TFST), defined as the time from the date of randomisation to the date of the first subsequent anticancer therapy or death, whichever occurred first; The data maturity of TFST was 47%, which is more mature than results for PFS-2.
- Progression-free survival on subsequent treatment (PFS-2), defined as the time from the date of randomisation to the date of disease progression on the next anti-cancer therapy following study treatment or death by any cause, whichever occurred first. Data for PFS-2 are immature but show a numerical benefit for niraparib (HR 0.81; 95% CI 0.58, 1.140; [redacted]). As of the data cut-off of 17 May 2019 for reporting, in the ITT population, 81.1% of niraparib treated patients and 78.5% of RS treated patients were censored; as such, the data maturity is only 20%. The niraparib group of the ITT population achieved a median PFS-2 of [redacted] months. The median PFS-2 in the RS group was not estimable due to the immaturity of the data.

6.1.3.2 *Safety and adverse events*

An overview of treatment-emergent adverse events (TEAEs) for the two treatment arms from the PRIMA trial is presented in Table 1. In the safety population, the majority of patients across both treatment groups experienced at least 1 TEAE, including 478 (98.8%) of 484 subjects who received niraparib and 224 (91.8%) of 244 subjects who received RS. The high rate of TEAEs in the RS group indicates the severity of the subjects' underlying OC signs and symptoms and the burden of chemotherapy. The proportions of patients experiencing a grade ≥3 AEs were 65.3% and 6.6% in the niraparib and RS groups, respectively. In the niraparib group, 12.0% of AEs resulted in treatment discontinuation compared to 2.5% in the RS group. In both treatment arms 0.4% of patients experienced an AE leading to death.

Table 1: Frequency of adverse events in the PRIMA trial.

Type of adverse event	Niraparib (N=484) Number of patients (%)	Placebo (N=244) Number of patients (%)

Any AE	478 (98.8%)	224 (91.8%)
Any AE of grade 3 or 4	341 (70.5%)	46 (18.9%)
Any ADR	466 (96.3%)	168 (68.9%)
Any ADR of grade 3 or 4	316 (65.3%)	16 (6.6%)
Any SAE	156 (32.2%)	32 (13.1%)
Any serious ADR	118 (24.4%)	6 (2.5%)
AEs leading to treatment discontinuation	58 (12.0%)	6 (2.5%)
AEs leading to dose reduction	343 (70.9%)	20 (8.2%)
AEs leading to dose interruption	385 (79.5%)	44 (18.0%)
AEs leading to an outcome of death	2 (0.4%)	1 (0.4%)

Source: CSR and PRIMA Table 2 (1,22)

Abbreviations: ADR, adverse drug reaction (treatment-related AE); AE, adverse event; N, total number of patients in the safety population; SAE, serious AE.

The most common AEs occurring in ≥10% of patients of either treatment arm are presented in Table 2. The most common grade ≥3 AEs in the niraparib group were anaemia (31.0%), thrombocytopenia (28.7%), and a decreased platelet count (13.0%).

Table 2: Most common adverse events of grade 3 and 4 in the PRIMA trial.

MedDRA preferred term	Niraparib (N=484) Number of patients (%)	Placebo (N=244) Number of patients (%)
Anaemia	150 (31.0%)	4 (1.6%)
Thrombocytopenia	139 (28.7%)	1 (0.4%)
Platelet count decreased	63 (13.0%)	0
Neutropenia	62 (12.8%)	3 (1.2%)
Fatigue	9 (1.9%)	1 (0.4%)
Abdominal pain	7 (1.4%)	1 (0.4%)
Nausea	6 (1.2%)	2 (0.8%)
Insomnia	4 (0.8%)	1 (0.4%)
Vomiting	4 (0.8%)	2 (0.8%)
Headache	2 (0.4%)	0
Constipation	1 (0.2%)	0

Source: CSR and PRIMA Table 2 (1,22)

Abbreviation: MedDRA, medical dictionary for regulatory activities; RS, routine surveillance.

6.1.4 Olaparib (relevant for clinical question 1)

6.1.4.1 Proportion of patients who experienced grade 3 and 4 adverse events

There were no AEs with an outcome of death (grade 5). AEs of grade 3 and 4 were reported in 39.2 (33.3; 45.2)% of patients receiving olaparib and 18.5 (11.8; 25.1)% of patients receiving

placebo(23). Of these AEs, the most commonly observed were blood and lymphatic system disorders, gastrointestinal disorders, investigations and general disorders and administration-site condition. Anaemia and neutropenia were the only AEs of grade 3 and 4 reported in ≥5% of patients Table 3. Adverse drug reactions of grade 3–4 was not reported.

Table 3: Most common adverse events of grade 3 and 4 in the SOLO1 trial.

MedDRA preferred term	Olaparib (N=260) Number of patients (%)	Placebo (N=130) Number of patients (%)
Anaemia	56 (22%)	2 (2%)
Neutropenia	22 (9%)	6 (5%)
Fatigue or asthenia	10 (4%)	2 (2%)
Diarrhoea	8 (3%)	0
Abdominal pain	4 (2%)	1 (1%)
Thrombocytopenia	2 (1%)	2 (2%)
Nausea	2 (1%)	0
Headache	1 (<1%)	3 (2%)
Vomiting	1 (<1%)	1 (1%)
Dizziness	0	1 (<1%)

Source: SOLO publication Table 2 (24) and EPAR Table 46 (23)
Abbreviations: AE, adverse event; N, total number of patients in the safety population; MedDRA, Medical Dictionary for Regulatory Activities.

6.2 Clinical evidence: Other data sources

Evidence from the ovarian cancer database affiliated to the university of Edinburgh was used to inform subsequent treatment rates and to validate the overall survival extrapolations used in the model. The Edinburgh database contains long-term follow-up data on patients diagnosed with OC in the South East region of Scotland (N > 4,000). Data were available for patients with newly diagnosed OC who had not received any active maintenance therapy. This database was used, as only very limited data is available for the Danish OC cohort. The database was used to inform the split on the different subsequent treatment options in second line. To validate the overall survival extrapolations for RS, log-term data from the Edinburgh database was used, to ensure that the extrapolations was clinical plausible. Data from the Edinburgh database was validated by clinical experts, which concluded that the Edinburgh database was transferable to the Danish OC cohort in regard to patient characteristics.

Baseline patient- and disease characteristics of the Edinburgh database were suitably similar to those observed in the routine surveillance arm of the PRIMA trial. This warranted the use of such evidence database to aid selection of appropriate survival distributions for the economic analysis Table 4. It should be highlighted that the patient population in the Edinburgh database are a slightly more

severe patient group, than the one in PRIMA. Based on this the prediction of long-term survival from this patient population should serve as a minimum benchmark for PRIMA RS, as the severity of disease is associated with a bad prognosis and low survival rates. However, it should be mentioned that there is a potential risk of overestimating the survival gain for niraparib and thus, also the additional costs associated with treatment with niraparib.

Table 4: Comparison of PRIMA RS cohort and the Edinburgh Ovarian Cancer Database cohort baseline patient and disease characteristics.

Characteristic	Edinburgh database [redacted])	PRIMA RS cohort (n=246)
Age (median)	[redacted]	62 (33-88)
Histological type		
Serous	[redacted]	93.5%
Endometroid	[redacted]	3.7%
Other	[redacted]	2.4%
Primary cancer site		
Ovary	[redacted]	81.7%
Fallopian tube	[redacted]	13.%
Peritoneum	[redacted]	5.3%
FT/ovary	[redacted]	0%
FIGO stage at diagnosis		
IIIA	[redacted]	1.6%
IIIB	[redacted]	4.9%
IIIC	[redacted]	56.1%
III NS	[redacted]	1.6%
IV	[redacted]	35.5%
ECOG		
0	[redacted]	70.7%
1	[redacted]	29.3%
2	[redacted]	-
3	[redacted]	-

Abbreviations: ECOG, European Oncology Cooperative Group; FIGO, International Federation of Gynecology and Obstetric; RS, routine surveillance.

6.3 CLINICAL QUESTIONS

The 26th of November 2020, GSK received the protocol from the Danish Medicines Council (DMC) for evaluating niraparib as first line maintenance treatment for patients with ovarian cancer (OC). The protocol consisted of five clinical questions listed below(3):

1. Value of niraparib compared to olaparib for maintenance treatment of newly diagnosed patients with advanced BRCA-mutated ovarian-, fallopian tube- and primary peritoneal cancer, that is in complete or partial response to platinum-based chemotherapy (PBC).
2. Value of niraparib compared to bevacizumab for newly diagnosed patients with advanced non-BRCA mutated, HRD-positive high grade ovarian-, fallopian tube- and peritoneal cancer, that is in complete or partial response to PBC and are candidates for bevacizumab.
3. Value of niraparib compare to bevacizumab for newly diagnosed patients with advanced non-BRCA mutated, HRD-negative high-grade ovarian-, fallopian tube- and peritoneal cancer, that respond complete or partial to PBC and are candidates for bevacizumab.
4. value of niraparib compared to placebo as maintenance treatment of newly diagnosed patients with advanced, non-BRCA mutation, HRD-positive high-grade OC that are in complete or partial response to PBC and are not candidates for bevacizumab.
5. value of niraparib compared to placebo as maintenance treatment for newly diagnosed patients with advanced non-BRCA mutation, HRD-negative high-grade OC that are in complete or partial response to PBC and are not candidates for bevacizumab.

The comparisons and different (sub)populations requested for this application is illustrated in Table 5. However, due to the heterogeneity in the study designs and populations, it was not possible to answer all the desired clinical questions an explanation for the included populations and comparators are described in Section 6.4.

Table 5: The five clinical questions provided in the protocol from the DMC.

Clinical question	Population	Comparator(s) for niraparib
1	Stage III-IV HRD-positive patients with a BRCA mutation.	Olaparib
2	Stage III-IV HRD-positive patients without a BRCA mutation, with more than ≥1 cm rest tumor or *inoperable.*	Bevacizumab
3	Stage III-IV HRD-negative patients without BRCA mutation, with more than ≥1 cm rest tumor or *inoperable.*	Bevacizumab
4	Stage III HRD-positive patients without a BRCA mutation, with less than *≤1 cm rest tumor,*	RS/placebo
5	Stage III HRD-negative patients without a BRCA mutation, with less than ≤ 1 cm rest tumor.	RS/placebo

Abbreviation: HRD, Homologous recombination deficiency; BRCA, Breast Cancer.

6.4 Comparators

Due to the heterogeneity in the clinical trial designs and populations, summarised below, a reliable evaluation of the comparative efficacy of niraparib versus olaparib and niraparib versus bevacizumab using indirect treatment comparison (ITC) techniques was deemed invalid.

6.4.1.1 Reasoning behind the included comparators

The feasibility of ITC between these 3 first-line (niraparib, olaparib and bevacizumab) treatment options for ovarian cancer patients has been investigated, and it has been concluded that several confounding factors preclude an objective systematic comparison between the randomised controlled trials included in this application.

6.4.1.1.1 Difference between the PRIMA trial (niraparib) and SOLO-1 trial (olaparib)

The PRIMA trial enrolled patients with a high risk of disease recurrence and as such the study population differed markedly from the population enrolled in the other first-line maintenance trials. The SOLO-1 trial only recruited ovarian cancer patients with a BRCA mutation (BRCAm). Furthermore, the ITT population included stage III patients with no visible residual disease (NVRD) following primary debulking surgery, a patient subgroup which was not included in the PRIMA trial. Retrospective studies have shown that patients with NVRD after primary debulking surgery have a better prognosis compared to those with visible residual disease, especially patients with stage III disease (25,26). This suggests that the SOLO-1 ITT population had a better prognosis than the PRIMA BRCAm population. The presence of residual disease following debulking surgery (cytoreduction) is a treatment effect modifier, thus an indirect comparison between the PRIMA BRCAm subgroup and the ITT population in SOLO-1 is likely to be biased.

As the comparison of niraparib and olaparib will produce biased results, a cost minimization analysis was conducted, where the effect of the two treatments were set equal. This was done to enable a comparison of costs between the two treatment options niraparib and olaparib, to reflect clinical practice to some extent. Time to treatment discontinuation from the PRIMA trial was used to inform the treatment duration of olaparib.

6.4.1.1.2 Differences between the PRIMA trial (niraparib) and GOG-0218 and ICON7 trials (bevacizumab)

In the GOG-0218 and ICON7 trials, bevacizumab was co-administered with chemotherapy and continued into the maintenance phase of the first-line regimen. Currently no methods are available that can accurately adjust the data to isolate the treatment effect of bevacizumab in the maintenance phase and thus permit a reliable comparison with niraparib. Furthermore, the PRIMA and ICON-7 trials did not report primary debulking surgery (PDS) and interval debulking surgery (IDS) rates and subsequent residual disease, therefore no comparison between niraparib and bevacizumab could be made for this analysis.

BRCA and homologous recombination status were not analysed in GOG-0218 and ICON7, why the proportion of patients with deleterious mutations or other genomic instability is unknown. Patients with HRD positive BRCAm generally has a better prognosis compared to patients with non-BRCA (BRCAwt) and homologous recombination proficiency (HRP)(3,10). In PRIMA, the patient population was presented by homologous recombination status (HRD/HRP) and within HRD by BRCA status

(BRCAm/BRCAwt). This results in an unknown difference in important prognostic factors, which are considered to make any comparisons between the data invalid.

Due to important differences in the clinical trial designs and confounding factors, it has been concluded that neither indirect nor narrative comparisons on the comparative efficacy of niraparib versus bevacizumab are meaningful. This has also previously been confirmed by the Danish Medicines Council(27). Bevacizumab is included as a subsequent treatment option in the model.

6.5 TARGET POPULATION AND COMPARATORS

Due to the heterogeneity in the study designs and population, it was not possible to include all the desired comparators requested in the five clinical questions. The value of niraparib compared to olaparib for the HRD positive BRCA mutated patients was requested in clinical question 1. Due to the heterogeneity in the study designs and populations included in the PRIMA and SOLO-1 trial explained in section 6.4.1.1.1, it was not possible to conduct a reliable ITC and therefore, a cost minimization analysis was adopted for this comparison.

It was not possible to compare niraparib to bevacizumab in clinical question 2 and 3, as the PRIMA and ICON-7 trials did not report PDS and IDS rates and subsequent residual disease, explained in section 6.4.1.1.2. Because of this, no comparison between niraparib and bevacizumab could be made, and it was therefore not possible to answer the clinical questions individually. The HRD-positive non-BRCA (clinical question 2 and 4), will be compared to RS and the HRD-negative non-BRCA (clinical question 3 and 5) will be compared to RS as well. Three populations will therefore be used in answering the five clinical questions. An overview of the included populations and comparators are summarized in Table 6. One more population (overall population) was included in the model, this population was not requested in any clinical question. However, this population was included as niraparib is indicated for maintenance treatment irrespective of biomarker status. The overall population can be switch on manually in the model, as it is not a part of the base-case analysis.

Table 6: Population and comparators included in the model.

Clinical questions	Population	Comparator	Data used	Model population name
1	Stage III-IV HR-deficient/HRD-positive BRCAm. Only patients with a BRCA mutation are included.	Olaparib	The effect of niaparib and olaparib is assumed equal and a cost minimization analysis is performed for this population. Data will be informed from the PRIMA and SOLO-1 trial. SPC and treatment guidelines are used to inform dosing for olaparib.	HR-deficient BRCAmut
2 and 4	Stage III-IV HR-defient/HRD-positive, non-BRCA (BRCAwt). Patients without a BRCA mutation, these patients make up the	Routine surveliance	The HRD BRCAwt population will be compared to RS, using niraparib and RS data from the PRIMA trial and the Edinburgh OC database.	HR-deficient BRCAwt

	rest of the HRd-positive group.			
3 and 5	Stage III-IV HR-proficient/HRD-negative non-BRCA (BRCAwt). Patients without a BRCA mutation that are HRD-negative in the PRIMA trial referred to as HRP.	Routine surveillance	The HRP population will be compared to RS. Data from the PRIMA trial and Edinburgh OC database will be used.	HR-proficient

Abbreviations: BRCAm, BRCA mutation; BRCAwt, BRCA wildtype; RS, Routine surveillance.

7 METHODS

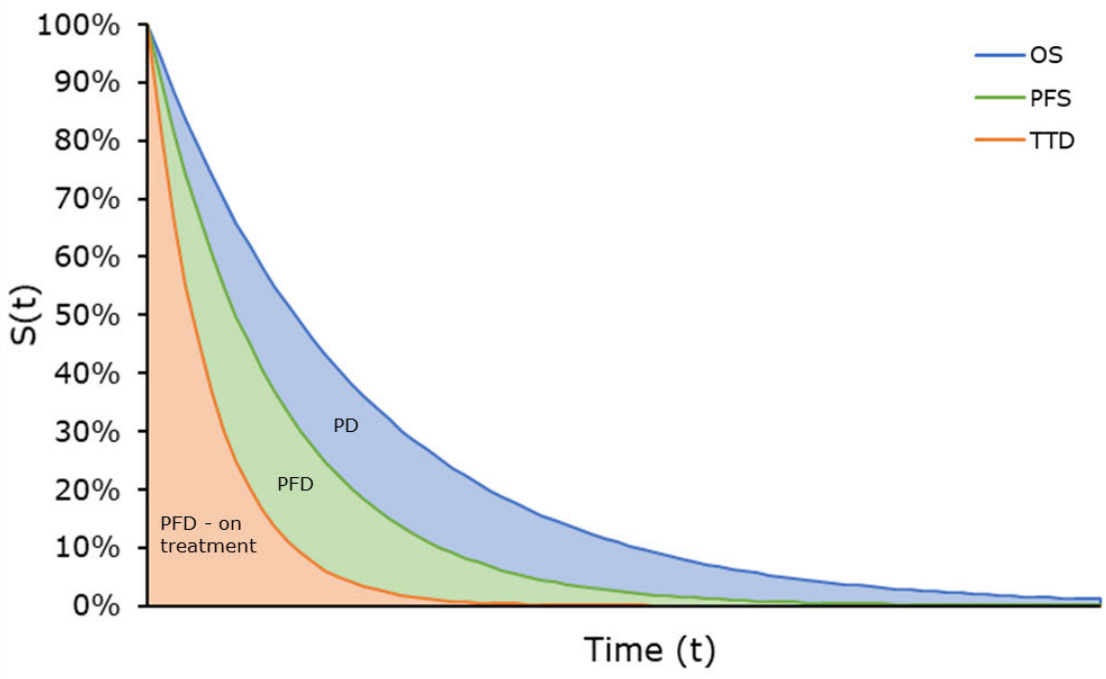
7.1 OVERVIEW

A partitioned survival model (PSM) was developed to model the costs associated with receiving treatment with niraparib over a 30-year time horizon.

7.2 MODEL STRUCTURE

A three-state cohort-based PSM was developed to assess the costs of niraparib for the first-line maintenance treatment of patients with OC. The model includes three mutually exclusive health states, Progression-free disease (PFD), progressed disease (PD), and Death, from any cause. An illustration of the model state structure is provided in Figure 1. With the PFD health state patients may be on or off maintenance treatment, as determined by a time to treatment discontinuation (TTD) curve. The three states are mutually exclusive and fully exhaustive, meaning that patients must occupy one of the states at any given time.

Figure 1: Model schematic.



Abbreviations: PD, progressed disease; PFD, progression-free disease; PFS, progression-free survival; OS, overall survival; s(t), survival at time t; TTD, time to treatment discontinuation

The selected health states used in the model are consistent with the clinical endpoints assessed in the PRIMA trial including the primary endpoint of PFS, and the secondary endpoint of OS. PFD state membership will be estimated from the extrapolated PFS Kaplan-Meier (KM) curve, the state

membership of the dead state is estimated using the extrapolated OS KM curve (Death=1-OS), and finally the PD state membership is estimated to be the difference between the OS and PFS curves (PD=OS-PFS). The OS curve is limited by the general mortality of the background population, this is done as patients with an OC diagnosis are not assumed to live longer than the background population.

7.2.1 Time horizon

A time horizon of 30 years is chosen for this economic evaluation, as this time horizon will capture all costs associated with treatment of OC for the maintenance phase and subsequent treatment lines. This time horizon was adopted as no patients were still alive after 30 years.

7.2.2 Cycle length

A monthly cycle length was adopted; this cycle length is in line with the PRIMA time-to-event survival analysis. A cycle is defined as 30.44 days (365.25 days/12 months). Half cycle correction is applied to the model, assuming that costs is incurred on average mid-way through a cycle.

7.2.3 Perspective

The model takes a restricted societal perspective as recommended by DMC methods' guideline(28). The model will, therefore, include drug costs, administration costs, monitoring costs, AE costs, patient – and transportation costs associated with the included treatment options.

7.2.4 Discounting

A discount rate of 3,5% was adopted in this model, based on the recommendation provided by the Danish ministry of finance (29). The used discount rate is in line with the recommended for the chosen time horizon.

7.3 MODELLING EFFECTIVENESS

7.3.1 Estimation of survival curves

Efficacy data were used directly from PRIMA to extrapolate survival curves for the (sub)population for PFS, TTD and OS for both niraparib and routine surveillance. Parametric models were fitted to the niraparib and RS PLD to provide long-term extrapolations for PFS. At the time of data cut off (May 17, 2019) there were 232/487 events (47,6% maturity) in the niraparib arm and 155/246 events in the RS arm (63% maturity). After a median follow-up of approximately 13.8 months, the median PFS was 13.77 and 8.15 months for niraparib and RS, respectively.(1) To apply a 30-year time horizon in the economic analysis, extrapolation beyond the follow-up period was required. Extrapolated curves were fitted with formulae which ensured PFS and TTD is always less than OS.

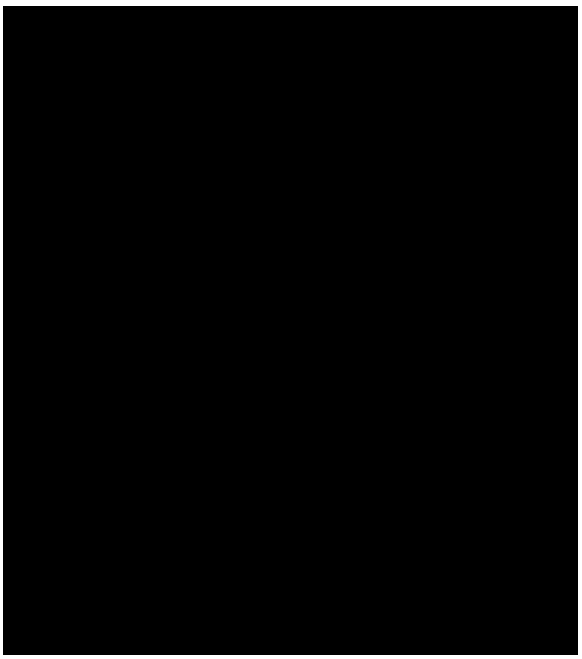
7.3.1.1 Parametric curve fitting

For treatments included in the PRIMA study, survival curves were fitted to the time-to-event patient level data (PLD), based on Decision Support Unit (DSU) guidance from the National Institute for Health and Care Excellence (NICE).(30) Survival curves for all endpoints were fitted using individually modelled standard parametric curves: exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma.[1] Additionally, dependent parametric curves were also fitted to the PLD. Here the parametric curves were fitted to the RS and niraparib arms simultaneously with a covariate for treatment (reference=RS arm). As per the NICE DSU guidelines six parametric curves were jointly fitted to the data: exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma.

For all curves presented in the following sections, the following key criteria were applied to select the base case curves:

- Assessment of proportional hazard assumption: Inspection of the log cumulative hazards (Figure 2) and Schoenfeld residual plot (Figure 3) suggests that the relative hazards are likely to vary over time. The hazards appear not to be proportional in the two treatment arms. Looking at the log-cumulative hazards (Figure 2), the hazard is not constant over time, however the curves do not intersect. The residual plot in Figure 3 does not suggest a non-random pattern against time. Based on this, proportional hazard (PH) is not considered plausible, and as such, it is not possible to conclude that the PH assumption between niraparib and RS holds.
- Visual inspection of survival curve fit to KM data from the PRIMA trial
- Inspection of log-cumulative hazard plots (to assess the behaviour of the hazard over time)
- Statistical model fit, as measured by the Akaike's Information Criterion (AIC)/ Bayesian Information Criterion (BIC)
- Clinical plausibility of long-term extrapolation compared to real world data from the Edinburgh ovarian cancer database.

Figure 2: PFS cumulative log-log plot for the ITT data set.



Abbreviations: PFS, progression free survival; ITT, intention to treat

Figure 3: PFS Schoenfeld residuals plot for the ITT data set.

Abbreviations: PFS, progression free survival; ITT, intention to treat

7.3.2 Subgroup survival analysis

Survival analysis conducted for the populations requested in the clinical questions, HRD-positive with a BRCA mutation (question 1), HRD-positive without a BRCA mutation (question 2 and 4) and HRD-negative patients without a BRCA mutation (question 3 and 5). PFS, OS and TTD endpoints were analyzed for all subgroups. Landmark survival rates and survival curves for all the subgroups are provided in Appendix 11.1.1.1.1.1.

7.3.2.1 HRD-positive BRCA mutated (BRCAm)

A subgroup of all patients with homologous recombination deficiency (HRD) who additionally had a *BRCA* mutation (HRD positive *BRCAm*) were analysed in this subgroup survival analysis.

7.3.2.1.1 Progression-free survival

Six standard parametric independent models were therefore fitted to each arm of the study data; exponential, Weibull, Gompertz, log-logistic, log-normal and the generalised gamma. A summary of the goodness-of-fit statistics for the PFS extrapolations is available in Table 7.

Table 7: AIC and BIC statistical goodness of fit data for PFS HR-deficient BRCAm data set (independent models)

Rank	Distribution	Niraparib		RS	
		AIC	BIC	AIC	BIC
6	Exponential	461.55	464.57	309.48	311.74
4	Weibull	451.55	457.59	307.61	312.14

Rank	Distribution	Niraparib		RS	
		AIC	BIC	AIC	BIC
5	Gompertz	457.18	463.23	310.90	315.42
2	**Log-logistic**	**449.99**	**456.04**	**304.02**	**308.55**
1	Log-normal	449.09	455.14	302.50	307.03
3	Generalised gamma	451.09	460.16	303.82	310.61

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival

The best statistically fitting model was the log-normal, closely followed by the log-logistic as these scored the lowest AIC and BIC. However, the second-best fitting distribution log-logistic was deemed more plausible and was therefore chosen.

7.3.2.1.2 Overall survival

Six standard parametric independent models were fitted to each arm of the study data; exponential, Weibull, Gompertz, log-logistic, log-normal and the generalised gamma. A summary of the goodness-of-fit statistics for the OS extrapolations is available in Table 8. The generalised gamma did not converge to the available data for either niraparib or RS. It could therefore not be plotted or included in the table below.

Table 8: AIC and BIC statistical goodness of fit data for OS HRD positive BRCAm (independent models).

Rank	Distribution	Niraparib		RS	
		AIC	BIC	AIC	BIC
4	Exponential	133.36	136.38	55.13	57.40
5	Weibull	121.17	127.22	307.61	312.14
3	Gompertz	123.32	129.37	51.41	55.93
2	**Log-logistic**	**121.03**	**127.08**	**50.45**	**54.97**
1	Log-normal	120.32	126.37	50.03	54.55
	Generalised Gamma	N/A	N/A	N/A	N/A

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, Overall survival.

The best statistically fitting model was the log-normal, closely followed by the log-logistic as these scored the lowest AIC and BIC. In general, the parametric models fitted to the data, produced a wide range of extrapolations, which made reasonable visual predictions for the most suitable curve difficult to predict. The second-best fitting model log-logistics was used to extrapolate OS for HRD positive BRCAm, as this was thought to produce the most reliable results.

7.3.2.1.3 Time to treatment discontinuation

Six standard parametric independent models were fitted to each arm of the study data; exponential, Weibull, Gompertz, log-logistic, log-normal and the generalised gamma. A summary of the goodness-of-fit statistics for the TTD extrapolations is available in Table 9. The generalised gamma distribution did not converge to the available data for either niraparib or RS. It could therefore not be plotted or included in the table below.

Table 9: AIC and BIC statistical goodness of fit data for TTD HR-deficient BRCAm data set (independent models)

Rank	Distribution	Niraparib		RS	
		AIC	BIC	AIC	BIC
2	Exponential	605.57	608.60	355.59	357.85
3	Weibull	606.11	612.15	347.55	352.07
1	**Gompertz**	**604.64**	**610.69**	**352.33**	**356.86**
4	Log-logistic	609.57	615.61	345.97	350.50
5	Log-normal	615.99	622.03	345.17	349.69
6	Generalised Gamma	N/A	N/A	N/A	N/A

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival

The Gombertz was the best fitting distribution to the model and was therefore chosen to fit data for the TTD.

7.3.2.2 HRD-positive without BRCA mutation (BRCAwt)

A subgroup of all HRD-positive patients without a BRCA mutation who had the standard wild-type genetic make-up in the BRCA gene (HRD *BRCA*wt) were analysed in this subgroup survival analysis.

7.3.2.2.1 Progression-free survival

Six standard parametric independent models were fitted to each arm of the study data; exponential, Weibull, Gompertz, log-logistic, log-normal and the generalised gamma. A summary of the goodness-of-fit statistics for the PFS extrapolations is available in Table 10. The generalised gamma distribution did not converge to the available data for niraparib and so it could not be plotted or included in the table below.

Table 10: AIC and BIC statistical goodness of fit data for PFS HR-deficient BRCAwt data set (independent models)

Rank	Distribution	Niraparib		RS	
		AIC	BIC	AIC	BIC
3	Exponential	283.68	286.22	246.35	248.36
4	Weibull	283.96	289.04	246.20	250.21

Rank	Distribution	Niraparib		RS	
		AIC	BIC	AIC	BIC
5	Gompertz	285.44	290.53	248.34	252.36
2	**Log-logistic**	**282.71**	**287.80**	**240.91**	**244.93**
1	Log-normal	281.39	286.48	239.16	243.17
	Generalised Gamma	N/A	N/A	237.07	243.09

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival; RS, routine surveillance.

The best statistical fitting model was the log normal. However, all the parametric models fitted well do the data. The second-best fitting model log-logistic was chosen, as this was more plausible.

7.3.2.2.2 Overall survival

Six standard parametric independent models were fitted to each arm of the study data; exponential, Weibull, Gompertz, log-logistic, log-normal and the generalised gamma. A summary of the goodness-of-fit statistics for the OS extrapolations is available in Table 11. The generalised gamma did not converge to the available data for either niraparib or RS. It could therefore not be plotted or included in the table below.

Table 11: AIC and BIC statistical goodness of fit data for OS HRD positive non-BRCA (independent models).

Rank	Distribution	Niraparib		RS	
		AIC	BIC	AIC	BIC
4	Exponential	79.46	82.00	73.67	75.68
3	Weibull	77.21	82.30	73.02	77.03
5	Gompertz	76.84	81.93	74.35	78.37
2	**Log-logistic**	77.41	82.50	72.87	76.88
1	Log-normal	77.44	82.52	72.05	76.07
	Generalised Gamma	N/A	N/A	N/A	N/A

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, Overall survival.

The best statistically fitting model was the log-normal, closely followed by the log-logistic as these scored the lowest AIC and BIC. In general, the parametric models fitted to the data, produced a wide range of extrapolations, which made reasonable visual predictions for the most suitable curve difficult to predict. The second-best fitting model log-logistic was used to extrapolate OS for HRD positive non-BRCA, as this was thought to produce the most reliable results.

7.3.2.2.3 Time to treatment discontinuation

Six standard parametric independent models were fitted to each arm of the study data; exponential, Weibull, Gompertz, log-logistic, log-normal and the generalised gamma. A summary of the

goodness-of-fit statistics for the TTD extrapolations is available in Table 12. The generalised gamma distribution did not converge to the available data for either niraparib or RS. It could therefore not be plotted or included in the table below.

Table 12: AIC and BIC statistical goodness of fit data for TTD HR-deficient BRCAwt data set (independent models)

Rank	Distribution	Niraparib		RS	
		AIC	BIC	AIC	BIC
3	Exponential	423.30	425.85	268.68	270.69
5	Weibull	425.15	430.24	267.34	271.35
4	Gompertz	423.75	428.84	270.18	274.19
1	**Log-logistic**	**422.65**	**427.74**	**264.42**	**268.44**
2	Log-normal	423.05	428.13	265.38	269.39
	Generalised Gamma	N/A	N/A	N/A	N/A

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; TTD, time to treatment discontinuation; RS, routine surveillance.

The best fitting model was the log-logistic, this was also deemed the most plausible distribution on visual inspection and was therefore included.

7.3.2.3 HRD-negative without a BRCA mutation (HRP)

A subgroup of all patients with HRD-negative non-BRCA (HR-proficient) status was analysed in the subgroup survival analysis.

7.3.2.3.1 Progression-free survival

Six standard parametric independent models were therefore fitted to each arm of the study data; exponential, Weibull, Gompertz, log-logistic, log-normal and the generalised gamma. A summary of the goodness-of-fit statistics for the PFS extrapolations is available in Table 13.

Table 13: AIC and BIC statistical goodness of fit data for PFS HRD non-BRCA data set (independent models)

Rank	Distribution	Niraparib		RS	
		AIC	BIC	AIC	BIC
5	Exponential	770.42	773.55	363.37	365.76
4	Weibull	759.63	765.89	363.61	368.38
6	Gompertz	770.66	776.92	364.37	369.13
3	**Log-logistic**	**744.14**	**750.40**	**349.05**	**353.81**
2	Log-normal	737.56	743.82	346.83	351.59
1	Generalised Gamma	727.97	737.36	335.58	342.73

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival; RS, routine surveillance.

The best statistically fitting model was the generalized gamma, however, on visual inspection of the survival curves this did not fit the data very well. The log-logistic model fitted the data better and was deemed more plausible, for that reason this model was chosen.

7.3.2.3.2 Overall survival

Six standard parametric independent models were fitted to each arm of the study data; exponential, Weibull, Gompertz, log-logistic, log-normal and the generalised gamma. A summary of the goodness-of-fit statistics for the OS extrapolations is available in Table 14. The generalised gamma did not converge to the available data for either niraparib or RS. It could therefore not be plotted or included in the table below.

Table 14: AIC and BIC statistical goodness of fit data for OS HRD-negative non-BRCA data set (independent models)

Rank	Distribution	Niraparib		Routine surveillance	
		AIC	BIC	AIC	BIC
5	Exponential	251.77	254.90	176.85	179.24
3	Weibull	242.51	248.77	169.55	174.32
4	Gompertz	247.75	254.01	171.12	175.89
2	**Log-logistic**	**241.73**	**247.99**	**169.58**	**174.35**
1	Log-normal	239.16	245.42	169.53	174.29
	Generalised Gamma	N/A	N/A	N/A	N/A

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival; RS routine surveillance.

The best statistically fitting model was the log-normal, closely followed by the log-logistic as these scored the lowest AIC and BIC. In general, the parametric models fitted to the data, produced a wide range of extrapolations, which made reasonable visual predictions for the most suitable curve difficult to predict. The Weibull and the gompertz underestimate OS at 5 and 10 years. In addition, the exponential overestimate OS at 5 and 10 years. Due to the uncertainty in the results these curves were not considered any further in this economic analysis. The log-logistic model was used to extrapolate OS for HRD-negative non-BRCA, as this was though to produce the most reliable results.

7.3.2.3.3 Time to treatment discontinuation

Six standard parametric independent models were fitted to each arm of the study data; exponential, Weibull, Gompertz, log-logistic, log-normal and the Generalised Gamma. A summary of the goodness-of-fit statistics for the TTD extrapolations is available in Table 15. For the generalised gamma, the distribution did not converge for the niraparib available data and so it could not be plotted or included in the table below.

Table 15: AIC and BIC statistical goodness of fit data for TTD HRD non-BRCA data set (independent models)

Rank	Distribution	Niraparib	RS

		AIC	BIC	AIC	BIC
3	Exponential	869.27	872.40	407.90	410.28
2	**Weibull**	**865.62**	**871.88**	**406.52**	**411.29**
4	Gompertz	869.96	876.22	409.88	414.64
1	Log-logistic	861.87	868.13	394.45	399.21
5	Log-normal	871.06	877.32	394.40	399.16
	Generalised Gamma	N/A	N/A	395.35	402.50

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; TTD, time to treatment discontinuation; RS, routine surveillance.

The best fitting model was the log-logistic. In general, all the parametric models fitted well to the data. The second-best fitting model Weibull was chosen, as this was thought to produce the most reliable results.

An overview of the chosen distributions to extrapolate PFS, OS and TTD data for the included populations are summarized in Table 16.

Table 16: Overview of the included parametric models for the extrapolation of PFS, OS and TTD.

Endpoint	HRD-positiv BRCA mutated	HRD-positive BRCAwt	HRD-negative BRCAwt
Progression free survival			
Niraparib	PRIMA study, Log-logistic	PRIMA study, Log-logistic	PRIMA study, Log-logistic
Routine surveillance	PRIMA study, Log-logistic	PRIMA study, Log-logistic	PRIMA study, Log-logistic
Olaparib (BRCAm only)	N/A	N/A	N/A
Overall survival			
Niraparib	PRIMA study, Log-logistic	PRIMA study, Log-logistic	PRIMA study, Log-logistic
Routine surveillance	PRIMA study, Log-logistic	PRIMA study, Log-logistic	PRIMA study, Log-logistic
Olaparib (BRCAm only)	N/A	N/A	N/A
Time to treatment discontinuation			
Niraparib	PRIMA study, gompertz With a three-year stopping rule	PRIMA study, Log-logistic	PRIMA study, Weibull
Routine surveillance	PRIMA study, gompertz	PRIMA study, Log-logistic	PRIMA study, Weibull
Olaparib (HR-d BRCAm only)	Assumed equal to niraparib with a two-year stopping rule	N/A	N/A

Abbreviations: BRCA, breast cancer susceptibility gene; HRD, homologous recombinant deficient; PFS, progression free survival; OS, overall survival; N/A, not applicable.

7.4 COSTS

7.4.1 Treatment acquisition

Niraparib is available as a 100 mg capsule, the recommended starting dose is 200 mg (two 100-mg capsules), taken once daily and for those patients who weigh ≥77 kg and have baseline platelet count ≥150,000/µL, the recommended starting dose is 300 mg (three 100-mg capsules), taken once daily. Treatment is given until disease progression or unacceptable toxicity. The cost per pack (56 x 1 hard tablet) of niraparib in PTC is DKK 41,340.00(31).

7.4.1.1 Dosing

Within the PRIMA trial, the original protocol initially started patients on 300 mg OD, however a subsequent protocol amendment allowed patients who weigh < 77 kg and /or have baseline platelet count < 150,000/µL, to initiate on 200 mg OD. The dose intensity recorded in the PRIMA trial was [redacted] mg.(22) An analysis of patient level data by treatment cycle, equal to one model cycle, demonstrates that average cycle starting-dose down-titrated rapidly before plateauing out just above [redacted] OD, as shown in Figure 4.

Figure 4: Average starting dose by cycle for the niraparib ITT dataset of the PRIMA trial.

Cycle	2	4	6	8	10	12
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: CSR(32)
Abbreviations: ITT, intention to treat

A second analyses was conduced to explore the actual dose received by patients over the first 12 months of the PRIMA trial. Figure 5 demonstrates how the dose received quickly reduces over the first few cycles before stabilising. It also shows an increasing proportion of patients receiving a 100 mg daily dose over time ([redacted] of patients with a dose of 100 mg by month 12).

Figure 5: Niraparib dose level by month on treatment.

The efficacy data behind this economic analysis are driven by the actual dose received in the PRIMA trial, and as such, given the evidence presented above, it was concluded appropriate to use the actual dose observed in the PRIMA trial, in the base-case. The actual dose was preferred to the average dose as it alleviates the need for wastage to be incorporated into the calculations. It is possible to choose fixed dose or individual dose in the model. A scenario analysis was performed on both the fixed and individualized dosing.

7.4.1.2 Drug acquisition costs

The acquisition costs for niraparib and the included comparators in the model are illustrated in Table 17. As niraparib and olparib is oral treatment regimes no administration costs were applied. There

are no costs associated with routine surveillance, as all patients included in the model will receive cytoreductive surgery and/or chemotherapy prior to first line maintenance treatment. Acquisition costs were applied in the model in line with how the treatment was received in the PRIMA study. TTD extrapolations were used to estimate duration of treatment with niraparib.

Table 17: Summary of drug related costs.

Items	Niraparib	Olaparib	RS
Protocol dosing per administration	200 mg (2x100mg tablets)	300	N/A
Frequency of administration	Once daily	Twice daily	N/A
List price treatment cost (PTC)	DKK 41.340 per pack of 56 tablets	DKK 18.219,87 per pack of 100mg and 150 mg 56 tablets	DKK 0
Average daily dose	[redacted], dose intensity in the PRIMA trial	600 mg, from the SmPC of olaparib.	-
Administration cost per cycle	N/A	N/A	N/A
Stopping rule	Patients discontinue at 3 years	Patients discontinue at 2 years	N/A

Abbreviations: mg, milligram; N/A, not applicable; SmPC, Summary of Product Characteristics.

7.4.2 Homologous recombination deficiency test

Homologous recombination repair deficiency (HRD) is a frequent feature of high-grade serous ovarian, fallopian tube and peritoneal carcinoma (HGSC) and is associated with sensitivity to PARPi therapy. HRD testing provides an opportunity to optimize the use of PARPi in treatment of patients with OC (33). Before enrollment in the PRIMA trial, tumor samples from the patients underwent central testing to identify those with homologous-recombination deficiency (myChoice test, Myriad Genetics). HRD was defined as the presence of a BRCA deleterious mutation, a score of at least 42 on the myChoice test, or both (test scores can range from 1 to 100) (1). The list price of a Myriad myChoice® CDx test was on October 23, 2019 $4,040 (34). The price was converted into Danish

crowns DKK 24,711.47[1]. HRD test costs are applied as a one-off cost in the model and can be included if desired in the "cost inputs" sheet. The HRD test is evaluated in a scenario analysis.

7.4.3 Disease management costs

Disease management costs are calculated for the treatment alternatives included in the model. Costs of outpatient visits are calculated assuming 30-minute physician time. The hourly salary of a chief physician and attending physician was used to generate an average hourly salary, as there are no requirements for which doctor will attend the consultation. Danish reference grouper (DRG, 2021) was used to estimate the unit costs for a CT scan (30PR06 – DKK 2,007).

Patients on treatment with niraparib will be assessed by a consulting physician once every month, to monitor treatment effect and AEs. The most common AEs associated with treatment with niraparib is heamatologic. It is therefore important to monitor the patients blood count closely the first month, as most AEs will present within the first month of treatment. The patient will have a blood sample done every week, the first month of treatment, reducing to once every month in cycle 2+. The patient will not be called in for a consultation after each blood count, the patient will be contacted if there are abnormalities in the blood count. It should be noted that the most effective treatment of AEs is dose reduction or dose interruption. The costs of complete blood count was derived from Rigshopitalets lab portal, only relevant blood samples for the OC patients were included in the costs, based on insights from the clinic (35). The included blood samples are summarized in Appendix 11.1.1.1.1.3.

It is anticipated that niraparib patients will be required to undertake additional blood pressure and heart rate monitoring (weekly in the first two months of treatment and monthly thereafter until the patient discontinue treatment). The hourly nurse salary was used in estimating the unit costs, assuming 15-minute consultation each time. No additional CT-scans were required for treatment with niraparib.

Patients in the olaparib arm were assessed by a consulting physician once every month and had a complete blood count test monthly, reducing to once every three months when off treatment whilst progression-free. Upon disease progression, outpatient consultations were made monthly. For both treatments blood tests were carried out every three months throughout all stages. Disease management costs and resource use for the included treatments are summarized in Table 18.

[1] Exchange rate, currency US dollars 611.67 (January 12th 2021)(42).

Table 18: Disease management resource use and unit costs.

Intervention	Health state	Out-patient visit oncology	CT scan	Complete blood count	Blood pressure & heart rate *	Total cost per cycle
Unit cost (DKK)		**524**	**2,007**	**382**	**138.50**	
Niraparib	PFD on-treatment (cycle 1)	1.0	0.3	4.0	4.0	**3,208.1**
	PFD on-treatment (cycle 2)	1.0	0.3	1.0	4.0	**2,062.1**
	PFD on treatment (cycle 3+)	1.0	0.3	1.0	1.0	**1,646.6**
	PFD off-treatment	0.3	0.3	0.3	0.0	**873.9**
	PD	1.0	0.3	0.3	0.0	**1,240.7**
Olaparib	PFD on-treatment	1.0	0.3	1.0	0.0	**1,508.1**
	PFD off-treatment	0.3	0.3	0.3	0.0	**873.9**
	PD	1.0	0.3	0.3	0.0	**1,240.7**
RS	PFD on-treatment	0.3	0.3	0.3	0.0	**873.9**
	PFD off-treatment	0.3	0.3	0.3	0.0	**873.9**
	PD	1.0	0.3	0.3	0.0	**1,240.7**

Abbreviations: CT, computerised tomography; PD, progressed disease; PFD, progression-free disease; RS, routine surveillance

* Blood pressure and heart rate monitoring assumed to be the same cost as out-patient visit

7.4.4 Patient and transportation costs

Patient cost were calculated in line with the recommendation for valuation of unit costs provided by DMC. The unit cost per hours used is assumed to be DKK 179 per hour. Based on the estimated 14-kilometer distance to the hospital recommended by DMC, an estimated 30 minutes were assumed used on transportation. Transportation costs are calculated in line with guidance provided by DMC. The estimated average distance to and from the hospital is assumed to be 28 kilometers and an additional price of DKK 3.52 per kilometer. The majority of patients will receive more than one examination at the same visit to the hospital. Therefore, patient and transportation costs will be calculated based on the examinations from Table 18 where most visits are required. A summary of patient and transportation costs can be found in Table 19.

Table 19: Patient and transportation unit costs.

Intervention	Health state	Patient costs	Transpor-tation costs	Total patient cost per cycle (DKK)	Total transport cost per cycle (DKK)
Unit cost (DKK)		179.00	98.84	--	--
Niraparib	PFD on treatment (cycle 1)	4.0	4.0	716.00	395.36
	PFD on treatment (cycle 2)	4.0	4.0	716.00	395.36
	PFD on treatment (cycle 3+)	1.0	1.0	179.00	98.84
	PFD off treatment	0.3	0.3	53.70	29.65
	PD	1.0	1.0	179.00	98.84
Olaparib	PFD on treatment	1.0	1.0	179.00	98.84
	PFD off treatment	0.3	0.3	53.70	29.65
	PD	1.0	1.0	179.00	98.84
RS	PFD on treatment	0.3	0.3	53.70	29.65
	PFD off treatment	0.3	0.3	53.70	29.65
	PD	1.0	1.0	179.00	98.84

Abbreviations: PFD, progression free disease; PD, progressed disease.

7.4.5 Adverse event management costs

Treatment-related AEs grade ≥3 that are reported in ≥5% of patients in the treatment groups were included. For niraparib and RS the AE rates were sourced from the PRIMA trial. Corresponding AE data for olaparib were sourced from the SOLO-1 trial. Management of the included AEs have been validated by KOL. Costs were obtained from the 2021 DRG reference costs and the DMC valuation of unit costs. AEs were incorporated as one-off events and the cost were applied to the first cycle of the model, under the assumption that AEs are likely to occur soon after treatment initiation. The AE costs are summarized in Table 20.

Table 20: Unit costs of grade ≥3 AEs.

Grade ≥ 3 AE	Mean unit costs (DDK)	Type of management	Source
Anaemia	4,732	Ambulant blood transfusion, 1 day once every month	16PR02: Blood transfusion, others
Thrombocytopenia	511.50	30 min telephone consultation with a doctor.	DMC valuation of unit costs is used to calculate an average cost. Chief physician: DKK 1,282/hour Attending physician: DKK 764/hour
Platelet count decreased	511.50	30 min telephone consultation with a doctor.	Same method was applied as for thrombocytopenia
Neutropoenia	511.50	30 min telephone consultation with a doctor.	Same method was applied as for thrombocytopenia
Hypertension	NA	No treatment is required	NA
Fatigue/asthenia	NA	No treatment is required	NA
Lymphopenia	NA	No treatment is required	NA
Neutrophil count decreased	511.50	30 min telephone consultation with a doctor.	Same method was applied as for thrombocytopenia

Abbreviations: AE, adverse event.

7.4.6 Subsequent treatment costs

Following disease progression from first-line maintenance therapy, patients will receive several subsequent treatment regimens over the course of their care. The subsequent treatment options included in the model are based on Danish clinical practice and the Danish Gynecological Cancer Group (DGCG) and the European Society of Gynecological Oncology (ESGO) guidelines. Subsequent treatment helps to provide the overall survival for patients in the study, and it would therefore be wrong not to include these costs in the model, as the observed OS also depends on the patients' subsequent lines of treatment.

No data was available for Denmark on the percentage split in patients receiving which treatments in subsequent lines. Data from the Edinburgh OC database has proven to reflect Danish clinical practice and was therefore used to define this split. Clinicians with specialty in OC were asked to validate this assumption. The subsequent treatment regimens applied in the model are summarized in Table 21 . In the absence of published data for olaparib, subsequent treatment regimens were assumed equal to that of niraparib.

Table 21: Base-case second-line subsequent treatment regimens, derived from KOL input and weighted by the proportion of patients who remain platinum-sensitive following first-line treatment.

Primary treatment	Secondary treatment	Overall (PRIMA CSR Table 14,2,6,2a)	HR-deficient BRCAmut (assumed same as overall)	HR-deficient BRCAwt	HR-proficient (assumed same as overall)
Niraparib	Carboplatin	29,16%	29,16%	23,48%	29,16%
	Cisplatin	3,29%	3,29%	2,02%	3,29%
	Taxane	12,73%	12,73%	6,88%	12,73%
	Doxorubicin	20,33%	20,33%	16,60%	20,33%
	Gemcitabine	15,61%	15,61%	12,96%	15,61%
	Bevacizumab	8,01%	8,01%	4,86%	8,01%
	Cyclophosphamide	0,62%	0,62%	0,81%	0,62%
	PARP inhibitor	0,00%	0,00%	0,00%	0,00%
Olaparib (assumed equal to niraparib in absence of SOLO-1 data)	Carboplatin	29,16%	29,16%	N/A	N/A
	Cisplatin	3,29%	3,29%	N/A	N/A
	Taxane	12,73%	12,73%	N/A	N/A
	Doxorubicin	20,33%	20,33%	N/A	N/A
	Gemcitabine	15,61%	15,61%	N/A	N/A
	Bevacizumab	8,01%	8,01%	N/A	N/A
	Cyclophosphamide	0,62%	0,62%	N/A	N/A
	PARP inhibitor	0,00%	0,00%	N/A	N/A
RS	Carboplatin	35,77%	35,77%	33,33%	35,77%
	Cisplatin	2,44%	2,44%	1,59%	2,44%
	Taxane	12,20%	12,20%	5,28%	12,20%
	Doxorubicin	26,83%	26,83%	20,63%	26,83%
	Gemcitabine	17,89%	17,89%	14,29%	17,89%
	Bevacizumab	8,96%	8,96%	7,14%	8,96%
	Cyclophosphamide	0,81%	0,81%	0,79%	0,81%
	PARP inhibitor	4,47%	4,47%	5,56%	4,47%

Abbreviations: BRCA, breast cancer susceptibility gene; PD(L)-1, programmed death ligand 1

Subsequent treatment drug costs were calculated based on available formulations, recommended dose and duration from promedicin.dk and pack sizes and unit costs from medicinpriser.dk. The recommended dose of subsequent treatment was based on SmPC and relevant trial protocol doses (3,31,36). As chemotherapy are administered in different ways and the dose are often individualized based on weight etc. Different dose assumptions (area under the curve, body area surface, and fixed) are included in the model, based on the recommended.

The included treatment regimes and the data underlying the calculations are illustrated in Table 22. A cost of DKK 1,670 (2021 reference costs–13MA98, MCD13-1-dagsgroup) were applied for the

intravenously administered chemotherapies (37). Treatment with PARPi incurred no administration costs, as this is an oral treatment regimen.

Table 22: Subsequent treatment drug costs and unit size. Sourced from Medicinpriser.dk.

Subsequent treatment class	Subsequent treatment combination	Treatment	Pack size	List price per pack (DKK)	Unit size
Carboplatin	Carboplatin only	Carboplatin	1	203	450
	Carboplatin w/gemcitabine	Carboplatin	1	203	450
	Carboplatin w/gemcitabine	Gemcitabine	1	1000	1000
	Carboplatin w/paclitaxel	Carboplatin	1	203	450
	Carboplatin w/paclitaxel	Paclitaxel	1	1500	150
Cisplatin	Cisplatin	Cisplatin	1	109	50
Taxane	Carboplatin w/paclitaxel	Carboplatin	1	203	450
	Carboplatin w/paclitaxel	Paclitaxel	1	1500	150
	Docetaxel	Docetaxel	1	150	80
	Paclitaxel	Paclitaxel	1	1500	150
	Paclitaxel albumin	Paclitaxel albumin	1	1500	150
Doxorubicin	Doxorubicin	Doxorubicin	1	120	50
	Doxorubicin hydrochloride	Doxorubicin hydrochloride	1	2551.09	10
	Liposomal doxorubicin hydrochloride	Liposomal doxorubicin hydrochloride	1	2551.09	10
	Pegylated liposomal doxorubicin	Pegylated liposomal doxorubicin	1	2551.09	10
	Pegylated liposomal doxorubicin hydrochloride	Pegylated liposomal doxorubicin hydrochloride	1	2551.09	10
Gemcitabine	Carboplatin w/gemcitabine	Carboplatin	1	203	450
	Carboplatin w/gemcitabine	Gemcitabine	1	203	450
	Gemcitabine	Gemcitabine	1	1000	1000
	Gemcitabine hydrochloride	Gemcitabine hydrochloride	1	1000	1000
Bevacizumab	Bevacizumab	Bevacizumab	1	2090.82	100
	Bevacizumab	Bevacizumab	1	7707.76	400
Cyclophosphamide	Cyclophosphamide	Cyclophosphamide	100	1241	50
PARP inhibitor	Niraparib	Niraparib	56	41340	100
	Olaparib	Olaparib	56	18219.87	100

The rationale behind the dose, frequency and treatment duration included in the model are summarized in Table 23.

Table 23: Subsequent treatment dose and frequency of cycle. Sorced from SmPC (38) and DGCG treatment guidelines (39).

Treatment	Dose	Frequency of cycle and treatment duration	Source
Carboplatin	Dose based on creatinine clearance rates plus twenty-five multiplied by the AUC (5mg/mL/min)	Repeated every 21 days for up to 6 cycles	SmPC for Carboplatin(38). DGCG treatment guidelines(39).
Gemcitabine	Dose based on body surface area and calculated as 1000mg/m2	Repeated twice every 21 days for up to 6 cycles	SmPC for Gemcitabine(38). DGCG treatment guidelines(39).
Paclitaxel	Dose based on body surface area of patient population and calculated as 175 mg/m2	Repeated every 21 days for up to 6 cycles	SmPC for Paclitaxel(38). DGCG treatment guidelines(39).
Cisplatin	Based on body surface area of patient population and calculated as 100 mg/m2	Repeated every 21 days for up to 6 cycles	SmPC for Cisplatin(38). DGCG treatment guidelines(39).
Docetaxel	Based on body surface area of patient population and calculated as 100 mg/m2	Repeated every 21 days for up to 6 cycles	SmPC for Docetaxel(38). DGCG treatment guidelines(39).
Doxorubicin	Based on body surface area of patient population and calculated as 70 mg/m2	Repeated every 21 days for up to 6 cycles	SmPC for Doxorubicin(38). DGCG treatment guidelines(39).
Bevacizumab	7.5 mg per kg	Repeated every 21 days for up to 12 cycles	ICON-7 protocol maintenance dose(40).
Cyclophosphamide	Fixed 50 mg dose	Repeated twice every 28 days for up to 6 cycles.	SmPC for Cyclophosphamide(38). Treatment guideline from Region Sealand (Roskilde)(41).
Niraparib	300 mg OD	Daily for up to [redacted] months based on niraparib CDF report	UK Cancer Drugs Fond (CDF) systemic anti-cancer therapy (SACT), data collected from real world use of niraparib in the UK, this is assumed a conservative estimate for the treatment duration of PARPi in second line. ENGOT-OV16/NOVA protocol dose(10).
Olaparib	600 mg OD	Daily for up to [redacted] months based on niraparib CDF report	UK Cancer Drugs Fond (CDF) systemic anti-cancer therapy (SACT), data collected from real world use of PARPi in the UK, this is assumed to be a conservative estimate for the use of PARPi in second line. SOLO-2 protocol dose(24).

The cost of subsequent treatments is applied as a one-off cost upon progression. A modelling approach in which time to event data were used to explicitly model when patients receive subsequent treatment over time was considered. However, as there is uncertainty surrounding which regimens are received and when, it was deemed more appropriate to apply a simpler approach within the economic analysis using the Edinburgh OC database. Furthermore, the regimens (specifically chemotherapy) are not expected to differ largely between treatments and hence the main difference between applying one-off costs or explicitly tracking when patients receive them

would be down to discounting only. The total costs per subsequent treatment class and line of treatment for each comparator are summarised in Table 24.

Table 24: Total subsequent treatment costs per treatment in second-line.

Primary treatment	Subsequent treatment	Total cost (DKK) per treatment class in second-line	Total costs (DKK)
Niraparib	Carboplatin	6,835.24	64,168.18
	Cisplatin	415.15	
	Taxane	3,468.84	
	Doxorubicin	34,485.34	
	Gemcitabine	5,084.35	
	Bevacizumab	13,753.96	
	Cyclophosphamide	125.28	
	PARP inhibitor	0	
Olaparib (HR-d BRCAmut only)	Carboplatin	6,835.24	64,168.18
	Cisplatin	415.15	
	Taxane	3,468.84	
	Doxorubicin	34,485.34	
	Gemcitabine	5,084.35	
	Bevacizumab	13,753.96	
	Cyclophosphamide	125.28	
	PARP inhibitor	0	
Routine surveillance	Carboplatin	8,385.76	97,908.61
	Cisplatin	308.20	
	Taxane	3,322.83	
	Doxorubicin	45,513.18	
	Gemcitabine	5,827.32	
	Bevacizumab	15,387.85	
	Cyclophosphamide	165.35	
	PARP inhibitor*	18,998.14	

8 ASSUMPTIONS/BASE-CASE SETTINGS

Key assumptions underpinning the cost analysis are presented in Table 25.

Table 25: Model assumptions.

Category	Assumption	Justification
Population and comparators	The PRIMA trial is representative of patient population receiving first-line maintenance treatment with niraparib and RS for patients in the ITT population.	The clinical trial population for PRIMA compared maintenance therapy with niraparib versus placebo in patients with platinum-sensitive, recurrent, high-grade, serous ovarian, fallopian tube, or primary peritoneal cancer who had previously received one platinum-based regimens and were responsive (partial or complete) to their last platinum-based chemotherapy.
Model structure and settings	Partitioned survival model	Reflective of the natural history of the disease and a well-accepted model structure in oncology.
	Restricted societal perspective	In line with DMC methods guideline.
	30 year time horizon	Patient are not assumed to be on treatment with PARPi after 30 years.
	3.5% per annum discount rate for costs	In line with the DMC methods guideline and the recommended from the Danish finance ministry.
	Half cycle correction applied	Assuming a cost or outcome is incurred on average mid-way through a cycle.
Clinical effectiveness	Treatment effect remains for the duration of the time horizon.	Aligned with existing PSM models within ovarian cancer.
	Treatment effect is not impacted by treatment stopping rules.	Aligned with clinical evidence observed in PARPi first-line trials (SOLO-1).
	Active treatment OS is estimated based on the HR	HR override the naive extrapolation approach, and applies a HR on the curve of routine surveillance to estimate the curve of Niraparib.
	The log-logistic distribution provides an appropriate PFS extrapolation for niraparib and RS.	The log-logistic distribution for PFS is the best statistically fitting curve and was selected by clinicians as clinically plausible.
	The log-logistic distribution provides an appropriate OS extrapolation for RS.	The log-logistic distribution is the second best statistically fitting curve and was selected by clinicians as clinically plausible.
AEs	Grade ≥ 3 AEs ≥5% are included and assumed occur in the first cycle of the model time horizon. The same was adopted for the included comparators.	AE are likely to occur very soon after treatment and only require acute care. This is consistent to the modelling approaches adopted in previous submissions(24).
Cost and resource use inputs	Treatment discontinuation for niraparib is set to 3 years and olaparib is set to 2 years.	As a treatment duration of 2 years is stated in Danish treatment guidelines for olaparib and was therefore used. No stopping rule is available for niraparib, however, a 3-year

Category	Assumption	Justification
		treatment duration was implemented in the PRIMA trial and protocol. Based on this and clinical insights a 3-year stopping rule was implemented for niraparib.
	No administration costs for oral maintenance or subsequent chemotherapy treatments.	Oral treatments
	Monitoring requirements and resource use are consistent across all active treatments (with the exception of additional monitoring for niraparib within the first 3 months of treatment).	There is no evidence that suggest that monitoring should differ largely between the subgroups and active treatments (KOL inputs).
	Subsequent treatment is applied as a one-off cost upon disease progression.	In line with previous HTA appraisals, and not expected to impact results as subsequent treatment is similar between active treatments.
	Patients are not allowed to receive a PARPi after a PARPi.	In line with Danish guidelines on OC.
	Subsequent treatment regimens are based on DK clinical expert opinion and Edinburgh cancer database.	Assumed to be more aligned with clinical practice that PRIMA trial data.
	Olaparib subsequent treatment regimens are aligned with niraparib.	In absence of data it is assumed that subsequent treatments are aligned between active treatments.
	Costs for subsequent chemotherapy regimens classes are calculated based on a straight average, as opposed to a weighted average	Subsequent chemotherapy costs have a minor impact on the cost, hence a straight average calculation is sufficient.

Abbreviations: AE, adverse events; BRCA, breast cancer susceptibility gene; HR, hazard ratio; NICE, National Institute for Health and Excellence; OC, ovarian cancer; PARPi, PARP inhibitor; PBC, platinum-based chemotherapy; PFS, progression-free survival; OS, overall survival; RS, routine surveillance; TTD, time to treatment discontinuation; HTA, Health Technology Assessment; KOL, Key Opinion Leader; DMC, Danish Medicines Council.

9 RESULTS

9.1 BASE-CASE

Base-case results for niraparib compared to RS and olaparib for the HRD positive BRCAm population resulted in total costs of [redacted] for niraparib, DKK 785,514 for olaparib. The incremental difference between niraparib and olaparib is [redacted]. Base-case results are summarized in Table 26.

Table 26: Base-case results comparing niraparib to RS for the HRD positive BRCAm population (clinical question 1).

Treatment	Niraparib (DKK)	Olaparib (DKK)	Incremental Costs olaparib versus niraparib (DKK)
Treatment costs	[redacted]	661,212	[redacted]
Disease monitoring costs	61,111	54,165	6,946
Subsequent treatment costs	55,096	59,416	-4,320
AE costs	1,515	1,030	485
Patient costs	17,118	6,319	10,799
Transportation costs	4,200	3,371	829
Total costs	[redacted]	**777,603**	[redacted]

Base-case results for niraparib compared to RS for the HRD positive non-BRCA population resulted in total costs of [redacted] for niraparib and DKK 156,453 for RS. The incremental difference between niraparib and RS is [redacted]. Base-case results are summarized in Table 27.

Table 27: Base-case results comparing niraparib to RS for the HRD positive non-BRCA population (clinical question 2 and 4).

Treatment	Niraparib (DKK)	Routine surveillance (DKK)	Incremental Costs versus RS (DKK)
Treatment costs	[redacted]	0	[redacted]
Disease monitoring costs	76,292	67,092	9,200
Subsequent treatment costs	43,962	82,331	-39,369

AE costs	1,515	76	1,439
Patient costs	16,004	4,844	11,160
Transportation costs	5,239	4,671	568
Total costs	[redacted]	**159,013**	[redacted]

Base-case results for niraparib compared to RS for the HRD negative non-BRCA population resulted in total costs of [redacted] for niraparib and DKK 140,186 for RS. The incremental difference between niraparib and RS is [redacted]. Base-case results are summarized in Table 28.

Table 28: Base-case results comparing niraparib to RS for the HRD negative non-BRCA population (clinical question 3 and 5).

Treatment	Niraparib (DKK)	Routine surveillance (DKK)	Incremental Costs versus RS (DKK)
Treatment costs	[redacted]	0	[redacted]
Disease monitoring costs	61,512	39,703	21,809
Subsequent treatment costs	62,776	94,424	-33,648
AE costs	1,515	76	1,439
Patient costs	9,821	3,006	6,815
Transportation costs	4,887	2,744	2,143
Total costs	[redacted]	**141,953**	[redacted]

9.2 SCENARIO ANALYSIS

9.2.1 Results from the scenario analysis

The results from the scenario analysis that are most sensitive to change, and has the biggest impact on the results, will be presented for the included populations. The stopping rule and fixed dosed are also presented. The results from the scenario analysis are summarized in Table 29. The full scenario analysis is provided in Appendix 11.1.1.1.1.4.

Table 29: Most sensitive results from the Scenario analysis

	Niraparib (DKK)	RS (DKK)	Olaparib (DKK)	Incremental niraparib vs RS (DKK)	Incremental niraparib vs olaparib (DKK)
HRD positive BRCAm					
HR-deficient BRCAmut pop -	[redacted]	50,691	749,500	[redacted]	[redacted]

Include subsequent TX					
HR-deficient BRCAmut pop - TTD - Generalised Gamma	[redacted]	334,435	525,350	[redacted]	[redacted]
HR-deficient BRCAmut pop - Stopping rule - No tx cap	[redacted]	334,518	1,169,050	[redacted]	[redacted]
HR-deficient BRCAmut pop - Dosing - Fixed dose	[redacted]	334,518	857,678	[redacted]	[redacted]
HRD positive non-BRCA					
HR-deficient BRCAwt pop - OS - Exponential	[redacted]	251,028	N/A	[redacted]	N/A
HR-deficient BRCAwt pop - OS - Generalised Gamma	[redacted]	288,699	N/A	[redacted]	N/A
HR-deficient BRCAwt pop - Stopping rule - No tx cap	[redacted]	192,056	N/A	[redacted]	N/A
HR-deficient BRCAwt pop - Dosing - Fixed dose	[redacted]	192,056	N/A	[redacted]	N/A
HRD negative non-BRCA					
HR-proficient pop – OS – Generalised Gamma	[redacted]	134,654	N/A	[redacted]	N/A
HR-proficient pop - TTD - Generalised Gamma	[redacted]	176,635	N/A	[redacted]	N/A

HR-proficient pop - Stopping rule - No tx cap	[redacted]	176,448	N/A	[redacted]	N/A
HR-proficient pop - Dosing - Fixed dose	[redacted]	176,448	N/A	[redacted]	N/A

9.3 DURATION SPENT IN EACH HEALTH STATE

The duration of time spent in each health state PF, progression free and PD, progressed disease for the included populations and comparators are illustrated in Table 30. Only the health states for which there is costs and resources associated with are illustrated.

Table 30: Mean duration in health state (undiscounted).

Duration in health state (months) – HRD positive BRCAm			
Health state	PF	PD	Total
Niraparib	[redacted]	[redacted]	[redacted]
Olaparib	[redacted]	[redacted]	[redacted]
RS	[redacted]	[redacted]	[redacted]
Duration in health state (months) – HRD positive non-BRCA			
Health state	PF	PD	Total
Niraparib	[redacted]	[redacted]	[redacted]
RS	[redacted]	[redacted]	[redacted]
Duration in health state (months) – HRD negative non-BRCA			
Health state	PF	PD	Total
Niraparib	[redacted]	[redacted]	[redacted]
RS	[redacted]	[redacted]	[redacted]

Abbreviations: PF, progression free; PD, progressed disease; HRD, homologous recombination deficiency; HRP, homologous recombination proficiency.

Table 31: Figure 6: Mean time on treatment (months) for the included populations and comparators. The table shows both time on treatment and time on treatment, half-cycle corrected.

Mean time on treatment (months) – HRD positive BRCAm		
Health state	Time on TX	Time on TX, half-cycle corrected
Niraparib	[redacted]	[redacted]
Olaparib	[redacted]	[redacted]
RS	[redacted]	[redacted]
Mean time on treatment (months) – HRD positive non-BRCA		
Health state	Time on TX	Time on TX, half-cycle corrected
Niraparib	[redacted]	[redacted]
RS	[redacted]	[redacted]
Mean time on treatment (months) – HRD negative non-BRCA		
Health state	Time on TX	Time on TX, half-cycle corrected
Niraparib	[redacted]	[redacted]
RS	[redacted]	[redacted]

Abbreviations: PF, progression free; PD, progressed disease; HRD, homologous recombination deficiency; HRP, homologous recombination proficiency; TX, treatment.

9.4 BUDGET IMPACT ANALYSIS

9.4.1 Method

The budget impact analysis is calculated as per DMC method guidelines. The costs of niraparib will be compared to olaparib and RS in the scenario where niraparib is recommended as standard of care, for first line maintenance treatment of patients with OC in Denmark. The budget impact is calculated per 1 year over a 5-year period, using non-discounted values.

9.4.1.1 Patient population

The patient population described in the protocol provided by DMC is used, an estimated 300 new patients are eligible for first line treatment each year.

- 60 patients are HRD positive BRCAmut (clinical question 1)
- 37 patients are HRD positive non-BRCA, candidates for bevacizumab (clinical question 2)
- 53 patients are HRD negative non-BRCA, candidates for bevacizumab (clinical question 3).
- 63 patients are HRD positive non-BRCA, not candidates for bevacizumab (clinical question 4)
- 87 patrients are HRD negative non-BRCA, not candidates for bevacizumab (clinical question 5).

9.4.1.2 Market share

The market share for the presented patient populations included in the budget impact analysis are summarized in the following tables. This is for patients who are eligible for fist line treatment with a PARP inhibitor.

Table 32: Market share for niraparib, RS and olaparib for the HRD positive BRCAm population (clinical question 1).

Not recommended as standard of care							Recommended as standard of care				
Year	1	2	3	4	5		1	2	3	4	5
Niraparib	0%	0%	0%	0%	0%		55%	75%	80%	80%	80%
Olaparib	80%	80%	80%	80%	80%		25%	5%	0%	0%	0%
RS	20%	20%	20%	20%	20%		20%	20%	20%	20%	20%

Table 33: Market share for niraparib, RS and olaparib for the HRD positive non-BRCA population, candidates for bevacizumab (clinical question 2).

Not recommended as standard of care							Recommended as standard of care				
Year	1	2	3	4	5		1	2	3	4	5
Niraparib	0%	0%	0%	0%	0%		65%	75%	80%	80%	80%
Olaparib	0%	0%	0%	0%	0%		0%	0%	0%	0%	0%
RS	100%	100%	100%	100%	100%		35%	25%	20%	20%	20%

Table 34: Market share for niraparib, RS and olaparib for the HRD negative non-BRCA population, candidates for bevacizumab (clinical question 3).

Not recommended as standard of care							Recommended as standard of care				
Year	1	2	3	4	5		1	2	3	4	5
Niraparib	0%	0%	0%	0%	0%		65%	75%	80%	80%	80%
Olaparib	0%	0%	0%	0%	0%		0%	0%	0%	0%	0%
RS	100%	100%	100%	100%	100%		35%	25%	20%	20%	20%

Table 35: Market share for niraparib, RS and olaparib for the HRD positive non-BRCA population, not candidates for bevacizumab (clinical question 4).

Not recommended as standard of care							Recommended as standard of care				
Year	1	2	3	4	5		1	2	3	4	5
Niraparib	0%	0%	0%	0%	0%		65%	75%	80%	80%	80%
Olaparib	0%	0%	0%	0%	0%		0%	0%	0%	0%	0%
RS	100%	100%	100%	100%	100%		35%	25%	20%	20%	20%

Table 36: Market share for niraparib, RS and olaparib for the HRD negative non-BRCA population, not candidates for bevacizumab (clinical question 5).

Not recommended as standard of care							Recommended as standard of care				
Year	1	2	3	4	5		1	2	3	4	5
Niraparib	0%	0%	0%	0%	0%		65%	75%	80%	80%	80%
Olaparib	0%	0%	0%	0%	0%		0%	0%	0%	0%	0%
RS	100%	100%	100%	100%	100%		35%	25%	20%	20%	20%

9.4.1.3 Costs

Costs from the economic model are embedded in the budget impact analysis, based on parametric curves included in the cost model. The budget impact includes the same costs as applied to the cost model, with exception of patient and transportation costs as per DMC methods guideline. The budget impact analysis will not include discounted costs.

9.4.2 Results

The estimated budget impact on PTC-level (AIP) if niraparib is recommended as standard of care are presented in the following tables.

9.4.2.1 HRD positive BRCAm population (clinical question 1)

The budget impact with a recommendation of niraparib as standard of care for patients with an HRD positive BRCAm is [redacted] for year 1, and [redacted] for year 5. Summarized in Table 37.

Table 37: Budget impact for HRD positive BRCAm population (clinical question 1).

Budget impact	Year 1	Year 2	Year 3	Year 4	Year 5
No recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

9.4.2.2 HRD positive non-BRCA population, candidates for bevacizumab (clinical question 2)

The budget impact with a recommendation of niraparib as standard of care for patients with an HRD positive non-BRCA, candidates for bevacizumab is [redacted] for year 1 and [redacted] for year 5. Summarized in Table 38.

Table 38:Budget impact for HRD positive non-BRCA population, candidates for bevacizumab (clinical question 2).

Budget impact	Year 1	Year 2	Year 3	Year 4	Year 5
No recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

9.4.2.3 HRD negative non-BRCA population, candidates for bevacizumab (clinical question 3)

The budget impact with a recommendation of niraparib as standard of care for patients with an HRD negative non-BRCA, candidates for bevacizumab is [redacted] for year 1 and [redacted] for year 5. Summarized in Table 38.

Table 39:Budget impact for HRD positive non-BRCA population, candidates for bevacizumab (clinical question 2).

Budget impact	Year 1	Year 2	Year 3	Year 4	Year 5
No recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

9.4.2.4 *HRD positive non-BRCA population, not candidates for bevacizumab (clinical question 4)*

The budget impact with a recommendation of niraparib as standard of care for patients with an HRD positive non-BRCA, not canddates for bevacizumab is [redacted] for year 1 and [redacted] for year 5. Summarized in Table 38.

Table 40:Budget impact for HRD positive non-BRCA population, not candidates for bevacizumab (clinical question 4).

Budget impact	Year 1	Year 2	Year 3	Year 4	Year 5
No recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

9.4.2.5 *HRD negative non-BRCA population, not candidates for bevacizumab (clinical question 5)*

The budget impact with a recommendation of niraparib as standard of care for patients with an HRD negative non-BRCA, not candidates for bevacizumab is [redacted] year 1, and [redacted] year 5. Summarized in Table 41.

Table 41: Budget impact for HRD negative non-BRCA population, not candidates for bevacizumab (clinical question 5).

Budget impact	Year 1	Year 2	Year 3	Year 4	Year 5
No recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

10 Discussion

Treatment with niraparib is associated with significant additional costs compared to RS for the HRD positive non-BRCA and HRD negative non-BRCA population. Niraparib prolongs PFS and the time on treatment is therefore also prolonged, which contributes to the increased costs of treatment with niraparib compared to RS. The costs are primarily driven by treatment acquisition costs of niraparib. For the HRD positive BRCAm population treatment with niraparib was associated with additional costs. In the two studies PRIMA and SOLO-1 different duration of treatment was used, which means that patients were treated with niraparib for 3 years and 2 years for olaparib. This results in additional costs associated with one year of treatment, which are not attributed to olaparib.

11 REFERENCES

1. González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med [Internet]. 2019 Dec 19 [cited 2021 Jan 5];381(25):2391–402. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa1910962

2. Den samfundsøkonomiske diskonteringsrente Den anbefalede samfundsøkonomiske diskonteringsrente. 2018.

3. Medicinrådets protokol for vurdering af niraparib 1.linje OC [Internet]. [cited 2021 Jan 5]. Available from: https://medicinraadet.dk/media/frzbgcod/medicinrådets-protokol-for-vurdering-af-niraparib-til-nydiagnosticeret-kræft-i-æggestokkene-vers-1-0_adlegacy.pdf

4. Retningslinier for visitation, diagnostik, behandling og opfølgning af epitelial ovarie-, tuba-og primaer peritonealcancer samt borderline tumorer 5. udgave 2016.

5. Dansk Gynaekologisk Cancer Database Landsdaekkende klinisk database for gynaekologisk kraeft [Internet]. 2017 [cited 2021 Jan 5]. Available from: www.rkkp.dk

6. NORDCAN - Association of the Nordic Cancer Registries. Æggestok, æggeleder mv. Aldersstandardiseret relativ overlevelse [Internet]. [cited 2021 Jan 5]. Available from: https://www-dep.iarc.fr/NORDCAN/DK/table23.asp?registry=208&sex=2&time=5&sort=0&submit=%A0%A0Udf%F8r%A0%A0

7. Bell D, Berchuck A, Birrer M, Chien J, Cramer DW, Dao F, et al. Integrated genomic analyses of ovarian carcinoma. Nature [Internet]. 2011 Jun 30 [cited 2021 Jan 5];474(7353):609–15. Available from: https://pubmed.ncbi.nlm.nih.gov/21720365/

8. Zhang S, Royer R, Li S, McLaughlin JR, Rosen B, Risch HA, et al. Frequencies of BRCA1 and BRCA2 mutations among 1,342 unselected patients with invasive ovarian cancer. Gynecol Oncol [Internet]. 2011 May 1 [cited 2021 Jan 5];121(2):353–7. Available from: https://pubmed.ncbi.nlm.nih.gov/21324516/

9. Bolton KL, Chenevix-Trench G, Goh C, Sadetzki S, Ramus SJ, Karlan BY, et al. Association between BRCA1 and BRCA2 Mutations and Survival in Women with Invasive Epithelial Ovarian Cancer. JAMA - J Am Med Assoc [Internet]. 2012 Jan 25 [cited 2021 Jan 5];307(4):382–90. Available from: https://pubmed.ncbi.nlm.nih.gov/22274685/

10. Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med [Internet]. 2016 Dec [cited 2021 Jan 5];375(22):2154–64. Available from: https://pubmed.ncbi.nlm.nih.gov/27717299/

11. Takaya H, Nakai H, Takamatsu S, Mandai M, Matsumura N. Homologous recombination deficiency status-based classification of high-grade serous ovarian carcinoma. Sci Rep [Internet]. 2020 Dec 17 [cited 2021 Jan 5];10(1):2757. Available from: http://www.nature.com/articles/s41598-020-59671-3

12. Mirza MR, Åvall Lundqvist E, Birrer MJ, dePont Christensen R, Nyvang GB, Malander S, et al. Niraparib plus bevacizumab versus niraparib alone for platinum-sensitive recurrent ovarian cancer (NSGO-AVANOVA2/ENGOT-ov24): a randomised, phase 2, superiority trial. Lancet Oncol [Internet]. 2019 Oct 1 [cited 2021 Jan 5];20(10):1409–19. Available from: https://pubmed.ncbi.nlm.nih.gov/31474354/

13. Mirza MR, Coleman RL, González-Martín A, Moore KN, Colombo N, Ray-Coquard I, et al. The forefront of ovarian cancer therapy: update on PARP inhibitors [Internet]. Vol. 31, Annals of Oncology. Elsevier Ltd; 2020 [cited 2021 Jan 5]. p. 1148–59. Available from: https://pubmed.ncbi.nlm.nih.gov/32569725/

14. Forslag til national guideline for genetisk udredning af patienter med ovariecancer [Internet]. [cited 2021 Jan 5]. Available from: http://dgcg.dk/images/Grupper/Ovariecancergruppen/Retningslinier2016/nye_filer/Kap_5.pdf

15. Zejula | European Medicines Agency [Internet]. [cited 2021 Jan 5]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/zejula

16. Medicinrådets behandlingsvejledning vedrørende lægemidler til BRCA-muteret kræft i æggestokkene, æggelederne eller primær kræft i bughinden [Internet]. 2020 [cited 2021 Jan 5]. Available from: https://medicinraadet.dk/media/ibkdjfqg/medicinrådets_behandlingsvejledning_vedr-_lægemidler_til_brca-mutereret_kræft_i_æggestokkene-vers-_1-0_adlegacy.pdf

17. CHMP. ANNEX I SUMMARY OF PRODUCT CHARACTERISTICS.

18. Monberg MJ, Hall JP, Moon R, Higson O, McLaurin K, Dalvi T. Real-world bevacizumab utilization and outcomes in first-line ovarian cancer. J Clin Oncol. 2019 May 20;37(15_suppl):5578–5578.

19. Hanker LC, Loibl S, Burchardi N, Pfisterer J, Meier W, Pujade-Lauraine E, et al. The impact of second to sixth line therapy on survival of relapsed ovarian cancer after primary taxane/platinum-based therapy. Ann Oncol [Internet]. 2012 Oct [cited 2021 Jan 5];23(10):2605–12. Available from: https://pubmed.ncbi.nlm.nih.gov/22910840/

20. Martín-Cameán M, Delgado-Sánchez E, Piñera A, Diestro MD, De Santiago J, Zapardiel I. The role of surgery in advanced epithelial ovarian cancer [Internet]. Vol. 10, ecancermedicalscience. ecancer Global Foundation; 2016 [cited 2021 Jan 5]. Available from: /pmc/articles/PMC4990056/?report=abstract

21. Nick AM, Coleman RL, Ramirez PT, Sood AK. A framework for a personalized surgical approach to ovarian cancer [Internet]. Vol. 12, Nature Reviews Clinical Oncology. Nature Publishing Group; 2015 [cited 2021 Jan 5]. p. 239–45. Available from: /pmc/articles/PMC4528308/?report=abstract

22. Tesaro/GSK. Clinical Study Report PR-5017-C: A Phase 3, randomized, double-bline, placebo-controlled, multicenter study of niraparib maintenance treatment in patients with advanced ovarian cancer following response on front-line platinum-based chemotherapy. (2019). [Internet]. [cited 2021 Jan 5]. Available from: https://www.google.com/search?rlz=1C1GCEA_enDK889DK889&q=Tesaro/GSK.+Clinical+Stu

dy+Report+PR-5017-C:+A+Phase+3,+randomized,+double-bline,+placebo-controlled,+multicenter+study+of+niraparib+maintenance+treatment+in+patients+with+advanced+ovarian+cancer+following+response+on+front-line+platinum-based+chemotherapy.+(2019).&spell=1&sa=X&ved=2ahUKEwjV7IrOr4XuAhXJVsAKHdwSBbIQBSgAegQIBBA4&biw=925&bih=747&dpr=1.13

23. CHMP. Committee for Medicinal Products for Human Use (CHMP) Assessment report [Internet]. 2019 [cited 2021 Jan 13]. Available from: www.ema.europa.eu/contact

24. Moore K, Colombo N, Scambia G, Kim B-G, Oaknin A, Friedlander M, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med [Internet]. 2018 Dec 27 [cited 2021 Jan 10];379(26):2495–505. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa1810858

25. Hamilton CA, Miller A, Miller C, Krivak TC, Farley JH, Chernofsky MR, et al. The impact of disease distribution on survival in patients with stage III epithelial ovarian cancer cytoreduced to microscopic residual: A gynecologic oncology group study. Gynecol Oncol [Internet]. 2011 Jun 17 [cited 2021 Jan 5];122(3):521–6. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/21683993/?tool=EBI

26. Elattar A, Bryant A, Winter-Roach BA, Hatem M, Naik R. Optimal primary surgical treatment for advanced epithelial ovarian cancer [Internet]. Vol. 2011, Cochrane Database of Systematic Reviews. John Wiley and Sons Ltd; 2011 [cited 2021 Jan 6]. Available from: https://pubmed.ncbi.nlm.nih.gov/21833960/

27. Danish Medicines Council. Baggrund for Medicinrådets anbefaling vedrørende niraparib som mulig standardbehandling til kræft i æggestokkene, æggelederne eller primær kræft i bughinden. [Internet]. Version 1.0. [cited 2021 Jan 6]. Available from: https://medicinraadet.dk/media/ayefu1dv/baggrund-for-medicinraadets-anbefaling-vedr-niraparib-til-kraeft-i-aeggestokkene-aeggelederne-eller-primaer-kraeft-i-bughinden-vers-1-0-m-bilag_adlegacy.pdf

28. Medicinrådet. Medicinrådets metodevejledning for vurdering af nye laegemidler.

29. Finansministeriet. Dokumentationsnotat for den samfundsøkonomiske diskonteringsrente.

30. Latimer NR. Survival analysis for economic evaluations alongside clinical trials - Extrapolation with patient-level data: Inconsistencies, limitations, and a practical guide. Med Decis Mak. 2013 Aug;33(6):743–54.

31. Forside - www.medicinpriser.dk [Internet]. [cited 2020 Sep 9]. Available from: https://medicinpriser.dk/

32. Tesaro I. A Study of Niraparib Maintenance Treatment in Patients With Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy [Internet]. Clinical Trials NCT02655016. 2020. 1–13641 p. Available from: https://clinicaltrials.gov/ct2/show/study/NCT02655016

33. Miller RE, Leary A, Scott CL, Serra V, Lord CJ, Bowtell D, et al. ESMO recommendations on predictive biomarker testing for homologous recombination deficiency and PARP inhibitor benefit in ovarian cancer. Ann Oncol [Internet]. 2020 Dec 1 [cited 2021 Jan 8];31(12):1606–22. Available from: https://doi.org/10.1016/j.annonc.2020.08.2102

34. myChoice® CDx | Myriad Genetics, Inc. [Internet]. [cited 2021 Jan 8]. Available from: https://myriad.com/products-services/precision-medicine/mychoice-cdx/

35. Klinisk biokemisk afdeling - Metodeliste [Internet]. [cited 2021 Jan 5]. Available from: https://labportal.rh.dk/Metodeliste.asp

36. pro.medicin.dk – information om medicin [Internet]. [cited 2021 Jan 11]. Available from: https://pro.medicin.dk/

37. DRG-takster 2021 - Sundhedsdatastyrelsen [Internet]. [cited 2021 Jan 11]. Available from: https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2021

38. Søg - Produktresuméer [Internet]. [cited 2021 Jan 11]. Available from: http://www.produktresume.dk/AppBuilder/search

39. Klinisk Retningslinje │Kraeft DGCG.

40. Stark D, Nankivell M, Pujade-Lauraine E, Kristensen G, Elit L, Stockler M, et al. Standard chemotherapy with or without bevacizumab in advanced ovarian cancer: Quality-of-life outcomes from the International Collaboration on Ovarian Neoplasms (ICON7) phase 3 randomised trial. Lancet Oncol [Internet]. 2013 Mar [cited 2021 Jan 6];14(3):236–43. Available from: https://pubmed.ncbi.nlm.nih.gov/23333117/

41. Cyclophosphamid - Region Sjælland [Internet]. [cited 2021 Feb 23]. Available from: https://www.regionsjaelland.dk/sundhed/geo/roskildesygehus/Afdelinger/dermatologisk-afdeling/hudsygdomme/Tablet-behandling/Sider/Cyclophosphamid.aspx

42. Exchange rates [Internet]. [cited 2021 Jan 12]. Available from: https://www.nationalbanken.dk/en/statistics/exchange_rates/Pages/Default.aspx

11.1.1.1.1.1 Subgroup independent survival analyses

This appendix details results from the independent survival analysis conducted for four subgroups (HR-deficient, HR-deficient *BRCAm*, HR-deficient *BRCA*wt and HR-proficient). The methods described in Section 7.3 were also adopted here. PFS and TTD endpoints were analyses for all subgroups; however, due to level of data immaturity, OS was only analysed for the HR-proficient population (16% maturity).

HR-deficient BRCAm

A subgroup of all patients with homologous recombination deficiency (HR-deficient) who additionally had a *BRCA* mutation (HR-deficient *BRCAm*) were analysed in this subgroup survival analysis.

Progression-free survival

Six standard parametric independent models were therefore fitted to each arm of the study data; exponential, Weibull, Gompertz, log-logistic, log-normal and the generalised gamma. A summary of the goodness-of-fit statistics for the PFS extrapolations is available in Table 42. Table 43 outlines the landmark PFS rates for niraparib and RS.

Table 42: AIC and BIC statistical goodness of fit data for PFS HR-deficient BRCAm data set (independent models).

Distribution	Niraparib		RS	
	AIC	BIC	AIC	BIC
Exponential	461.55	464.57	309.48	311.74
Weibull	451.55	457.59	307.61	312.14
Gompertz	457.18	463.23	310.90	315.42
Log-logistic	449.99	456.04	304.02	308.55
Log-normal	449.09	455.14	302.50	307.03
Generalised gamma	451.09	460.16	303.82	310.61

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.

Table 43: Niraparib and RS landmark survival rates for PFS HR-deficient BRCAm (independent models).

Distribution	Intervention	Years					
		1	2	3	5	10	20

Exponential	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PFS, progression-frees survival; RS, Routine surveillance

Figure 6: PFS survival analysis curves for niraparib HR-deficient BRCAm dataset.

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival

Figure 7: PFS survival analysis curves for RS HR-deficient BRCAm dataset.

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival; RS, routine surveillance

Time to treatment discontinuation

Six standard parametric independent models were fitted to each arm of the study data; exponential, Weibull, Gompertz, log-logistic, log-normal and the generalised gamma. A summary of the goodness-of-fit statistics for the TTD extrapolations is available in Table 44. Table 45 outlines the landmark TTD rates for niraparib and RS. The generalised gamma distribution did not converge to the available data for either niraparib or RS. It could therefore not be plotted or included in the tables or figures below.

Table 44: AIC and BIC statistical goodness of fit data for TTD HR-deficient BRCAm data set (independent models).

Distribution	Niraparib		RS	
	AIC	BIC	AIC	BIC
Exponential	605.57	608.60	355.59	357.85
Weibull	606.11	612.15	347.55	352.07
Gompertz	604.64	610.69	352.33	356.86
Log-logistic	609.57	615.61	345.97	350.50
Log-normal	615.99	622.03	345.17	349.69

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival

Table 45: Niraparib and RS landmark survival rates for TTD HR-deficient BRCAm data set (independent models).

Distribution	Intervention	Years					
		1	2	3	5	10	20
Exponential	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: RS, Routine surveillance; TTD, time to treatment discontinuation

Figure 8: TTD survival analysis curves for niraparib HR-deficient BRCAm dataset.

Abbreviations: KM, Kaplan-Meier; TTD, time to treatment discontinuation

Figure 9: TTD survival analysis curves for RS HR-deficient BRCAm dataset.

Abbreviations: KM, Kaplan-Meier; TTD, time to treatment discontinuation; RS, routine surveillance

HR-deficient BRCAwt

A subgroup of all patients with homologous recombination deficiency (HR-deficient) who had the standard wild-type genetic make-up in the BRCA gene (HR-deficient *BRCA*wt) were analysed in this subgroup survival analysis.

Progression-free survival

Six standard parametric independent models were fitted to each arm of the study data; exponential, Weibull, Gompertz, log-logistic, log-normal and the generalised gamma. A summary of the goodness-of-fit statistics for the PFS extrapolations is available in Table 46. Table 47 outlines the landmark PFS rates for niraparib and RS. The generalised gamma distribution did not converge to the available data for niraparib and so it could not be plotted or included in the tables or figures below.

Table 46: AIC and BIC statistical goodness of fit data for PFS HR-deficient BRCAwt data set (independent models).

Distribution	Niraparib		RS	
	AIC	BIC	AIC	BIC
Exponential	283.68	286.22	246.35	248.36
Weibull	283.96	289.04	246.20	250.21
Gompertz	285.44	290.53	248.34	252.36
Log-logistic	282.71	287.80	240.91	244.93
Log-normal	281.39	286.48	239.16	243.17
Generalised Gamma	N/A	N/A	237.07	243.09

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival; RS, routine surveillance.

Table 47: Niraparib and RS landmark survival rates for PFS HR-deficient BRCAwt (independent models).

Distribution	Intervention	Years					
		1	2	3	5	10	20
Exponential	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Distribution	Intervention	Years					
		1	2	3	5	10	20
Log-logistic	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: RS, Routine surveillance

Figure 10: PFS survival analysis curves for niraparib HR-deficient BRCAwt dataset

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival

Figure 11: PFS survival analysis curves for RS HR-deficient BRCAwt dataset

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival; RS, Routine surveillance

Time to treatment discontinuation

Six standard parametric independent models were fitted to each arm of the study data; exponential, Weibull, Gompertz, log-logistic, log-normal and the generalised gamma. A summary of the goodness-of-fit statistics for the TTD extrapolations is available in Table 48. Table 49 outlines the landmark TTD rates for niraparib and RS. The generalised gamma distribution did not converge to the available data for either niraparib or RS. It could therefore not be plotted or included in the tables or figures below.

Table 48: AIC and BIC statistical goodness of fit data for TTD HR-deficient BRCAwt data set (independent models).

Distribution	Niraparib		RS	
	AIC	BIC	AIC	BIC
Exponential	423.30	425.85	268.68	270.69
Weibull	425.15	430.24	267.34	271.35
Gompertz	423.75	428.84	270.18	274.19
Log-logistic	422.65	427.74	264.42	268.44
Log-normal	423.05	428.13	265.38	269.39

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; TTD, time to treatment discontinuation; RS, routine surveillance

Table 49: Niraparib and RS landmark survival rates for TTD HR-deficient BRCAwt (independent models).

Distribution	Intervention	Years					
		1	2	3	5	10	20
Exponential	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: RS, Routine surveillance; TTD, time to treatment discontinuation

Figure 12: TTD survival analysis curves for niraparib HR-deficient BRCAwt dataset.

Abbreviations: KM, Kaplan-Meier; TTD, time to treatment discontinuation

Figure 13: TTD survival analysis curves for RS HR-deficient BRCAwt dataset.

Abbreviations: KM, Kaplan-Meier; RS, Routine surveillance; TTD, time to treatment discontinuation

HR-proficient

A subgroup of all patients without homologous recombination deficiency (HR-proficient) was analysed in the subgroup survival analysis.

Progression-free survival

Six standard parametric independent models were therefore fitted to each arm of the study data; exponential, Weibull, Gompertz, log-logistic, log-normal and the generalised gamma. A summary of the goodness-of-fit statistics for the PFS extrapolations is available in Table 50. Table 51 outlines the landmark PFS rates for niraparib and RS.

Table 50: AIC and BIC statistical goodness of fit data for PFS HR-proficient data set (independent models).

Distribution	Niraparib		RS	
	AIC	BIC	AIC	BIC
Exponential	770.42	773.55	363.37	365.76
Weibull	759.63	765.89	363.61	368.38
Gompertz	770.66	776.92	364.37	369.13
Log-logistic	744.14	750.40	349.05	353.81

Log-normal	737.56	743.82	346.83	351.59
Generalised Gamma	727.97	737.36	335.58	342.73

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival; RS, routine surveillance

Table 51: Niraparib and RS landmark survival rates for PFS HR-proficient (independent models).

Distribution	Intervention	Years					
		1	2	3	5	10	20
Exponential	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: RS, Routine surveillance; PFS, progression-free survival

Figure 14: PFS survival analysis curves for niraparib HR-proficient dataset.

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival

Figure 15: PFS survival analysis curves for RS HR-proficient dataset.

Abbreviations: KM, Kaplan-Meier; RS, Routine surveillance; PFS, progression-free survival

Overall survival

Six standard parametric independent models were fitted to each arm of the study data; exponential, Weibull, Gompertz, log-logistic, log-normal and the generalised gamma. A summary of the goodness-of-fit statistics for the OS extrapolations is available in Table 52. Table 53 outlines the landmark OS rates for niraparib and RS. The generalised gamma did not converge to the available data for either niraparib or RS. It could therefore not be plotted or included in the tables or figures below.

Table 52: AIC and BIC statistical goodness of fit data for OS HR-proficient data set (independent models).

Distribution	Niraparib		Routine surveillance	
	AIC	BIC	AIC	BIC
Exponential	251.77	254.90	176.85	179.24
Weibull	242.51	248.77	169.55	174.32
Gompertz	247.75	254.01	171.12	175.89
Log-logistic	241.73	247.99	169.58	174.35
Log-normal	239.16	245.42	169.53	174.29

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival; RS routine surveillance

Table 53: Niraparib and RS landmark survival rates for OS HR-proficient data set (independent models).

Distribution	Intervention	Years					
		1	2	3	5	10	20
Exponential	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: RS, Routine surveillance; OS, overall survival

Figure 16: OS survival analysis curves for niraparib HR-proficient dataset.

Abbreviations: KM, Kaplan-Meier; OS, overall survival

Figure 17: OS survival analysis curves for RS HR-proficient-neg dataset.

Abbreviations: KM, Kaplan-Meier; RS, routine surveillance; OS, overall survival

Time to treatment discontinuation

Six standard parametric independent models were fitted to each arm of the study data; exponential, Weibull, Gompertz, log-logistic, log-normal and the Generalised Gamma. A summary of the goodness-of-fit statistics for the TTD extrapolations is available in Table 54. Table 55 outlines the landmark TTD rates for niraparib and RS. For the generalised gamma, the distribution did not converge for the niraparib available data and so it could not be plotted or included in the tables or figures below.

Table 54: AIC and BIC statistical goodness of fit data for TTD HR-proficient data set (independent models).

Distribution	Niraparib		RS	
	AIC	BIC	AIC	BIC
Exponential	869.27	872.40	407.90	410.28
Weibull	865.62	871.88	406.52	411.29
Gompertz	869.96	876.22	409.88	414.64
Log-logistic	861.87	868.13	394.45	399.21
Log-normal	871.06	877.32	394.40	399.16
Generalised Gamma	N/A	N/A	395.35	402.50

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; TTD, time to treatment discontinuation; RS, routine surveillance

Table 55: Niraparib and RS landmark survival rates for TTD HR-proficient (independent models).

Distribution	Intervention	Years					
		1	2	3	5	10	20
Exponential	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: RS, Routine surveillance; TTD, time tot treatment discontinuation

Figure 18: TTD survival analysis curves for niraparib HR-proficient.

Abbreviations: KM, Kaplan-Meier; RS, Routine surveillance; TTD, time tot treatment discontinuation

Figure 19: TTD survival analysis curves for RS HR-proficient.

Abbreviations: KM, Kaplan-Meier; RS, Routine surveillance; TTD, time tot treatment discontinuation

11.1.1.1.1.2 Dependent survival analysis

In Section 7.3.1.1, dependent fitted extrapolation models were deemed inappropriate to extrapolate the PFS data beyond the KM data for the ITT dataset. In this appendix, the dependent model extrapolations for the ITT, HR-deficient, HR-deficient *BRCAm*, HR-deficient *BRCA*wt and HR-proficient populations. The PFS endpoint was analysed for all subgroups, however due to level of data immaturity OS was only analysed for the HR-proficient population (16% maturity). For each outcome, the six standard parametric models where fit to the data.

Progression-free survival

ITT

Table 56: Niraparib and RS landmark ITT PFS survival rates (dependent curves)

Distribution	Intervention	Years					
		1	2	3	5	10	20
Exponential	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: RS, Routine surveillance; PFS, progression-free survival

Table 57: AIC and BIC statistical goodness of fit data for the ITT PFS data set (dependent models)

Distribution	AIC	BIC
Exponential	2990.25	2999.45
Weibull	2962.73	2976.52
Gompertz	2990.24	3004.04
Log-logistic	2922.46	2936.25
Log-normal	2901.00	2914.79
Generalised gamma	2881.33	2899.72

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival

Figure 20: Niraparib ITT PFS extrapolation (dependent models)

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival

Figure 21: RS ITT PFS extrapolation (dependent models)

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival; RS, routine surveillance

HR-deficient

Table 58: Niraparib and RS landmark HR-deficient PFS survival rates (dependent models)

Distribution	Intervention	Years					
		1	2	3	5	10	20
Exponential	Niraparib						
	RS						
Weibull	Niraparib						
	RS						
Gompertz	Niraparib						
	RS						
Log-logistic	Niraparib						
	RS						
Log-normal	Niraparib						
	RS						
Generalised gamma	Niraparib						
	RS						

Abbreviations: PFS, progression-free survival; RS, Routine surveillance

Table 59: AIC and BIC statistical goodness of fit data for the HR-deficient PFS data set (dependent models)

Distribution	AIC	BIC
Exponential	1299.59	1307.44
Weibull	1284.84	1296.60
Gompertz	1297.52	1309.28
Log-logistic	1273.44	1285.20
Log-normal	1269.39	1281.15
Generalised gamma	1270.92	1286.61

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival

Figure 22: Niraparib HR-deficient PFS extrapolation (dependent models)

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival

Figure 23: RS HR-deficient PFS extrapolation (dependent models)

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival; RS, routine surveillance

HR-deficient BRCAm

Table 60: Niraparib and RS landmark HR-deficient BRCAm PFS survival rates (dependent models)

Distribution	Intervention	Years					
		1	2	3	5	10	20
Exponential	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PFS, progression-free survival; RS, Routine surveillance

Table 61: AIC and BIC statistical goodness of fit data for the HR-deficient BRCAm PFS data set (dep. models)

Distribution	AIC	BIC
Exponential	771.03	777.84
Weibull	758.33	768.56
Gompertz	767.11	777.33
Log-logistic	752.18	762.4
Log-normal	749.59	759.81
Generalised gamma	751.3	764.93

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival

Figure 24: Niraparib HR-deficient BRCAm PFS extrapolation (dependent models)

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival

Figure 25: RS dependent curve HR-deficient BRCAm PFS extrapolation (dependent models)

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival; RS, routine surveillance

HR-deficient BRCAwt

Table 62: Niraparib and RS landmark HR-deficient BRCAwt PFS survival rates (dependent models)

Distribution	Intervention	Years					
		1	2	3	5	10	20
Exponential	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: RS, Routine surveillance

Table 63: AIC and BIC statistical goodness of fit data for the HR-deficient BRCAwt PFS data set (dep. models)

Distribution	AIC	BIC
Exponential	530.03	536.04
Weibull	528.16	537.17
Gompertz	531.95	540.96
Log-logistic	522.35	531.36
Log-normal	520.12	529.13
Generalised gamma	521.23	533.24

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival

Figure 26: Niraparib HR-deficient BRCAwt PFS extrapolation (dependent models)

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival

Figure 27: RS HR-deficient BRCAwt PFS extrapolation (dependent models)

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival; RS, routine surveillance

HR-proficient

Table 64: Niraparib and RS landmark HR-proficient PFS survival rates (dependent models)

Distribution	Intervention	Years					
		1	2	3	5	10	20
Exponential	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PFS, progression-free survival; RS, Routine surveillance

Table 65: AIC and BIC statistical goodness of fit data for the HR-proficient PFS data set (dependent models)

Distribution	AIC	BIC
Exponential	1133.79	1140.83
Weibull	1122.58	1133.13
Gompertz	1135.51	1146.06
Log-logistic	1091.37	1101.93
Log-normal	1082.72	1093.27
Generalised gamma	1059.94	1074.01

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival

Figure 28: Niraparib dependent curve HR-proficient PFS extrapolation

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival

Figure 29: RS dependent curve HR-proficient PFS extrapolation

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival; RS, Routine surveillance

Overall survival

HR-proficient

Table 66: Niraparib and RS landmark HR-proficient OS survival rates (dependent curves)

Distribution	Intervention	Years					
		1	2	3	5	10	20
Exponential	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OS, overall survival; RS, Routine surveillance

Table 67: AIC and BIC statistical goodness of fit data for the HR-proficient OS data set (dependent models)

Distribution	AIC	BIC
Exponential	428.62	435.66
Weibull	410.07	420.62
Gompertz	417.10	427.65
Log-logistic	409.33	419.88
Log-normal	406.69	417.24
Generalised gamma	406.84	420.91

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, Overall survival

Figure 30: Niraparib dependent curve HR-proficient OS extrapolation

Abbreviations: KM, Kaplan-Meier; OS, overall survival

Figure 31: RS dependent curve HR-proficient OS extrapolation

Abbreviations: KM, Kaplan-Meier; OS, overall survival; RS, routine surveillance.

11.1.1.1.1.3 Included blood count

Table 68: Unit costs of standard blood count of patients with OC.

	Type	Unit costs [DKK]	Source
Liver enzymes	P-ALAT Albumin Basic phosphatase Bilirubin INR Lactahydrogenase	28 28 28 28 13 28	Rigshospitalets lab portal (Metodeliste)
Fluid and electrolytes	Albumin Creatinine eGFR Potassium Sodium	28 28 0 16 16	Rigshospitalets lab portal (Metodeliste)
P-Cancer-antigen 125	CA-125	109	Rigshospitalets lab portal (Metodeliste)
Hematology	Erythrocytes Leucocytes Thrombocytes	31 0 0	Rigshospitalets lab portal (Metodeliste)
Total (DKK)		382	

11.1.1.1.1.4 Scenario analysis

Table 69: The full scenario analysis for HRD positive BRCAm, HRD positive non-BRCA and HRD negative non-BRCA.

		Niraparib	RS	Olaparib	Incremental costs	
Scenario	**Scenario Label**	Costs	Costs	Costs	Niraparib vs RS	Niraparib vs Olaparib
1	HR-deficient BRCAmut pop - PFS - Exponential	[redacted]	335695,8293	855415,3052	[redacted]	[redacted]
2	HR-deficient BRCAmut pop - PFS - Weibull	[redacted]	338822,1311	861734,2973	[redacted]	[redacted]
3	HR-deficient BRCAmut pop - PFS - Gompertz	[redacted]	338352,9262	863041,9545	[redacted]	[redacted]
4	HR-deficient BRCAmut pop - PFS - Lognormal	[redacted]	334859,815	856671,4219	[redacted]	[redacted]
5	HR-deficient BRCAmut pop - PFS - Generalized Gamma	[redacted]	331633,2967	856644,6214	[redacted]	[redacted]

6	HR-deficient BRCAmut pop - OS - Exponential	[redacted]	475254,0595	987159,2046	[redacted]	[redacted]
7	HR-deficient BRCAmut pop - OS - Weibull	[redacted]	303566,203	851081,9787	[redacted]	[redacted]
8	HR-deficient BRCAmut pop - OS - Gompertz	[redacted]	324827,3419	846118,5067	[redacted]	[redacted]
9	HR-deficient BRCAmut pop - OS - Lognormal	[redacted]	341699,3779	866924,3731	[redacted]	[redacted]
10	HR-deficient BRCAmut pop - OS - Generalised Gamma	[redacted]	432724,496	925389,9023	[redacted]	[redacted]
11	HR-deficient BRCAmut pop - OS - HR approach	[redacted]	334518,0805	863210,5015	[redacted]	[redacted]

12	HR-deficient BRCAmut pop - TTD - Exponential	[redacted]	334813,6146	853227,1459	[redacted]	[redacted]
13	HR-deficient BRCAmut pop - TTD - Weibull	[redacted]	334480,0233	860061,6755	[redacted]	[redacted]
14	HR-deficient BRCAmut pop - TTD - Gompertz	[redacted]	334810,7488	857838,9389	[redacted]	[redacted]
15	HR-deficient BRCAmut pop - TTD - Log-logistic	[redacted]	334891,4954	862530,0721	[redacted]	[redacted]
16	HR-deficient BRCAmut pop - TTD - Generalized Gamma	[redacted]	334435,0836	525349,9146	[redacted]	[redacted]
17	HR-deficient BRCAmut pop - Model wastage	[redacted]	334518,0805	856323,163	[redacted]	[redacted]

18	HR-deficient BRCAmut pop - Dosing - Individualized dose	[redacted]	334518,0805	857678,1063	[redacted]	[redacted]
19	HR-deficient BRCAmut pop - Dosing - Fixed dose	[redacted]	334518,0805	857678,1063	[redacted]	[redacted]
20	HR-deficient BRCAmut pop - Include subsequent TX	[redacted]	50691,25931	749500,3589	[redacted]	[redacted]
21	HR-deficient BRCAmut pop - Stopping rule - No tx cap	[redacted]	334518,0805	1169049,626	[redacted]	[redacted]
22	HR-deficient BRCAmut pop - HRD test cost - exclude	[redacted]	334518,0805	857678,1063	[redacted]	[redacted]

23	HR-deficient BRCAwt pop - PFS - Exponential	[redacted]	193081,3448	N/A	[redacted]	[redacted]
24	HR-deficient BRCAwt pop - PFS - Weibull	[redacted]	194412,6032	N/A	[redacted]	[redacted]
25	HR-deficient BRCAwt pop - PFS - Gompertz	[redacted]	192785,4682	N/A	[redacted]	[redacted]
26	HR-deficient BRCAwt pop - PFS - Lognormal	[redacted]	192814,7545	N/A	[redacted]	[redacted]
27	HR-deficient BRCAwt pop - PFS - Generalized Gamma	[redacted]	181523,7536	N/A	[redacted]	[redacted]
28	HR-deficient BRCAwt pop - OS - Exponential	[redacted]	251028,4696	N/A	[redacted]	[redacted]

29	HR-deficient BRCAwt pop - OS - Weibull	[redacted]	172276,608	N/A	[redacted]	[redacted]
30	HR-deficient BRCAwt pop - OS - Gompertz	[redacted]	161935,7515	N/A	[redacted]	[redacted]
31	HR-deficient BRCAwt pop - OS - Lognormal	[redacted]	203795,6259	N/A	[redacted]	[redacted]
32	HR-deficient BRCAwt pop - OS - Generalised Gamma	[redacted]	288699,4015	N/A	[redacted]	[redacted]
33	HR-deficient BRCAwt pop - OS - HR approach	[redacted]	192055,9315	N/A	[redacted]	[redacted]
34	HR-deficient BRCAwt pop - TTD - Exponential	[redacted]	192227,2266	N/A	[redacted]	[redacted]

35	HR-deficient BRCAwt pop - TTD - Weibull	[redacted]	192073,4297	N/A	[redacted]	[redacted]
36	HR-deficient BRCAwt pop - TTD - Gompertz	[redacted]	192415,532	N/A	[redacted]	[redacted]
37	HR-deficient BRCAwt pop - TTD - Log-logistic	[redacted]	192493,84	N/A	[redacted]	[redacted]
38	HR-deficient BRCAwt pop - TTD - Generalized Gamma	[redacted]	191908,1772	N/A	[redacted]	[redacted]
39	HR-deficient BRCAwt pop - Model wastage	[redacted]	192055,9315	N/A	[redacted]	[redacted]
40	HR-deficient BRCAwt pop - Dosing - Individualized dose	[redacted]	192055,9315	N/A	[redacted]	[redacted]

41	HR-deficient BRCAwt pop - Dosing - Fixed dose	[redacted]	192055,9315	N/A	[redacted]	[redacted]
42	HR-deficient BRCAwt pop - Include subsequent TX	[redacted]	76682,60342	N/A	[redacted]	[redacted]
43	HR-deficient BRCAwt pop - Stopping rule - No tx cap	[redacted]	192055,9315	N/A	[redacted]	[redacted]
44	HR-deficient BRCAwt pop - HRD test cost - exclude	[redacted]	192055,9315	N/A	[redacted]	[redacted]
45	HR-proficient - PFS - Exponential	[redacted]	176686,5261	N/A	[redacted]	[redacted]
46	HR-proficient - PFS - Weibull	[redacted]	177146,886	N/A	[redacted]	[redacted]

47	HR-proficient - PFS - Gompertz	[redacted]	173640,8128	N/A	[redacted]	[redacted]
48	HR-proficient - PFS - Lognormal	[redacted]	176801,0164	N/A	[redacted]	[redacted]
49	HR-proficient - PFS - Generalised Gamma	[redacted]	171417,6916	N/A	[redacted]	[redacted]
50	HR-proficient - OS - Exponential	[redacted]	204224,2666	N/A	[redacted]	[redacted]
51	HR-proficient - OS - Weibull	[redacted]	165626,4725	N/A	[redacted]	[redacted]
52	HR-proficient - OS - Gompertz	[redacted]	160796,9973	N/A	[redacted]	[redacted]
53	HR-proficient - OS - Lognormal	[redacted]	182661,0085	N/A	[redacted]	[redacted]

54	HR-proficient - OS - Generalised Gamma	[redacted]	134653,799	N/A	[redacted]	[redacted]
55	HR-proficient - OS - HR approach	[redacted]	176448,3158	N/A	[redacted]	[redacted]
56	HR-proficient - TTD - Exponential	[redacted]	176493,8689	N/A	[redacted]	[redacted]
57	HR-proficient - TTD - Weibull	[redacted]	176507,0877	N/A	[redacted]	[redacted]
58	HR-proficient - TTD - Gompertz	[redacted]	176560,0099	N/A	[redacted]	[redacted]
59	HR-proficient - TTD - Log-logistic	[redacted]	176632,6727	N/A	[redacted]	[redacted]
60	HR-proficient - TTD - Generalised Gamma	[redacted]	176635,0749	N/A	[redacted]	[redacted]

61	HR-proficient - Model wastage	[redacted]	176448,3158	N/A	[redacted]	[redacted]
62	HR-proficient - Dosing - Individualized dose	[redacted]	176448,3158	N/A	[redacted]	[redacted]
63	HR-proficient - Dosing - Fixed dose	[redacted]	176448,3158	N/A	[redacted]	[redacted]
64	HR-proficient - Include subsequent TX	[redacted]	45529,45239	N/A	[redacted]	[redacted]
65	HR-proficient - Stopping rule - No tx cap	[redacted]	176448,3158	N/A	[redacted]	[redacted]
66	HR-proficient - HRD test cost - exclude	[redacted]	176448,3158	N/A	[redacted]	[redacted]

Medicinrådet

Medicinrådets protokol for vurdering af niraparib til 1. linje vedligeholdelsesbehandling af avanceret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

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

Om protokollen

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

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

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

Godkendt af Medicinrådet 26. november 2020
Dokumentnummer 99073
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Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
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Indhold

1 Begreber og forkortelser

CI	Konfidensinterval
BRCA	*Breast Cancer* (tumorsuppressorgen)
EMA	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EPAR	*European Public Assessment Report*
FDA	*U.S. Food and Drug Administration*
FIGO	*International Federation of Gynecology and Obstetrics* (system til at inddele kræftsygdomme I stadier fra I-IV)
GRADE	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HR	*Hazard ratio*
HRD	Homolog rekombinationsdefekt (*homologous recombination repair deficiency*)
ITT	*Intention-to-treat*
OR	*Odds ratio*
OS	Samlet overlevelse (*Overall survival*)
PARP	Poly-ADP-Ribose-Polymerase
PARPi	Poly-ADP-Ribose-Polymerasehæmmer (*inhibitor*)
PFS	Progressionsfri overlevelse (*progression free survival*)
PICO	Population, intervention, komparator og effektmål (*Population, Intervention, Comparator and Outcome)*
PP	*Per-protocol*
RCT	Randomiseret kontrolleret studie *(Randomised Controlled Trial)*
RR	Relativ risiko
SMD	*Standardized Mean Difference*

2 Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra GlaxoSmithKline Limited, som ønsker, at Medicinrådet vurderer niraparib til 1. linje vedligeholdelsesbehandling af high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden. Vi modtog den foreløbige ansøgning den 11. august 2020.

2.1 Kræft i æggestokkene, æggelederne eller primær bughulekræft

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

Kræft i æggestokkene er den fjerde hyppigste kræftdødsårsag hos kvinder i Danmark. Der diagnosticeres omkring 450-550 nye tilfælde om året, og ved udgangen af 2016 levede 4697 kvinder med diagnosen [1,2]. Kræft i æggestokkene udgør i alt 2,8 % af alle kræfttilfælde hos kvinder, og livstidsrisikoen for at udvikle sygdommen er ca. 2 %. Median alder for diagnosen er 63 år, og overlevelsen er afhængig af alder ved diagnosen samt sygdomsstadiet (FIGO stadium, herfra blot benævnt stadium). 5-års overlevelsesrater for stadium I, II, III og IV er henholdsvis 93, 76, 41 og 23 % med faldende respektive værdier ved stigende alder på diagnosetidspunktet [3,4]. Tidlige stadier af sygdommen er ofte asymptomatiske på grund af æggestokkenes frie beliggenhed i det lille bækken. Således har ca. 70-80 % af patienter med kræft i æggestokkene på diagnosetidspunktet lokal spredning eller avanceret sygdom (stadium II-IV) [1], hvilket er kraftigt medvirkende til en samlet 5-års overlevelse på ca. 40-50 % [4,5].

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

Mutationer i *Breast Cancer* (BRCA) 1 eller 2-genet er en væsentlig arvelig risikofaktor for udviklingen af kræft i æggestokkene. Forekomsten er ca. 15-20 % med en højere forekomst hos patienter med HGSC [6–8]. BRCA-mutationer kan være både arvelige eller somatiske. I dansk klinisk praksis behandles disse på samme måde, hvorved BRCA-mutationer i denne protokol bruges som fællesbetegnelse for begge typer. Patienter med BRCA-mutation har generelt en bedre prognose, da mutationerne medfører et signifikant bedre respons på både platin-baseret kemoterapi og hæmmere af Poly-ADP-Ribose-Polymerase (PARPi) [9–12].

BRCA er involveret i homolog rekombination, som er en vital celleproces til reparation af DNA-skader [9,13]. Tumorer med BRCA-mutation vil oftest også have homolog rekombinationsdefekt (HRD), men HRD kan også forekomme i ikke-BRCA-muterede tumorer. Flere studier har dokumenteret HRD i op mod 40 % af platin-sensitive tumorer i æggestokkene uden BRCA-mutation, hvorved gruppen med HRD er op mod dobbelt så stor som gruppen med BRCA-mutation [7,12,14–16]. I studierne var HRD defineret som enten BRCA-mutation eller en genomisk ustabilitetsscore over 42 målt vha. MYRIAD myChoice CDx. Dette er en kompleks molekylærbiologisk analyse, der kombinerer genomic scar assays, hhv. ”Telomeric Allelic Imbalance”, ”Loss Of Heterozygosity” og ”Large Scale Transition” med en samlet tærskelværdi på 42 til bestemmelse af HRD positivitet.

Det anbefales i dag, at alle patienter med kræft i æggestokkene udredes i forhold til BRCA-mutationsstatus [17], men der findes ingen nationale guidelines i forbindelse med udredning af HRD-status. Derfor vil det forventes, at en væsentlig gruppe af danske patienter uden påvist BRCA-mutation har tumorer, der udviser HRD. *U.S. Food and Drug Administration* (FDA) har i 2020 godkendt et companion diagnostics til at identificere HRD i high grade kræft i æggestokkene [18]. Denne diagnostiske metode er anvendt i flere

kliniske forsøg med PARPi i Danmark, heriblandt på Herlev Hospital, Odense Universitetshospital, Rigshospitalet og Aarhus Universitetshospital, hvor mere end 100 patienter er blevet testet [11,12,15,19].

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

2.2 Niraparib

Niraparib blev den 29. oktober 2020 godkendt af Europakomissionen til vedligeholdelsesbehandling af nydiagnosticerede patienter med avanceret high-grade kræft i æggestokkene, æggelederne og primær kræft i bughinden, som responderer på platinbaseret kemoterapi (komplet eller partiel respons). Niraparib er desuden godkendt som monoterapi til vedligeholdelsesbehandling af platinsensitiv recidiverende high-grade serøst karcinom i æggestokkene [20]. I 2010 blev niraparib betegnet som *orphan drug* af EMA [20].

Medicinrådet anbefaler niraparib til 2. linje vedligeholdelsesbehandling af patienter med påvist BRCA-mutation under forudsætning af, at der ikke er behandlet med PARPi i 1. linje [21].

Standarddoseringen af niraparib er på 3 kapsler af 100 mg dagligt indtil sygdomsprogression, eller 2 kapsler af 100 mg dagligt, hvis patienten vejer under 77 kg eller opfylder anden klinisk risikoparameter [22]. Dette er tilfældet for omkring 70 % af patienterne.

Niraparib tilhører gruppen af selektive PARPi, der hæmmer aktivering af enzymerne, PARP-1, -2 og -3 [20]. PARP indgår i cellens DNA-reparationsrespons, hvor de faciliterer reparation af enkeltstrengsbrud på DNA'et. Hæmning af denne proces resulterer i yderligere brud på DNA'et kaldet DNA dobbeltstrengsbrud. Disse brud repareres normalt via homolog rekombination, men i celler med HRD (som er tilfældet i BRCA mutationer), vil dobbeltstrengsbrud akkumulere og medføre celledød i tumoren [23]. Niraparib udviser, ligesom andre PARPi, en større effekt i tumorer med enten påvist BRCA-mutation eller HRD. Dog er der også påvist en mindre, men signifikant, øgning af PFS hos patienter uden hverken BRCA-mutation eller HRD ved 2. linje vedligeholdelsesbehandling af platinsensitive HGSC tumorer i æggestokkene [12].

2.3 Nuværende behandling

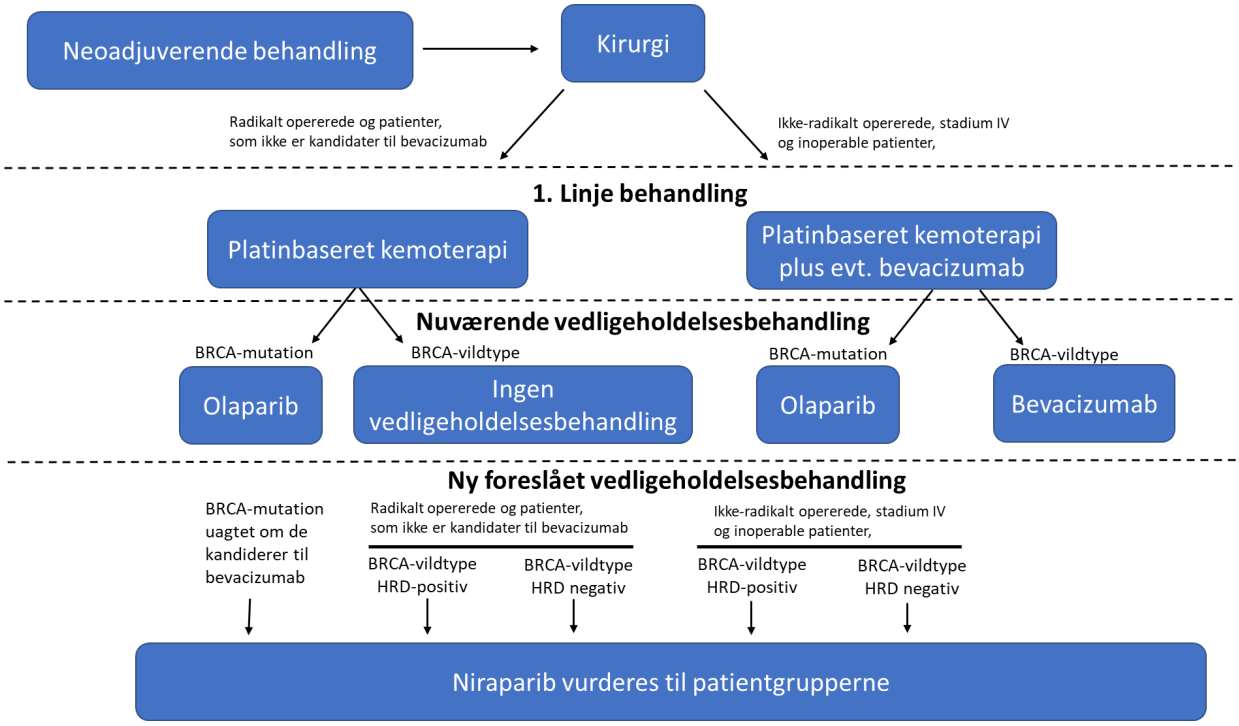
Det overordnede mål for behandlingen af kræft i æggestokkene er helbredelse, alternativt at forlænge overlevelsen og/eller at øge livskvaliteten. Den primære behandling er kirurgisk, hvor målet er at fjerne alt synligt kræftvæv (radikal operation) samt korrekt stadieinddeling [1,24]. Dette opnås for ca. 70 % af patienter med stadium III eller IV enten primært eller efter indledende kemoterapi [4]. Efterfølgende behandling afhænger af patientens sygdomsstadie, operationsresultat og sundhedsmæssige status. I klinisk praksis skelnes der mellem patienter, hvor der er efterladt mindre end eller mere end eller lig med 1 cm tumorvæv efter operation.

Patienter i stadium IIB-IV uden makroskopisk tumorvæv efter operation (< 1 cm) behandles som standard med adjuverende platinbaseret kombinationskemoterapi bestående af carboplatin og paclitaxel. Behandlingen gives i 6 serier, med mindre der opstår progression eller uacceptabel toksicitet [25]. Patienter med BRCA-mutation, som responderer på kemoterapibehandlingen, tilbydes vedligeholdelsesbehandling med olaparib i en standarddosering på 2 tabletter af 150 mg per styk 2 gange dagligt i 2 år eller indtil

progression eller uacceptabel toksicitet [21]. Patienter uden BRCA-mutation tilbydes ikke yderligere vedligeholdelsesbehandling.

Patienter i stadium III med efterladt makroskopisk tumorvæv efter operation (≥ 1 cm) samt patienter i stadium IV og inoperable patienter behandles som standard også med carboplatin og paclitaxel. Patienter med BRCA-mutation tilbydes vedligeholdelsesbehandling med olaparib som beskrevet ovenfor, hvorimod patienter uden BRCA-mutation kan tilbydes behandling med bevacizumab i kombination med og/eller efter kemoterapibehandlingen [25].

Størstedelen af patienterne (60-80 %) responderer på førstelinjebehandlingen, men omkring 80 % af disse vil opleve tilbagefald inden for 2-3 år efter afsluttet kemoterapi [1]. Disse patienter har generelt dårligere prognose end nydiagnosticerede patienter og vil typisk opleve kortere progressionsfri overlevelse (PFS) efter gentagne kemoterapibehandlingslinjer [26]. Det nuværende behandlingsforløb, samt hvorledes niraparib vil indtræde ved en eventuel anbefaling, er illustreret i figur 1.



Figur 1: Niraparibs indplacering som vedligeholdelsesbehandling efter den nuværende 1. linjebehandling med platinbaseret kemoterapi af kræft i æggestokkene. EMA-indikationen for niraparib dækker alle patienter med nydiagnosticeret kræft i æggestokkene, der responderer på platin, men den samlede patientpopulation opdeles i denne protokol for at belyse effekterne i de forskellige subgrupper, BRCA-mutation, BRCA-vildtype med/uden HRD og bevacizumab/ikke-bevacizumabkandidater.

Denne protokol vedrører kun 1. linjebehandling, hvorfor der ikke gives nærmere beskrivelse af efterfølgende behandling af platinsensitiv recidiverende kræft i æggestokkene.

3 Kliniske spørgsmål

Medicinrådet bruger kliniske spørgsmål til vores vurderinger af lægemidlers værdi for patienterne. Til hvert spørgsmål knytter sig en definition af patientgruppen (population), af det lægemiddel vi undersøger (interventionen), af den behandling vi sammenligner med (komparator(er)) og af effektmålene.

Det overordnede kliniske spørgsmål opdeles, da den nuværende standardbehandling varierer, afhængig af om patienten har en påvist BRCA-mutation, og om de kandiderer til bevacizumab. Derfor er det relevant at tage stilling til niraparibs kliniske værdi overfor tre forskellige standardbehandlinger. Patienter med BRCA-mutation vil med nuværende praksis modtage olaparib monoterapi, uagtet om de kandiderer til bevacizumab eller ej. Denne population vil derfor indeholde både patienter med stadium III og stadium IV BRCA-muteret high-grade kræft i æggestokkene uagtet operationsstatus. Nuværende praksis for vedligeholdelsesbehandling af patienter uden BRCA-mutation afhænger af om de kandiderer til bevacizumab eller ej. Derfor opdeles denne population efter stadium samt operationsresultat, som beskrevet nedenfor.

Yderligere bemærkes det, at subpopulationen af patienter uden BRCA-mutation men med diagnosticeret HRD potentielt kan opnå en anden klinisk værdi ved niraparibbehandling end den samlede ikke-BRCA-muterede population. Derfor er det relevant at opdele den ikke-BRCA-muterede population i HRD og ikke-HRD, når den kliniske værdi skal estimeres. Derudover bemærkes det, at en anden PARPi, olaparib, aktuelt behandles af Medicinrådet med en indikation, der kræver diagnosticeret HRD.

3.1 Klinisk spørgsmål 1

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

Population
Nydiagnosticerede patienter med avanceret (stadium III-IV) BRCA-muteret high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden, som responderer på platinbaseret kemoterapi (komplet eller partiel respons).

Intervention
Niraparib som beskrevet i 2.2.

Komparator
Olaparib.

Effektmål
De valgte effektmål står i tabel 1.

Klinisk spørgsmål 2

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

Population
Nydiagnosticerede patienter med avanceret (stadium III-IV) ikke-BRCA-muteret, HRD-positiv high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden, som responderer på platinbaseret

kemoterapi (komplet eller partiel respons), og som vurderes at være kandidater til bevacizumab (patienter med mere end eller lig med 1 cm efterladt tumorvæv, patienter med efterladt tumorvæv udenfor bughulen (stadium IV), og patienter, som er primært og/eller sekundært (interval kirurgi) inoperable).

Intervention
Niraparib som beskrevet i 2.2.

Komparator
Bevacizumab.

Effektmål
De valgte effektmål står i tabel 1.

Klinisk spørgsmål 3

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

Population
Nydiagnosticerede patienter med avanceret (stadium III-IV) ikke-BRCA-muteret, HRD-negativ high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden, som responderer på platinbaseret kemoterapi (komplet eller partiel respons), og som vurderes at være kandidater til bevacizumab (patienter med mere end eller lig med 1 cm efterladt tumorvæv, patienter med efterladt tumorvæv udenfor bughulen (stadium IV), og patienter, som er primært og/eller sekundært (intervalkirurgi) inoperable).

Intervention
Niraparib som beskrevet i 2.2.

Komparator
Bevacizumab.

Effektmål
De valgte effektmål står i tabel 1.

Klinisk spørgsmål 4

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

Population
Nydiagnosticerede patienter med stadium III, ikke-BRCA-muteret, HRD-positiv high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden, som responderer på platinbaseret kemoterapi (komplet eller partiel respons), og som har mindre end 1 cm tumorvæv efterladt efter operation.

Intervention
Niraparib som beskrevet i 2.2.

Komparator
Ingen vedligeholdelsesbehandling.

Effektmål
De valgte effektmål står i tabel 1.

Klinisk spørgsmål 5

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

Population
Nydiagnosticerede patienter med stadium III, ikke-BRCA-muteret, HRD-negativ high-grade kræft i æggestokkene, æggelederne eller primær kræft i bughinden, som responderer på platinbaseret kemoterapi (komplet eller partiel respons), og som har mindre end 1 cm tumorvæv efterladt efter operation.

Intervention
Niraparib som beskrevet i 2.2.

Komparator
Ingen vedligeholdelsesbehandling

Effektmål
De valgte effektmål står i tabel 1.

3.2 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, vi har nævnt i tabel 1. For hvert effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel (MKRF). I det følgende afsnit argumenterer vi for valget af effektmål og de mindste klinisk relevante forskelle.

Tabel 1. Effektmål.

Effektmål	Vigtighed	Effektmålsgruppe	Måleenhed	Mindste klinisk relevante forskel	
				BRCA-mutation eller HRD-positiv	**BRCA-vildtype og HRD-negativ**
Samlet overlevelse (OS)	Kritisk	Dødelighed	Median OS i antal måneder	En forskel på 4 måneder	En forskel på 3 måneder
			OS rate ved 5 år	En forskel på 5 procentpoint	
Progressions-fri overlevelse (PFS)	Kritisk	Livskvalitet samt alvorlige symptomer og bivirkninger	Median PFS i antal måneder	En forskel på 6 måneder	En forskel på 3 måneder
			PFS rate ved 2 år	En forskel på 10 procentpoint	En forskel på 5 procentpoint
Bivirkninger	Kritisk	Livskvalitet samt alvorlige symptomer og bivirkninger	Andel af patienter, som ophører behandling pga. bivirkninger	En forskel på 5 procentpoint	
			Andel af patienter, som oplever en eller flere grad 3-4 bivirkninger	En forskel på 10 procentpoint	
			Kvalitativ gennemgang af bivirkningstyperne med henblik på at vurdere alvorlighed, håndterbarhed og tyngde af bivirkningerne	Kvalitativ vurdering	
Livskvalitet	Vigtig	Livskvalitet samt alvorlige symptomer og bivirkninger	Andel af patienter, der ikke viser statistisk signifikant forværring i livskvalitet	En forskel på 10 procentpoint	

For alle effektmål ønsker vi data med længst mulig opfølgningstid, med mindre andet er angivet.

3.2.1 Kritiske effektmål

Samlet overlevelse

Forbedret samlet overlevelse (OS) med mindst mulig toksicitet er det optimale mål for kræftbehandling. OS defineres som tiden fra randomisering eller behandlingsstart til død uanset årsag. For OS anvendes to mål til at vurdere den absolutte effekt: median OS og OS-rate. De to mål supplerer hinanden.

Kræft i æggestokkene er en livstruende sygdom, og fagudvalget betragter derfor OS som et kritisk effektmål. For patienter med kræft i æggestokkene stadie III-IV er 5-årsoverlevelsen ca. 30 % med median OS på ca. 3 år [4]. Fagudvalget vurderer derfor, at en absolut forskel i OS-rate ved 5 år på 5 procentpoint og en absolut forskel for median OS på 4 måneder mellem intervention og komparator er klinisk relevant. For ikke-BRCA muterede patienter er prognoserne generelt dårligere. Ved sammenligning af OS på tværs af kohortestudier er der rapporteret hazard ratios omkring 0,6-0,8, hvilket viser en øget overlevelse for patienter med BRCA-mutation [6,27]. Fagudvalget vurderer, at en forskel i median OS på 3 måneder er klinisk relevant for ikke-

BRCA muterede patienter for at afspejle de dårligere generelle prognoser. Fagudvalget vurderer, at patienter med HRD har en sammenlignelig prognose med BRCA-muterede patienter. Derfor er de reducerede mindste klinisk relevante forskelle kun gældende for de HRD-negative patienter.

Progressionsfri overlevelse

Progressionsfri overlevelse (PFS) defineres som tiden fra randomisering eller behandlingsstart til første dokumentation af progression i henhold til Response Evaluation Criteria i Solid Tumors (RECIST)-kriterierne [28] eller til død.

PFS anvendes som surrogatmål for OS og livskvalitet inden for området. Hvis der ikke findes modne data på OS, vil fagudvalget anvende data på PFS som surrogatmål for OS. PFS påvirkes ikke af akkumulerede effekter af efterfølgende behandlinger på samme måde som OS, og data må forventes at have nået en større modenhed for PFS, hvilket medfører sikrere estimater. Fagudvalget er dog opmærksomme på, at validiteten af PFS som surrogat er uklar, fordi sammenhængen mellem OS og PFS ikke er dokumenteret for behandling af kræft i æggestokkene. Tværtimod viste to nylige metaanalyser af behandling af kræft i æggestokkene mangel på sammenhæng mellem PFS og OS ud fra hazard ratios [29,30]. Dog viste den ene analyse en bedre korrelation ved at sammenligne forskelle i medianer mellem kontrol og aktive behandlinger for PFS og OS [30]. Fagudvalget sætter derfor højere krav til effekten på PFS end på OS, hvilket er afspejlet i effektmålenes indplacering i effektmålsgruppe (se tabel 1).

PFS ved vedligeholdelsesbehandling afspejler desuden tiden til næste linje med platinbaseret kemoterapi. Længden af det platinfrie interval er bestemmende for valg af efterfølgende behandling, og fagudvalget anser dette som en vigtig patientrelateret parameter.

Fagudvalget vurderer på denne baggrund, at PFS er et kritisk effektmål. For populationen med BRCA-mutation er PFS-raten ved 2 år ca. 40 %, og median PFS er ca. 14 måneder [31]. Fagudvalget vurderer derfor, at en absolut forskel i PFS-rate ved 2 år på 10 procentpoint og en absolut forskel på median PFS på 6 måneder mellem intervention og komparator er klinisk relevant. Populationen uden BRCA-mutation har en dårligere prognose i forhold til PFS med en forventet PFS-rate ved 2 år på ca. 20 % og median PFS på ca. 10 måneder [19]. Fagudvalget vurderer derfor, at en absolut forskel i PFS-rate ved 2 år på 5 procentpoint og en forskel på median PFS på 3 måneder er klinisk relevant for ikke-BRCA-muterede patienter. Fagudvalget vurderer, at patienter med HRD har en sammenlignelig prognose med BRCA-muterede patienter. Derfor er de reducerede mindste klinisk relevante forskelle kun gældende for de HRD-negative patienter.

Bivirkninger

Bivirkninger (toksicitet) belyser de negative konsekvenser, patienterne kan opleve ved behandling med lægemidlet. Forbedret OS med mindst mulig toksicitet er det optimale mål for kræftbehandling. Fagudvalget anser derfor bivirkninger som et kritisk effektmål. Effektmålet vurderes samlet ud fra behandlingsophør på grund af bivirkninger, bivirkninger grad 3-4 samt en kvalitativ gennemgang af bivirkningerne. Behandlingsophør på grund af bivirkninger og bivirkninger grad 3-4 er to kvantitative opgørelser, som belyser henholdsvis tolerabilitet og hyppigheden af alvorlige og livstruende bivirkninger.

<u>Behandlingsophør på grund af bivirkninger</u>

Fagudvalget ønsker en opgørelse over forskellen i andel af patienter, som ophører behandling grundet bivirkninger ved længst mulig opfølgningstid. Fagudvalget vurderer, at en mindste klinisk relevant forskel er 5 procentpoint.

Bivirkninger grad 3-4

Forekomst af bivirkninger grad 3-4, defineret i henhold til National Cancer Institute CTCAE, version 4.0 [32], er et udtryk for alvorlig, men ikke fatal toksicitet af lægemidlet.

Fagudvalget ønsker en opgørelse over andelen af patienter, som oplever en eller flere bivirkninger af grad 3 og/eller 4 ved længst mulig opfølgningstid. Fagudvalget vurderer, at en mindste klinisk relevant forskel er 10 procentpoint.

Kvalitativ gennemgang af bivirkningerne

Fagudvalget ønsker en kvalitativ gennemgang af de konkrete bivirkninger forbundet med niraparib samt komparatorer med henblik på at vurdere bivirkningernes alvorlighed, hyppighed og håndterbarhed. Ansøger bedes bidrage med bivirkningsdata fra både kliniske studier samt lægemidlernes produktresumé.

Fagudvalget er meget opmærksomme på, at op til 80 % af bivirkningerne forbundet med behandling med PARP-hæmmere er håndterbare og dosistitrerbare. Fagudvalget vil tage højde for dette i den samlede kategorisering.

3.2.2 Vigtige effektmål

Livskvalitet

Ændring i livskvalitet er et patientrelevant effektmål, som kan give indblik i, hvordan lægemidlernes fordele og ulemper samlet set påvirker patienten. Baseline FACT-O TOI-score er uafhængigt prognostisk for PFS og OS, hvor forbedring sammenlignet med forværring i livskvalitet er forbundet med forlænget PFS og OS hos kvinder med kræft i æggestokkene [33]. På baggrund af dette betragter fagudvalget livskvalitet som et vigtigt effektmål for alle prognosegrupper.

Livskvalitet kan for patienter med kræft i æggestokkene måles med forskellige spørgeskemaer. Fagudvalget ønsker livskvalitet opgjort som andel patienter, der ikke viser en signifikant forværring i livskvalitet vha. spørgeskemaet EORTC-QLQ-OV28:

- EORTC-QLQ-OV28 eller C-30. European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30 (EORTC QLQ-C30) er et hyppigt anvendt generisk måleredskab, som består af fem funktionsskalaer, tre symptomskalaer og en 'global' livskvalitetsskala. Der anvendes en scoringsskala fra 0-100 [34]. EORTC Quality of Life Group and the Quality of Life Unit har udviklet og valideret et supplement til dette, som er specifikt for kræft i æggestokkene, -OV28 [35]. Det foretrækkes, at ansøger leverer data fra det specifikke spørgeskema, -OV28.

Hvis der foreligger data fra EORTC-QLQ-OV28 vil vurderingen baseres på dette. Hvis dette ikke er tilgængeligt, men ansøger har data for et andet måleinstrument, ønsker fagudvalget at se en opgørelse for dette. Denne opgørelse skal inkludere en beskrivelse af værktøjet samt argumentation og dokumentation for mindste klinisk relevant forskel. Alternative måleinstrumenter kunne være:

- Functional Assessment of Cancer Therapy-Ovarian (FACT-O). FACT-O er et sygdomsspecifikt spørgeskema, som anvendes til vurdering af helbredsrelateret livskvalitet hos patienter med kræft i æggestokkene. Spørgeskemaet består af fem domæner (fysisk velvære, socialt velvære, følelsesmæssigt velvære, funktionelt velvære og øvrige bekymringer), som scores på en 5-point Likertskala fra 0 (ingen) til 4 (rigtig meget). En høj samlet score repræsenterer høj livskvalitet [36].

- FACT Ovarian Symptom Index (FOSI). FOSI er et valideret 8-spørgsmåls måleinstrument omhandlende sygdomsrelaterede symptomer. Spørgsmålene er taget fra FACT-O-spørgeskemaet. Scoreskalaen går fra 0 (alvorlige symptomer) til 32 (ingen symptomer) [37].

- EQ-5D: EQ-5D er et velvalideret generisk spørgeskema, som anvendes til vurdering af helbredsrelateret livskvalitet (EuroQol Group). Spørgeskemaet består af fem dimensioner (bevægelighed, personlig pleje, sædvanlige aktiviteter, smerte/ubehag og angst/depression). Spørgeskemaet indeholder desuden en visuel analog skala (VAS), der går fra 0 (værst tænkeligt helbred) til 100 (bedst tænkeligt helbred) [38].

Fagudvalget vurderer, at en forskel på 10 procentpoint i andel patienter, der ikke viser forværring i livskvalitet mellem lægemidlerne, er klinisk relevant.

4 Litteratursøgning

Medicinrådet har på baggrund af den foreløbige ansøgning undersøgt, om der findes en eller flere fuldtekstartikler publiceret i videnskabelige, fagfællebedømte tidsskrifter, hvor niraparib er sammenlignet direkte med olaparib, bevacizumab og placebo for henholdsvis klinisk spørgsmål 1, 2-3 og 4-5.

Klinisk spørgsmål 1:

Medicinrådet har ikke fundet fuldtekstartikler, der indeholder en direkte sammenligning mellem niraparib og olaparib. Derfor skal ansøger søge efter artikler til en indirekte sammenligning. Søgestrengen fremgår nedenfor. Derudover skal ansøger konsultere Det Europæiske Lægemiddelagenturs (EMA) European public assessment reports (EPAR) for både det aktuelle lægemiddel og dets komparator(er).

Søgestreng til PubMed:

Sæt	Søgetermer	Kommentarer
1	Ovarian Neoplasms[mh]	Termer for population
2	(ovary[ti] OR ovari*[ti]) AND (cancer[ti] OR carcinoma*[ti] OR neoplasm*[ti] OR tumor*[ti] OR tumour*[ti])	
3	Fallopian Tube Neoplasms[mh]	
4	(fallopian tube*[ti] OR tubal[ti] OR oviduct[ti] OR tuba[ti]) AND (cancer[ti] OR carcinoma*[ti] OR neoplasm*[ti] OR tumor*[ti] OR tumour*[ti])	
5	Peritoneal Neoplasms[mh]	
6	(peritoneal[ti] OR peritoneum[ti] OR serous surface papillary[ti] OR extra-ovarian serous[ti] OR primary serous papillary[ti]) AND (cancer[ti] OR carcinoma*[ti] OR neoplasm*[ti] OR tumor*[ti] OR tumour*[ti])	
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	
8	newly diagnosed[tiab]	
9	1L[tiab] OR firstline[tiab] OR first-line[tiab] OR frontline[tiab] OR front-line[tiab] OR primary treatment[tiab] OR primary therapy[tiab]	
10	#7 AND (#8 OR #9)	
11	niraparib[nm] OR niraparib[tiab] OR Zejula*[tiab] OR olaparib[nm] OR olaparib[tiab] OR Lynparza*[tiab] OR Bevacizumab[mh] OR bevacizumab[tiab] OR Avastin*[tiab] OR Mvasi*[tiab] OR HRD[tiab] OR homologous recombination[tiab]	Termer for lægemidler og HRD defekt
12	#10 AND #11	Kombination population og lægemidler

13	Randomized Controlled Trial[pt] OR Controlled Clinical Trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR Clinical Trials as Topic[mh:noexp] OR randomly[tiab] OR trial[ti]	Filter til identifikation af randomiserede forsøg
14	#12 AND #13	
15	Animals[mh] NOT Humans[mh]	Eksklusion af dyr og irrelevante pub.typer
16	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR case report[ti]	
17	Review[pt] OR Systematic Review[pt] OR Meta-Analysis[pt] OR review[ti] OR meta-analys*[ti]	
18	#15 OR #16 OR #17	
19	**#14 NOT #18**	**Resultater til screening - alle kliniske spørgsmål**

Søgestreng til CENTRAL:

Sæt	**Søgetermer**	**Kommentarer**
1	[mh "Ovarian Neoplasms"]	Termer for populationen
2	((ovary OR ovari*) AND (cancer OR carcinoma* OR neoplasm* OR tumor* OR tumour*)):ti,kw	
3	[mh "Fallopian Tube Neoplasms"]	
4	((fallopian next tube* OR uterine next tube* OR tubal OR oviduct OR tuba) AND (cancer OR carcinoma* OR neoplasm* OR tumor* OR tumour*)):ti,kw	
5	[mh "Peritoneal Neoplasms"]	
6	((peritoneal OR peritoneum OR serous surface papillary OR extra-ovarian serous OR primary serous papillary) AND (cancer OR carcinoma* OR neoplasm* OR tumor* OR tumour*)):ti,kw	
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	
8	("newly diagnosed"):ti,ab	
9	(1L OR firstline OR first-line OR frontline OR front-line OR "primary treatment" OR "primary therapy"):ti,ab	
10	#7 AND (#8 OR #9)	
11	(niraparib OR Zejula* OR olaparib OR Lynparza* OR bevacizumab OR Avastin* OR Mvasi* OR HRD OR "homologous recombination"):ti,ab,kw	Termer for lægemidler og HRD defekt
12	#10 AND #11	Kombination population og lægemidler
13	("conference abstract" OR review):pt OR (abstract OR meeting OR review):ti OR (abstract OR meeting):so	Eksklusion irrelevante pub.typer
14	(clinicaltrials.gov OR trialsearch):so	
15	NCT*:au	
16	#13 OR #14 OR #15	
17	#12 NOT #16	**Resultater til screening - alle kliniske spørgsmål**

Ansøger skal ekskludere artikler med andre populationer end de, der er specificeret i protokollen, og artikler der ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

Klinisk spørgsmål 2-3:

Medicinrådet har ikke fundet fuldtekstartikler, der indeholder en direkte sammenligning mellem niraparib og bevacizumab. Derfor skal ansøger søge efter artikler til en indirekte sammenligning. Søgestrengen fremgår nedenfor. Derudover skal ansøger konsultere Det Europæiske Lægemiddelagenturs (EMA) European public assessment reports (EPAR) for både det aktuelle lægemiddel og dets komparator(er).

Søgestreng til PubMed:

Se søgestreng under klinisk spørgsmål 1

Søgestreng til CENTRAL:

Se søgestreng under klinisk spørgsmål 1

Ansøger skal ekskludere artikler med andre populationer end de, der er specificeret i protokollen, og artikler, der ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

Klinisk spørgsmål 4-5

Medicinrådet har fundet følgende fuldtekstartikel/fuldtekstartikler, som indeholder en direkte sammenligning mellem niraparib og placebo.

- González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2019;381(25):2391–402. [39]

Det er ikke tilstrækkeligt datagrundlag til en komplet besvarelse af det kliniske spørgsmål, da data ikke er opdelt efter de relevante subpopulationer. For at besvare de kliniske spørgsmål skal HRD-positivgruppen opdeles, så den ikke indeholder BRCA-muterede patienter. Dette kan eventuelt opnås fra artiklens datasæt, men det fremgår ikke af de umiddelbart publicerede data. Fagudvalget er dog opmærksomme på, at data er blevet præsenteret på ESMO kongressen 2019 med ovenstående opdeling i subpopulationer, hvorved det forventes, at data kan være tilgængelige. Derudover indeholder studiet kun patienter, der kandiderer til bevacizumab ifølge dansk praksis.

Ansøger skal derfor undersøge, om der findes andre fuldtekstartikler, som indeholder de angivne mangler. Søgestrengen fremgår nedenfor.

Ansøger skal på baggrund af artiklerne lave en indirekte sammenligning til at besvare den del af det kliniske spørgsmål, som den direkte sammenligning ikke kan besvare.

Ansøger skal derudover konsultere Det Europæiske Lægemiddelagenturs (EMA) European public assessment reports (EPAR) for både det aktuelle lægemiddel og dets komparator(er).

Søgestreng til PubMed:

Se søgestreng under klinisk spørgsmål 1

Søgestreng til CENTRAL:

Se søgestreng under klinisk spørgsmål 1

Virksomheden skal ekskludere artikler med andre populationer end de, der er specificeret i protokollen, og artikler, der ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

Kriterier for litteratursøgning

Ansøger skal søge relevant litteratur i databaserne PubMed og CENTRAL (via Cochrane Library). Ansøger skal dokumentere søgningen for hver af de to databaser, f.eks. i form af et skærmklip eller en downloadet søgestrategi. Eventuelle ændringer/tilføjelser til søgestrategien skal fremgå af dokumentationen.

Kriterier for udvælgelse af litteratur

Ansøger skal screene de artikler, der identificeres ved databasesøgningerne, for overensstemmelse med de i protokollen definerede kliniske spørgsmål samt kriterier for studie- og publikationstype(r). Det vil sige, at ansøger skal ekskludere artikler med andre populationer end de i protokollen specificerede. Dette gælder ligeledes for artikler, som ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

Den ansøgende virksomhed skal ved screening af artikler ekskludere først på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå af en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et flowdiagram som beskrevet i PRISMA-Statement (http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx).

Ved usikkerheder om, hvorvidt en artikel på titel- og abstractniveau lever op til inklusions- og eksklusionskriterierne, skal virksomheden anvende et forsigtighedsprincip til fordel for artiklen, hvorved fuldtekstartiklen skal vurderes.

5 Databehandling og -analyse

Ansøger skal bruge Medicinrådets ansøgningsskema til sin endelige ansøgning. Vær opmærksom på følgende:

Studier og resultater

- Beskriv de inkluderede studier og baselinekarakteristikken af studiepopulationerne.
- Angiv, hvilke studier/referencer der er benyttet til at besvare hvilke kliniske spørgsmål.
- Brug som udgangspunkt ansøgningsskemaet til ekstraktion af al relevant data.
- Krydstjek de ekstraherede data med de resultater, der fremgår af de relevante EPARs.
- Angiv årsager, hvis der er uoverensstemmelser mellem resultaterne fra artikler og EPARs.
- Angiv årsager, hvis der er uoverensstemmelser i forhold til PICO mellem protokollen og studierne.
- Vurdér, hvordan uoverensstemmelserne påvirker estimaterne.

Statistiske analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Udfør en komparativ analyse for hvert enkelt effektmål på baggrund af de ekstraherede data.
- Hvis data for et effektmål ikke er baseret på alle deltagere i et studie, skal ansøger ikke gøre forsøg på at erstatte manglende data med en meningsfuld værdi.
- Angiv for hvert effektmål og studie, hvilken analysepopulation (f.eks. intention to treat (ITT), per-protocol) der er anvendt.
- Angiv en sensitivitetsanalyse baseret på ITT-populationen, hvis den komparative analyse ikke er baseret herpå.
- Angiv for hvert effektmål og studie, hvilken statistisk analysemetode, der er anvendt.
- Basér de statistiske analyser for dikotome effektmål på den relative forskel.
- Beregn den absolutte forskel med udgangspunkt i den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen (jævnfør Appendiks 5 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).

- Foretag eventuelt en indirekte analyse, hvis der ikke foreligger direkte sammenlignende studier, og hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Anvend eventuelt Buchers metode for indirekte justeret sammenligning.

Metaanalyser

- Foretag en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt, hvis der er mere end ét sammenlignende studie.
- Basér metaanalyser vedr. effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, på standardized mean difference (SMD). Omregn den estimerede SMD til den foretrukne skala for effektmålet (jævnfør Appendiks 7 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Udfør alene netværksmetaanalyse i de undtagelsesvise situationer, hvor Medicinrådet specifikt beder om det i protokollen. Redegør i disse tilfælde for, i hvilken grad antagelserne om transitivitet og konsistens er opfyldt (gerne ved hjælp af passende statistiske metoder).
- Begrund for alle statistiske analyser valget mellem 'fixed effects'- og 'random effects'-modeller.
- Beskriv den anvendte metode detaljeret.

Narrative analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Syntetisér data narrativt, hvis det ikke er en mulighed at udarbejde komparative analyser baseret på statistiske metoder.
- Beskriv studie- og patientkarakteristika samt resultater fra de inkluderede studier narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er).
- Beskriv forskelle mellem studier og vurdér, hvorvidt resultaterne er sammenlignelige.

Særlige forhold i denne protokol

Vær opmærksom på, at Medicinrådets sekretariat forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans, uanset valg af analysemetode.

6 Evidensens kvalitet

Medicinrådet anvender GRADE (Grading of Recommendations, Assessments, Development and Evaluation) til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Evidensens kvalitet fortæller, i hvor høj grad vi kan have tiltro til den evidens, vi baserer vurderingen af lægemidlets værdi på.

7 Andre overvejelser

Det ønskes, at ansøger redegør for en mulig strategi til at diagnosticere HRD i dansk klinisk praksis, da diagnosen af HRD er afgørende for at identificere patienter, der potentielt kan modtage niraparib til indikationen.

Fagudvalget ønsker en opgørelse af tid til progression på den efterfølgende behandling (PFS2) for at supplere data for PFS og for at opnå et indblik i patienternes forløb efter 1. progression ved behandling med niraparib.

Fagudvalget ønsker informationer, der kan belyse en vurdering af, hvorvidt og hvordan indførelsen af den ansøgte intervention i dansk klinisk praksis vil påvirke behandlinger i efterfølgende behandlingslinjer, hvad angår type, varighed og forventet effekt.

8 Relation til behandlingsvejledning

Fagudvalget vil i forbindelse med vurderingen af niraparib tage stilling til, hvor det foreløbig kan placeres i Medicinrådets behandlingsvejledning for lægemidler til BRCA-muteret kræft i æggestokkene, æggelederne eller primær kræft i bughinden.

9 Referencer

1. Mosgaard BJ, Pedersen LK, Bjørn SF, Christiansen T, Markauskas A, Lund B, et al. Retningslinier for visitation, diagnostik, behandling og opfølgning af epitelial ovarie-, tuba- og primær peritonealcancer samt borderline tumorer. Kapitel 1: Introduktion. 2016;(5):1–9.
2. NORDCAN - Association of the Nordic Cancer Registries. Kræftstatistik: Nøgetal og figurer. 2017.
3. NORDCAN - Association of the Nordic Cancer Registries. Æggestok, æggeleder mv. 5-års aldersspecifik relativ overlevelse, diagnoseår 2012-2016. 2017.
4. Dansk Gynækologisk Cancer Database. Landsdækkende klinisk database for gynækologisk kræft. National Årsrapport 2017/2018 og 2018/2019. 2019.
5. NORDCAN - Association of the Nordic Cancer Registries. Æggestok, æggeleder mv. Alders-standardiseret relativ overlevelse (2012-2016), alder 0-89. 2017.
6. Bolton KL, Chenevix-Trench G, Goh C, Sadetzki S, Ramus SJ, Karlan BY, et al. Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer. JAMA. 2012;307(4):382–90.
7. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature. 2011;474(7353):609–15.
8. Zhang S, Royer R, Li S, McLaughlin JR, Rosen B, Risch HA, et al. Frequencies of BRCA1 and BRCA2 mutations among 1,342 unselected patients with invasive ovarian cancer. Gynecol Oncol. 2011;121(2):353–7.
9. Hoppe MM, Sundar R, Tan DSP, Jeyasekharan AD. Biomarkers for homologous recombination deficiency in cancer. J Natl Cancer Inst. 2018;110(7):704–13.
10. Huang Y. Association of BRCA1/2 mutations with ovarian cancer prognosis: An updated meta-analysis. Medicine (Baltimore). 2018;97(2):e9380.
11. Ray-Coquard I, Pautier P, Pignata S, Pérol D, González-Martín A, Berger R, et al. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. N Engl J Med. 2019;381(25):2416–28.
12. Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med. 2016;375(22):2154–64.
13. Pellegrino B, Mateo J, Serra V, Balmaña J. Controversies in oncology: are genomic tests quantifying homologous recombination repair deficiency (HRD) useful for treatment decision making? ESMO open. 2019;4(2):e000480.
14. Takaya H, Nakai H, Takamatsu S, Mandai M, Matsumura N. Homologous recombination deficiency status-based classification of high-grade serous ovarian carcinoma. Sci Rep. 2020;10(1):1–8.
15. Mirza MR, Åvall Lundqvist E, Birrer MJ, dePont Christensen R, Nyvang GB, Malander S, et al. Niraparib plus bevacizumab versus niraparib alone for platinum-sensitive recurrent ovarian cancer (NSGO-AVANOVA2/ENGOT-ov24): a randomised, phase 2, superiority trial. Lancet Oncol. 2019;20(10):1409–19.
16. Mirza MR, Coleman RL, González-Martín A, Moore KN, Colombo N, Ray-Coquard I, et al. The forefront of ovarian cancer therapy: update on PARP inhibitors. Ann Oncol. 2020;31(9):1148–59.
17. Charlotte Lautrup, Uffe Birk Jensen, Anders Bojesen, Mads Thomassen, Thomas van Overeem Hansen, Anne-Marie Gerdes, Jan Blaakær, Henrik Roed, Ulla Peen, Karina Dahl Steffensen, Bente Lund, Lotte Nedergaard Thomsen EH. Forslag til national guideline for genetisk udredning af

patienter med ovariecancer . 2018. 1-4 sider.

18. MYRIAD ONCOLOGY. MYRIAD myChoice CDx [internet]. [citeret 20. august 2020]. Tilgængelig fra: https://myriad-oncology.com/mychoice-cdx/

19. Coleman RL, Fleming GF, Brady MF, Swisher EM, Steffensen KD, Friedlander M, et al. Veliparib with first-line chemotherapy and as maintenance therapy in ovarian cancer. N Engl J Med. 2019;381(25):2403–15.

20. European Medicines Agency EMA. Zejula EPAR. 2017.

21. Medicinrådet. Medicinrådets behandlingsvejledning vedrørende lægemidler til BRCA-muteret kræft i æggestokkene, ægge-lederne eller primær kræft i bughinden. 2020.

22. European Medicines Agency E. Zejula SmPC. 2020.

23. O'Connor MJ. Targeting the DNA Damage Response in Cancer. Mol Cell. 2015;60(4):547–60.

24. Mosgaard BJ, Pedersen LK, Bjørn SF, Christiansen T, Markauskas A, Lund B, et al. Retningslinier for visitation, diagnostik, behandling og opfølgning af epitelial ovarie-, tuba- og primær peritonealcancer samt borderline tumorer. Kapitel 3: Kirurgisk behandling af epitheliale ovarietumorer. 2019;(6):1–19.

25. Mosgaard BJ, Pedersen LK, Bjørn SF, Christiansen T, Markauskas A, Lund B, et al. Retningslinier for visitation, diagnostik, behandling og opfølgning af epitelial ovarie-, tuba- og primær peritonealcancer samt borderline tumorer. Kapitel 5: Ikke-kirurgisk behandling af epiteliale tumorer. 2019;(6):1–36.

26. Hanker LC, Loibl S, Burchardi N, Pfisterer J, Meier W, Pujade-Lauraine E, et al. The impact of second to sixth line therapy on survival of relapsed ovarian cancer after primary taxane/platinum-based therapy. Ann Oncol. 2012;23(10):2605–12.

27. Zhong Q, Peng H-L, Zhao X, Zhang L, Hwang W-T. Effects of BRCA1- and BRCA2-related mutations on ovarian and breast cancer survival: a meta-analysis. Clin Cancer Res. 2015;21(1):211–20.

28. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228–47.

29. Paoletti X, Lewsley LA, Daniele G, Cook A, Yanaihara N, Tinker A, et al. Assessment of Progression-Free Survival as a Surrogate End Point of Overall Survival in First-Line Treatment of Ovarian Cancer: A Systematic Review and Meta-analysis. JAMA Netw open. 2020;3(1):e1918939.

30. Sjoquist KM, Lord SJ, Friedlander ML, John Simes R, Marschner IC, Lee CK. Progression-free survival as a surrogate endpoint for overall survival in modern ovarian cancer trials: a meta-analysis. Ther Adv Med Oncol. 2018;10(6):1758835918788500.

31. Moore K, Colombo N, Scambia G, Kim B-G, Oaknin A, Friedlander M, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med. 2018;379(26):2495–505.

32. National Institute of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. 2009.

33. Phippen NT, Secord AA, Wolf S, Samsa G, Davidson B, Abernethy AP, et al. Quality of life is significantly associated with survival in women with advanced epithelial ovarian cancer: An ancillary data analysis of the NRG Oncology/Gynecologic Oncology Group (GOG-0218) study. Gynecol

Oncol. 2017;147(1):98–103.

34. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365–76.

35. Greimel E, Bottomley A, Cull A, Waldenstrom A-C, Arraras J, Chauvenet L, et al. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-OV28) in assessing the quality of life of patients with ovarian cancer. Eur J Cancer. 2003;39(10):1402–8.

36. Basen-Engquist K, Bodurka-Bevers D, Fitzgerald MA, Webster K, Cella D, Hu S, et al. Reliability and validity of the functional assessment of cancer therapy-ovarian. J Clin Oncol. 2001;19(6):1809–17.

37. Beaumont J, Yount S, Lalla D, Lubeck D, Derynck M, Karlan B, et al. Validation of the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) Symptom Index (FOSI) in a phase II clinical trial of pertuzumab in patients with advanced ovarian cancer. J Clin Oncol. 2007;25(18_suppl):16021.

38. EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990;16(3):199–208.

39. González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2019;381(25):2391–402.

10 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende kræft i æggestokkene

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11 Versionslog

Version	**Dato**	***Ændring***
1.0	26.11.2020	Godkendt af Medicinrådet.