Medicinrådet

# Bilag til Medicinrådets anbefaling vedrørende olaparib til behandling af BRCA-muteret metastatisk kastrationsresistent prostatakræft-vers. 1.0

*Vers. 1.0*

# Bilagsoversigt

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Medicinrådet

# Medicinrådets sundheds-økonomiske afrapportering

# Olaparib

*BRCA1/2-muteret metastaserende kastrationsresistent prostatacancer*

Version 1.0

## Om Medicinrådet

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

## Dokumentets formål

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

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

| Dokumentoplysninger | |
|---|---|
| **Godkendelsesdato** | 15. december 2021 |
| **Dokumentnummer** | 130987 |
| **Versionsnummer** | 1.0 |



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# Indholdsfortegnelse

# 1. Begreber og forkortelser

| | |
|---|---|
| **AIP** | Apotekernes indkøbspris |
| **BSA** | Kropsoverfladeareal |
| **BSC** | *Best supportive care* |
| **CRPC** | Kastrationsresistent prostatakræft |
| **DKK** | Danske kroner |
| **DRG** | Diagnose Relaterede Grupper |
| **HR** | Hazard Ratio |
| **I.V.** | Intravenøst |
| **mCRPC** | Metastatisk kastrationsresistent prostatakræft |
| **NHA** | *New hormone agent*, nyt hormonmiddel |
| **PSA** | Prostataspecifikt antigen |
| **RDI** | Relativ dosisintensitet |
| **PFS** | Progressionsfri overlevelse |
| **SAIP** | Sygehusapotekernes indkøbspris |
| **SPC** | Produkters produktresuméer |
| **SRE** | Skeletrelaterede hændelser |
| **TTD** | Tid til behandlingsophør |

# 2. Konklusion

**Inkrementelle omkostninger og budgetkonsekvenser**

### Patienter, der er taxan-naive og vil modtage docetaxel

I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for olaparib ca. [redacted] DKK pr. patient sammenlignet med docetaxel. Når analysen er udført med apotekernes indkøbspris (AIP), er de inkrementelle omkostninger til sammenligning ca. 604.000 DKK pr. patient.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af olaparib som mulig standardbehandling vil være ca. [redacted] DKK i det femte år efter en anbefaling. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 26,1 mio. DKK i det femte år.

### Patienter, der tidligere har modtaget taxaner og vil modtage cabazitaxel

I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for olaparib ca. [redacted] DKK pr. patient sammenlignet med cabazitaxel. Når analysen er udført med AIP, er de inkrementelle omkostninger til sammenligning ca. 414.000 DKK pr. patient.

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

### Patienter, der ikke har andre behandlingsalternativer og vil modtage BSC

I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for olaparib ca. [redacted] DKK pr. patient sammenlignet med BSC. Når analysen er udført med AIP, er de inkrementelle omkostninger til sammenligning ca. 633.000 DKK pr. patient.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af olaparib som mulig standardbehandling vil være ca. [redacted] DKK i det femte år efter en anbefaling. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 5,2 mio. DKK i det femte år.

Der er stor usikkerhed vedr. testomkostningerne, fordi der på nuværende tidspunkt ikke testes rutinemæssigt for BRCA1/2-mutationer i mCRPC-patienter, og der ikke eksisterer en teststrategi. Det har stor betydning for analysens resultat, da de inkrementelle omkostninger i stor grad drives af testomkostningerne for olaparib.

# 3. Introduktion

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af olaparib som mulig standardbehandling på danske hospitaler til BRCA1/2-muteret metastatisk kastrationsresistent prostatakræft (mCRPC).

Analysen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra AstraZeneca. Medicinrådet modtog ansøgningen den 11. august 2021.

## 3.1 Patientpopulation

Prostatakræft er den hyppigste kræftform hos mænd i Danmark. Prostatakræft viser sig især efter 60-årsalderen [1]. Patienter med prostatakræft, der endnu ikke har modtaget ADT eller responderer på behandling med ADT, kaldes kastrationssensitive. De fleste kastrationssensitive prostatakræfttilfælde vil over tid udvikle sig til kastrationsresistente. Patienter med kastrationsresistent prostatakræft (CRPC) opdeles i to grupper i forhold til tilstedeværelse af metastaser. mCRPC defineres som prostatakræft med påviste metastaser involverende enten knogler, lymfeknuder uden for det lille bækken eller parenkymatøse organer. Fagudvalget vurderer, at maksimalt 5 % af patienter med mCRPC har mutationer i *breast cancer* (BRCA) 1- eller 2-genet. Tilstedeværelsen af BRCA1/2-mutationer hos patienter med mCRPC er forbundet med en dårlig prognose relativt til patienter uden BRCA-mutationer [2,3]. Fagudvalget vurderer, at ca. 1.500 patienter årligt diagnosticeres med mCRPC. Dermed forventer fagudvalget, at maksimalt ca. 75 patienter årligt vil have mCRPC med BRCA1/2-mutationer.

Yderligere information om sygdomsområdet kan findes i Medicinrådets vurderingsrapport.

### 3.1.1 Komparator

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

*Klinisk spørgsmål 1:*

Hvilken værdi har olaparib sammenlignet med docetaxel for patienter med BRCA1/2-muteret metastaserende kastrationsresistent prostatakræft, der er progredieret på enten enzalutamid eller abirateron?

*Klinisk spørgsmål 2:*

Hvilken værdi har olaparib sammenlignet med cabazitaxel for patienter med BRCA1/2-muteret metastaserende kastrationsresistent prostatakræft, der er progredieret efter behandling med enzalutamid eller abirateron samt docetaxel?

*Klinisk spørgsmål 3:*

Hvilken værdi har olaparib sammenlignet med *'best supportive care'* (BSC) for patienter med BRCA-muteret metastaserende kastrationsresistent prostatakræft, der ikke har andre behandlingsalternativer?

# 4. Vurdering af den sundhedsøkonomiske analyse

I sin ansøgning har ansøger indsendt en sundhedsøkonomisk analyse, der består af en omkostningsanalyse og en budgetkonsekvensanalyse. I omkostningsanalysen estimeres de inkrementelle omkostninger pr. patient for olaparib sammenlignet med hhv.:

- Docetaxel for patienter, der ikke har modtaget taxaner (docetaxel og/eller cabazitaxel).
- Cabazitaxel for patienter, der tidligere har modtaget docetaxel.
- BSC for patienter, der ikke har andre behandlingsalternativer.

Medicinrådet vurderer nedenfor den sundhedsøkonomiske analyse, som ansøger har indsendt.

## 4.1 Antagelser og forudsætninger for modellen

I fraværet af *head-to-head*-sammenligninger mellem olaparib og dets komparatorer, vælger ansøger at foretage en systematisk litteratursøgning for at identificere relevante studier, der kan anvendes i en indirekte sammenligning.

### Patienter, der er taxan-naive og vil modtage docetaxel

Sammenligningen mellem olaparib og docetaxel er lavet på baggrund af en indirekte sammenligning mellem studierne PROfound [4] og Swami [5]. PROfound er et randomiseret fase III-studie, der undersøger effekten af olaparib overfor et nyt hormonmiddel (NHA; enzalutamid og abirateron), mens Swami er et *real-world evidence*-studie, der undersøger effekten af docetaxel sammenlignet med NHA i patienter med metastatisk prostatakræft, der tidligere har været behandlet med NHA. Ansøger argumenterer for, at Swami-data betragtes som det bedst tilgængelige observationelle data til at informere om effektivitet af docetaxel sammenlignet med NHA. Ansøger vælger at opdele patientpopulationen fra PROfound-studiet i mindre subpopulationer og undersøger effekten af olaparib overfor docetaxel i patienter, der er taxan-naive, som Swami-studiet undersøger.

I sin indirekte analyse bruger ansøger NHA, som komparator for interventioner (olaparib og docetaxel), fordi NHA er en fælles komparator fra PROfound- og Swami-studiet. Ansøger finder den relative effekt fra Swami-studiet og anvender hazard ratio (HR)

direkte på time-to-event data for NHA-armen fra PROfound-studiet til at estimere effekten af docetaxel.

Patienter, der tidligere har modtaget taxaner og vil modtage cabazitaxel

Sammenligningen mellem olaparib og cabazitaxel er lavet på baggrund af en indirekte sammenligning mellem studierne PROfound og CARD [6]. CARD er et randomiseret fase III-studie, der undersøger effekten af cabazitaxel overfor NHA i patienter med mCRPC, der tidligere har modtaget behandling med docetaxel og en NHA. Ansøger vælger også at opdele patientpopulationen fra PROfound-studiet og undersøge effekten af olaparib overfor cabazitaxel i subpopulationen, der er taxan-behandlede.

I sin indirekte analyse bruger ansøger NHA, som komparator for interventioner (olaparib og cabazitaxel), fordi NHA er en fælles komparator fra PROfound- og CARD-studiet. Ansøger finder den relative effekt fra CARD-studiet og anvender HR direkte på *time-to-event* data for NHA-armen fra PROfound-studiet til at estimere effekten af cabazitaxel.

Patienter, der ikke har andre behandlingsalternativer og vil modtage BSC

Sammenligningen mellem olaparib og BSC er lavet på baggrund af data fra PROfound-studiet. I mangel på bedre data antager ansøger, at data fra NHA-armen kan anvendes som proxy for BSC til at modellere samlet overlevelse (OS) og progression. Ansøger argumenterer, at det er et konservativt valg, da genbehandling med NHA kan forventes at have en højere effektivitet end behandling med BSC. Ansøger pointerer også, at det potentielt kan overestimere omkostningerne for BSC. I denne sammenligning har ansøger valgt at anvende den fulde populationen fra PROfound-studiet med BRCA1/2-mutationer, hvor der indgår patienter, der både er taxan-naive og taxan-behandlede.

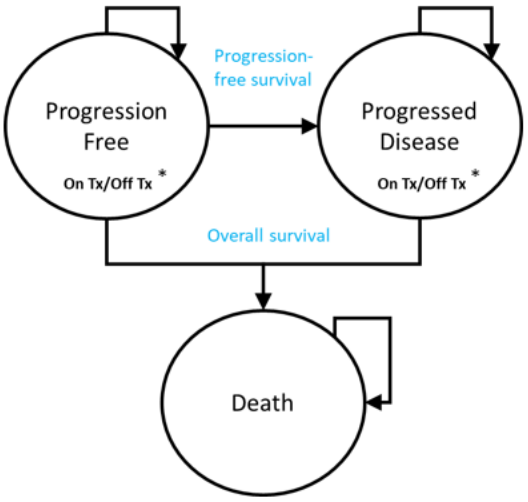
### 4.1.1 Modelbeskrivelse

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

Modellen indeholder en række sygdomsstadier, som patienterne skifter mellem i takt med sygdomsprogression. Ansøgers model består af tre stadier: progressionsfri overlevelse, post-progression og stadiet død. Se Figur 1 for de forskellige sygdomsstadier, og hvordan patienten kan bevæge sig mellem dem.

Alle patienter starter i sygdomsstadiet progressionsfri overlevelse, hvorfra deres bevægelse gennem modellen bestemmes ud fra ekstrapoleret time-to-event-data. Patientens tid i stadiet progressionsfri overlevelse bestemmes ud fra progressionsfri overlevelses (PFS)-data fra PROfound-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 fra PROfound-studiet som den andel af patienter, der hverken er i progressionsfri overlevelse eller død. Fra post-progression kan patienten udelukkende bevæge sig til stadiet død. Andelen af patienter i stadiet død bliver estimeret ud fra OS-data fra PROfound-studiet.

Modellen har en cykluslængde på 30,44 dage, hvilket, ansøger argumenterer, er passende, da det vil opfange forskelle i omkostninger mellem modellens cykler. Ansøger har anvendt *half-cycle correction* i modellen.




**Figur 1. Beskrivelse af modelstrukturen i omkostningsanalysen**

**Medicinrådets vurdering af ansøgers model**

Medicinrådet vurderer, at der er betydelig usikkerhed ved de anvendte studier i ansøgers analyse, da disse er baseret på en indirekte sammenligning af studier. Medicinrådet accepterer dog ansøgers tilgang, da kvantitative estimater er nødvendige i sundhedsøkonomiske analyser, og fordi fagudvalget, jf. vurderingsrapporten, finder at olaparib er en lovende behandling, selvom datagrundlaget er for usikkert till at fastlægge, om der er en bedre effekt end docetaxel, cabazitaxel og BSC.

*Medicinrådet accepterer ansøgers tilgang vedr. ansøgers model.*

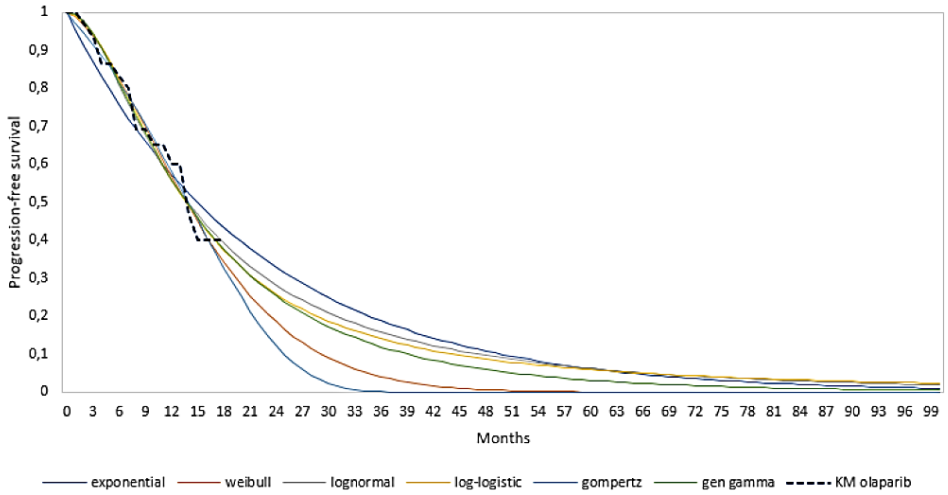
### 4.1.2 Modelantagelser og -beskrivelse

Sammenligning med docetaxel

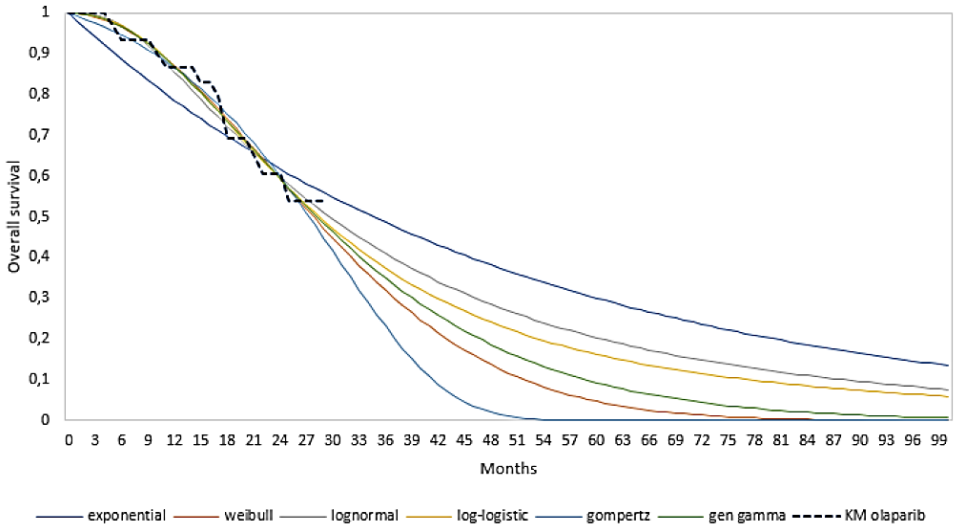
Ansøger modellerer tiden i de forskellige stadier ved at anvende ekstrapolerede Kaplan-Meier (KM)-data for PFS og OS. Dette er nødvendigt, da opfølgningen i PROfound-studiet er kortere end den anvendte tidshorisont.

Ansøger har anvendt den parametriske funktion Gompertz til at ekstrapolere PFS for olaparib for taxan-naive patienter, se Figur 2. For OS har ansøger valgt at ekstrapolere data med den parametriske funktion Weibull for olaparib, se Figur 3. Disse parametriske funktioner er valgt, da de, jf. AIC- og BIC-værdierne, har det bedste statistiske fit. For docetaxel anvender ansøger de samme parametriske funktioner til at ekstrapolere data for PFS og OS, men anvender derudover en HR på 1,0 overfor NHA armen til at genere data for PFS og en hazard ratio på 1,29 overfor NHA armen til at genere data for OS for docetaxel som kan ses i Figur 4 og Figur 5.

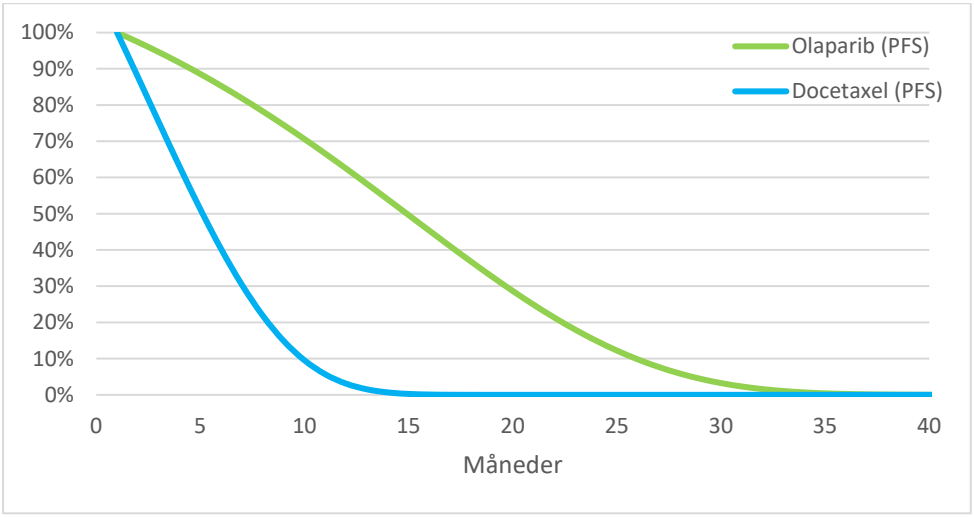
Ansøger antager, at behandlingsvarigheden for olaparib er lig tid til progression, mens docetaxel behandles i op til 10 cykler, hvis ikke patienterne er progredieret inden. Ansøger argumenterer for, at dette stemmer overens med dansk klinisk praksis, da progression er et udtryk for, at behandlingen ikke virker, og man vil derfor skifte patienten til en anden behandling som følge af progression.



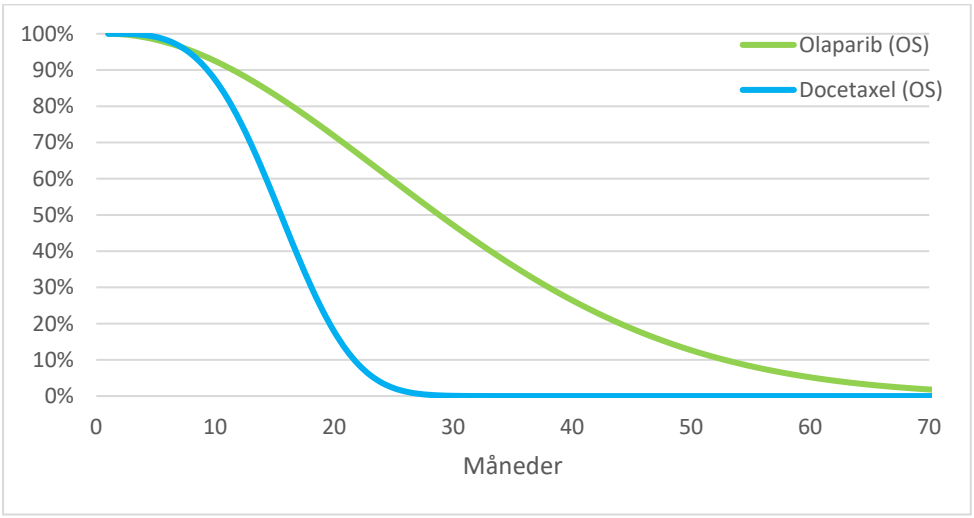

**Figur 2. PFS for olaparib for patienter, der er taxan-naive**




**Figur 3. OS for olaparib for patienter, der er taxan-naive**




**Figur 4. PFS for docetaxel for patienter, der er taxan-naive**

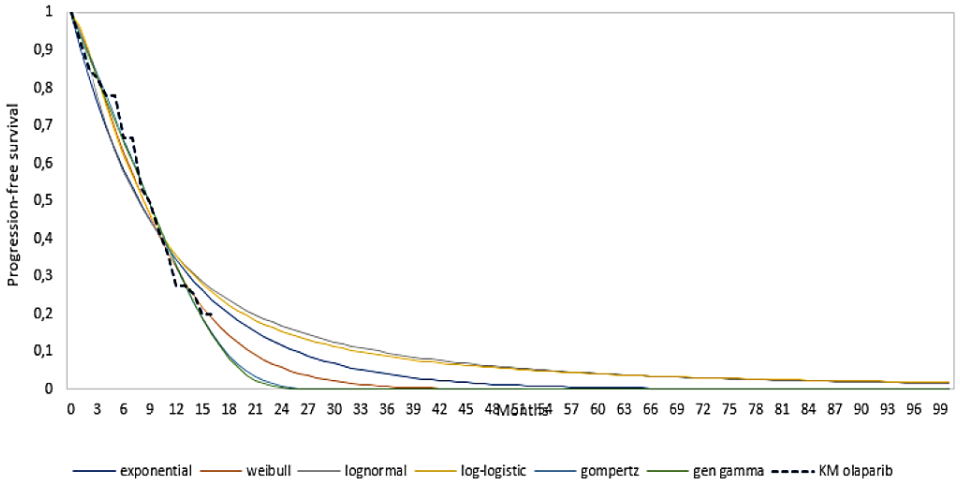



**Figur 5. OS for docetaxel for patienter, der er taxan-naive**

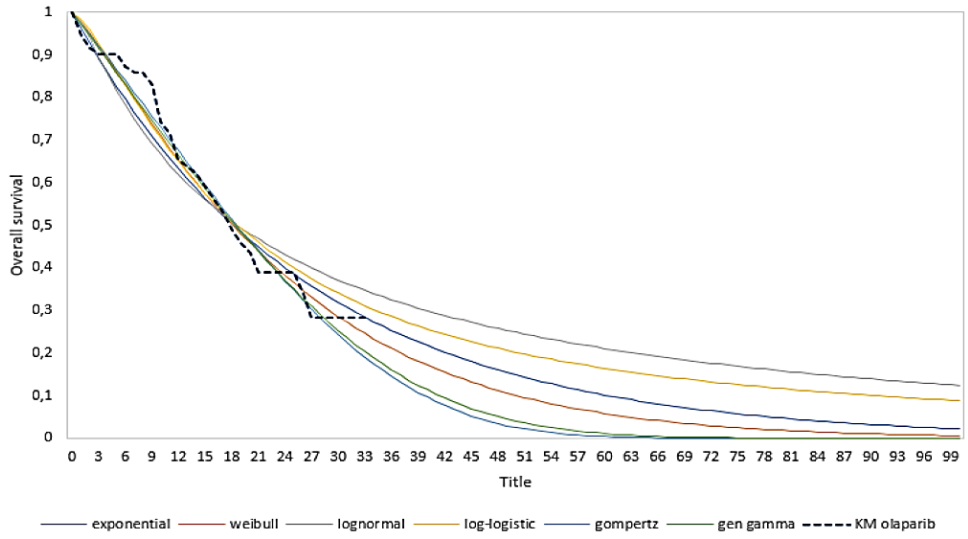
### Sammenligning med cabazitaxel

Ansøger har anvendt den parametriske funktion Gompertz til at ekstrapolere PFS for olaparib for taxan-behandlede patienter, se Figur 4. For OS har ansøger valgt at ekstrapolere data med den parametriske funktion Weibull for olaparib, se Figur 5. Disse parametriske funktioner er valgt, da de, jf. AIC- og BIC-værdierne, har det bedste statistiske fit. For cabazitaxel anvender ansøger de samme parametriske funktioner til at ekstrapolere data for PFS og OS, men anvender derudover en HR på 0,54 overfor NHA armen til at genere data for PFS og en hazard ratio på 0,64 overfor NHA armen til at genere data for OS for docetaxel som kan ses i Figur 8 og Figur 9.

Ansøger antager, at behandlingsvarigheden for olaparib er lig tid til progression, mens cabazitaxel behandles i op til 8 cykler, hvis ikke patienterne er progredieret inden.

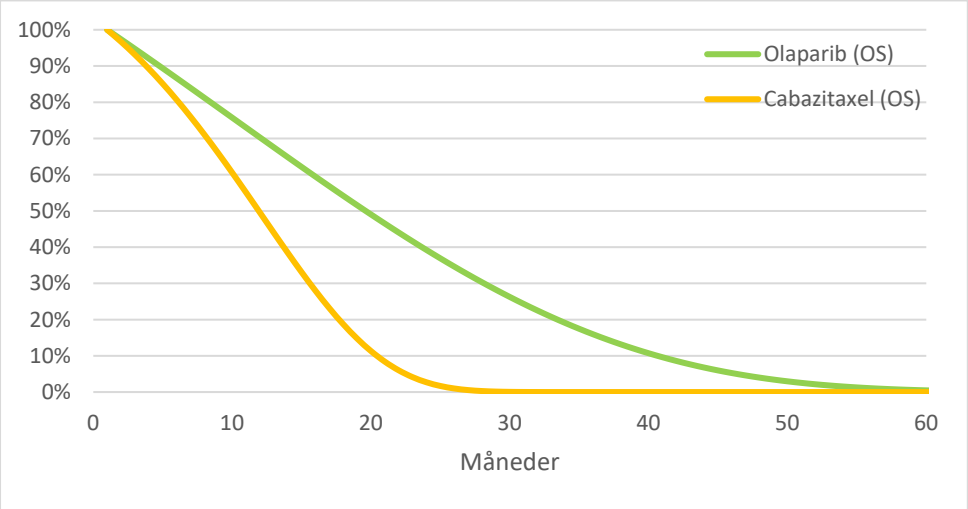



**Figur 6. PFS olaparib for patienter, der er taxan-behandlede**




**Figur 7. OS for olaparib for patienter, der er taxan-behandlede**


**Figur 8. PFS cabazitaxel for patienter, der er taxan-behandlede**

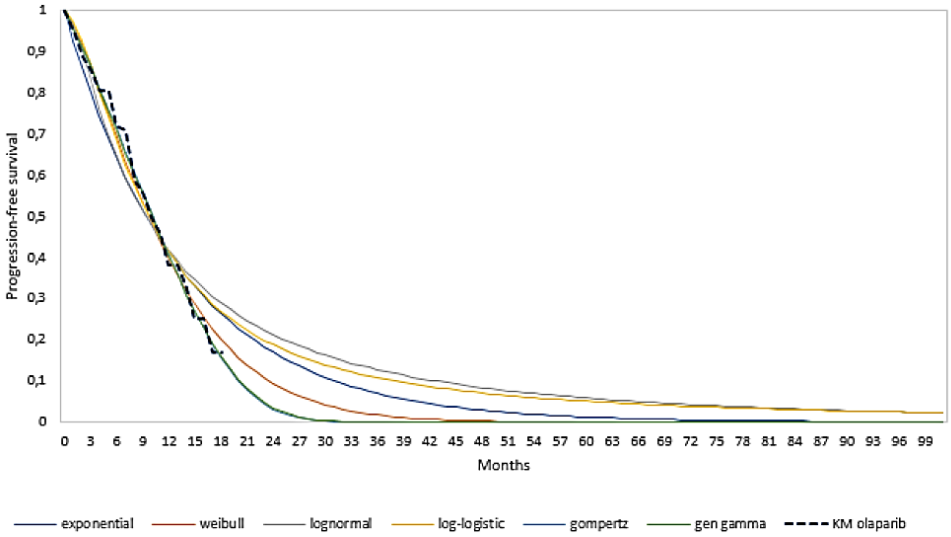



**Figur 9. OS for cabazitaxel for patienter, der er taxan-behandlede**

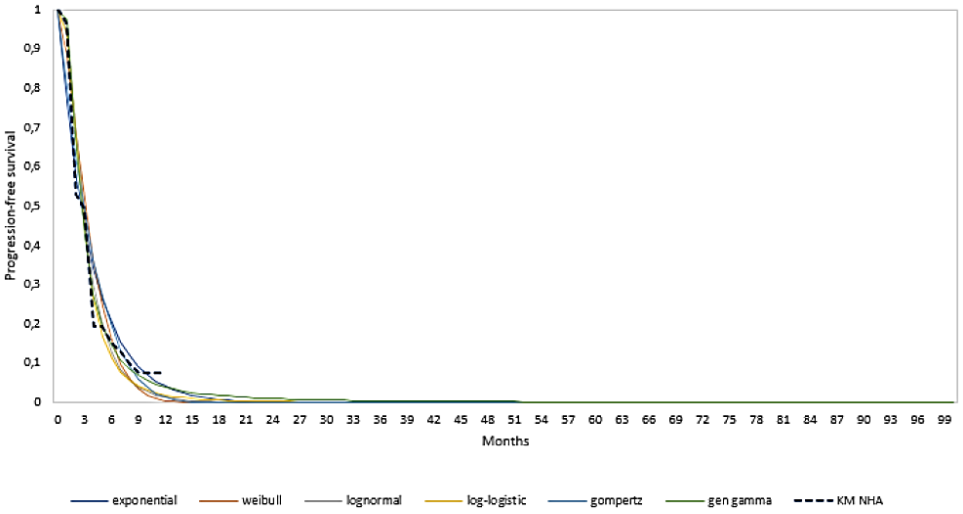
### Sammenligning med BSC

Ansøger har anvendt den parametriske funktion Gompertz til at ekstrapolere PFS for både olaparib og BSC for både taxan-naive og taxan-behandlede patienter, se Figur 6 og Figur 7. For OS har ansøger valgt at ekstrapolere data med den parametriske funktion Weibull for både olaparib og BSC, se Figur 8 og Figur 9. Disse parametriske funktioner er valgt, da de, jf. AIC- og BIC-værdierne, har det bedste statistiske fit.

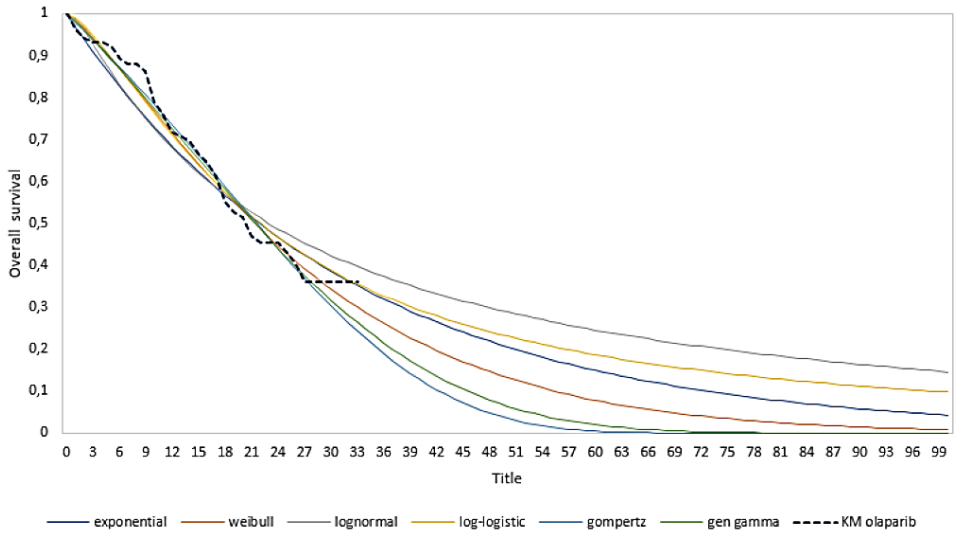
Ansøger antager, at behandlingsvarigheden for olaparib og BSC er lig tid til progression.



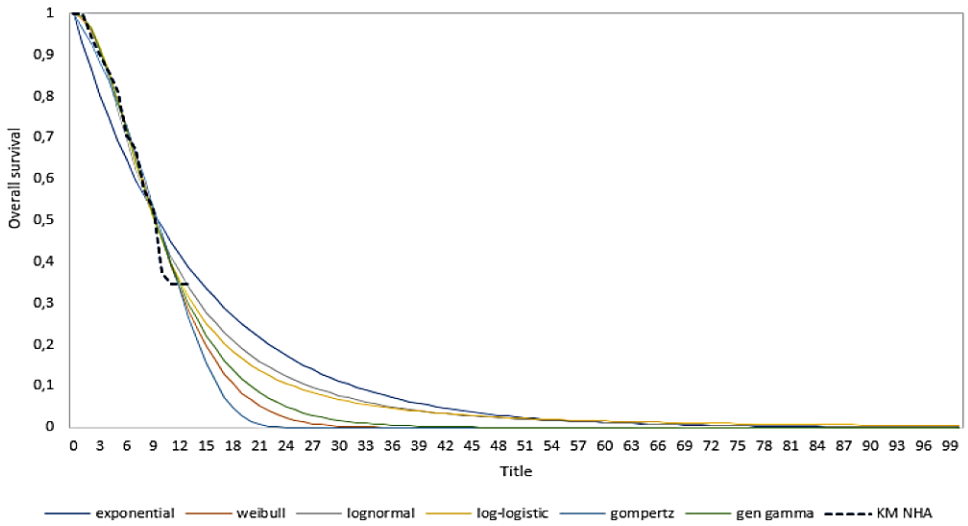

**Figur 10. PFS for olaparib for patienter, der er både er taxan-naive og taxan-behandlede**




**Figur 11. PFS for BSC for patienter, der er både er taxan-naive og taxan-behandlede**




**Figur 12. OS for olaparib for patienter, der er både er taxan-naive og taxan-behandlede**




**Figur 13. OS for BSC for patienter, der er både er taxan-naive og taxan-behandlede**

**Medicinrådets vurdering af ansøgers modelantagelser**

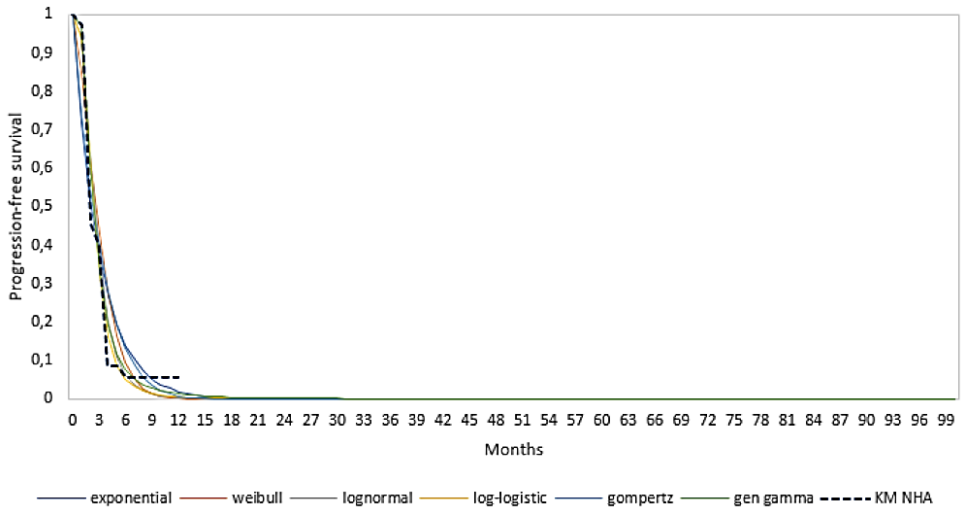
Jf. vurderingsrapporten vurderer fagudvalget, at det ikke er muligt at vurdere om der er forskel i effekt og bivirkninger mellem olaparib, docetaxel og cabazitaxel på baggrund af data. Dog mener fagudvalget, at data peger i retning af at olaparib kunne have en bedre effekt end komparatorerne. Derfor vælger Medicinrådet at præsentere en hovedanalyse, hvor der antages en effekt af olaparib overfor hhv. docetaxel og cabazitaxel. Medicinrådet vælger derudover at udarbejde to følsomhedsanalyser, der undersøger scenarierne, hvor der ikke antages at være forskel i effekt mellem olaparib og hhv. docetaxel og cabazitaxel. I de to følsomhedsanalyser antages effekten, tiden i de forskellige sygdomsstadier og bevægelse gennem modellen at være ens for både

olaparib, docetaxel og cabazitaxel. PFS- og OS-data fra olaparib-armen i PROfound-studiet anvendes til at modellere patienternes bevægelse gennem modellen.

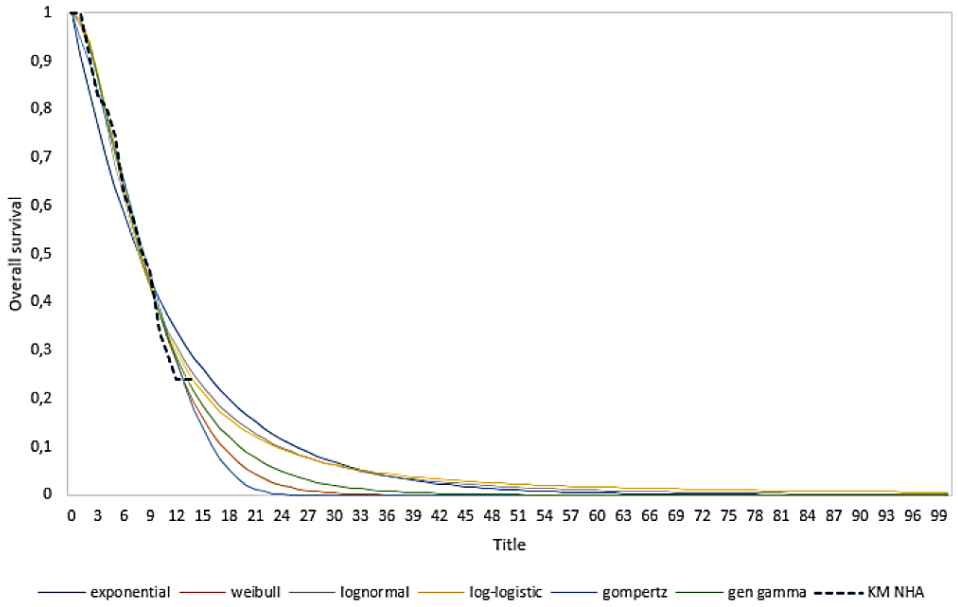
For sammenligning med docetaxel accepterer Medicinrådet ansøgers valg af parametrisk funktion for PFS, hvorimod fagudvalget vurderer, at OS for docetaxel estimeres kortere i modellen, end hvad de oplever i dansk klinisk praksis. Derfor vælger Medicinrådet at ændre HR for docetaxel overfor NHA, så den gennemsnitlige overlevelse stiger fra 8,9 måneder til 15 måneder. For sammenligning med cabazitaxel accepterer Medicinrådet ansøgers valg af parametrisk funktion for PFS og OS.

For sammenligning med BSC accepterer Medicinrådet anvendelsen af data for NHA som proxy for modellering af effekten af BSC. Dog vurderer fagudvalget, at ansøgers valg af subpopulation, som både inkluderer taxan-naive og taxan-behandlede patienter, ikke repræsenterer den efterspurgte patientpopulation i protokollen. Fagudvalget vurderer derimod, at subpopulation, der kun inkluderer taxan-behandlede patienter, bedre afspejler den efterspurgte population i protokollen. Denne subpopulation er ligeledes anvendt i sammenligningen med cabazitaxel. Medicinrådet vælger derfor at anvende data fra taxan-behandlede patienter til sammenligningen med BSC i Medicinrådets hovedanalyse.

Ansøger har anvendt den parametriske funktion Gompertz til at ekstrapolere PFS for både olaparib og BSC for taxan-behandlede patienter, se Figur 6 og Figur 14. Fagudvalget finder ansøgers ekstrapolering af PFS for olaparib og BSC acceptable. For OS har ansøger valgt at ekstrapolere data med den parametriske funktion Weibull for både olaparib og BSC, se Figur 7 og Figur 15. Fagudvalget vurderer, at ansøgers valgte parametriske funktioner overestimerer den gennemsnitlige overlevelse for både olaparib og BSC, når det drejer sig om patienter, som er progredieret på både docetaxel og cabazitaxel. I stedet vurderer fagudvalget, at Gompertz-funktionen i større grad repræsenterer den gennemsnitlige overlevelse, hvorfor Medicinrådet anvender denne i egen hovedanalyse. Derfor ændres OS for olaparib fra 27,0 måneder til 20,9 måneder, mens OS for BSC ændres fra 10,6 måneder til 9,2 måneder. Ydermere ændres PFS for olaparib fra 11,2 måneder til 9,9 måneder, mens PFS for BSC ændres fra 4,1 måneder til 3,5 måneder. Dette ændrer behandlingslængden for olaparib og vurderes at have mindre betydning for analysens resultat.




**Figur 14. PFS for BSC for patienter, der er taxan-behandlede**




**Figur 15. OS for BSC for patienter, der er taxan-behandlede**

Estimaterne for PFS, OS og behandlingsvarighederne for hver sammenligning er præsenteret i Tabel 1.

**Tabel 1. Gennemsnitlig tid i behandling, tid til progression og samlet overlevelse**

| Behandling | Behandlingsvarighed [måneder] | PFS [måneder] | OS [måneder] |
|---|---|---|---|
| **Sammenligning med docetaxel** | | | |
| Olaparib | 14,7 | 14,7 | 30,3 |
| Docetaxel | 5,1 | 5,1 | 15,0 |

| Behandling | Behandlingsvarighed [måneder] | PFS [måneder] | OS [måneder] |
|---|---|---|---|
| **Sammenligning med cabazitaxel** | | | |
| Olaparib | 9,9 | 9,9 | 23,9 |
| Cabazitaxel | 5,5 | 5,5 | 12,6 |
| **Sammenligning med BSC** | | | |
| Olaparib | 9,9 | 9,9 | 20,9 |
| BSC | 3,5 | 3,5 | 9,2 |

*Progressionsfri overlevelse (PFS), samlet overlevelse (OS).

*Medicinrådet accepterer ansøgers antagelser, men udarbejder to følsomhedsanalyser, der undersøger ens effekt af olaparib overfor docetaxel og cabazitaxel. Medicinrådet ændrer subpopulationen for sammenligningen med BSC og ændrer valg af ekstrapolation for OS for både olaparib og BSC.*

### 4.1.3 Analyseperspektiv

I overensstemmelse med Medicinrådets metoder har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en tidshorisont på 10 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.

Dette er valgt, da ansøger argumenterer for, at den gennemsnitlige behandlingslængde (af både 1. og 2. linjebehandling) ligger inden for denne tidshorisont. Det betyder ikke, at patienterne modtager behandling med olaparib i hele tidshorisonten, men at analysen opfanger alle direkte og afledte økonomiske forskelle mellem olaparib og komparatorer set over en tidshorisont på 10 år.

*Medicinrådet accepterer ansøgers valg vedr. analyseperspektiv.*

## 4.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af olaparib sammenlignet med hhv. docetaxel, cabazitaxel og BSC. Ansøger har inkluderet lægemiddelomkostninger, hospitalsomkostninger og patientomkostninger.

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

### 4.2.1 Lægemiddelomkostninger

Ansøger har, jf. *Metodevejledning for omkostningsanalyser af nye lægemidler og indikationer i hospitalssektoren,* estimeret lægemiddelomkostninger på baggrund af apotekernes indkøbspris (AIP). Doser anvendt i ansøgers analyse er hentet i de respektive produktresuméer (SPC'er).

Den anbefalede dosis af olaparib er 300 mg oralt to gange dagligt. Hertil anvender ansøger en relativ dosisintensitet (RDI) på 91,5 % for olaparib fra PROfound-studiet svarende til en gennemsnitlig daglig dosis på 549 mg.

Den anbefalede dosis af docetaxel er 75 mg/$m^2$ i.v. i kombination med 10 mg prednisolon hver 3. uge op til 10 serier.

Den anbefalede dosis af cabazitaxel er 20 mg/$m^2$ i.v. i kombination med 10 mg prednisolon hver 3. uge, jf. vurderingsrapporten.

Ansøger antager, at BSC består af en række forskellige lægemidler:

- Morfin, der administreres oralt hver 12. time dagligt á 10 mg.
- Denosumab, der administreres subkutant én gang hver 4. uge á 120 mg.
- Domperidon, der administreres oralt tre gange dagligt á 30 mg.
- Ondansetron administreres 1-2 timer før kemobehandling á 16 mg og derefter en gang dagligt á 16 mg i højst 5 dage.
- Prednisolon, der administreres oralt en gang dagligt á 25 mg.

Ansøger antager, at alle patienter sideløbende vil blive co-medicineret med et eller flere af følgende lægemidler:

- Zoledronsyre, der administreres intravenøst hver 3,5 uge á 4 mg.
- Antihistamin, der administreres oralt én gang dagligt á 25 mg.
- Esomeprazole, der administreres oralt én gang dagligt á 20 mg.
- Dexamethasone, der administreres oralt én gang dagligt á 8 mg.
- Ondansetron, der administreres per oralt á 8 mg 1-2 timer før kemoterapi eller radiografi efterfulgt á 8 mg 12 timer senere i 5 dage.
- Filgrastim, der administreres intravenøst op til fem gange hver tredje uge á 5 mikrogram (0,5 ME)/kg/døgn.

Ansøger antager, at fordelingen af patienter, der modtager co-medicinering, varierer alt efter, hvilken behandling patienterne modtager.

Ved lægemidler doseret efter kropsvægt og kropsoverfladeareal (BSA) anvender ansøger en gennemsnitlig vægt på 80 kg fra PROfound-studiet og en gennemsnitlig BSA på 1,91 m2 fra Sacco et. al [7].

**Medicinrådets vurdering af ansøgers antagelser vedr. lægemiddelomkostninger**
Medicinrådet accepterer ansøgers antagelse vedr. RDI for olaparib. Fagudvalget er opmærksom på, at ansøger ikke har inkluderet præ-medicinering forbundet med administrering af cabazitaxel og docetaxel, hvorfor Medicinrådet vælger at inkludere dette. For patienter, der modtager docetaxel, vil patienterne præ-medicineres med 50 mg prednisolon fem gange oralt ifm. kemoterapi. For patienter, der modtager cabazitaxel, vil patienterne præ-medicineres med 40 mg methylprednisolon i.v. og 2 mg clemastin i.v. en gang før administrering med cabazitaxel. Denne ændring vurderes at have lille betydning for analysens resultat.

Medicinrådet har udskiftet AIP med sygehusapotekernes indkøbspris (SAIP), se Tabel 2 for olaparib, docetaxel, cabazitaxel, prednisolon, methylprednisolon og clemastin.

**Tabel 2. Anvendte lægemiddelpriser, SAIP (september 2021)**

| Lægemiddel | Styrke | Pakkings-størrelse | Pris [DKK] | Betingede pris* [DKK] | Kilde |
|---|---|---|---|---|---|
| Olaparib | 300 mg | 56 stk. | [redacted] | [redacted] | Amgros |
| Docetaxel | 20 mg/ml | 1 ml | [redacted] | | Amgros |
| Cabazitaxel | 60 mg/1,5 ml | 1,5 ml | [redacted] | | Amgros |
| Prednisolon | 5 mg | 100 stk. | [redacted] | | Amgros |
| Methylprednisolon | 40 mg/ ml | 1 ml | [redacted] | | Amgros |
| Clemastin | 1 mg/ml | 10 ml | [redacted] | | Amgros |

*AstraZeneca har tilbudt en pris betinget af at olaparib bliver anbefalet til én af de tre kliniske spørgsmål.

Fagudvalget vurderer, at ansøgers antagelse vedr. BSC ikke repræsenterer dansk klinisk praksis. Fagudvalget forklarer, at BSC daglig består af 10 mg prednisolon eller 0,5 mg dexamethason, 10 mg morfin og månedlig administrering af 120 mg denosumab. Denne ændring vurderes at have lille betydning for analysens resultat. Medicinrådet ændrer derfor lægemidlerne for BSC og udskifter AIP med SAIP i Medicinrådets hovedanalyse, se Tabel 3.

**Tabel 3. Anvendte lægemiddelpriser for BSC, SAIP (september 2021)**

| Lægemiddel | Styrke | Pakkings-størrelse | Pris [DKK] | Kilde |
|---|---|---|---|---|
| Contalgin | 10 mg | 100 stk. | [redacted] | Amgros |
| Denosumab | 120 mg/1,7 ml | 1,7 ml. | [redacted] | Amgros |
| Prednisolon | 25 mg | 10 stk. | [redacted] | Amgros |
| Dexamethason | 1 mg | 100 stk. | [redacted] | Amgros |

Fagudvalget vurderer, at ansøgers antagelse vedr. lægemidler, der indgår i co-medicinering, ligeledes ikke repræsenterer dansk klinisk praksis. Fagudvalget forklarer, at følgende lægemidler indgår i co-medicinering: 120 mg denosumab, der administreres subkutant hver 4. uge, 10 mg prednisolon, der administreres oralt én gang dagligt, 25 mg antihistamin, der administreres oralt én gang dagligt og 10 mg domperidon, der administreres oralt tre gange dagligt. Denne ændring vurderes at have lille betydning for analysens resultat. Medicinrådet ændrer derfor, hvilke lægemidler der indgår i co-medicinering, se Tabel 4. Medicinrådet ændrer også fordelingen af lægemidler for co-medicinering, se Tabel 5 .

**Tabel 4. Anvendte lægemiddelpriser for co-medicinering, SAIP (september 2021)**

| Lægemiddel | Styrke | Pakningsstørrelse | Pris [DKK] | Kilde |
|---|---|---|---|---|
| Antihistamin | 25 mg | 100 stk. | [redacted] | Amgros |
| Denosumab | 120 mg | 1 stk. | [redacted] | Amgros |
| Domperidon | 10 mg | 30 stk. | [redacted] | Amgros |
| Prednisolon | 5 mg | 100 stk. | [redacted] | Amgros |

**Tabel 5. Fordeling af lægemidler til co-medicinering**

| Lægemiddel | Olaparib | BSC | Cabazitaxel | Docetaxel |
|---|---|---|---|---|
| Antihistamin | 65 % | 0 % | 100 % | 100 % |
| Denosumab | 10 % | 0 % | 0 % | 0 % |
| Domperidon | 10 % | 0 % | 100 % | 5 % |
| Prednisolon | 100 % | 5 % | 100 % | 100 % |

*Medicinrådet accepterer ansøgers valg vedr. lægemiddelomkostninger og RDI, men ændrer ansøgers antagelse vedr. lægemidler, der indgår i BSC og co-medicinering, samt ændrer fordelingen for co-medicinering. Medicinrådet tilføjer omkostninger forbundet med præmedicinering for docetaxel og cabazitaxel i Medicinrådets hovedanalyse.*

### 4.2.2 Hospitalsomkostninger

Til beregning af hospitalsomkostningerne har ansøger inkluderet omkostninger forbundet til administration, monitorering, bivirkninger, testomkostninger og terminale omkostninger.

#### Administrationsomkostninger

Ansøger inkluderer administrationsomkostninger forbundet med administreringen af cabazitaxel og docetaxel, der administreres i.v. Som enhedsomkostning for

administration af i.v.-behandling anvender ansøger DRG-taksten 12MA98 (MDC12 1-dagsgruppe, pat. mindst 7 år, DRG-takster 2021), svarende til 1681 kr.

Ansøger inkluderer ikke administrationsomkostninger for olaparib, fordi det administreres oralt. Ydermere, vælger ansøger ikke at inkludere administrationsomkostninger for hverken BSC eller co-medicinering, fordi de fleste lægemidler administreres oralt eller gives i forbindelse med de initierende behandlinger.

**Medicinrådets vurdering af ansøgers antagelser vedr. administrationsomkostninger**
Medicinrådet accepterer ansøgers tilgang til estimering af administrationsomkostninger. Dog har fagudvalget vurderet, at patienter, der modtager cabazitaxel, også vil modtage præmedicinering med methylprednisolon og clemastin, der administreres i.v. Derfor tillægger Medicinrådet et ekstra administrationsbesøg for patienter, der modtager cabazitaxel, i forbindelse med administrering af præ-medicinering. Denne ændring vurderes at have minimal betydning for analysens resultat.

Anvendte enhedsomkostninger kan ses i Tabel 6.

**Tabel 6. Omkostninger til lægemiddeladministration**

| | Enhedsomkostning [DKK] | Kilde |
|---|---|---|
| Ambulant besøg - konsultation | 1.681 | 12MA98 - DRG-2021 |

*Medicinrådet accepterer ansøgers tilgang vedr. administrationsomkostninger, men inkluderer et ekstra administrationsbesøg i forbindelse med præ-medicinering af cabazitaxel.*

### Monitoreringsomkostning

Ansøger inkluderer monitoreringsomkostninger i form af 2021 DRG-takster samt omkostninger til Rigshospitalets Labportal. Ansøger antager, at ressourceforbruget af hospitalsydelser ikke er afhængigt af, hvilken behandlingslinje patienten modtager (hhv. 1.- eller 2. linjebehandling), men udelukkende varierer, afhængigt af om patienten modtager aktiv behandling eller ej.

Ansøger inkluderer omkostninger til monitorering af patienterne, der modtager aktiv og inaktiv behandling og differentierer mellem monitorering i hhv. de første 3 måneder og fra 4. måned. I monitoreringsomkostningerne har ansøger inkluderet kontrolbesøg i form af ambulante besøg, et besøg hos en specialiseret sygeplejerske, CT-scanning, blodprøver og test for prostataspecifikt antigen (PSA).

**Medicinrådets vurdering af ansøgers antagelser vedr. monitoreringsomkostninger**
Idet ansøger anvender DRG-takster til at estimere omkostninger til monitorering, vælger Medicinrådet at ekskludere omkostninger til blodprøver og PSA-test, da de vil være inkluderet i DRG-taksten anvendt som enhedsomkostning for et ambulant besøg i forbindelse med monitorering. Denne ændring er gældende for patienter i både aktiv og inaktiv behandling og vurderes at have minimal betydning for analysens resultat. Medicinrådet vælger også at ekskludere specialiseret sygeplejebesøg, da fagudvalget vurderer, at det normalt indgår i det ambulante besøg. Denne ændring er gældende for

patienter i både aktiv og inaktiv behandling og vurderes at have minimal betydning for analysens resultat.

Derudover vurderer Medicinrådet, at ansøgers antagelse om forskellige monitoreringsfrekvenser i hhv. de første 3 måneder og fra 4. måned ikke afspejler dansk klinisk praksis, hvorfor Medicinrådet ændrer monitoreringsfrekvensen for ambulant besøg og CT-scanning. Denne ændring vurderes at have lille betydning for analysens resultat. Medicinrådet accepterer ansøgers valg af DRG-takster til at estimere omkostninger til ambulant besøg og CT-scanning.

Fagudvalget er opmærksom på, at ansøger ikke har inkluderet knoglescanning, som patienterne får foretaget i forbindelse med monitorering af deres sygdom. Medicinrådet vælger derfor at inkludere dette hver 3. måned i Medicinrådets analyse og anvender DRG-taksten 30PR17 (Røntgenundersøgelse (alm), kompliceret), svarende til 744 kr.

Anvendte ressourceforbrug for patienter i aktiv behandling og patienter i inaktiv behandling kan ses i hhv. Tabel 7 og Tabel 8, og enhedsomkostningerne kan ses i Tabel 9.

**Tabel 7. Ressourceforbrug for monitorering ved aktiv behandling**

| Ressource | Olaparib | BSC | Cabazitaxel/docetaxel |
|---|---|---|---|
| Ambulant besøg | Hver 4. uge | Hver 6. måned | Hver 3. uge |
| CT-scanning | Hver 3. måned | - | Hver 3. måned |
| Knoglescanning | Hver 3. måned | - | Hver 3. måned |

**Tabel 8. Ressourceforbrug for monitorering ved inaktiv behandling**

| Ressource | Olaparib/cabazitaxel/docetaxel | BSC |
|---|---|---|
| Ambulant besøg | Hver 3. måned | Hver 6. måned |
| CT-scanning | Hver 3. måned | - |
| Knoglescanning | Hver 3. måned | - |

**Tabel 9. Enhedsomkostninger til monitorering**

| Ressource | Enhedsomkostning | Kilde |
|---|---|---|
| Ambulant besøg | 1.681 | 12MA98 – DRG-2021 |
| CT-scanning | 2.007 | 30PR06 - DRG-2021 |
| Knoglescanning | 744 | 30PR17 – DRG – 2021 |

*Medicinrådet ekskluderer omkostninger til specialiseret sygeplejebesøg, blodtest og PSA-test samt ændrer på monitoreringsfrekvensen for patienter i aktiv og inaktiv behandling.*

*Medicinrådet tilføjer knoglescanning hver 3. måned og accepterer ansøgers tilgang vedr. valg af DRG-takster.*

### Bivirkningsomkostninger

Ansøger har inkluderet omkostninger forbundet med bivirkninger ved behandlingsstart og begrunder det med, at bivirkninger forekommer oftere ved behandlingsstart med olaparib og komparatorerne. Ansøgers model benytter frekvenser for bivirkninger af grad 3+ som mål for bivirkningerne, der forekommer i mere end 2 % af patienterne.

### Sammenligning med BSC

For olaparib og BSC har ansøger benyttet de rapporterede bivirkningsrater fra PROfound-studiet. Ressourcerne brugt i forbindelse med de forskellige bivirkninger har ansøger baseret på 2021 DRG-takster.

Ansøger har inkluderet omkostninger til skeletrelaterede hændelser (SRE). Ansøger har ikke mulighed for at opgøre det totale antal SRE for olaparib og komparatorerne. Derfor bruger ansøger andelen af patienter, der oplever mindst én SRE ved progression, og anvender det i modellen. For olaparib og BSC anvender ansøger PROfound-studiet til at informere omkring forekomsten af SRE. Ydermere anvender ansøger fordelingen af SRE fra AFFIRM-studiet [8] og antager, at fordelingen er gældende for alle de patienter, der oplever en SRE. Ressourcerne brugt i forbindelse med de forskellige SRE har ansøger baseret på DRG-takster.

### Sammenligning med docetaxel

Ansøger anvender TAX 327-studiet [9] til at belyse bivirkninger for docetaxel. Ansøger antager, at sandsynligheden for, at patienter, der modtager docetaxel, vil opleve mindst én SRE, er den samme som for patienter i BSC.

### Sammenligning med cabazitaxel

Ansøger anvender CARD-studiet [6] til at informere omkring de rapporterede bivirkninger for cabazitaxel + prednisolon. Studiet rapporterede frekvenser for bivirkninger af grad 3+ i mere end 3 % af patienterne. Ansøger antager, at sandsynligheden for, at patienter, der modtager cabazitaxel, vil opleve mindst én SRE, er den samme som for patienter i BSC.

**Medicinrådets vurdering af ansøgers antagelser vedr. bivirkningsomkostninger**

Medicinrådet accepterer ansøgers tilgang til estimering af bivirkningsomkostninger og SRE for sammenligningen med docetaxel, cabazitaxel og BSC. Dog vurderer fagudvalget, at ansøgers antagelse vedr. ambulant behandling ifm. behandling af grad 3 dyspnø og opkast ikke afspejler dansk klinisk praksis, da patienterne vil blive indlagt til udredning. Medicinrådet vælger derfor at udskifte ansøgers anvendte DRG-takst for dyspnø til 04MA23 (Symptomer fra luftveje) svarende til 19.691 kr. og udskifte anvendte DRG-takst for opkast til 06MA11 (Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag) svarende til 5.130 kr. Denne ændring vurderes at have lille betydning for analysens resultat. Bivirkningsfrekvenser kan ses i Tabel 10, mens anvendte takster kan ses i Tabel 11. Frekvenser for SRE kan ses i Tabel 12, mens anvendte takster kan ses i Tabel 13.

**Tabel 10. Rapporterede bivirkningsfrekvenser ved behandling med olaparib, docetaxel, cabazitaxel og BSC**

| | Olaparib [%] | Docetaxel [%] | Cabazitaxel [%] | BSC [%] |
|---|---|---|---|---|
| Anæmi | 22,66 % | 8,00 % | 5,00 % | 5,38 % |
| Neutropeni | 3,91 % | 44,72 % | 32,00 % | 0,00 % |
| Trombocytopeni | 3,52 % | 3,20 % | 1,00 % | 0,00 % |
| Pneumoni | 3,13 % | 0,00 % | 0,00 % | 2,31 % |
| Urinvejsinfektion | 1,95 % | 0,00 % | 0,00 % | 3,85 % |
| Sepsis | 1,17 % | 0,00 % | 3,30 % | 2,31 % |
| Lungeemboli | 2,73 % | 0,00 % | 0,00 % | 0,77 % |
| Dyspnø | 2,34 % | 0,00 % | 0,60 % | 0,00 % |
| Opkast | 2,34 % | 0,00 % | 1,20 % | 0,77 % |
| Asteni | 1,56 % | 3,97 % | 0,00 % | 3,08 % |
| Træthed | 1,56 % | 3,97 % | 5,00 % | 2,31 % |
| Hypertension | 1,17 % | 2,38 % | 0,00 % | 2,31 % |

**Tabel 11. Enhedsomkostninger for bivirkningerne**

| | Enhedsomkostning [DKK] | Kilde |
|---|---|---|
| Anæmi | 6.042 | 16PR01 – DRG-2021 |
| Neutropeni | 1.681 | 12MA98 – DRG-2021 |
| Trombocytopeni | 6.042 | 16PR01 – DRG-2021 |
| Pneumoni | 36.514 | 04MA13 – DRG-2021 |
| Urinvejsinfektion | 24.431 | 11MA07 – DRG-2021 |
| Sepsis | 42.770 | 18MA01 – DRG-2021 |
| Lungeemboli | 31.012 | 04MA04 – DRG-2021 |
| Dyspnø | 19.691 | 04MA23 – DRG-2021 |
| Opkast | 5.130 | 06MA11 – DRG-2021 |
| Asteni | 1.681 | 12MA98 – DRG-2021 |

| | Enhedsomkostning [DKK] | Kilde |
|---|---|---|
| Træthed | 1.681 | 12MA98 – DRG-2021 |
| Hypertension | 7.078 | 05MA11 – DRG-2021 |

**Tabel 12. Rapporterede skeletrelaterede hændelser samt fordelingen**

| Skeletrelateret hændelser | Fordeling (%) | Sandsynlighed for skeletrelateret hændelse (%) | |
|---|---|---|---|
| | | Olaparib | Docetaxel, Cabazitaxel & BSC |
| Medullært tværsnitssyndrom | 19,20 % | 23,58 % | 27,94 % |
| Patologisk fraktur | 10,93 % | | |
| Strålebehandling for knoglemetastaser | 63,47 % | | |
| Operation for knoglemetastaser | 6,40 % | | |

**Tabel 13. Enhedsomkostninger for skeletrelaterede hændelser**

| | Enhedsomkostning [DKK] | Kilde |
|---|---|---|
| Medullært tværsnitssyndrom | 66.938 | 01MA02 – DRG - 2021 |
| Patologisk fraktur | 90.959 | 08MP22 – DRG - 2021 |
| Strålebehandling for knoglemetastaser | 93.155 | 27MP05 – DRG - 2021 |
| Operation for knoglemetastaser | 25.533 | 08MP63 – DRG - 2021 |

*Medicinrådet accepterer ansøgers tilgang vedr. bivirkningsomkostninger og skeletrelaterede hændelser for sammenligning med docetaxel, cabazitaxel og BSC, men udskifter anvendte DRG-takster for dyspnø og opkast.*

### Terminale omkostninger

Ansøger har valgt at inkludere terminale omkostninger forbundet med palliativ pleje, hvor ansøger antager, at 25 % af patienterne vil modtage palliativ pleje. Til estimering af omkostningerne har ansøger anvendt DRG-taksten 11MA98 (Sygdomme i prostata, ondartet sygdom, pat. mindst 18 år), svarende til 32.869 kr.

**Medicinrådets vurdering af ansøgers antagelser vedr. terminale omkostninger**
Fagudvalget vurderer, at ansøgers andel af patienter, der vil modtage palliativ pleje, ikke er korrekt. Derimod vurderer fagudvalget, at 10 % af patienterne, der enten modtager docetaxel eller cabazitaxel, vil modtage palliativ pleje. For patienter, der vil modtage BSC, vurderer fagudvalget, at 50 % vil modtage palliativ pleje. Medicinrådet ændrer derfor andelen af patienter, der vil modtage palliativ pleje ifm. hvert klinisk spørgsmål. Denne ændring vurderes at have lille betydning for analysens resultat.

*Medicinrådet ændrer ansøgers andel for patienter, der vil modtage palliativ pleje og accepterer ansøgers antagelse for estimering af omkostningerne.*

### Testomkostninger

Ansøger har inkluderet testomkostninger forbundet med testning af BRCA1- og BRCA2-mutation. Ansøger anvender testen: *DNA(spec.)-BRCA1-gen;sekv.var.* baseret på oplysninger fra Rigshospitalets Labportal og antager en enhedsomkostning på 4.113 DKK pr. test.

Ydermere vælger ansøger, at anvende prævalensen for BRCA1/2-mutationer fra PROfound-studiet på 9,7 % til at estimere omkostningerne forbundet med test af BRCA1/2-mutationer [10].

**Medicinrådets vurdering af ansøgers antagelser vedr. testomkostninger**
Der testes ikke rutinemæssigt for BRCA1/2-mutationer hos patienter med mCRPC, men fagudvalget understreger, at dette vil være en forudsætning for ibrugtagning af olaparib, hvis Medicinrådet vælger at anbefale olaparib.

Medicinrådet vurderer, at ansøgers estimater for test af BRCA1/2-mutationer er underestimeret, da ansøger kun har valgt at bruge en test. Fagudvalget forklarer, at patienter kan testes for BRCA1/2-mutationer ifm. tre forskellige test; germline (test på blod), somatisk (test på arkiveret væv) eller frit cirkulerende tumor DNA. Fagudvalget har svært ved at udtale sig omkring den præcise teststrategi, men finder det mest sandsynligt, at patienter oftest vil testes for BRCA1/2-mutationer igennem både en germline og en somatisk test, fordi det repræsenterer dansk klinisk praksis ifm. testning af BRCA1/2-mutationer inden for æggestokkekræft. Det kan dog være svært at opnå nok væv til en somatisk test af BRCA1/2-mutationer, hvorfor man i stedet kan vælge at lave en yderligere vævsanalyse i form af frit cirkulerende tumor DNA. Fagudvalget kan dog ikke vurdere, hvornår test på frit cirkulerende tumor væv vil ibrugtages, fordi det er et nyt område for fagudvalget.

Medicinrådet vælger at anvende en samlet testomkostning forbundet med test af BRCA1/2-mutationer i form af både en germline og somatisk test i Medicinrådets hovedanalyse. Denne ændring vurderes at have stor betydning for analysens resultat. Afdeling for Genomisk Medicin på Rigshospitalet oplyser, at en germline test koster 4.500 DKK, og en somatisk test koster 6.500 DKK. Medicinrådet vurderer, at ansøgers estimat for prævalens af BRCA1/2-mutation ikke er repræsentativt for dansk klinisk praksis, hvorfor Medicinrådet ændrer prævalensen til 5 %, jf. protokollen. Denne ændring vurderes at have stor betydning for analysens resultat. Dermed bliver den gennemsnitlige testomkostning 220.000 DKK pr. patient med BRCA1/2-mutationer.

Eftersom der ikke eksisterer en teststrategi for test af BRCA1/2-mutationer i mCRPC-patienter, skal resultatet af testomkostninger tolkes med stor usikkerhed, fordi valg af test har stor indflydelse på omkostningerne. Derfor vælger Medicinrådet at lave en følsomhedsanalyse, hvor der kun anvendes en germline test til at teste for BRCA1/2-mutationer.  Dermed bliver den gennemsnitlige testomkostning 90.000 DKK pr. patient med BRCA1/2-mutationer.

*Medicinrådet ændrer antallet af test samt enhedsomkostningen forbundet med testene. Ydermere ændrer Medicinrådet prævalensen for BRCAm. Medicinrådet udarbejder derudover en følsomhedsanalyse, hvor kun en germline test anvendes.*

### 4.2.3 Efterfølgende behandling

Ansøger inkluderer omkostninger til efterfølgende behandling, da OS forventes at afspejle både effekten af 1. linjebehandling, men også effekten af de efterfølgende behandlingslinjer. Ansøger antager, at patienter, som progredierer, vil modtage én af nedenstående behandlinger:

- Docetaxel: 75 mg/m2 intravenøst i kombination med 10 mg prednisolon hver 3. uge i 10 cyklusser
- Cabazitaxel: 20 mg/m2 intravenøst i kombination med 10 mg prednisolon hver 3. uge i 7 cyklusser
- Radium-223: 55 kBq/kg intravenøst hver 4. uge i 6 cyklusser
- BSC: Ansøger antager, at den gennemsnitlige behandlingslængde er 6,6 måneder, hvilket svarer til den gennemsnitlige behandlingslængde for de andre øvrige behandlingsalternativer (cabazitaxel, docetaxel, abirateron, enzalutamid, og radium-223).

#### Sammenligning med docetaxel

Ansøger antager, at 52,03 % af patienterne, der behandles med olaparib, vil progrediere og modtage 2. linjebehandling, som ansøger baserer på estimater fra PROfound-studiet. For docetaxel antager ansøger, at 57,50 % af patienterne vil progrediere og modtage 2. linjebehandling, som ansøger baserer på estimater fra CARD-studiet. Hertil antager ansøger, at andelen af patienter, der progredierer og modtager efterfølgende behandling, er ens for cabazitaxel og docetaxel. Fordelingen af efterfølgende behandling er ligeledes baseret på data fra PROfound-studiet og CARD-studiet.

#### Sammenligning med cabazitaxel

Ansøger antager, at 52,03 % af patienterne, der behandles med olaparib, vil progrediere og modtage 3. linjebehandling, som ansøger baserer på estimater fra PROfound-studiet. For cabazitaxel antager ansøger, at 57,50 % af patienterne vil progrediere og modtage 3. linjebehandling, som ansøger baserer på estimater fra CARD-studiet. Fordelingen af efterfølgende behandling er ligeledes baseret på data fra PROfound-studiet og CARD-studiet.

### Sammenligning med BSC

Ansøger antager, at 52,03 % af patienterne, der behandles med olaparib, vil progrediere og modtage 4. linjebehandling. Både estimaterne for andelen af patienter, der modtager efterfølgende behandling, og fordelingen af efterfølgende behandling for olaparib og BSC er baseret på PROfound-studiet.

**Medicinrådets vurdering af ansøgers antagelser vedr. efterfølgende behandling**

Medicinrådet har udskriftet AIP for lægemiddelpriser til efterfølgende behandling med SAIP for de lægemidler, der ikke allerede er blevet præsenteret tidligere, se Tabel 14.

Fagudvalget vurderer, at der er flere patienter, der progredierer til næste behandlingslinje, end hvad ansøger har antaget, hvorfor Medicinrådet vælger at ændre andelen af patienter, der modtager efterfølgende behandling efter at være progredieret på olaparib, cabazitaxel og docetaxel til 70 %. Fagudvalget vurderer derudover, at ansøgers antagelse vedr. patienter, der progredierer på BSC, ikke er rimelig, da BSC er den sidste behandlingslinje, hvorfor patienter ikke kan progrediere herfra. Derfor ændrer Medicinrådet denne andel til 0 %, se Tabel 15. Denne ændring vurderes at have lille betydning for analysens resultat.

Fagudvalget er uenige i ansøgers fordeling fra PROfound-studiet for efterfølgende behandling, hvorfor Medicinrådet vælger at ændre fordelingen. Denne ændring vurderes at have lille betydning for analysens resultat. Fagudvalgets estimering af fordelingen af efterfølgende behandling kan ses i Tabel 16.

Fagudvalget vurderer, at ansøgers antagelser vedr. behandlingsvarigheden for efterfølgende behandling er overestimeret, hvorfor Medicinrådet vælger at ændre dette, se Tabel 17. For docetaxel ændrer Medicinrådet den gennemsnitlige behandlingsvarighed fra 10 til 7 cykler svarende til 5,5 måneder. For cabazitaxel og BSC accepterer Medicinrådet ansøgers gennemsnitlige behandlingsvarighed. For radium-223 ændrer Medicinrådet den gennemsnitlige behandlingsvarighed fra 6 cykler svarende til 5,5 måneder til 3,48 cykler svarende til 3,8 måneder.

**Tabel 14. Anvendte lægemiddelpriser for efterfølgende behandling, SAIP (oktober 2021)**

| Lægemiddel | Styrke | Pakningsstørrelse | Pris [DKK] | Kilde |
|---|---|---|---|---|
| Radium-223 | 6,6 MBq | 1 stk. | [redacted] | Amgros |

**Tabel 15. Andel patienter, der progredierer og modtager efterfølgede behandling**

| | Tidligere behandling | |
|---|---|---|
| For sammenligning med docetaxel | Olaparib | Docetaxel |
| | 70,00 % | 70,00 % |
| | Olaparib | Cabazitaxel |

| | Tidligere behandling | |
|---|---|---|
| For sammenligning med cabazitaxel | 70,00 % | 70,00 % |
| For sammenligning med BSC | Olaparib | BSC |
| | 70,00 % | 0,00 % |

**Tabel 16. Fordeling af patienter, der modtager efterfølgende behandling**

| Tidligere behandling | Efterfølgende behandling | | | | |
|---|---|---|---|---|---|
| | Olaparib | Cabazitaxel | Docetaxel | Radium-223 | BSC |
| Sammenligning med docetaxel | | | | | |
| Olaparib | 0 % | 0 % | 100 % | 0 % | 0 % |
| Docetaxel | 0 % | 95 % | 0 % | 5 % | 0 % |
| Sammenligning med cabazitaxel | | | | | |
| Olaparib | 0 % | 95 % | 0 % | 5 % | 0 % |
| Cabazitaxel | 0 % | 0 % | 0 % | 90 % | 10 % |
| Sammenligning med BSC | | | | | |
| Olaparib | 0 % | 0 % | 0 % | 90 % | 10 % |
| BSC | 0 % | 0 % | 0 % | 0 % | 0 % |

**Tabel 17. Gennemsnitlig behandlingsvarighed for efterfølgende behandling**

| Efterfølgende behandling | Behandlingslængde |
|---|---|
| Docetaxel | 7 cyklusser (med en cykluslængde på 3 uger) |
| Cabazitaxel | 7 cyklusser (med en cykluslængde på 3 uger) |
| Radium-223 | 3,48 cyklusser (med en cykluslængde på 4 uger) |

*Medicinrådet ændrer andelen af patienter, der progredierer til næste behandlingslinje. Medicinrådet ændrer derudover fordelingen for efterfølgende behandling samt behandlingsvarigheden.*

### 4.2.4 Patientomkostninger

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

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

Ansøger antager forskellige varigheder i forbindelse med monitorering, hvor et ambulant besøg varer 20 minutter, og CT-scanning varer 30 minutter. Ansøger vælger at skelne mellem aktiv og inaktiv behandling, se hhv. Tabel 19 og Tabel 20.

**Medicinrådets vurdering af ansøgers antagelser vedr. patientomkostninger**
Medicinrådet accepterer ansøgers estimerede patienttid, men vælger at inkludere patienttid til knoglescanning, hvilket varer 30 minutter, se Tabel 18. Denne ændring vurderes at have lille betydning for analysens resultat.

Medicinrådet accepterer ansøgers tilgang til estimering af patientomkostninger for både aktiv og inaktiv behandling, men ændrer frekvensen for estimerede patientomkostninger, således dette stemmer overens med ændringer i monitorering, se Tabel 19 og Tabel 20. Denne ændring vurderes at have lille betydning for analysens resultat.

**Tabel 18. Estimat af effektiv patienttid**

| | Patienttid [minutter] |
|---|---|
| Ambulant besøg | 20 |
| Specialiseret sygeplejebesøg | 20 |
| CT-scanning | 30 |
| Knoglescanning | 30 |

**Tabel 19. Estimerede patientomkostninger for patienter i aktiv behandling pr. måned**

| | Olaparib | BSC | Cabazitaxel | Docetaxel |
|---|---|---|---|---|
| Patienttid, besøg [timer] | 0,66 | 0,06 | 1,30 | 0,81 |
| Patienttid, transport [antal gange] | 3,32 | 0,33 | 7,12 | 4,22 |

**Tabel 20. Estimerede patientomkostninger for patienter i inaktiv behandling pr. måned**

| | Olaparib | BSC | Cabazitaxel | Docetaxel |
|---|---|---|---|---|
| Patienttid, besøg [timer] | 0,44 | 0,11 | 0,44 | 0,44 |
| Patienttid, transport [antal gange] | 1,98 | 0,66 | 1,98 | 1,98 |

*Medicinrådet tilføjer knoglescanning og* ændrer antallet af besøg på hospitalet, så dette stemmer overens med ændringerne i monitorering, jf. afsnit 4.2.2.

## 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. Ansøger har foretaget følgende følsomhedsanalyser, som er udført for alle tre kliniske spørgsmål:

**Tabel 21. Følsomhedsanalyser og beskrivelse**

| Følsomhedsanalyse | Beskrivelse |
|---|---|
| Tidshorisont | Ændrer tidshorisonten til hhv. 5 år og 15 år |
| Diskonteringsrate | Ændrer diskonteringsraten til hhv. 0 % og 5 % |
| Ekstrapolering af OS for olaparib og NHA | Ændrer ekstrapolering fra en Weibull-funktion til en generalized gamma-funktion |
| | Ændrer ekstrapolering fra en Weibull-funktion til en Gompertz-funktion |
| Ekstrapolering af PFS for olaparib og NHA | Ændrer ekstrapolering fra en Gompertz-funktion til en Weibull-funktion |
| | Ændrer ekstrapolering fra en Gompertz-funktion til en generalized gamma-funktion |
| Estimering af behandlingsvarighed | Ændrer antagelsen fra behandling indtil progression til at anvende TTD-data fra PROfound-studiet og ekstrapolationen Gompertz |
| | Ændrer antagelsen fra behandling indtil progression til at anvende TTD-data fra PROfound-studiet og ekstrapolationen generalized gamma |
| Testomkostninger | Ekskluderer testomkostninger for BRCA1 & BRCA2 |

| Følsomhedsanalyse | Beskrivelse |
|---|---|
| Efterfølgende behandling | Ekskluderer efterfølgende behandling |
| Bivirkningsomkostninger | Ekskluderer omkostninger til bivirkninger |
| SRE-omkostninger | Ekskluderer omkostninger til SRE |
| Monitoreringsomkostninger | Ekskluderer omkostninger til monitorering |
| Patienttid og transportomkostninger | Ekskluderer omkostninger til patienttid og transport |
| Prisen på olaparib | Varierer prisen på olaparib ± 20 % |

**Medicinrådets vurdering af ansøgers valg af følsomhedsanalyser**
Medicinrådet vælger ikke at præsentere ansøgers følsomhedsanalyser vedr. tidshorisont, diskontering, ekstrapolering af PFS, ekstrapolering af OS, estimering af behandlingsvarighed, testomkostninger til efterfølgende behandling, bivirkningsomkostninger, SRE-omkostninger, monitoreringsomkostninger og patienttid, transportomkostninger og prisen på olaparib, da disse ikke vurderes at være klinisk plausible i dansk klinisk praksis.

Medicinrådet vælger at udarbejde en følsomhedsanalyse på testomkostningerne for BRCA1/2-mutationer, fordi der ikke eksisterer nogen teststrategi for patienter med mCRPC. Derfor skal resultaterne tolkes med stor forsigtighed, fordi valg af test har stor indflydelse på analysens resultat. Derfor vælger Medicinrådet at udarbejde en følsomhedsanalyse, hvor der kun testes med en germline test. På baggrund af ansøgers høringssvar har sekretariatet tilføjet en følsomhedsanalyse hvor BRCA1/2-muterede patienter estimeres at udgøre en større del af den samlede patientpopulation.

Medicinrådet vælger derudover at udarbejde to følsomhedsanalyser, der undersøger scenarierne, hvor der ikke antages at være forskel i effekt mellem olaparib og hhv. docetaxel og cabazitaxel. I de to følsomhedsanalyser antages effekten, tiden i de forskellige sygdomsstadier og bevægelse gennem modellen at være ens for både olaparib, docetaxel og cabazitaxel. Slutteligt udføres der følsomhedsanalyser af Medicinrådets hovedanalyser, hvor den betingede pris på olaparib ikke anvendes X

*Medicinrådet vælger ikke at præsentere ansøgers følsomhedsanalyser, men præsenterer i stedet Medicinrådets egne følsomhedsanalyser vedr. testomkostninger for BRCA1/2-mutation, ændring af prævalens for BRCA1/2-muterede patienter, omkostningsminimeringsanalyse mellem olaparib, docetaxel og cabazitaxel og anvendelse af den ikke betingede pris på olaparib.*

## 4.4 Opsummering af basisantagelser

I Tabel 22 opsummeres basisantagelserne i henholdsvis ansøgers og Medicinrådets hovedanalyse.

**Tabel 22. Basisantagelser for ansøgers og Medicinrådets hovedanalyse**

| Basisantagelser | Ansøger | Medicinrådet |
|---|---|---|
| **Sammenligning med docetaxel** | | |
| Tidshorisont | 10 år | 10 år |
| Diskonteringsrate | 3,5 % | 3,5 % |
| Inkluderede omkostninger | Lægemiddelomkostninger<br>Hospitalsomkostninger<br>Efterfølgende behandling<br>Patientomkostninger | Lægemiddelomkostninger<br>Hospitalsomkostninger<br>Efterfølgende behandling<br>Patientomkostninger |
| Behandlingslinje | Efter NHA | Efter NHA |
| Behandlingslængder<br>Intervention:<br>Komparator: | <br>Olaparib: 14,7 måneder<br>Docetaxel: 5,1 måneder | <br>Olaparib: 14,7 måneder<br>Docetaxel: 5,1 måneder |
| Parametriske funktioner for PFS<br>Intervention:<br>Komparator: | <br>Gompertz<br>Gompertz | <br>Gompertz<br>Gompertz |
| Parametriske funktioner for OS<br>Intervention:<br>Komparator: | <br>Weibull<br>Weibull | <br>Weibull<br>Weibull |
| Inkludering af spild | Nej | Nej |
| **Sammenligning med cabazitaxel** | | |
| Tidshorisont | 10 år | 10 år |
| Diskonteringsrate | 3,5 % | 3,5 % |
| Inkluderede omkostninger | Lægemiddelomkostninger<br>Hospitalsomkostninger<br>Efterfølgende behandling<br>Patientomkostninger | Lægemiddelomkostninger<br>Hospitalsomkostninger<br>Efterfølgende behandling<br>Patientomkostninger |
| Behandlingslinje | Efter NHA og docetaxel | Efter NHA og docetaxel |

| Basisantagelser | Ansøger | Medicinrådet |
|---|---|---|
| Behandlingslængder | | |
| Intervention: | Olaparib: 9,9 måneder | Olaparib: 9,9 måneder |
| Komparator: | Cabazitaxel: 5,5 måneder | Cabazitaxel: 5,5 måneder |
| Parametriske funktioner for PFS | | |
| Intervention: | Gompertz | Gompertz |
| Komparator: | Gompertz | Gompertz |
| Parametriske funktioner for OS | | |
| Intervention: | Weibull | Weibull |
| Komparator: | Weibull | Weibull |
| Inkludering af spild | Nej | Nej |
| **Sammenligning med BSC** | | |
| Tidshorisont | 10 år | 10 år |
| Diskonteringsrate | 3,5 % | 3,5 % |
| Inkluderede omkostninger | Lægemiddelomkostninger<br>Hospitalsomkostninger<br>Efterfølgende behandling<br>Patientomkostninger | Lægemiddelomkostninger<br>Hospitalsomkostninger<br>Efterfølgende behandling<br>Patientomkostninger |
| Behandlingslinje | Når der ikke er flere behandlingsalternativer | Når der ikke er flere behandlingsalternativer |
| Behandlingslængder | | |
| Intervention: | Olaparib: 11,2 måneder | Olaparib: 9,9 måneder |
| Komparator: | BSC: 4,1 måneder | BSC: 3,5 måneder |
| Population | Samlet population (taxan-naive og taxan-behandlede patienter) | Taxan-behandlede patienter |
| Parametriske funktioner for PFS | | |
| Intervention: | Gompertz | Gompertz |
| Komparator: | Gompertz | Gompertz |
| Parametriske funktioner for OS | | |
| Intervention: | Weibull | Gompertz |
| Komparator: | Weibull | Gompertz |

| Basisantagelser | Ansøger | Medicinrådet |
|---|---|---|
| Inkludering af spild | Nej | Nej |

# 5. Resultater

## 5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse med undtagelse af de væsentligste ændringer, der fremgår af Tabel 22.

### Sammenligning med docetaxel

Den gennemsnitlige inkrementelle omkostning pr. patient bliver [redacted] DKK i Medicinrådets hovedanalyse. Størstedelen af omkostningerne forekommer dog de første år af behandlingsforløbet. Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient 604.000 DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 23.

### Sammenligning med cabazitaxel

Den gennemsnitlige inkrementelle omkostning pr. patient bliver [redacted] DKK i Medicinrådets hovedanalyse. Størstedelen af omkostningerne forekommer dog de første år af behandlingsforløbet. Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient 414.000 DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 24.

### Sammenligning med BSC

Den gennemsnitlige inkrementelle omkostning pr. patient bliver [redacted] DKK i Medicinrådets hovedanalyse. Størstedelen af omkostningerne forekommer dog de første år af behandlingsforløbet. Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient 633.000 DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 25.

**Tabel 23. Resultatet af Medicinrådets hovedanalyse ved sammenligning med docetaxel, DKK, diskonterede tal**

| | Olaparib | Docetaxel | Inkrementelle omkostninger |
|---|---|---|---|
| Lægemiddelomkostninger | [redacted] | [redacted] | [redacted] |
| Hospitalsomkostninger | 67.586 | 62.265 | 5.321 |
| Efterfølgende behandling | [redacted] | [redacted] | [redacted] |

| | Olaparib | Docetaxel | Inkrementelle omkostninger |
|---|---|---|---|
| Patientomkostninger | 12.934 | 5.304 | 7.630 |
| Testomkostninger | 220.000 | 0 | 220.000 |
| **Totale omkostninger** | [redacted] | [redacted] | [redacted] |

**Tabel 24. Resultatet af Medicinrådets hovedanalyse ved sammenligning med cabazitaxel, DKK, diskonterede tal**

| | Olaparib | Cabazitaxel | Inkrementelle omkostninger |
|---|---|---|---|
| Lægemiddelomkostninger | [redacted] | [redacted] | [redacted] |
| Hospitalsomkostninger | 54.407 | 80.718 | -26.310 |
| Efterfølgende behandling | [redacted] | [redacted] | [redacted] |
| Patientomkostninger | 10.119 | 5.038 | 5.080 |
| Testomkostninger | 220.000 | 0 | 220.000 |
| **Totale omkostninger** | [redacted] | [redacted] | [redacted] |

**Tabel 25. Resultatet af Medicinrådets hovedanalyse ved sammenligning med BSC, DKK, diskonterede tal**

| | Olaparib | BSC | Inkrementelle omkostninger |
|---|---|---|---|
| Lægemiddelomkostninger | [redacted] | [redacted] | [redacted] |
| Hospitalsomkostninger | 64.770 | 38.930 | 25.840 |
| Efterfølgende behandling | [redacted] | [redacted] | [redacted] |
| Patientomkostninger | 8.968 | 2.692 | 6.276 |
| Testomkostninger | 220.000 | 0 | 220.000 |
| **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 26.

**Tabel 26. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalysen, DKK**

| Scenarie | Inkrementelle omkostninger |
|---|---|
| **Resultatet af hovedanalysen for sammenligning med docetaxel** | [redacted] |
| Tester for BRCA1/2-mutationer kun via germline test | [redacted] |
| Antager ens effekt mellem olaparib og docetaxel | [redacted] |
| Anvendelse af ikke-betingede pris på olaparib | [redacted] |
| Ændrer prævalensen for BRCA1/2-mutationer til 9,7 % | [redacted] |
| **Resultatet af hovedanalysen for sammenligning med cabazitaxel** | [redacted] |
| Tester for BRCA1/2-mutationer kun via germline test | [redacted] |
| Antager ens effekt mellem olaparib og cabazitaxel | [redacted] |
| Anvendelse af ikke-betingede pris på olaparib | [redacted] |
| Ændrer prævalensen for BRCA1/2-mutationer til 9,7 % | [redacted] |
| **Resultatet af hovedanalysen for sammenligning med BSC** | [redacted] |
| Tester for BRCA1/2-mutationer kun via germline test | [redacted] |
| Anvendelse af ikke-betingede pris på olaparib | [redacted] |
| Ændrer prævalensen for BRCA1/2-mutationer til 9,7 % | [redacted] |

# 6. Budgetkonsekvenser

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

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

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

## 6.1 Estimat af patientantal og markedsandel

Ansøger anvender den samlede mandlige befolkning i Danmark som udgangspunkt, hvor patientantallet estimeres ud fra den samlede forekomst af prostatakræft, andelen af patienter med metastatisk sygdom, andelen af patienter, der modtager 1. linjebehandling med NHA, andelen af patienter, der modtager 2. linjebehandling, og andelen patienter med BRCA1/2-mutation.

Ansøger har antaget, at:

- Der er 52 patienter med BRCA 1/2-muteret metastaserende kastrationsresistent prostatakræft, der er progredieret på enten enzalutamid eller abirateron pr. år, som kandidater til behandling med olaparib, hvoraf ansøger antager, at olaparib vil have et stigende markedsoptag til 67 % i år 5.
- Der er 30 patienter med BRCA 1/2-muteret metastaserende kastrationsresistent prostatakræft, der er progredieret på enten enzalutamid eller abirateron samt docetaxel pr. år, som kandidater til behandling med olaparib, hvoraf ansøger antager, at olaparib vil have et stigende markedsoptag til 67 % i år 5.
- Der er 14 patienter med BRCA 1/2-muteret metastaserende kastrationsresistent prostatakræft, der er progredieret på enzalutamid eller abirateron, docetaxel og cabazitaxel pr. år, som kandidater til behandling med olaparib, hvoraf ansøger antager, at olaparib vil have et stigende markedsoptag til 67 % i år 5.

Ansøger antager, at 6 % af patienterne vil modtage olaparib, hvis det ikke anbefales som standardbehandling.

**Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse**
Fagudvalget er blevet konsulteret i forhold til patientantal, hvis olaparib anbefales som mulig standardbehandling, og hvis ikke olaparib anbefales. Fagudvalget finder ansøgers antagelse rimelig, at der er 52 patienter, der er progredieret på enten enzalutamid eller abirateron pr. år, som kandidater til behandling med olaparib.

Fagudvalget finder ansøgers antagelse, at der er 25 patienter, der er progredieret på enten enzalutamid eller abirateron samt docetaxel pr. år, som kandidater til behandling med olaparib, overestimeret. Fagudvalget vælger derfor at nedjustere patienttallet til 25 patienter pr. år, som kandidater til behandling med olaparib.

Fagudvalget finder ansøgers antagelse, at der er 10 patienter, der er progredieret på enzalutamid eller abirateron, docetaxel og cabazitaxel pr. år, som kandidater til behandling med olaparib, overestimeret. Fagudvalget vælger derfor at nedjustere patienttallet til 10 patienter pr. år, som kandidater til behandling med olaparib.

**Tabel 27. Medicinrådets estimat af antal nye patienter pr. år for sammenligning med docetaxel**

| | År 1 | År 2 | År 3 | År 4 | År 5 |
|---|---|---|---|---|---|
| | | | Anbefales | | |
| Olaparib | 34 | 37 | 41 | 44 | 47 |

| | År 1 | År 2 | År 3 | År 4 | År 5 |
|---|---|---|---|---|---|
| Docetaxel | 18 | 15 | 11 | 8 | 5 |
| | | | **Anbefales ikke** | | |
| Olaparib | 0 | 2 | 2 | 3 | 3 |
| Docetaxel | 52 | 50 | 50 | 49 | 49 |

**Tabel 28. Medicinrådets estimat af antal nye patienter pr. år for sammenligning med cabazitaxel**

| | År 1 | År 2 | År 3 | År 4 | År 5 |
|---|---|---|---|---|---|
| | | | **Anbefales** | | |
| Olaparib | 17 | 18 | 20 | 21 | 23 |
| Cabazitaxel | 8 | 7 | 5 | 4 | 2 |
| | | | **Anbefales ikke** | | |
| Olaparib | 0 | 1 | 1 | 1 | 2 |
| Cabazitaxel | 25 | 24 | 24 | 24 | 23 |

**Tabel 29. Medicinrådets estimat af antal nye patienter pr. år for sammenligning med BSC**

| | År 1 | År 2 | År 3 | År 4 | År 5 |
|---|---|---|---|---|---|
| | | | **Anbefales** | | |
| Olaparib | 7 | 7 | 8 | 8 | 9 |
| BSC | 3 | 3 | 2 | 2 | 1 |
| | | | **Anbefales ikke** | | |
| Olaparib | 0 | 0 | 0 | 1 | 1 |
| BSC | 10 | 10 | 10 | 9 | 9 |

*Medicinrådet accepterer ansøgers antagelser vedr. budgetkonsekvensanalyse for sammenligningen mellem olaparib og komparatorerne. Medicinrådet udfører sin egen budgetkonsekvensanalyse, hvor patientantallet for sammenligning med cabazitaxel er ændret til 25 patienter pr. år, og patientantallet for sammenligning med BSC er ændret til 10 patienter pr. år.*

## 6.2 Medicinrådets budgetkonsekvensanalyse

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

- For sammenligning mellem olaparib og docetaxel: 52 patienter
- For sammenligning mellem olaparib og cabazitaxel: 25 patienter
- For sammenligning mellem olaparib og BSC: 10 patienter.

### Sammenligning med docetaxel

Medicinrådet estimerer, at anvendelse af olaparib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i det femte år efter en anbefaling. Resultatet er præsenteret i Tabel 30. Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 26,1 mio. DKK i år 5.

### Sammenligning med cabazitaxel

Medicinrådet estimerer, at anvendelse af olaparib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i det femte år efter en anbefaling. Resultatet er præsenteret i Tabel 31. Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 8,5 mio. DKK i år 5.

### Sammenligning med BSC

Medicinrådet estimerer, at anvendelse af olaparib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i det femte år efter en anbefaling. Resultatet er præsenteret i Tabel 32. Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 5,2 mio. DKK i år 5.

**Tabel 30. Medicinrådets analyse af totale budgetkonsekvenser for sammenligning med docetaxel, 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 sammenligning med cabazitaxel, 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 32. Medicinrådets analyse af totale budgetkonsekvenser for sammenligning med BSC, 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

#### Sammenligning med docetaxel

Ved samme antagelser som i Medicinrådets hovedanalyse for budgetkonsekvenser, men hvor man kun tester BRCA1/2-mutationer via germline test, vil omkostningerne i år 5 være ca. [redacted] DKK, se Tabel 33.

Ved samme antagelser som i Medicinrådets hovedanalyse for budgetkonsekvenser, men hvor antagelsen om, at olaparib har ens effekt overfor docetaxel, vil omkostningerne i år 5 være ca. [redacted] DKK, se Tabel 34.

Ved samme antagelser som i Medicinrådets hovedanalyse for budgetkonsekvenser, men med den ikke-betingede pris på olaparib, vil omkostningerne i år 5 være ca. [redacted] DKK, se Tabel 35.

Ved samme antagelser som i Medicinrådets hovedanalyse for budgetkonsekvenser, men hvor prævalensen for BRCA1/2-muterede patienter ændres til 9,7 % i stedet for 5 %, vil omkostningerne i år 5 være ca. [redacted] DKK, se Tabel 36.

#### Sammenligning med cabazitaxel

Ved samme antagelser som i Medicinrådets hovedanalyse for budgetkonsekvenser, men hvor man kun tester BRCA1/2-mutationer via germline test, vil omkostningerne i år 5 være ca. [redacted] DKK, se Tabel 37.

Ved samme antagelser som i Medicinrådets hovedanalyse for budgetkonsekvenser, men hvor antagelsen om, at olaparib har en effekt overfor cabazitaxel, vil omkostningerne i år 5 være ca. [redacted] DKK, se Tabel 38.

Ved samme antagelser som i Medicinrådets hovedanalyse for budgetkonsekvenser, men med den ikke-betingede pris på olaparib, vil omkostningerne i år 5 være ca. [redacted] DKK, se Tabel 39.

Ved samme antagelser som i Medicinrådets hovedanalyse for budgetkonsekvenser, men hvor prævalensen for BRCA1/2-muterede patienter ændres til 9,7 % i stedet for 5 %, vil omkostningerne i år 5 være ca. [redacted] DKK, se Tabel 40.

### Sammenligning med BSC

Ved samme antagelser som i Medicinrådets hovedanalyse for budgetkonsekvenser, men hvor man kun tester BRCA1/2-mutationer via germline test, vil omkostningerne i år 5 være ca. [redacted] DKK, se Tabel 41.

Ved samme antagelser som i Medicinrådets hovedanalyse for budgetkonsekvenser, men med den ikke-betingede pris på olaparib, vil omkostningerne i år 5 være ca. [redacted] DKK, se Tabel 42.

Ved samme antagelser som i Medicinrådets hovedanalyse for budgetkonsekvenser, men hvor prævalensen for BRCA1/2-muterede patienter ændres til 9,7 % i stedet for 5 %, vil omkostningerne i år 5 være ca. [redacted] DKK, se Tabel 43.

**Tabel 33. Medicinrådets analyse af totale budgetkonsekvenser, hvor BRCA1/2-mutationer kun testes via germline test, for sammenligning med docetaxel i 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, hvor olaparib har ens effekt overfor docetaxel, for sammenligning med docetaxel i 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 med den ikke-betingede pris på olaparib, for sammenligning med docetaxel i 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 36. Medicinrådets analyse af totale budgetkonsekvenser, hvor prævalensen for BRCA1/2-muterede patienter ændres, for sammenligning med docetaxel i 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 37. Medicinrådets analyse af totale budgetkonsekvenser, hvor BRCA1/2-mutationer kun testes via germline test, for sammenligning med cabazitaxel i 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 38 Medicinrådets analyse af totale budgetkonsekvenser, hvor olaparib har ens effekt overfor cabazitaxel, for sammenligning med cabazitaxel i 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 39. Medicinrådets analyse af totale budgetkonsekvenser med den ikke-betingede pris på olaparib, for sammenligning med cabazitaxel i 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 40. Medicinrådets analyse af totale budgetkonsekvenser, hvor prævalensen for BRCA1/2-muterede patienter ændres, for sammenligning med cabazitaxel i 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. Medicinrådets analyse af totale budgetkonsekvenser, hvor BRCA1/2-mutationer kun testes via germline test, for sammenligning med BSC i 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. Medicinrådets analyse af totale budgetkonsekvenser med den ikke-betingede pris på olaparib, for sammenligning med BSC i 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. Medicinrådets analyse af totale budgetkonsekvenser, hvor prævalensen for BRCA1/2-muterede patienter ændres, for sammenligning med BSC i mio. DKK, ikke-diskonterede tal**

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

# 7. Diskussion

Behandling med olaparib er forbundet med inkrementelle omkostninger på [redacted] DKK sammenlignet med behandling med docetaxel, inkrementelle omkostninger på [redacted] DKK sammenlignet med behandling med cabazitaxel og inkrementelle omkostninger på [redacted] DKK sammenlignet med behandling med BSC. De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne og testomkostningerne for olaparib.

Jf. vurderingsrapporten vurderer fagudvalget, at det ikke er muligt at vurdere om der er forskel i effekt og bivirkninger mellem olaparib, docetaxel og cabazitaxel på baggrund af data. Dog mener fagudvalget, at data peger i retning af at olaparib kunne have en bedre effekt end komparatorerne. Derfor vælger Medicinrådet at præsentere en hovedanalyse, hvor der antages en effekt af olaparib overfor hhv. docetaxel og cabazitaxel. Medicinrådet vælger derudover at udarbejde to følsomhedsanalyser, der undersøger scenarierne, hvor der ikke antages at være forskel i effekt mellem olaparib og hhv. docetaxel og cabazitaxel. I de to følsomhedsanalyser antages effekten, tiden i de forskellige sygdomsstadier og bevægelse gennem modellen at være ens for både olaparib, docetaxel og cabazitaxel. PFS- og OS-data fra olaparib-armen i PROfound-studiet anvendes til at modellere patienternes bevægelse gennem modellen.

Behandling med olaparib er forbundet med inkrementelle omkostninger på [redacted] DKK, hvis der antages ens effekt mellem olaparib og docetaxel. Behandling med olaparib er forbundet med inkrementelle omkostninger på [redacted] DKK, hvis der antages ens effekt mellem olaparib og cabazitaxel. De inkrementelle omkostninger skal tolkes med stor forsigtighed, da hovedanalysen og følsomhedsanalyserne belyser to forskellige scenarier, hvor olaparib hhv. har en effekt og ingen effekt overfor docetaxel og cabazitaxel. De reelle inkrementelle omkostninger er sandsynligvis et sted mellem de to præsenteret scenarier. X

Derudover er der stor usikkerhed vedr. testomkostningerne, fordi der på nuværende tidspunkt ikke testes rutinemæssigt for BRCA1/2-mutationer i mCRPC-patienter, og der ikke eksisterer en præcis teststrategi. Det har stor betydning for analysens resultat, da de inkrementelle omkostninger i stor grad drives af testomkostningerne for olaparib. Hvis der kun testes for BRCA1/2-mutationer via germline test, reduceres de inkrementelle omkostninger pr. patient med 130.000 for alle kliniske spørgsmål.

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# 9. Versionslog

| Versionslog | | |
|---|---|---|
| **Version** | **Dato** | **Ændring** |
| 1.0 | 15. december 2021 | Godkendt af Medicinrådet |

# 10. Bilag

## 10.1 Resultatet af ansøgers hovedanalyse

### Sammenligning med docetaxel

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient [redacted] DKK over en tidshorisont på 10 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 44.

### Sammenligning med cabazitaxel

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient [redacted] DKK over en tidshorisont på 10 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 45.

### Sammenligning med BSC

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient [redacted] DKK over en tidshorisont på 10 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 46.

**Tabel 44. Resultatet af ansøgers hovedanalyse for sammenligning med docetaxel, DKK, diskonterede tal**

| | Olaparib | Docetaxel | Inkrementelle omkostninger |
|---|---|---|---|
| Lægemiddelomkostninger | [redacted] | [redacted] | [redacted] |
| Hospitalsomkostninger | 96.804 | 55.761 | 41.043 |
| Efterfølgende behandling | [redacted] | [redacted] | [redacted] |
| Patientomkostninger | 16.146 | 4.754 | 11.392 |
| Testomkostninger | 42.402 | 0 | 42.402 |
| **Totale omkostninger** | [redacted] | [redacted] | [redacted] |

**Tabel 45. Resultatet af ansøgers hovedanalyse for sammenligning med cabazitaxel, DKK, diskonterede tal**

| | Olaparib | Cabazitaxel | Inkrementelle omkostninger |
|---|---|---|---|
| Lægemiddelomkostninger | [redacted] | [redacted] | [redacted] |
| Hospitalsomkostninger | 77.666 | 68.984 | 8.682 |
| Efterfølgende behandling | [redacted] | [redacted] | [redacted] |

| | Olaparib | Cabazitaxel | Inkrementelle omkostninger |
|---|---|---|---|
| Patientomkostninger | 12.676 | 5.712 | 6.963 |
| Testomkostninger | 42.402 | 0 | 42.402 |
| **Totale omkostninger** | [redacted] | [redacted] | [redacted] |

**Tabel 46. Resultatet af ansøgers hovedanalyse for sammenligning med BSC, DKK, diskonterede tal**

| | Olaparib | BSC | Inkrementelle omkostninger |
|---|---|---|---|
| Lægemiddelomkostninger | [redacted] | [redacted] | [redacted] |
| Hospitalsomkostninger | 84.332 | 56.150 | 28.182 |
| Efterfølgende behandling | [redacted] | [redacted] | [redacted] |
| Patientomkostninger | 14.306 | 5.385 | 8.922 |
| Testomkostninger | 42.402 | 0 | 42.402 |
| **Totale omkostninger** | [redacted] | [redacted] | [redacted] |

## 10.2 Resultatet af ansøgers budgetkonsekvensanalyse

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

### Sammenligning med docetaxel

Med ovenstående antagelser om patientantal og markedsandel estimerer ansøger, at anvendelse af olaparib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 47.

### Sammenligning med cabazitaxel

Med ovenstående antagelser om patientantal og markedsandel estimerer ansøger, at anvendelse af olaparib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 48.

### Sammenligning med BSC

Med ovenstående antagelser om patientantal og markedsandel estimerer ansøger, at anvendelse af olaparib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 49.

**Tabel 47. Ansøgers hovedanalyse for totale budgetkonsekvenser for sammenligning med docetaxel, 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 48. Ansøgers hovedanalyse for totale budgetkonsekvenser for sammenligning med cabazitaxel, 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 49. Ansøgers hovedanalyse for totale budgetkonsekvenser for sammenligning med BSC, 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 | 15.12.2021 |
| Leverandør | Astra Zeneca |
| Lægemiddel | Olaparib (lynparza) |
| Ansøgt indikation | Olaparib til behandling af patienter med metastatisk kastrationsresistent prostatakæft, som har gendefekten BRCA1/2-mutation i tre behandlingslinjer ved sygdomsprogression efter behandling med enzalutamid/abirateron. |

## Forhandlingsresultat

Amgros har opnået følgende pris på olaparib:

*Tabel 1: Forhandlingsresultat*

| Lægemiddel | Styrke/dosis | Pakningsstørrelse | AIP (DKK) | Nuværende SAIP (DKK) | Betinget pris SAIP*(DKK) | Rabatprocent ift. AIP |
|---|---|---|---|---|---|---|
| Olaparib | 100 mg | 56 stk. | 17.764,37 | [redacted] | [redacted] | [redacted] |
| Olaparib | 150 mg | 56 stk. | 17.764,37 | [redacted] | [redacted] | [redacted] |

[redacted]

Olaparib er inkluderet i det udbud, der netop er afsluttet på ovariecancer (niraparib og olaparib). Aftalen starter d. 1/4-2022. [redacted]

Amgros har været i dialog med leverandøren om hvornår den nye pris kan være gældende fra, såfremt denne indikation anbefales af Medicinrådet. Den nuværende aftale løber indtil slutningen af marts 2022, men indeholder en mulighed for prisjustering. [redacted]

## Informationer fra forhandlingen

[redacted]

- Udbuddet af lægemidlerne til ovariecancer blev gennemført i oktober/november med deadline d. 26/11-2021. Den pris leverandøren har budt ind med er gældende fra d. 1/4-2022.

[redacted]

## Konkurrencesituationen

[redacted]

## Status fra andre lande

Norge: Endnu ikke færdigbehandlet.[1]

England: Blev ikke anbefalet[2]

## Konklusion

[redacted]

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

[2] 1 Recommendations | Olaparib for previously treated BRCA-mutation positive hormone-relapsed metastatic prostate cancer | Olaparib for previously treated, hormone-relapsed metastatic prostate cancer with homologous recombination repair gene mutations [ID1640] | Consultations | NICE

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05. December 2021

**Re.: Assessment of Olaparib for BRCAm mCRPC**

AstraZeneca has received and read the assessment report concerning 'Olaparib for BRCAm mCRPC' and we hereby submit our hearing response letter.
We would like to thank the Fagudvalg for Prostate Cancer for a very comprehensive and attentive assessment, which is clearly reflective of careful consideration of the provided data for all of the three clinical questions.

We agree that the clinical documentation for Question #1 is weak and that an solid assessment vs docetaxel is difficult. We are pleased to note that for Question #2, Fagudvalget finds olaparib to be "a promising treatment with comparatively better median PFS and OS than what Fagudvalget has typically observed for cabazitaxel in clinical practice as well as in the CARD study". Fagudvalget also finds olaparib to be "a better tolerated treatment than cabazitaxel on selected important clinical parameters with expected lower frequency of neuropathy and febrile neutropenia".
For Question #3, we note that Fagudvalget finds Olaparib to be "an important targeted treatment for BRCAm mCRPC patients in good performance status who have no other treatment options left" (Question #3).
In conclusion following this, we note that Fagudvalget proposes that "the best placement for olaparib in the current treatment algorithm for mCRPC, would be after NHA and docetaxel". On balance of the available evidence, AstraZeneca finds this a reasonable proposal.

However, although we are pleased with the overall very positive tone and conclusions of the assessment, we must address a few important issues below.

**Clinical Question #2:**

Fagudvalget noted that there are differences between the study populations in the PROfound study (olaparib vs. NHA) and the CARD study (cabazitaxel vs. NHA), which makes a comparison of the results in these two studies difficult. In particular, the indication for olaparib based on the PROfound study included only BRCA-mutated patients.

Although the assessment report from Medicinrådet(DMC) mentions that a naïve comparison of the PROfound and CARD might underestimate the difference in effect between olaparib and cabazitaxel, it seems that Fagudvalget did not take the indirect comparison between olaparib and cabazitaxel into account. The indirect comparison suggested that olaparib reduced the risk of disease progression by 64% (HR 0.36; 95% CI: 0.20 – 0.64) vs cabazitaxel in the BRCAm population. In addition, the cross-over adjusted indirect comparison suggested that olaparib reduced the risk of death by 53% (HR 0.47; 95% CI: 0.12 – 1.79) vs cabazitaxel in the BRCAm population (Reason et al. 2021 [1]). The HR confidence interval for the OS comparison is very broad, as might be expected given that it is an indirect comparison based on a cross-over adjusted analysis for a subgroup. The PFS comparison has a much narrower HR confidence interval, partly because no cross-over

adjustment is needed for PFS as cross over occurs after progression. These results also indicate that the naïve comparison of the PROfound and CARD probably underestimates the difference in effect between olaparib and cabazitaxel, as suggested by Fagudvalget in the DMC report.
The CARD study had a similar study design as the PROfound study, with previous NHA treatment as inclusion criterion and with NHA as comparator to cabazitaxel. Hence, it is the most comparable study to use for an indirect comparison. Indeed, it was the only relevant trial identified in the systematic literature review. It is true that CARD did not include a BRCA-mutated population, but that should not necessarily affect the relative efficacy between cabazitaxel and NHA. Afterall, it is the relative efficacy that matters in an indirect comparison, even if there would be differences in absolute outcomes between BRCAm positive and BRCAm negative prostate cancer patients, with on average probably worse prognosis for BRCAm positive patients compared with BRCAm negative patients according to Fagudvalget.

**Clinical Question #3**

In the DMC assessment report, Fagudvalget noted that the OS HR for olaparib vs. NHA was 0.63 (95 % CI 0.39 – 1.04). They also suggest that the effect of olaparib compared with BSC is probably underestimated, partly due to cross over from NHA to olaparib in the control arm after progression, and partly due to the fact that retreatment with NHA is expected to have greater effect on OS than BSC.
Indeed 24 out of 35 (69%) of patients in the NHA-arm of the BRCAm, post-taxane subgroup crossed over to olaparib treatment and a cross-over adjusted indirect comparison does suggest that olaparib reduces the risk of death by 70% (HR 0.30; 95% CI 0.08 – 1.08) vs NHA in the post taxane, BRCAm population (AstraZeneca data on file [2]). Although not statistically significant, the cross-over adjusted results thus clearly indicate that the unadjusted OS HR is very likely underestimating the effect of olaparib compared with BSC, as also suggested by Fagudvalget.
Again we would like to emphasize that the OS analysis of a subgroup (post taxane) within a subgroup (BRCAm) makes it challenging to achieve statistical significance due to the small patient population of this subgroup. It's worth noting that if the BRCAm population regardless of prior taxane treatment is examined (overall approved indication by EMA), the OS HR point estimate for olaparib vs NHA was similarly 0.63 but with a significant confidence interval (95% CI 0.42–0.95). As was also noted by Fagudvalget, the similar HR clearly suggests that efficacy for the post-taxane BRCAm subgroup does not differ from that of the whole BRCAm group.
Although the assessment has not been able to categorize the added value for OS, we trust that these important considerations will be taken into account when the decision on the recommendation is made.

**BRCA testing**

The results from the PROfound study show that the combined prevalence of germline and/or somatic BRCA1/2 mutations is 9.7% of patients who were screened for participation in the study (De Bono et al [3]). However, in the assessment report, Fagudvalget estimate the prevalence at only 5%. Since the 5% estimate is used as the basis for calculating the costs of testing per patient (220.000 DKK) and since no reference is given for this estimate, we must insist that the DMC instead considers the available published high quality evidence on germline/somatic BRCA1/2 prevalence.
As mentioned, the PROfound study diagnostic screening identified no less than 269 patients with BRCA1/2 germline and/or somatic mutations from 2792 patients successfully tested, making this by far the most comprehensive prospective screening effort to date [3]. Since the PROfound screening has a large sample size and reflects exactly the eligible population, we believe this is the most appropriate estimate for the prevalence. However, the findings in the PROfound screening are in fact supported by other high impact

publications. Robinson et al. found a prevalence of 13% germline/somatic BRCA2 mutations in a population of mCRPC patients [4] and a recent study by Matteo et al., found an 8% prevalence [5].
The review article cited by the DMC assessment report (Messina et al. [6]) in section 3.1 discussing BRCA prevalence, cites Robinson et al [4] (13%), as well as a study by Pritchard et al., showing a prevalence of 0.9% and 5.3% respectively for BRCA1 and BRCA2 mutations [7]. However, importantly Pritchard et al. only analyzed germline mutations and did not include somatic mutations, which likely accounts for the lower observed prevalence in this study.
On balance, the frequently cited sequencing studies that have analyzed both somatic and germline BRCA1/2 mutations by NGS all report similar or higher prevalence as found in the PROfound screening. Hence, we strongly urge the DMC to use the 9.7% prevalence from the PROfound study as the basis for calculating the testing costs as opposed to the 5% estimate for which no reference or supporting data have been provided.
In addition, it's important to emphasize that the introduction of NGS-based BRCA testing will not only be for the immediate benefit of the identified BRCAm mCRPC patients eligible for olaparib. The implementation of routine NGS workflows for mCRPC will provide the framework for future biomarker-guided treatments that can then leverage the testing capabilities put in place by the practical implementation of the PROfound indication. Identification of germline BRCA2m patients will also help identify healthy family relatives at risk of developing prostate cancer, which is aligned with the recently announced intentions by DaProCa of prioritizing early detection of hereditary prostate cancer. Precision oncology has greatly improved treatment outcomes for other large patient groups such as breast cancer, lung cancer, and ovarian cancer and introduction of NGS-based BRCA testing for mCRPC will be an important first step to initiate the same development for prostate cancer patients.

We trust that these points are taken into consideration by the DMC for the final recommendation of olaparib for BRCAm mCRPC.

Sincerely
AstraZeneca A/S

Søren Clausen
Market Access Head

Mattias Ekman
Health Economist

Kim Hjort Jensen
Disease Area Specialist

References:


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Medicinrådet

# Medicinrådets vurdering vedrørende olaparib til behandling af BRCA1/2-muteret metastaserende kastrationsresistent prostatakræft

Version 1.0

## Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

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

## Om vurderingsrapporten

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

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

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

| **Dokumentoplysninger** | |
|---|---|
| **Godkendelsesdato** | 24. november 2021 |
| **Dokumentnummer** | 130205 |
| **Versionsnummer** | 1.0 |

# Indholdsfortegnelse

# 1. Medicinrådets konklusion

Medicinrådet har vurderet olaparib til behandling af patienter med metastatisk kastrationsresistent prostatakræft, som har gendefekten BRCA1/2-mutation i tre behandlingslinjer ved sygdomsprogression efter behandling med enzalutamid/abirateron.

Medicinrådet vurderer, at olaparib kan være en bedre behandling end docetaxel, cabazitaxel og især bedre end BSC. Medicinrådet vurderer desuden, at olaparib giver færre alvorlige bivirkninger end docetaxel og cabazitaxel, men flere alvorlige bivirkninger end BSC.

Datagrundlaget er dog utilstrækkeligt, hvorfor vurderingen er meget usikker. Det skyldes primært, at studierne ikke afspejler dansk klinisk praksis. Værdien af behandling med olaparib kan af samme grund ikke kategoriseres efter Medicinrådets metoder.



Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 24. november 2021

## 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

| | |
|---|---|
| **ADT:** | Androgen deprivationsterapi |
| **BSC:** | *Best supportive care* |
| **BRCA:** | *Breast cancer gene* |
| **DNA:** | Deoxyribonucleic Acid |
| **EMA:** | Det Europæiske Lægemiddelagentur *(European Medicines Agency)* |
| **EPAR:** | *European Public Assessment Report* |
| **EUnetHTA:** | *European Network for Health Technology Assessment* |
| **FACT-P:** | *Functional Assessment of Cancer Therapy – Prostate* |
| **FDA:** | *The Food and Drug Administration* |
| **FINOSE:** | Finland, Norge og Sveriges samarbejde om medicinske teknologivurderinger |
| **GRADE:** | System til at vurdere evidens *(Grading of Recommendations, Assessment, Development and Evaluation)* |
| **HRD:** | *Homologous recombination deficiency* |
| **HTA:** | Medicinsk teknologivurdering (Health Technology Assessment) |
| **IQWIG:** | *The Institute for Quality and Efficiency in Healthcare* |
| **ITT:** | *Intention to treat* |
| **LHRH:** | *Luteinising Hormone Releasing Hormone* |
| **mCRPC:** | Metastaserende kastrationsresistent prostatakræft *(metastatic castration-resistant prostata cancer*) |
| **MKRF:** | Mindste klinisk relevante forskel |
| **NHA:** | New Hormonal Agent (enzalutamid og abirateron) |
| **NICE:** | *The National Institute for Health and Care Excellence* |
| **OS:** | Samlet overlevelse *(overall survival)* |
| **PARP:** | Poly-ADP-ribose polymerase |
| **PFS:** | Progressionsfri overlevelse |

| | |
|---|---|
| **PICO:** | Population, intervention, komparator og effektmål *(Population, Intervention, Comparison and Outcome)* |
| **PP:** | Per protocol |
| **RECIST:** | *Response Evaluation Criteria in Solid Tumors* |
| **RR:** | Relativ risiko |
| **SMD:** | *Standardized Mean Difference* |

# 3. Introduktion

Formålet med Medicinrådets vurdering af olaparib til behandling af BRCA1/2-muteret metastaserende kastrationsresistent prostatakræft er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra AstraZeneca. Medicinrådet modtog ansøgningen den 11. august 2021.

De kliniske spørgsmål er:

- Hvilken værdi har olaparib sammenlignet med docetaxel for patienter med BRCA1/2-muteret metastaserende kastrationsresistent prostatakræft, der er progredieret på enten enzalutamid eller abirateron?
- Hvilken værdi har olaparib sammenlignet med cabazitaxel for patienter med BRCA1/2-muteret metastaserende kastrationsresistent prostatakræft, der er progredieret efter behandling med enzalutamid eller abirateron samt docetaxel?
- Hvilken værdi har olaparib sammenlignet med *best supportive care* (BSC) for patienter med BRCA-muteret metastaserende kastrationsresistent prostatakræft, der ikke har andre behandlingsalternativer?

## 3.1 Metastaserende kastrationsresistent prostatakræft

Prostatakræft er den hyppigste kræftform hos mænd i Danmark. Prostatakræft viser sig især efter 60-årsalderen [1]. I 2018 blev der registreret 4.674 nye sygdomstilfælde [1]. Ved udgangen af 2018 var antallet af mænd med prostatakræft i Danmark 42.318 [1].

Patienter med prostatakræft, der endnu ikke har modtaget endokrin behandling, herunder androgen deprivationsterapi (ADT), eller som responderer på den endokrine behandling, kaldes for hormonsensitive. Stort set alle hormonsensitive prostatakræfttilfælde vil over tid udvikle sig til kastrationsresistente. Kastrationsresistent prostatakræft (CRPC) defineres ved serum testosteron i kastrationsniveau[1] og sygdomsprogression enten biokemisk og/eller radiologisk [2]. Metastaserende CRPC (mCRPC) defineres som prostatakræft med påviste metastaser involverende enten knogler, lymfeknuder uden for det lille bækken og/eller parenkymatøse organer.

Man screener i dag ikke patienter med mCRPC for mutationer i BRCA-genet. Fagudvalget vurderer, at ca. 5 % af patienter med mCRPC har mutationer i *breast cancer* (BRCA) 1- eller 2-genet. Disse mutationer kan både være arvelige (germline) og somatiske (kun til stede i tumor). Tilstedeværelsen af BRCA1/2-mutationer hos patienter med mCRPC har i nogle studier vist sig at være forbundet med en dårligere prognose relativt til patienter uden BRCA-mutationer, mens andre studier ikke har vist en forskel[3][4]. I modsætning til andre kræftsygdomme (fx kræft i

[1] 0,5 ng/mL eller 1,7 nmol/L

æggestokkene) er betydningen af BRCA-mutationer ikke nær så velbeskrevet i litteraturen [3][5].

Fagudvalget vurderer, at ca. 1.500 patienter årligt diagnosticeres med mCRPC. Dermed forventer fagudvalget, at omkring 75 patienter årligt vil have mCRPC med BRCA1/2-mutationer. En oversigt over incidensen af patienter i de forskellige behandlingslinjer for mCRPC kan ses Figur 1.

## 3.2 Olaparib

Olaparib (Lynparza) er indiceret som monoterapi til behandling af voksne patienter med metastatisk kastrationsresistent prostatakræft, som har BRCA1/2-mutationer (germline eller somatiske) og har progredieret under tidligere behandling, der omfattede et nyt hormonmiddel (NHA; enzalutamid og abirateron, se afsnit 3.3).

Den anbefalede dosis af olaparib er 300 mg (2 x 150 mg tabletter) indtaget to gange dagligt, svarende til en samlet daglig dosis på 600 mg. Behandlingen gives indtil progression eller uacceptabel toksicitet.

Olaparib inhiberer humane poly (ADP-ribose) polymeraseenzymer (PARP-1, PARP-2 og PARP-3) og hæmmer dermed tumorvækst. PARP'er er nødvendige for effektiv reparation af enkeltstrengsbrud på deoxyribonucleic acid (DNA). Når olaparib bindes til det aktive site på PARP-enzymet, blokeres for reparation af enkeltstrengs DNA-brud, og der akkumuleres DNA-skader, som fører til dobbeltstrengsbrud. Pga. mutation i BRCA-genet kan dobbeltstrengsbrud ikke repareres, hvilket slutteligt forårsager kræftcellens død. Til forskel fra raske celler har kræftceller ofte defekter i deres DNA-reparationsmekanismer, hvilket gør dem mere sårbare overfor hæmning af PARP-enzymerne. Erfaringer fra kræft i æggestokkene indikerer, at effekten af PARP-inhibition synes at være særlig udtalt hos patienter med BRCA1/2-mutation [6].

Olaparib er også godkendt af EMA til behandling af kræft i bughinden, brystkræft, æggestokkræft og bugspytkirtelkræft. Medicinrådet har anbefalet olaparib som mulig standardbehandling til patienter med nydiagnosticeret avanceret high-grade BRCA-muteret kræft i æggestokkene, æggelederne eller primær kræft i bughinden.

## 3.3 Nuværende behandling

Mænd med mCRPC er uhelbredeligt syge, hvorfor sigtet med behandlingen er palliation og levetidsforlængelse. Patienterne behandles livslangt med ADT, enten ved bilateral orkiektomi (kirurgisk fjernelse af testikler) eller medicinsk kastration med *Luteinising Hormone Releasing Hormone* (LHRH)-analoger [7]. Herudover behandles patienter med mCRPC i dansk klinisk praksis med docetaxel, cabazitaxel, abirateron (alle 3 inklusive lav-dosis + prednisolon), enzalutamid og radium-223 diklorid [7]. Docetaxel (75 mg/m$^2$) gives som intravenøs dosis hver 3. uge i op til 10 serier eller til progression eller uacceptabel toxicitet. Cabazitaxel (20 mg/m$^2$) gives også intravenøst hver 3. uge og fortsættes til progression eller uacceptabel toxicitet. For docetaxel gives median 6-7 behandlingsserier, og for cabazitaxel gives median 5-6 behandlingsserier.

Der findes ikke god evidens for den optimale sekvens af de anbefalede behandlinger for mCPRC. Sekvensen af behandlinger afhænger af den enkelte patients tidligere behandling, typen af sygdomsprogression og sygdomsbyrde samt performance status (metode til at graduere patienters helbredsstatus med henblik på at vurdere, hvorvidt en patient forventes at have gavn af f.eks. kemoterapi og strålebehandling).

Ca. 2/3 patienter har ingen eller få symptomer og er i god performance status (0-1). Disse patienter behandles i 1. linje med enzalutamid eller alternativt abirateron [7,8]. I 2. linje anvendes docetaxel, og i 3. linje kan anvendes cabazitaxel. Fagudvalget vurderer, at den forventede gennemsnitlige overlevelse for disse patienter efter enzalutamid eller abirateron er ca. 18 mdr. med nuværende behandlingsmuligheder. Fagudvalget vurderer, at den gennemsnitlige overlevelse vil være lidt dårligere for patienter med BRCA1/2-muteret mCRPC.

Ca. 1/3 patienter er enten symptomatiske og i performance status 1-2 eller patienter med hurtig progression på ADT i den hormonsensitive fase af prostatakræft eller patienter med viscerale metastaser. Denne gruppe behandles oftest med docetaxel i 1. linje, såfremt der ikke er givet docetaxel i den 'tidlige' hormonsensitive fase [7,8]. Patienter med mCRPC, som progredierer efter 1. linje docetaxel, behandles med enten enzalutamid eller cabazitaxel i 2. linje. Patienter genbehandles som udgangspunkt ikke med samme stof [8]. Fagudvalget vurderer, at den forventede overlevelse for disse patienter, som har fået docetaxel og herefter enzalutamid, er ca. 12 mdr. med nuværende behandlingsmuligheder. Fagudvalget vurderer, at den gennemsnitlige overlevelse vil være lidt dårligere for patienter med BRCA1/2-muteret mCRPC.

Radium-223 anvendes til patienter med symptomatiske knoglemetastaser uden viscerale metastaser eller betydelig lymfeknudeinvolvering, og som tidligere har modtaget mindst 2 linjer behandling for mCRPC eller ikke er egnede til anden mCRPC behandling.

Patienter, der ikke har flere behandlingsmuligheder, behandles med BSC. Der er stor variation i patienternes helbredsstatus, når de udelukkende tilbydes BSC. En større andel af patienterne har på dette tidspunkt fremskreden sygdom og dårlig almentilstand, og disse patienter kandiderer ikke til ny aktiv CRPC-behandling. En mindre gruppe af patienterne har fortsat god almentilstand (ECOG: 0-1), og til disse patienter mangler lige nu effektive behandlingsalternativer.

Behandling med BSC har til formål at reducere sygdomsbyrden og lindre symptomer og består i Danmark typisk af denosumab, contalgin (morfin) og binyrebarkhormon (prednisolon eller dexamethason). Fagudvalget vurderer, at den forventede overlevelse for disse patienter uden flere behandlingsmuligheder er 9 mdr. med BSC. Fagudvalget vurderer, at den gennemsnitlige overlevelse vil være lidt dårligere for patienter med BRCA1/2-muteret mCRPC.

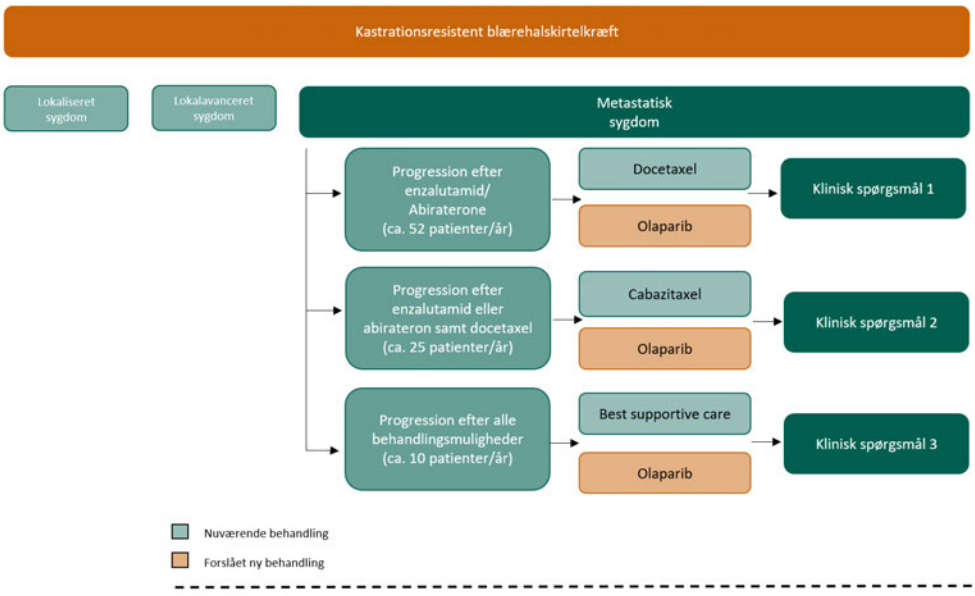
I Danmark screenes der ikke rutinemæssigt for BRCA-mutationer ved prostatacancer. Patienter med BRCA-mutationer behandles derfor efter nuværende guidelines på lige fod med andre patienter med mCRPC. De nuværende behandlingsregimer er derfor ikke godt belyst for patienter med BRCA-mutationer

Hvis olaparib anbefales af Medicinrådet som mulig standardbehandling, vil screening af patienter med mCRPC for BRCA1/2-mutationer være en forudsætning for ibrugtagning. Dette gøres allerede rutinemæssigt for patienter med kræft i æggestokkene og for en del patienter

med brystkræft. Fagudvalget bemærker, at kendskab til BRCA1/2-mutationer hos patienter med mCRPC vil give klinikerne mulighed for, for første gang at give en målrettet behandling til en lille gruppe patienter, som formentligt ville kunne få forbedret deres prognose.

Da størstedelen af danske patienter med mCRPC modtager kemoterapi ved progression på enzalutamid/abirateron, ønsker fagudvalget en sammenligning af olaparib overfor henholdsvis docetaxel og cabazitaxel (Figur 1). Ligeledes ønsker fagudvalget en analyse, hvor der sammenlignes med BSC, for at belyse effekten hos patienter, hvor øvrige behandlingsmuligheder er udtjente eller vurderet uegnede, dvs. patienter, som er progredieret på (enzalutamid eller abirateron) samt docetaxel og cabazitaxel eller ikke vurderes egnede til kemoterapi, men som fortsat har en helbredsstatus, som gør dem egnede til at modtage aktiv behandling (Figur 1). Fagudvalgets estimat af patientantal for de 3 behandlingslinjer kan ses i figur 1.

Fagudvalget finder det ikke relevant at sammenligne med Radium-223, da denne behandling kun gives i begrænset omfang.




**Figur 1. Simpel oversigt over nuværende behandling samt foreslået ny behandling i forhold til de tre kliniske spørgsmål**

# 4. Metode

Medicinrådets protokol for vurdering vedrørende olaparib til behandling af BRCA1/2-muteret metastaserende kastrationsresistent prostatakræft beskriver sammen med Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser, hvordan Medicinrådet vil vurdere lægemidlets værdi for patienterne.

# 5. Resultater

## 5.1 Klinisk spørgsmål 1

- Hvilken værdi har olaparib sammenlignet med docetaxel for patienter med BRCA1/2-muteret metastaserende kastrationsresistent prostatakræft, der er progredieret på enten enzalutamid eller abirateron?

### 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 4 fuldtekstartikler. Desuden indgår data fra EMA's EPAR for olaparib og docetaxel i ansøgningen. Sekretariatet har gennemgået ansøgers litteraturudvælgelse og ikke fundet anledning til at tilføje yderligere studier.

Tabel 1 viser et overblik over den litteratur, der anvendes i klinisk spørgsmål 1.

**Tabel 1. Oversigt over studier**

| Publikationer | Klinisk forsøg | NCT-nummer | Population |
|---|---|---|---|
| Kwon DH, Chou J, Yip SM, Reimers MA, Zhang L, Wright F, et al. Differential treatment outcomes in BRCA1/2-, CDK12-, and ATMmutated metastatic castration-resistant prostate cancer. Cancer. 2021. [9] | Forsøget har ikke et navn, men omtales Kwon et al. | Intet | mCPRC-patienter med DNA-mutationer (44 % med BRCA1/2-mutation) |
| Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. The New England journal of medicine. 2004;351(15):1502-12. [10] | TAX-327 | Intet | 1. linje mCRPC-patienter |
| Hussain M, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Survival with Olaparib in Metastatic Castration- Resistant Prostate Cancer. The New England journal of medicine. 2020;383(24):2345-57. [11]<br><br>de Bono J, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. | PROfound | NCT02987543 | mCRPC-patienter med BRCA1/2-mutation med progression efter enzalutamid/abirateron |

Olaparib for Metastatic Castration-Resistant Prostate Cancer. The New England journal of medicine. 2020;382(22):2091-102. [12]

Nedenfor beskrives de studier, som danner grundlag for vurderingen af effekten af olaparib overfor docetaxel.

**Studiekarakteristika**

PROfound

PROfound [12] sammenligner olaparib med genbehandling med *new hormonal agents* (NHA; enzalutamid eller abirateron) til patienter med metastaserende kastrationsresistent prostatakræft, som allerede er progredieret på NHA. Det er et multicenter fase III randomiseret open-label klinisk studie, hvor patienterne er randomiseret 2:1 til hhv. olaparib (300 mg 2 gange dagligt; n = 256) og NHA (enzalutamid 160 mg 1 gang dagligt eller abirateron 1000 mg 1 gang dagligt, n = 131). Begge behandlinger gives i kombination med ADT. Studiet er opdelt i en kohorte A og en kohorte B. Kohorte A (n = 245) består af patienter, som har mutationer i generne BRCA1, BRCA2 eller ATM-mutation, og kohorte B består af patienter, som har mutationer i generne BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D eller RAD54L.

En subgruppe til kohorte A er patienter med enten BRCA1- eller BRCA2-mutation (n = 160). Denne population omtales BRCAm. En yderligere opdeling består i, hvorvidt patienter med BRCA1/2-mutation har eller ikke har modtaget taxaner (docetaxel og/eller cabazitaxel; henholdsvis n = 107 og n = 53).

Det primære endepunkt er progressionsfri overlevelse (PFS) defineret som tid fra randomisering indtil *soft tissue disease progression* ifølge RECIST-kriterierne, *bone lesion progression* ifølge Prostate Cancer Clinical Trial Working Group 3 criteria eller død. Sekundære effektmål er blandt andet samlet overlevelse, sikkerhed og livskvalitet.

Data fra PROfound-studiet er tilgængelige fra to data cut-offs:

1. Den primære analyse med cut-off den 4. juni 2019 blev foretaget, efter 174 PFS-hændelser havde fundet sted i kohorte A. Data fra dette cut-off blev brugt i studiets endelige analyse af PFS.
2. Den endelige analyse med cut-off den 20. marts 2020 blev foretaget, efter 146 OS-hændelser havde fundet sted i kohorte A. Data fra dette data cut-off blev brugt i den endelig OS-analyse samt den endelige sikkerhedsanalyse.

Median opfølgningstid i studiet var 21,9 måneder i olaparibarmen og 21,0 måneder i NHA-armen.

**Vurdering af studiedesign:**
Komparator i studiet er genbehandling med NHA, hvilket ikke er dansk klinisk praksis. Fagudvalget vurderer, at genbehandling med NHA ikke forventes at have en særlig effekt og kan sidestilles med BSC.

Derudover er der i studiet mulighed for overkrydsning fra komparatorarmen til olaparib. I kohorte A+B krydsede 72 ud af 88 (82 %) over til olaparib ved progression, og i Kohorte A krydse 50 ud af 62 (80 %) over. Fagudvalget vurderer, at dette kan betyde, at effekten af olaparib sammenlignet med komparator er underestimeret i studiet.

Endeligt vurderer fagudvalget, at opfølgningstiden med *cut-off* den 20. marts 2020 er tilstrækkelig, da patienterne forventes at have en kortere median overlevelse med nuværende standardbehandling.

**Vurdering af baselinekarakteristika:**
I Tabel 2 nedenfor rapporteres de relevante baselinekarakteristika fra PROfound i forhold til kohorte A+B samt subpopulationerne BRCAm, BRCAm taxan-naive og BRCAm taxan-behandlede.

Fagudvalget bemærker, at patienterne i PROfound repræsenterer et bredt udsnit af patienter med mCRPC i forskellige behandlingslinjer, fordi der er forskel på, hvor mange behandlinger patienterne har fået, inden de er startet i studiet. Fagudvalget vurderer samtidig, at dette stemmer overens med dansk klinisk praksis, hvor patienter heller ikke følger en bestemt behandlingssekvens, og hvor omkring 1/3 af patienterne ville have modtaget docetaxel før NHA.

Fagudvalget kan ikke sammenholde baselinekarakteristika for studiedeltagerne med danske BRCA1/2-muterede mCRPC-patienter, da man ikke screener for disse mutationer på nuværende tidspunkt i dansk praksis. Fagudvalget vil i stedet sammenholde karakteristikken fra PROfound med den fulde population af mCRPC-patienter, som de kender fra dansk klinisk praksis. Fagudvalget vurderer her, at der overordnet set ikke er væsentlige forskelle mellem den fulde population i PROfound og den forventede population i dansk klinisk praksis.

Gruppen af taxan-naive patienter ser ud til at være yngre end den samlede gruppe, idet 27 % er over 65 år. Gennemsnitsalderen er for denne gruppe ikke opgjort af ansøger. Fagudvalget vurderer, at det er forventeligt, at taxan-naive patienter er lidt yngre, da de optræder tidligere i behandlingsalgoritmen, men alder vurderes ikke at have nogen væsentlig betydning for deres helbred og prognose.

**Tabel 2. Baselinekarakteristika i PROfound for kohorte A+B, BRCAm samt BRCAm med og uden tidligere taxan behandling**

| | Kohorte A+B | | BRCAm | | BRCAm, taxan-naive | BRCAm, taxan-behandlet |
|---|---|---|---|---|---|---|
| | Olaparib ( n = 256) | NHA (n = 131) | Olaparib (n = 102) | NHA (n = 58) | Olaparib (n = 30) | Olaparib (n = 72) |
| Mutation | | | | | | |
| BRCA1 | 8 (3) | 5 (4) | *Alle patienter har BRCA1/2-mutation* | *Alle patienter har BRCA1/2-mutation* | *Alle patienter har BRCA1/2-mutation* | *Alle patienter har BRCA1/2-mutation* |
| BRCA2 | 81 (32) | 47 (36) | | | | |
| ATM | 62 (24) | 24 (18) | | | | |
| CDK12 | 61 (24) | 28 (21) | | | | |
| Alder | | | | | | |
| ≥ 65, n (%) | 174 (68) | 97 (74) | 69 (68) | 37 (64) | 8 (27) | 47 (65) |
| Median | 69 (47-91) | 69 (49-87) | 68 (47-86) | 67 (49-86) | Ikke oplyst[a] | Ikke oplyst[a] |
| Metastaserende sygdom ved baseline, n (%) | | | | | | |
| Knogle, alene | 65 (25) | 36 (28) | N[a] (89)[b] | N[a] (86)[b] | 9 (30) | 22 (30) |
| Lunge | 43 (17) | 15 (12) | N[a] (23) | N[a] (16) | Ikke oplyst[a] | Ikke oplyst[a] |
| Lever | 25 (10) | 18 (14) | N[a] (12) | N[a] (17) | Ikke oplyst[a] | Ikke oplyst[a] |

| | Kohorte A+B | | BRCAm | | BRCAm, taxan-naive | BRCAm, taxan-behandlet |
|---|---|---|---|---|---|---|
| | **Olaparib ( n = 256)** | **NHA (n = 131)** | **Olaparib (n = 102)** | **NHA (n = 58)** | **Olaparib (n = 30)** | **Olaparib (n = 72)** |
| **ECOG-score ved baseline, n (%)** | | | | | | |
| 0 | 131 (51) | 55 (42) | 51 (50) | 22 (38) | 17 (57) | 34 (47) |
| 1 | 112 (44) | 71 (54) | 43 (42) | 33 (57)) | 12 (40) | 31 (43) |
| 2 | 13 (5) | 4 (3) | 8 (8) | 3 (5) | 1 (3) | 7 (10) |
| **PSA ved baseline,** | | | | | | |
| median (rækkevidde) | 68,2 (24,1-294,4) | 106,5 (37,2-326,6) | 57,5 (0,22-240) | 104,0 (1,85-7115) | Ikke oplyst[a] | Ikke oplyst [a] |
| **Tidligere taxanbehandling, n (%)** | | | | | | |
| Taxanbehandling | 170 (66) | 84 (64) | 72 (71) | 35 (60) | 0 % | 100 % |
| Docetaxel, alene | 115 (45) | 58 (44) | 41 (40)[c] | 18 (31)[c] | | Ikke oplyst [a] |
| Cabazitaxel, alene | 3 (1) | 0 | 2 (2)[c] | 1 (2)[c] | | Ikke oplyst [a] |
| Docetaxel og cabazitaxel | 51 (20) | 26 (20) | 18 (18)[c] | 10 (17)[c] | | Ikke oplyst [a] |

| | Kohorte A+B | | BRCAm | | BRCAm, taxan-naive | BRCAm, taxan-behandlet |
|---|---|---|---|---|---|---|
| | Olaparib ( n = 256) | NHA (n = 131) | Olaparib (n = 102) | NHA (n = 58) | Olaparib (n = 30) | Olaparib (n = 72) |
| **Tidligere NHA-behandling, n (%)** | | | | | | |
| Enzalutamid | 103 (40) | 54 (41) | 42 (41) | 29 (50) | Ikke oplyst[a] | Ikke oplyst[a] |
| Abirateron | 97 (38) | 54 (41) | 38 (37) | 21 (36) | | |
| Enzalutamid/abirateron | 51 (20) | 23 (18) | 20 (20) | 8 (14) | | |

[a] Ikke oplyst af ansøger.

[b] Disse data er oplyst af ansøger, men er ikke i overensstemmelse med data opgivet for den fulde population

[c] Tidligere taxan behandling for mCRPC.

Kwon et al.

Kwon et al. [9] er et multi-institutionelt retrospektivt kohortestudie blandt mCRPC-patienter med DNA-mutationer, herunder BRCA1/2-mutationer. Den totale population bestod af 149 patienter med mCRPC med DNA-mutationer, herunder havde 65 (44 %) BRCA1/2-mutation. I studiet undersøges sammenhængen mellem behandling i 1. og 2. linje og samlet overlevelse. Baseret på udtræk fra patientjournaler undersøges abirateron, enzalutamid, docetaxel og platinbaseret kemoterapi som 1. linjebehandling. I 2. linje undersøges abirateron, enzalutamid, docetaxel, platinbaseret kemoterapi, cabazitaxel og olaparib. For det kliniske spørgsmål er det analyserne af samlet overlevelse i 2. linje, som er relevante. Her indgik 67 patienter fra den samlede population (dvs. patienter med DNA-mutation men både med og uden BRCA1/2-mutationer), som i 1. linje havde modtaget enzalutamid eller abirateron. Analysen bestod af 21 patienter, som modtog docetaxel i den efterfølgende behandlingslinje.

*Vurdering af baselinekarakteristika:*

Blandt patienter, der var inkluderet i Kwon et al., var alder, stadie, PSA og Gleason Score sammenlignelig på tværs af BRCA1/2- og de øvrige DNA-mutationer (Tabel 1 i artiklen). Fagudvalget vurderer, at der overordnet set ikke er væsentlige forskelle mellem studiepopulationen i Kwon et al. og den forventede population i dansk klinisk praksis.

### 5.1.2 Databehandling og analyse

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

Til besvarelse af klinisk spørgsmål 1 har ansøger indsendt en deskriptiv sammenligning på baggrund af Kwon et al og PROfound for effektmålet samlet overlevelse. Ansøger har ikke identificeret studier med direkte sammenlignende data for effekten af olaparib over for docetaxel eller studier, der kan danne grundlag for en indirekte sammenligning for patienter med BRCA-mutationer som har modtaget behandling med enzalutamid eller abirateron. Fagudvalget har ikke kendskab til data fra kliniske studier, hvor effekten af docetaxel blandt mCRPC-patienter med BRCA1/2-mutation er undersøgt, og er derfor enige i ansøgers tilgang til vurderingen af samlet overlevelse.

For effektmålet median OS er de taxan-naive patienter fra BRCAm-subpopulation i PROfound anvendt til at estimere effekten af olaparib (n = 30) som første behandling efter NHA. Olaparib sammenlignes med resultaterne fra Kwon et al. samt fagudvalgets kliniske erfaringer vedr. effekten af docetaxel.

For effektmålet bivirkninger baseres en deskriptiv sammenligning på brug af kohorte A+B i PROfound-studiet samt EMA's produktresumé for olaparib og docetaxel. Fagudvalget bemærker, at uønskede hændelser er opgivet som grad 3 og derover og ikke som grad 3-4, som efterspurgt i protokollen. Fagudvalget vurderer, at dette ikke har en betydning for kategoriseringen af værdien af olaparib, fordi grad 5 uønskede hændelser kun udgør en lille andel, og accepterer derfor ansøgers tilgang.

For effektmålene progressionsfri overlevelse og livskvalitet er der ingen data tilgængelige, som muliggør en sammenligning mellem olaparib og docetaxel. For progressionsfri overlevelse sammenlignes resultaterne fra PRofound med fagudvalgets kliniske erfaringer vedr. effekten af docetaxel. For effektmålet livskvalitet anvendes alene data fra PROfound, hvor populationen af patienter med BRCA1/2-mutation beskrives, men uden opdeling i tidligere brug af taxaner.

### 5.1.3 Evidensens kvalitet

Da vurderingen af olaparib er baseret på en deskriptiv sammenligning med docetaxel, kan Medicinrådet ikke anvende GRADE til at vurdere kvaliteten af evidensen. Medicinrådet har vurderet studierne ved Cochrane risk of bias tool 2.0

Medicinråder vurderer evidensens kvalitet som meget lav, hvilket betyder, at nye studier 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 tilgængelige absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 1.

**Tabel 3. Resultater for klinisk spørgsmål 1**

| Effektmål | Målenhed (MKRF) | Vigtighed | PROfound olaparib | Kwon et al. samt EPAR docetaxel | Aggregeret værdi for effektmålet |
|---|---|---|---|---|---|
| Samlet overlevelse (OS) | Median OS i antal mdr.<br>(MKRF: 3 mdr.) | Kritisk | Ikke opnået ved en opfølgningstid på median 21 mdr. | 16,7 mdr. | Kan ikke kategoriseres |
| | OS-rate ved 1 år<br>(MKRF: 5 %-point) | Kritisk | Ca. 88 % [a] | Ca. 65 % [a] | |
| Uønskede hændelser/ bivirkninger | Andel af patienter med grad 5 bivirkninger<br>(MKRF: 5 %-point) | Kritisk | 2,3 % opgjort som AE | 0,3 % opgjort som AR | Kan ikke kategoriseres |
| | Andel af patienter med grad 3- 4 uønskede hændelser<br>(MKRF: 10 %-point) | Vigtigt | 52 % | Ikke opgjort | |
| | Kvalitativ gennemgang | Vigtigt | Se gennemgang | Se gennemgang | |
| Progressionsfri overlevelse (PFS) | Median i antal mdr.<br>(MKRF: 3 mdr.) | Vigtigt | [redacted] | Ikke opgjort | Kan ikke kategoriseres |
| | Rate ved 1 år<br>(MKRF: 10 %-point) | Vigtigt | Ikke opgjort | Ikke opgjort | |

| | | | | |
|---|---|---|---|---|
| Livskvalitet | Andelen af patienter, som oplever ≥ 10 points reduktion fra baseline ved kort (2-6 mdr.) og lang (> 6 mdr.) opfølgning (MKRF: 10 %-point) | Vigtigt | Ikke opgjort | Kan ikke kategoriseres |

| **Konklusion** | |
|---|---|
| **Samlet kategori for lægemidlets værdi** | Kan ikke kategoriseres.<br>Fagudvalget vurderer, at olaparib er en lovende behandling, men datagrundlaget er for usikkert til at fastlægge, om der er forskel i effekten mellem olaparib og docetaxel. Fagudvalget vurderer, at olaparib er en mere skånsom behandling end docetaxel. |
| **Kvalitet af den samlede evidens** | Meget lav |

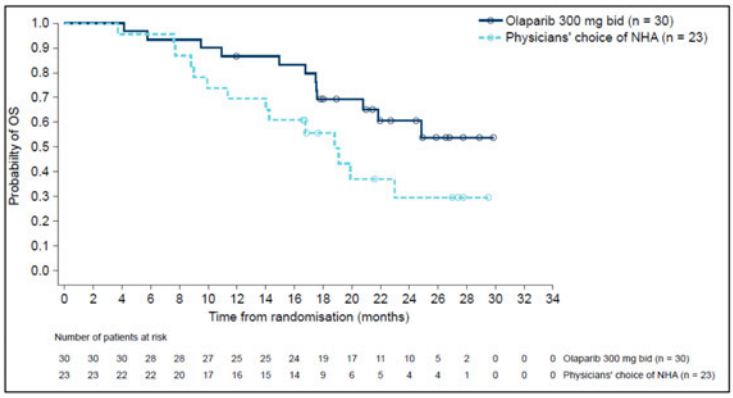
CI = konfidensinterval, HR = Hazard Ratio, OR = Odds Ratio, RR = relativ risiko.

a. Aflæst på Kaplan-Meier kurve.

**Samlet overlevelse**
Som beskrevet i protokollen er effektmålet samlet overlevelse kritisk for vurderingen af lægemidlets værdi for patienterne, fordi metastaserende kastrationsresistent prostatakræft er en dødelig sygdom.

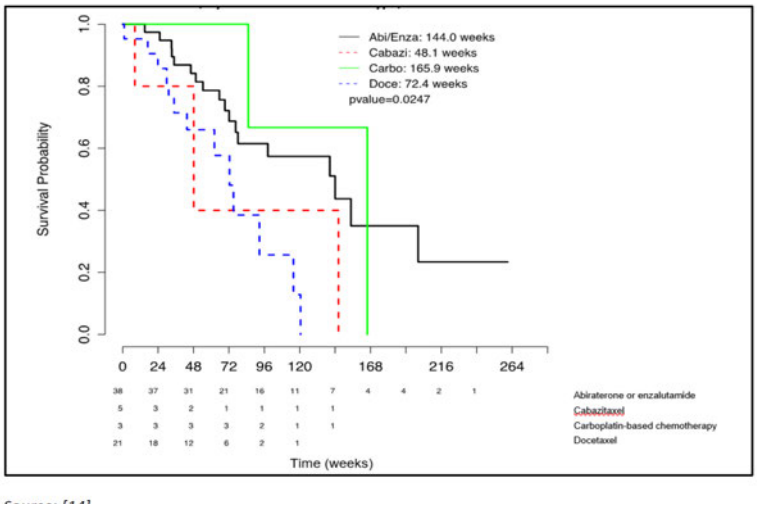
For olaparibarmen er median OS ikke opnået i PROfound hos gruppen af taxan-naive patienter med BRCA1/2-mutationer (n = 30). Aflæsning på den mørkeblå Kaplan-Meier kurve (figur 2) viser, at efter en median opfølgningstid på 21 mdr. er omkring 70 % af patienterne fortsat i live. Overlevelsesraten ved 1 år aflæses til at være ca. 88 % for olaparibarmen.

Median overlevelse for NHA-armene er i denne subgruppe 18,8 måneder, og overlevelsen efter 1 år aflæses til at være ca. 70 %.




**Figur 2. Kaplan-Meier kurve for effekten af olaparib (mørkeblå kurve) på overlevelse**

For docetaxel er median OS 16,7 måneder for patienter med DNA-mutation, der modtog docetaxel i Kwon et al. efter enzalutamid eller abirateron. OS-raten ved 1 år aflæses til at være ca. 65 %. Fagudvalget vurderer, at dette svarer nogenlunde til det kliniske billede af mCRPC-patienter med progression efter NHA, som modtager nuværende standardbehandling med docetaxel. Hos disse patienter i dansk klinisk praksis er BRCA1/2-mutationsstatus dog ukendt, hvilket behæfter vurderingen med usikkerhed. Da nogle studier indikerer, at BRCA-muterede patienter har dårligere effekt af behandling med docetaxel [3,5], ville disse patienters overlevelse teoretisk kunne være lavere end observeret i dette studie.




**Figur 3. Kaplan-Meier kurve for effekten af docetaxel (stiplet blå linje) på overlevelse**

Fagudvalget vurderer, at effekten på OS ikke kan kategoriseres grundet manglende komparative data for den relevante population. Fagudvalget vurderer, at overlevelsesraten ved 1 år på 88 %, samt at median OS ikke er nået efter median 21 måneders opfølgning, peger i retning af, at overlevelsen for patienter, der modtager olaparib, er bedre end docetaxel som følge ad deres kliniske erfaringer og data fra Kwon et al.

Sammenligningen med Kwon et al. er behæftet med stor usikkerhed. Dette skyldes, at der er tale om en deskriptiv sammenligning mellem behandlinger i to forskellige studier, hvoraf det ene er et observationelt studie, mens det andet er et randomiseret klinisk studie. Herudover tilføjer den manglende selektion af BRCA1/2-patienter i Kwon et al. usikkerhed til vurderingen.

Sammenlignes resultaterne for olaparibarmen i PROfound med fagudvalgets kliniske erfaringer, ser olaparib ud til at være mere effektivt end docetaxel, da fagudvalget estimerer, at nuværende median overlevelse for patienter med mCRPC, som er progredieret på enten enzalutamid eller abirateron, er under 18 måneder.

Der er manglende viden om generaliserbarheden til en dansk population, fordi der på nuværende tidspunkt ikke screenes for BRCA-mutation. Nogle studier har dog indikeret, at docetaxel kan være mindre effektivt i BRCA-muterede patienter, hvilket ville kunne underestimere effekten af olaparib i denne sammenligning.

**Progressionsfri overlevelse**
Som beskrevet i protokollen vurderer fagudvalget, at progressionsfri overlevelse (PFS) er et vigtigt effektmål, da det er et mål i sig selv at forsinke progressionen, fordi det betyder, at patienterne har længere tid med færre symptomer.

Da der ikke foreligger data, der muliggør en sammenligning af olaparibs og docetaxels effekt på PFS, kan værdien af olaparib ikke kategoriseres for dette effektmål. I PROfound

sås en median PFS på 13,6 mdr. ved behandling med olaparib i taxan-naive patienter med BRCA1/2-mutationer. Median PFS for behandling med NHA var 3,71 måneder. PFS på 13,6 måneder er betydende længere end fagudvalgets kliniske erfaring med docetaxel hos patienter, som progredierer på NHA, hvor median PFS estimeres til ca. 5-6 mdr. i gruppen, hvor BRCA-status er ukendt.

Fagudvalget vurderer derfor ud fra deres kliniske erfaring, at olaparib ser ud til at være mere effektivt til at forlænge PFS sammenlignet med docetaxel.

**Bivirkninger/uønskede hændelser**

Grad 5-bivirkninger

Fagudvalget vurderer, at grad 5-bivirkninger er særligt kritiske, idet de omhandler mortalitet som følge af behandlingen.

For olaparib viste data fra PROfound, at 6 ud af 256 patienter (2,3 %), der modtog olaparib, havde en grad 5 uønsket hændelse. Blandt disse patienter skete de fleste dødsfald mere end 30 dage efter den sidste dosis og var relateret til mCRPC. Der var 2 dødsfald, der blev vurderet, som muligvis er relateret til behandling med olaparib.

For docetaxel viste data fra TAX-327, som danner baggrund for EMA's produktresumé, at 2 ud af 662 (0,3 %), der modtog docetaxel, havde en grad 5 uønsket hændelse, der sandsynligvis var relateret til docetaxel. Patienterne havde mCRPC, men havde ikke tidligere modtaget behandling med enzalutamid eller abirateron.

Data for docetaxel og olaparib kan ikke sammenlignes, da det er opgjort som hændelser i PROfound og bivirkninger i TAX-327. For både docetaxel og olaparib var der få grad 5 uønskede hændelser og under den fastlagte MKRF på 5%-point. Fagudvalget vurderer derfor, at der er en ingen dokumenteret merværdi vedr. grad 5 bivirkninger.

Grad 3-4 uønskede hændelser og kvalitativ gennemgang af bivirkninger

Uønskede hændelser har betydning for den enkelte patients livskvalitet og efterlevelse af behandling. Fagudvalget anser derfor uønskede hændelser grad 3-4 som et vigtigt effektmål.

For olaparib viste data fra PROfound, at 133 ud af 256 patienter (52 %) behandlet med olaparib oplevede mindst en uønsket hændelse af grad ≥ 3.

For docetaxel viste data fra TAX-327, at 26 % oplevede bivirkninger grad 3-4.

Data for docetaxel og olaparib kan ikke sammenlignes for grad 3-4 bivirkninger, da de er opgjort som hændelser i PROFOUND og bivirkninger i TAX-327.

Som beskrevet i protokollen ønskes en kvalitativ gennemgang af bivirkningsprofilen for både olaparib og docetaxel baseret på EMA's produktresumé og fagudvalgets egen erfaring med behandling med docetaxel. Grundet usammenligneligheden af de kvantificerbare data vil fagudvalget lægge mest vægt på den kvalitative gennemgang.

*Olaparib*
Af EMA's produktresumé fremgår det, at behandling med olaparib monoterapi er forbundet med bivirkninger, som generelt er af let eller moderat sværhedsgrad, og som generelt ikke kræver afbrydelse af behandlingen. De hyppigst observerede bivirkninger var anæmi, kvalme, træthed, hovedpine, smagsforstyrrelser, hoste, neutropeni, dyspnø, hoste, svimmelhed, leukopeni, nedsat appetit, udmattelse, forstoppelse, opkast, diarré og trombocytopeni.

Bivirkningerne af grad ≥ 3, der forekom hos > 2 % af patienterne, var anæmi (16 %), neutropeni (5 %), træthed/asteni (5 %), leukopeni (3 %) og trombocytopeni (3 %).

De bivirkninger, der oftest medførte dosisafbrydelser og/eller dosisreduktioner i monoterapi, var anæmi (16,7 %), opkastning (6,3 %), kvalme (6,2 %), træthed/asteni (6,1 %) og neutropeni (6,0 %). De bivirkninger, der oftest medførte permanent seponering, var anæmi (1,7 %), trombocytopeni (0,8 %) træthed/asteni (0,7 %) og kvalme (0,7 %).

*Docetaxel*
Af EMA's produktresumé fremgår det, at de hyppigste bivirkninger for behandling af docetaxel på tværs sygdomme er reversibel neutropeni, anæmi, hårtab, kvalme, opkast, mundbetændelse, kraftløshed og diarré. De hyppigste (> 2 %) uønskede hændelser grad ≥ 3 forbundet ved docetaxel blandt mCRPC-patienter i TAX-327 er neutropeni (32 %), anæmi (4,9 %), træthed (3,9 %), infektioner (3,3 %) og kvalme (2,4 %).

Andre alvorlige hændelser, som påvirker patienterne, er dyspnø, ødemer og muskelsmerter. Derudover fremhæver fagudvalget neuropati, som forekommer hos en del patienter, og som kan være særligt invaliderende, fordi tilstanden kan blive kronisk.

Samlet vurdering af effektmålet bivirkninger/uønskede hændelser:

Samlet set kan effekten af olaparib overfor docetaxel vedr. bivirkninger/uønskede hændelser ikke kategoriseres, da der er forskel på, hvordan de er undersøgt for de to lægemidler. Der er alvorlige bivirkninger ved begge lægemidler. Bivirkningerne er generelt velkendte for begge lægemidler. Fagudvalget vurderer, at behandling med olaparib på udvalgte kliniske parametre (særligt febril neutropeni og kronisk neuropati) vil være bedre tolereret end behandling med docetaxel.

### Livskvalitet
Fagudvalget betragter livskvalitet som et vigtigt effektmål, idet behandling med olaparib er livsforlængende og ikke kurativ. I protokollen efterspurgte fagudvalget effektmålet opgjort som forskellen i andelen af patienter, som oplever ≥ 10 points reduktion fra baseline ved kort (mellem 2 og 6 måneder) og lang (> 6 måneder) opfølgningstid. Livskvaliteten er ikke opgjort som ønsket for olaparib. Ansøger har i stedet indleveret en gennemsnitlig ændring fra baseline i BRCAm-populationen for olaparib vs. NHA målt med FACT-P i PROfound.

Der foreligger ikke data, der muliggør en sammenligning af effekten på livskvalitet af olaparib overfor docetaxel. Derfor kan værdien af olaparib ikke kategoriseres vedr. livskvalitet. Fagudvalget beskriver i stedet livskvaliteten alene ud fra PROfound.

*Olaparib*
Livskvaliteten opgjort som FACT-P-score i gennemsnitlig ændring ift. baseline *(least sqaures mean)* var -5,2 (SD: 2,6) point hos patienter behandlet med olaparib og -9,7 (SD: 3,5) point hos patienter behandlet med NHA i PROfound.

### 5.1.5 Fagudvalgets konklusion

Den samlede værdi af olaparib sammenlignet med docetaxel til patienter med BRCA1/2-muteret metastaserende kastrationsresistent prostatakræft, der er progredieret på enten enzalutamid eller abirateron, kan ikke kategoriseres med Medicinrådets metoder. Da der ikke eksisterer gode kliniske data af effekten af docetaxel efter NHA blandt patienter med BRCA1/2-mutation, kan fagudvalget ikke med sikkerhed konkludere, om der er forskel i effekten mellem olaparib og docetaxel. Fagudvalget finder det dog sandsynligt, at olaparib kan være mere effektivt end docetaxel. Dette er baseret på fagudvalgets kliniske erfaringer med docetaxel i en samlet patientpopulation med og uden BRCA1/2-muteret mCRPC samt data fra Kwon et al. Specifikt er OS (88 % i live efter 1 år og median OS ikke nået ved 21 mdr.) samt median PFS for olaparib (13,6 mdr.) markant bedre end fagudvalgets erfaring med docetaxel i denne samlede population (median OS <18 mdr.; median PFS: 5-6 mdr.). Vurderingen er usikker, da der er tale om en deskriptiv sammenligning. Forskellen mellem olaparib og docetaxel kan være underestimeret, da studier har vist, at behandling med docetaxel kan have en dårligere effekt for BRCA-muterede patienter med mCRPC vs. patienter uden mutationer. Fagudvalget vurderer desuden, at behandling med olaparib på udvalgte kliniske parametre vil være bedre tolereret end behandling med docetaxel, hvor især antallet af patienter med kronisk neuropati og antallet af patienter, der indlægges med febril neutropeni, forventes at være betydeligt lavere. Derfor vil en aktiv målrettet behandling, der kan forsinke sygdomsudviklingen med færre bivirkninger sammenlignet med den nuværende standardbehandling være en gevinst for patienten.

## 5.2 Klinisk spørgsmål 2

- Hvilken værdi har olaparib sammenlignet med cabazitaxel for patienter med BRCA1/2-muteret metastaserende kastrationsresistent prostatakræft, der er progredieret efter behandling med [enzalutamid eller abirateron] samt docetaxel?

### 5.2.1 Litteratur

Ansøger anvender PROfound til at estimere effekten af olaparib. PROfound-studiet er beskrevet i afsnit 5.1.1. Ansøger anvender CARD-studiet til at estimere effekten af cabazitaxel. Tabel 4 i afsnit 5.1.1 viser et overblik over populationen af BRCAm-taxan-behandlede patienter, som er relevant for klinisk spørgsmål 2.

Ansøger har søgt litteratur med søgestrengen fra protokollen og har udvalgt 5 fuldtekstartikler. Sekretariatet har ikke tilføjet yderligere studier.

**Tabel 4. Oversigt over studier**

| Publikationer | Klinisk forsøg | NCT-nummer | Population |
|---|---|---|---|
| Hussain M, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer. The New England journal of medicine. 2020;383(24):2345-57. [11]<br><br>de Bono J, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. The New England journal of medicine. 2020;382(22):2091-102. [12] | PROfound | NCT02987543 | mCRPC-patienter med BRCA1/2-mutation med progression efter enzalutamid/abirateron og docetaxel/cabazitaxel (n = 72) |
| de Wit R, de Bono J, Sternberg CN, Fizazi K, Tombal B, Wülfing C, et al. Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. The New England journal of medicine. 2019;381(26):2506-18. [13]<br><br>Fizazi K, Kramer G, Eymard JC, Sternberg CN, de Bono J, Castellano D, et al. Quality of life in patients with metastatic prostate cancer following treatment with cabazitaxel versus abiraterone or enzalutamide (CARD): an analysis of a randomised, multicentre, open-label, phase 4 study. The Lancet Oncology. 2020;21(11):1513-25. [14]<br><br>Reason T, McCrea C, Hettle R, Ghate S, Poehlein CH, Olmos D. Indirect treatment comparison of the efficacy of olaparib 300 mg tablets BID and cabazitaxel 25 mg/m2 every 3 weeks plus daily prednisolone and granulocyte colony-stimulating factor in the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC). Journal of Clinical Oncology. 2021;39(15_suppl):5051- (ASCO 2021 poster) | CARD | NCT02485691 | mCRPC-patienter med progression efter docetaxel og enzalutamid/abirateron (n = 129) |

Nedenfor beskrives de studier og populationer, som danner grundlag for vurderingen af effekten af olaparib overfor cabazitaxel.

**Studiekarakteristika**

PROfound

PROfound-studiet er beskrevet i afsnit 5.1.1. Baselinekarakteristika for PROfound er beskrevet i Tabel 2. For klinisk spørgsmål 2 er det subgruppen af patienter med BRCA1/2-mutation, som tidligere har modtaget taxanbehandling (BRCAm-taxan-behandlede), som er relevant.

Fagudvalget vurderer, at patienternes alder og ECOG-score i subgruppen BRCAm-taxan-behandlede er sammenlignelig med den samlede population i PROfound og med den forventede populationen i dansk klinisk praksis. Det er dog vanskeligt at vurdere, om gruppen af taxan-behandlede adskiller sig fra de øvrige populationer i PROfound, da kun sparsomme baselinekarakteristika er tilgængelige fra ansøgers side. Dette kan have betydning for vurderingen af resultaterne, hvis der er forskelle i prognostiske faktorer.

CARD

CARD er randomineret studie, hvor effekten af cabazitaxel undersøges blandt patienter med metastaserende kastrationsresistent prostatakræft, der tidligere har modtaget docetaxel, og som er progredieret efter behandling med enzalutamid eller abirateron. Populationen bestod af i alt 255 patienter, hvoraf 129 blev randomiseret til at modtage cabazitaxel (25 mg/m$^2$) og 126 til kontrolarmen med enzalutamid (160 mg 1 gang dagligt) eller abirateron (1000 mg 1 gang dagligt). Fagudvalget bemærker yderligere, at dansk klinisk praksis er 20 mg/m$^2$, hvilket medfører færre bivirkninger. Fagudvalget bemærker, at studiepopulationen ikke er selekteret for patienter med BRCA1/2-mutation, hvilket kan skævvride en sammenligning til dansk klinisk praksis. For yderligere tilgængelige baggrundskarakteristika vurderer fagudvalget, at der overordnet set ikke er væsentlige forskelle mellem studiepopulationen i CARD og den forventede population i dansk klinisk praksis.

### 5.2.2 Databehandling og analyse

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

Ansøger har indsendt en publiceret *matching adjusted indirect comparison* (MAIC)-analyse, der beskriver den relative effekt mellem olaparib og cabazitaxel for effektmålene OS, PFS og uønskede hændelser. Fagudvalget vurderer, at den indsendte MAIC-analyse ikke kan ligge til grund for en kategorisering af værdien af olaparib overfor cabazitaxel, da populationerne i de to studier er for forskellige:

- Fagudvalget vurderer, at den manglende selektion af patienter med BRCA-1/2-mutation i CARD-studiet gør, at behandlinger, behandlingsrespons samt prognosen ikke kan sammenlignes med populationen i PROfound. Det er ikke muligt at vurdere, om dette betyder, at prognosen generelt er bedre eller værre i CARD-studiet end i PROfound, da fagudvalget ikke kender til studier, som har sammenlignet effekten af cabazitaxel i patienter med eller uden BRCA-mutationer i denne behandlingslinje.
- Der er forskel på, hvordan patienter blev behandlet forud for inklusionen i studiet. I begge studier har patienterne enten modtaget enzalutamid eller abirateron, men i

CARD-studiet måtte der ikke gå mere end 12 måneder, før patienterne progredierede på behandling med abirateron eller enzalutamid, hvis de skulle inkluderes i studiet. I PROfound-studiet måtte der gerne gå mere end 12 måneder, før progression efter behandling med abirateron eller enzalutamid var påbegyndt. Fagudvalget vurderer, at de fleste patienter vil opleve progression inden 12 mdr., og dermed forventes forskellen mellem studierne ikke at udgøre et stort problem.

- I CARD-studiet skulle patienter have modtaget mindst 3 serier docetaxel, før de startede i studiet, hvor PROfound-studiet inkluderer patienter, uanset om de tidligere har modtaget både docetaxel og cabazitaxel, kun docetaxel eller kun cabazitaxel. Dette medfører, at den relevante population for klinisk spørgsmål 2 i PROfound inkluderer patienter, der har modtaget docetaxel og/eller cabazitaxel. De patienter i PROfound, der både havde modtaget cabazitaxel og docetaxel (18 ud af 72 BRCAm-taxan-behandlede patienter) kan have en dårligere prognose vedr. OS end patienterne i CARD. Fagudvalget vurderer, at dette kan betyde, at effekten af olaparib sammenlignet med cabazitaxel kan være underestimeret. Endelig er der i PROfound-studiet overkrydsning til olaparib for ca. 80 % af patienterne i komparatorarmen. I CARD-studiet var overkrydsning fra komparator til cabazitaxel også tilladt men forekom i mindre grad. Fagudvalget vurderer, at dette kan betyde, at effekten af olaparib sammenlignet med cabazitaxel kan være underestimeret.

På baggrund af ovenstående har fagudvalget besluttet ikke at anvende ansøgers indirekte analyse (MAIC-analysen). I stedet vurderer fagudvalget værdien af olaparib overfor cabazitaxel ved en deskriptiv sammenligning af studiedata fra PROfound og CARD.

For effektmålet samlet overlevelse og PFS har fagudvalget anvendt subgruppen af patienter i PROfound med BRCA1/2-mutation, som progredierer efter at have modtaget enzalutamid/abirateron samt docetaxel og/eller cabazitaxel (n = 107). Denne population adskiller sig fra den ønskede population ved også at indeholde patienter, som modtog cabazitaxel. Subpopulationen i PROfound sammenlignes med den samlede patientpopulation fra CARD, som rummer mCRPC-patienter med progression efter docetaxel og enzalutamid/abirateron, som dog ikke er selekteret for mutationer, herunder BRCA1/2-mutationer.

For effektmålet bivirkninger/uønskede hændelser har fagudvalget valgt at sammenligne den totale population kohorte A+B i PROfound (beskrevet i afsnit 5.1.1) med populationen fra CARD. For begge populationer gælder, at bivirkninger er opgjort for grade 3 og derover og ikke grade 3-4, som efterspurgt i protokollen.

For effektmålet livskvalitet har ansøger indsendt data for den fulde BRCAm-population. Denne sammenligner fagudvalget deskriptivt med data fra CARD-studiet.

### 5.2.3 Evidensens kvalitet

Da vurderingen af olaparib er baseret på en deskriptiv sammenligning med cabazitaxel, kan Medicinrådet ikke anvende GRADE til at vurdere kvaliteten af evidensen.

Medicinrådet har dog vurderet studierne ved Cochrane risk of bias tool 2.0

Medicinrådet vurderer evidensens kvalitet som meget lav, hvilket betyder, at nye studier 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, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 2.

**Tabel 5. Resultater for klinisk spørgsmål 2**

| | | PROfound (taxan-behandlede) | | | | CARD | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Effektmål og vigtiged** | **Målenhed (MKRF)** | **Olaparib (95 % CI)** | **NHA (95 % CI)** | **Absolut forskel (95 % CI)** | **Relativ effektforskel (95 % CI)** | **Cabazitaxel (95 % CI)** | **NHA (95 % CI)** | **Absolut forskel (95 % CI)** | **Relativ effektforskel (95 % CI)** |
| Samlet overlevelse (OS) | Median i antal mdr. (MKRF: 3 mdr) | 17,5 mdr. | 11,9 mdr. | 5,6 mdr. | HR: 0,63 (0,39; 1,04) | 13,6 mdr. | 11,0 mdr. | 2,6 mdr. | HR: 0,64 (0,46; 0,89) |
| | Rate ved 1 år (MKRF: 5 %-point) | Ca. 65 % [a] | Ca. 50 % [a] | Ca. 15 % | | Ca. 60 % [a] | Ca. 50 % [a] | Ca. 10 % | |
| Progressionsfri overlevelse (PFS) | Median i antal mdr. (MKRF: 3 mdr.) | [redacted] | [redacted] | [redacted] | HR: [redacted] | 8,0 mdr. | 3,7 mdr. | 4,3 mdr. | HR: 0,54 (0,40; 0,73) |
| | Rate ved 1 år (MKRF: 10 %-point) | [redacted] | [redacted] | [redacted] | | Ca. 27 % | Ca. 7 % | Ca. 20 % | |
| Uønskede hændelser / bivirkninger | Andel af patienter med grad 5-bivirkninger (MKRF: 5 %-point) | 2,3 % | 2,3 % | 0,3 % (-3,17; 3,17) | RR: 1,02 (0,26-4,00) | 5,6 % | 11,3 % | 5,7 % | Ikke opgjort |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Andel af patienter med grad 3- 4 uønskede hændelser<br><br>(MKRF: 10 %-point) | 52 % | 40 % | 12 % (0,9; 22,9) | 56,3 % | 52,4 % | 3,9 % | |
| | Kvalitativ gennemgang | Se gennemgang | | | Se gennemgang | | | |
| Livskvalitet | Andelen af patienter, som oplever ≥ 10 points reduktion fra baseline ved kort (2-6 mdr.) og lang (> 6 mdr.) opfølgning (MKRF: 10 %-point) | Ikke gjort | | | Ikke opgjort | | | |

| **Konklusion** | |
|---|---|
| **Samlet kategori for lægemidlets værdi** | Kan ikke kategoriseres.<br><br>Fagudvalget vurderer, at olaparib er en lovende behandling, men datagrundlaget er for usikkert til at fastlægge, om der er forskel i effekten mellem olaparib og cabazitaxel. Fagudvalget vurderer, at olaparib er en mere skånsom behandling end cabazitaxel. |
| **Kvalitet af den samlede evidens** | Meget lav. |

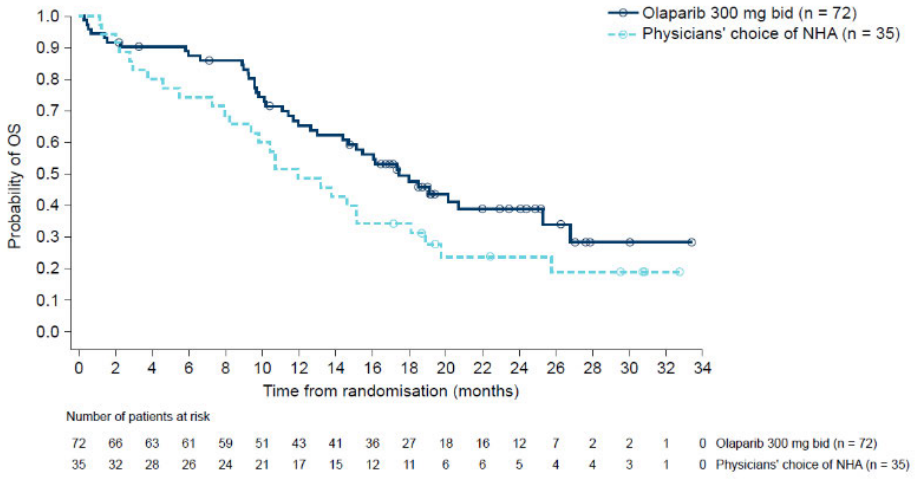
CI = konfidensinterval, HR = Hazard Ratio, RR = relativ risiko.

a. Aflæst af ansøger på Kaplan-Meier kurve.

**Samlet overlevelse**
Som beskrevet i protokollen er effektmålet samlet overlevelse (OS) kritisk for vurderingen af lægemidlets værdi for patienterne, fordi metastaserende kastrationsresistent prostatakræft er en dødelig sygdom.

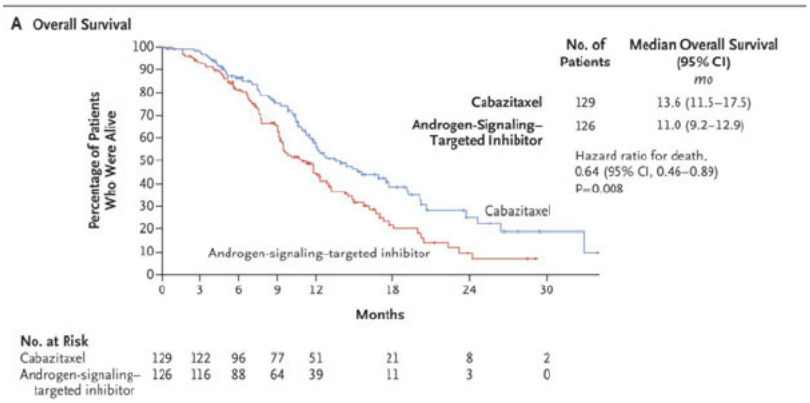
Effekten på OS viste en median OS på 17,5 måneder for olaparib og 11,9 måneder for NHA, hvilket svarer til en absolut forskel i median OS på 5,6 måneder. Den relative forskel, som fremgår af Tabel 5, var ikke signifikant (HR: 0,63 (0,39-1,04) i PROfound-populationen med 160 deltagere. Aflæsning på Kaplan-Meier plot (Figur 4) giver, at OS-raten ved 1 år var ca. 65 % for olaparib og ca. 50 % for NHA, hvilket svarer til en forskel på 15 %-point.

Fagudvalget fremhæver, at ca. 80 % krydsede over til at modtage olaparib i PROfound, hvilket medfører, at estimatet i NHA-gruppen kan være overestimeret.




**Figur 4. Kaplan-Meier plot for overlevelse i PROfound hos taxan-behandlede patienter med BRCA1/2-mutation**

Effekten på OS viste en median OS på 13,6 måneder over for cabazitaxel og 11,0 måneder for enzalutamid/abirateron, hvilket svarer til en absolut forskel i median OS på 2,6 måneder. Den relative forskel (HR: 0,64, 95 % CI 0,46-0,89), som fremgår af Tabel 5 , indikerer en signifikant forbedring i overlevelsen for patienter, der modtog cabazitaxel. Aflæsning på Kaplan-Meier plot (Figur 5) giver, at OS-raten ved 1 år var ca. 60 % for cabazitaxel og ca. 50 % for NHA, hvilket svarer til en forskel på 10 %-point.




**Figur 5. Kaplan-Meier plot for overlevelse i CARD**

Effekten af olaparib overfor cabazitaxel kan ikke kategoriseres for OS, pga. manglende komparative data. Fagudvalget vurderer, at data kunne tyde på en større overlevelsesgevinst for olaparib overfor cabazitaxel. Der lægges vægt på, at den absolutte forskel til komparator er en smule større i PROfound-studiet end i CARD-studiet (5,6 mdr. versus 2,3 mdr.), samt at median OS for olaparib er knap 4 måneder længere end median OS for cabazitaxel. Dog er den relative effektforskel i de to studier tilsvarende.

Sammenligningen mellem PROfound og CARD er behæftet med stor usikkerhed, da der er tale om en deskriptiv sammenligning mellem behandlinger i to forskellige studier. Effekten på OS kan være påvirket af senere behandlingslinjer, som kan være forskellige mellem studierne, ligesom overkrydsning kan udgøre et problem. Derudover kan den manglende selektion af BRCA1/2-patienter i CARD medføre, at patienterne i CARD har en bedre prognose end patienter i PROfound og dermed en risiko for underestimering af olaparibs effekt.

**Progressionsfri overlevelse**

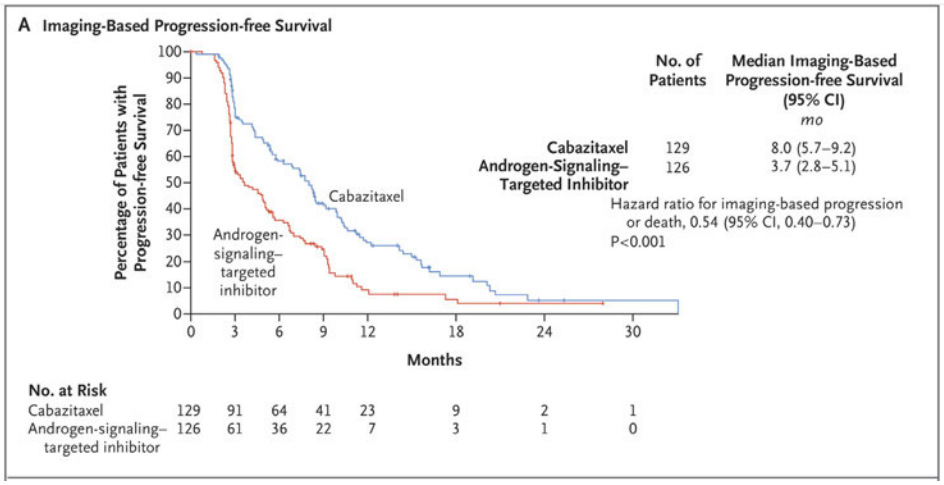
Som beskrevet i protokollen vurderer fagudvalget, at progressionsfri overlevelse (PFS) er et vigtigt effektmål, da det er et mål i sig selv at forsinke progressionen, fordi det betyder, at patienterne har længere tid med færre symptomer.

I PROfound sås en median PFS på [redacted] måneder ved behandling med olaparib og [redacted] måneder ved behandling med NHA, hvilket svarer til en forskel i median PFS på [redacted] måneder for olaparib overfor NHA. Den relative effektforskel var (HR[redacted]. Aflæsning på Kaplan-Meier plot (Figur 6) giver, at PFS-raten ved 1 år var ca [redacted] for olaparib og ca. [redacted] for NHA, hvilket svarer til en forskel på [redacted] %-point.

[redacted]

Figur 6 [redacted]

I CARD ses en median PFS på 8,0 måneder for cabazitaxel og 3,7 måneder for enzalutamid/abirateron, hvilket giver en absolut forskel i median PFS på 4,3 måned. Den relative forskel var (HR: 0,54 (0,40-0,73)) (Tabel ). Aflæsning på Kaplan-Meier plot (Figur 7) giver, at PFS-raten ved 1 år var ca. 27 % for cabazitaxel og ca. 7 % for NHA, hvilket svarer til en forskel på 20 %-point.




Figur 7. Kaplan-Meier plot for PFS i CARD

Olaparibs værdi overfor cabazitaxel kan ikke kategoriseres for PFS, pga. manglende komparative data. Fagudvalget vurderer, at median PFS er sammenlignelig i interventionsarmene i PROfound og CARD, men at den absolutte forskel til genbehandling med NHA er større for olaparib (7,1 mdr.) end for cabazitaxel (4,3 mdr.). Yderligere er den relative effektforskel større for olaparib overfor NHA end for cabazitaxel overfor NHA. Fagudvalget bemærker, at for PFS-raten ved 1 år er den absolutte forskel til komparator tilsvarende i de to studier, hvilket betyder, at man hen

over 1 år ikke helt kan undgå progression, men at tiden til denne måske kan forsinkes med olaparib sammenlignet med cabazitaxel.

Sammenligningen mellem PROfound og CARD er behæftet med usikkerhed, da der er tale om en deskriptiv sammenligning mellem behandlinger i to forskellige studier. Herudover kan den manglende selektion af BRCA1/2-patienter i CARD medføre en dårligere prognose blandt patienter i PROfound-studiet og dermed en risiko for underestimering af olaparibs effekt.

**Bivirkninger/uønskede hændelser**

### Bivirkninger grad 5

Fagudvalget vurderer, at grad 5-bivirkninger er særligt kritiske, idet de omhandler mortalitet som følge af behandlingen.

Data er opgjort som AE i begge studier. 6 ud af 256 patienter (2,3 %), der modtog olaparib, og 3 ud af 130 patienter (2,3 %), der modtog NHA, havde en grad 5 uønsket hændelse. De fleste dødsfald i begge arme skete efter 30 dage efter den sidste dosis og var relateret til mCRPC. Den absolutte forskel er beregnet til 0,3 % (-3,17; 3,17).

7 ud af 126 (5,5 %), der modtog cabazitaxel, og 14 ud af 124 patienter (11,3 %), der modtog enzalutamid eller abirateron, havde en uønsket hændelse grad 5, hvilket svarer til en absolut forskel på 5,8 %. Ingen af hændelserne var relateret til behandlingerne.

Der er ikke noget, der tyder på, at andelen af grad 5 uønskede hændelser er større ved olaparib end ved cabazitaxel. Fagudvalget vurderer derfor, at der er en ingen dokumenteret merværdi vedr. grad 5 bivirkninger.

### Grad 3-4 uønskede hændelser og kvalitativ gennemgang af bivirkninger

Uønskede hændelser har betydning for den enkelte patients livskvalitet og efterlevelse af behandling, og derfor anser fagudvalget uønskede hændelser grad 3-4 som et vigtigt effektmål.

133 ud af 256 patienter (52 %) behandlet med olaparib og 53 ud af 130 patienter (40 %), der modtog NHA, oplevede mindst en uønsket hændelse af grad ≥ 3 i PROfound. Dette svarer til en absolut forskel på 12 % (0,9-22,9). Den relative forskel var RR: 1,27 (1,00-1,61).

71 ud af 126 patienter (56,3 %), der modtog cabazitaxel, og 65 ud af 124 patienter (52,4 %), der modtog NHA, oplevede mindst en uønsket hændelse af grad ≥ 3 i CARD. Det svarer til en absolut forskel på 3,9 %.

Olaparibs værdi overfor cabazitaxel kan ikke kategoriseres for uønskede hændelser grad 3-4, pga. manglende komparative data. Fagudvalget bemærker, at hændelsesraterne for NHA i studierne var markant forskellige, hvilket gør det svært at sige noget om cabazitaxels og olaparibs potentielle indbyrdes forskel. Herudover er der forskel i behandlingslængden, som er længere for olaparib vs. cabazitaxel. Fagudvalget lægger derfor i sin vurdering af sikkerhed vægt på den kvalitative gennemgang nedenfor.

*Olaparib*
En kvalitativ gennemgang af bivirkninger for olaparib er gennemgået i afsnit 5.1.4.

*Cabazitaxel*
Af EMA's produktresumé fremgår det, at de hyppigste bivirkninger (≥ 10 %) for behandling med cabazitaxel af mCRPC-patienter var anæmi (97,3 %), leukopeni (95,6 %), neutropeni (93,5 %), thrombocytopeni (47,4 %) og diarré (46,6 %). De mest almindeligt forekommende (≥ 5 %) grad ≥ 3-bivirkninger var neutropeni (81,7 %), leukopeni (68,2 %), anæmi (10,5 %), febril neutropeni (7,5 %) og diarré 6,2 %. Dette gælder dog for dosis på 25 mg/m2, og som tidligere nævnt gives i Danmark dosis på 20 mg/m2, som er vist at være forbundet med færre bivirkninger og ingen nævneværdig forskel i effekt.

For 20 mg/m2 er neutropeni (37,8 %), leukopeni (21,7 %), anæmi (6,5 %), febril neutropeni (2,4 %) og diarre (3,5 %) de hyppigste grad ≥ 3-bivirkninger [15].

Behandlingsafbrydelse på grund af bivirkninger forekom hos 68 patienter (18,3 %), som modtog cabazitaxel. Den bivirkning, som hyppigst medførte seponering af cabazitaxel, var neutropeni.

Der er ligeledes risiko for dyspnø, ødemer og muskelsmerter om end det forekommer mindre hyppigt end ved docetaxel. Derudover fremhæver fagudvalget neuropati, som forekommer hos en mindre gruppe af patienter, men som kan være særligt invaliderende, fordi tilstanden kan blive kronisk.

Samlet vurdering af effektmålet bivirkninger/uønskede hændelser:

Samlet set kan effekten af olaparib overfor cabazitaxel mht. bivirkninger/uønskede hændelser ikke kategoriseres, pga. manglende komparative data.

Der er alvorlige men velkendte bivirkninger ved begge lægemidler. Cabazitaxel har mange af de samme bivirkninger som docetaxel, selvom de forekommer i mindre grad. Fagudvalget bemærker, at der vil være patienter som har tålt docetaxel dårligt og for eksempel har været indlagt med febril neutropeni og som fortsat har gener i form af for eksempel kronisk neuropati. Fagudvalget vurderer, at disse patienter formentlig vil være bedre tjent med behandling med olaparib end cabazitaxel.

**Livskvalitet**
Fagudvalget betragter livskvalitet som et vigtigt effektmål, idet behandling med olaparib er livsforlængende og ikke kurativ. I protokollen efterspurgte fagudvalget effektmålet opgjort som forskellen i andelen af patienter, som oplever ≥ 10 points reduktion fra baseline ved kort (mellem 2 og 6 måneder) og lang (> 6 måneder) opfølgningstid. Livskvaliteten er ikke opgjort som ønsket for olaparib. Ansøger har i stedet indleveret gennemsnitlig ændring fra baseline i BRCAm-populationen for olaparib vs. NHA målt med FACT-P i PROfound.

Da der ikke er indleveret data, der muliggør en deskriptiv sammenligning, kan værdien af olaparib ikke kategoriseres. Fagudvalget beskriver i stedet livskvaliteten i de to studier hver for sig.

Livskvaliteten opgjort som FACT-P-score i gennemsnitlig ændring ift. baseline *(least sqaures mean)* var -5,2 (SD: 2,6) point hos patienter behandlet med olaparib og -9,7 (SD: 3,5) point hos patienter behandlet med NHA i PROfound. Forskellen mellem grupperne var 4,45 (-4,01; 12,91) point. Der var dermed ikke en signifikant forskel i livskvaliteten mellem de to grupper.

I CARD er andelen af patienter, der oplever ≥ 10 points reduktion fra baseline, målt ved FACT-P, opgjort efter en median opfølgningstid på 22 uger for cabazitaxel og 12,5 uger for NHA. 32 ud af 108 (30 %) patienter, der modtog cabazitaxel, og 33 ud af 111 (29 %), der modtog NHA, oplevede en forværring i livskvalitet. 21 ud af 129, der modtog cabazitaxel (16 %), og 12 ud af 126 (10 %), der modtog NHS, var ikke med i opgørelsen, fordi de ikke havde gennemført spørgeskemaet.

Livskvaliteten opgjort som FACT-P-score i gennemsnitlig ændring ift. baseline *(least sqaures mean)* var -6,33 (SD: 2,81) point hos patienter behandlet med cabazitaxel og -10,91 (SD: 3,13) point hos patienter behandlet med NHA i CARD. Forskellen mellem grupperne var 4,58 (-1,36; 10,52) point. Der var dermed ikke en signifikant forskel i livskvaliteten mellem de to grupper.

Samlet set er det ikke muligt for fagudvalget at vurdere, om der er forskel mellem effekten af olaparib og cabazitaxel på livskvalitet. Der er ikke signifikant forskel til komparator for hverken cabazitaxel eller olaparib i nogen af studierne.

### 5.2.5 Fagudvalgets konklusion

Den samlede værdi af olaparib sammenlignet med cabazitaxel til patienter med BRCA1/2-muteret metastaserende kastrationsresistent prostatakræft, der er progredieret på enten enzalutamid eller abirateron samt docetaxel, kan ikke kategoriseres med Medicinrådets metoder.

Forskelle i studiedesign og manglende selektion af patienter med BRCA1/2-mutation i CARD betyder, at fagudvalget ikke med sikkerhed kan konkludere, om der er forskel i effekten mellem olaparib og cabazitaxel. Fagudvalget finder behandlingen lovende og hæfter sig især ved, at median OS og PFS på hhv. 17,5 mdr. og 9 mdr. ved behandling med olaparib er væsentlig bedre end fagudvalgets erfaring med cabazitaxel i den samlede population (OS: ca. 12 mdr.; PFS ca. 5-6 mdr.), og mere end der er observeret i CARD-studiet (OS: 13,6 mdr.; PFS 8,0 mdr.) for cabazitaxel.

Fagudvalget vurderer desuden, at behandling med olaparib på udvalgte kliniske parametre vil være bedre tolereret end behandling med cabazitaxel, hvor især antallet af patienter med kronisk neuropati og antallet af patienter, der indlægges med febril neutropeni, må forventes at være lavere. Derfor vil en aktiv målrettet behandling, der kan forsinke sygdomsudviklingen med færre bivirkninger sammenlignet med den nuværende standardbehandling være en gevinst for patienten.

## 5.3 Klinisk spørgsmål 3

- Hvilken værdi har olaparib sammenlignet med *best supportive care* (BSC) for patienter med BRCA-muteret metastaserende kastrationsresistent prostatakræft, der ikke har andre behandlingsalternativer?

### 5.3.1 Litteratur

PROfound-studiet, som ligger til grund for besvarelsen af klinisk spørgsmål 3, er beskrevet i afsnit 5.1.1. Den specifikke subpopulation i studiet, taxan-behandlede BRCAm-patienter, er beskrevet i afsnit 5.2.1 og Tabel 2. Populationen indeholder dog også en stor del patienter, som kun har været behandlet med én taxan-behandling tidligere udover NHA.

### 5.3.2 Databehandling og analyse

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

Interventions- og kontrolarmen i PROfound vurderes at være tilstrækkelig til at foretage en direkte sammenligning af effekten af olaparib over for BSC. Kontrolarmen i PROfound-studiet er en genbehandling med NHA, og selvom sekventiel behandling med NHA ikke er dansk standard, ønsker fagudvalget at se på data fra denne arm, fordi effekten af sekventiel behandling forventes at være meget lille og sammenlignelig med BSC. Fagudvalget bemærker dog, at dette kan betyde, at patienterne i NHA-gruppen kan have en bedre prognose end patienter, der i Danmark kun har BSC som behandlingsmulighed. Yderligere bemærker fagudvalget, at problematikken omkring overkrydsning til olaparib i komparator-armen også bidrager til usikkerhed i vurderingen af klinisk spørgsmål 3.

For effektmålene samlet overlevelse og progressionsfri overlevelse har ansøger anvendt subgruppen af taxan-behandlede patienter i PROfound med BRCA1/2-mutation med progression efter enten enzalutamid eller abirateron. Fagudvalget bemærker, at ikke alle patienterne i denne gruppe har modtaget både docetaxel og cabazitaxel, som var definitionen af populationen i protokollen (18 ud af 72 af modtaget behandling med både docetaxel og cabazitaxel). Dette ville være gældende for størstedelen af populationen i dansk klinisk praksis og betyder, at den pågældende population forventes at have en bedre prognose for overlevelse og PFS end den population, der er beskrevet i protokollen. Dette bidrager yderligere til usikkerheden af konklusionerne, men vil være ens for begge grupper i studiet.

For effektmålet bivirkninger/uønskede hændelser anvendes alle patienter i PROfound, der modtog mindst en dosis, som beskrevet i afsnit 5.2.1. For BSC gennemgår fagudvalget bivirkningsprofilen for de hyppigste lægemidler, der anvendes.

For effektmålet livskvalitet anvendes populationen af patienter med BRCA1/2-mutation, men uden opdeling i tidligere brug af taxaner.

### 5.3.3 Evidensens kvalitet

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

Medicinrådet vurderer evidensens kvalitet som meget lav, hvilket betyder, at nye studier med høj sandsynlighed kan ændre konklusionen.

Vurdering af risikoen for bias ved de enkelte studier fremgår af bilag 2.

### 5.3.4 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 3.

**Tabel 6. Resultater for klinisk spørgsmål 3**

| 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 i antal mdr. (MKRF: 3 mdr.) | Kritisk | 5,6 mdr. | Kan ikke kategoriseres | HR: 0,63 (0,39; 1,04) | Kan ikke kategoriseres | Kan ikke kategoriseres |
| | Rate ved 1 år (MKRF: 5 %-point) | | 17 %-point | Kan ikke kategoriseres | | | |
| Progressionsfri overlevelse (PFS) | Median i antal mdr. (MKRF: 3 mdr.) | Vigtigt | [redacted] | Kan ikke kategoriseres | [redacted] | Stor merværdi | **Stor merværdi** |
| | Rate ved 1 år (MKRF: 10 %-point) | Vigtigt | [redacted] | Kan ikke kategoriseres | | | |
| Uønskede hændelser / bivirkninger | Andel af patienter med grad 5 bivirkninger (MKRF: 5 %-point) | Kritisk | Ikke opgjort | Kan ikke kategoriseres | Ikke opgjort | Kan ikke kategoriseres | **Kan ikke kategoriseres** |
| | Andel af patienter med grad 3-4 uønskede hændelser (MKRF: 10 %-point) | Vigtigt | Ikke opgjort | Kan ikke kategoriseres | Ikke opgjort | Kan ikke kategoriseres | **Kan ikke kategoriseres** |
| | Kvalitativ gennemgang | Vigtigt | | | | | |
| Livskvalitet | Andelen af patienter, som oplever ≥ 10 points reduktion fra baseline ved kort (2-6 mdr.) og lang (> 6 mdr.) opfølgning (MKRF: 10 %-point) | Vigtigt | Ikke opgjort | Kan ikke kategoriseres | Ikke opgjort | Kan ikke kategoriseres | **Kan ikke kategoriseres** |

| Konklusion | |
|---|---|
| **Samlet kategori for lægemidlets værdi** | Kan ikke kategoriseres. Værdien kan ikke kategoriseres, fordi studiepopulationen ikke afspejler den danske patientpopulation. Fagudvalget vurderer, at olaparib har en bedre effekt end best supportive care (BSC), men kan ikke vurdere effektens størrelse. Fagudvalget vurderer, at der vil være flere bivirkninger forbundet med olaparib end ved BSC. |
| **Kvalitet af den samlede evidens** | Meget lav. |

CI = konfidensinterval, HR = Hazard Ratio, OR = Odds Ratio, RR = relativ risiko.

a. Aflæst af ansøger på Kaplan-Meier kurve.

**Samlet overlevelse (OS)**
Som beskrevet i protokollen er effektmålet samlet overlevelse kritisk for vurderingen af lægemidlets værdi for patienterne, fordi metastaserende kastrationsresistent prostatakræft er en dødelig sygdom.

Median OS for patienter behandlet med olaparib er 17,5 måneder og 11,9 måneder for patienter behandlet med NHA, hvilket er mere end fagudvalgets vurdering af medianoverlevelsen ved BSC (ca. 6-9 måneder).

Den absolutte forskel mellem grupperne er dermed 5,6 måneder, hvilket overstiger den mindste klinisk relevante forskel på 3 måneder. Punktestimatet for den absolutte effektforskel afspejler dermed en klinisk relevant effektforskel. Dog findes der ikke en standardmetode til at beregne konfidensintervallet for forskellen i median. Derfor kan den foreløbige værdi af olaparib ikke kategoriseres efter Medicinrådets metoder.

OS-raten ved 1 år er 67 % i olaparib-armen mod 50 % i NHA-armen. Det svarer til en absolut forskel på 17 %-point, hvilket overstiger den mindste klinisk relevante forskel på 5 %-point. Punktestimatet for den absolutte effektforskel afspejler dermed en klinisk relevant effektforskel. Dog findes der ikke en standardmetode til at beregne konfidensintervallet for forskellen i rate. Derfor kan den foreløbige værdi af olaparib ikke kategoriseres efter Medicinrådets metoder.

Den relative effektforskel er ikke signifikant for HR: 0,63 (95 % CI 0,39; 1,04). Punktestimatet for HR er tilsvarende for BRCAm-populationen med et signifikant konfidensinterval (0,43-0,95). Analysen af subgruppen, som er efterspurgt i dette spørgsmål (BRCAm, taxan-behandlede), har ikke tilstrækkelig styrke til at kunne finde en statistisk signifikant forskel, men analysen tyder ikke på, at effekten i denne population adskiller sig fra den samlede population.

Effekten af olaparib overfor BSC kan ikke kategoriseres for OS, pga. usikkerhed omkring populationens generaliserbarhed til den population i dansk klinisk praksis, som får BSC (indirekthed). Fagudvalget vurderer, at data tyder på, at olaparib har en større effekt på OS end BSC. Yderligere vurderes effekten af olaparib at være underestimeret på grund af dels overkrydsning fra NHA til olaparib, og dels at NHA forventes at have en lidt større effekt på OS, end hvis der var sammenlignet med BSC.

**Progressionsfri overlevelse**
PFS for patienter behandlet med olaparib er [redacted] og [redacted] for patienter behandlet med NHA. Det svarer til en absolut forskel på [redacted], hvilket overstiger den mindste klinisk relevante forskel på 3 måneder. Punktestimatet for den absolutte effektforskel afspejler dermed en klinisk relevant effektforskel. Dog findes der ikke en standardmetode til at beregne konfidensintervallet for forskellen i median. Derfor kan den foreløbige værdi af olaparib ikke kategoriseres efter Medicinrådets metoder.

Ved 1 år er forskellen i PFS-rate [redacted], hvilket overstiger den mindste klinisk relevante forskel på 10 %-point. Punktestimatet for den absolutte effektforskel afspejler dermed en klinisk relevant effektforskel. Dog findes der ikke en standardmetode til at

beregne konfidensintervallet for forskellen i rate. Derfor kan den foreløbige værdi af olaparib ikke kategoriseres efter Medicinrådets metoder.

Baseret på den relative effektforskel (HR: [redacted] som fremgår af Tabel 6, har olaparib foreløbigt en stor merværdi vedr. PFS.

Fagudvalget vurderer, at olaparib har en stor merværdi vedr. PFS. Der er opnået stor merværdi for den relative effektforskel. De absolutte forskelle underbygger denne værdi, da forskellen for median PFS og PFS-raten ved 1 år overstiger den mindste klinisk relevante forskel væsentligt.

**Bivirkninger/uønskede hændelser**

### Bivirkninger grad 5

Fagudvalget vurderer, at grad 5-bivirkninger er særligt kritiske, idet de omhandler mortalitet som følge af behandlingen.

6 ud af 256 patienter (2,3 %), der modtog olaparib, havde grad 5-bivirkninger. Fagudvalget har ikke et estimat for, hvor mange patienter, der dør af bivirkninger ved behandling med BSC. Dermed kan den absolutte eller relative forskel ikke estimeres. Fagudvalget vurderer derfor, at værdien af olaparib ikke kan kategoriseres vedr. grad 5-bivirkninger.

### Grad 3-4 uønskede hændelser og kvalitativ gennemgang af bivirkninger

Uønskede hændelser har betydning for den enkelte patients livskvalitet og efterlevelse af behandling. Fagudvalget anser derfor uønskede hændelser grad 3-4 som et vigtigt effektmål. Ansøger for dette effektmål har indleveret uønskede hændelser ≥ 3. Fagudvalget vurderer, at dette ikke har en betydning for kategoriseringen af værdien af olaparib, fordi grad 5 uønskede hændelser udgør en lille andel.

133 ud af 256 patienter (52 %) behandlet med olaparib oplevede mindst én uønsket hændelse af grad ≥ 3. De hyppigste alvorlige uønskede hændelser for olaparib er beskrevet i afsnit 5.1.4. Det er ikke muligt at lave samme opgørelse for patienter, der modtager BSC, da behandlingen af disse patienter varierer. Fagudvalget lægger i stedet vægt på en kvalitativ gennemgang af de tre hyppigst brugte lægemidler, morfin, denosumab og prednisolon.

For morfin er de hyppigste bivirkninger forbundet med behandling (> 10 %) forstoppelse og kvalme. Andre hyppige bivirkninger er svimmelhed, delir, fald, søvnløshed, hovedpine, hyperhidrose (ekstrem svedproduktion), appetitløshed, mundtørhed, opkast, mavesmerter, udslæt og utilpashed.

For denosumab er de hyppigste bivirkninger forbundet med behandling (> 10 %) muskuloskeletale smerter, hypocalcæmi og diarré. Herudover er der risiko for kæbeosteonekrose.

For prednisolon fremhæver fagudvalget ændring af humør, søvn og appetit, mavesår, diabetes, knogleskørhed, muskelsvækkelse og hudblødninger som de vigtigste bivirkninger.

For en kvalitativ gennemgang af uønskede hændelser vedr. olaparib henvises til afsnit 5.1.4.

Samlet vurdering af effektmålet bivirkninger/uønskede hændelser:

Fagudvalget vurderer, at der vil være flere bivirkninger forbundet med olaparib end ved BSC. Omvendt vurderer fagudvalget, at sygdomsbyrden og dermed forekomsten af uønskede hændelser vil være mere fremtrædende hos patienter, der ikke modtager en aktiv behandling.

**Livskvalitet**
Fagudvalget betragter livskvalitet som et vigtigt effektmål, idet behandling med olaparib er livsforlængende og ikke kurativ. I protokollen efterspurgte fagudvalget effektmålet opgjort som forskellen i andelen af patienter, som oplever ≥ 10 points reduktion fra baseline ved kort (mellem 2 og 6 måneder) og lang (> 6 måneder) opfølgningstid. Ansøger har i stedet indleveret gennemsnitlig ændring fra baseline i BRCAm-populationen målt med FACT-P. Dermed kan værdien af olaparib ikke kategoriseres. Fagudvalget vil i stedet præsentere ændringen i livskvalitet fra baseline ligesom i klinisk spørgsmål 2.

Livskvaliteten opgjort som FACT-P-score var i gennemsnit *(least sqaures mean)* -5,2 (SD: 2,6) point i forhold til baseline hos patienter behandlet med olaparib. Hos patienter behandlet med NHA var forværringen i gennemsnit -9,7 (SD: 3,5) point. Forskellen mellem grupperne var 4,45 (-4,01; 12,91) point. Der var dermed ikke en signifikant forskel i livskvaliteten mellem de to grupper.

### 5.3.5 Fagudvalgets konklusion

Den samlede værdi af olaparib sammenlignet med BSC (typisk denosumab, contalgin og binyrebarkhormon) til patienter med BRCA-muteret metastaserende kastrationsresistent prostatakræft, der ikke har andre behandlingsalternativer, kan ikke kategoriseres pga. indirekthed i forhold til den danske patientpopulation. Fagudvalget vurderer, at olaparib samlet set har en bedre effekt end BSC. Fagudvalget vurderer, at data tyder på, at olaparib er bedre end BSC i forhold til både OS (median 17,5 mdr.) og PFS (median 9,0 mdr.), hvor median OS forventes at være 6-9 måneder. Yderligere vurderes effekten af olaparib på OS at være underestimeret på grund af dels overkrydsning fra NHA til olaparib, og dels at NHA som komparator forventes at have en større effekt, end hvis der var sammenlignet med BSC. Vurderingen er forbundet med usikkerhed.

Fagudvalget vurderer, at der vil være flere bivirkninger forbundet med olaparib end ved BSC. Omvendt vurderer fagudvalget, at sygdomsbyrden og dermed forekomsten af uønskede hændelser vil være mere fremtrædende hos patienter, der ikke modtager en aktiv behandling.

Samlet set vurderer fagudvalget, at olaparib er en vigtig målrettet behandling til patienter med god helbredsstatus og som har BRCA1/2-muteret mCRPC, der ikke har andre behandlingsmuligheder tilbage.

# 6. Andre overvejelser

### Overvejelser omkring test for BRCA-mutationer

Der testes ikke rutinemæssigt for BRCA1/2-mutationer hos patienter med mCRPC i Danmark, men fagudvalget understreger, at dette vil være en forudsætning for ibrugtagning af olaparib. Patienter kan testes for BRCA1/2-mutationer ved tre forskellige test; germline (test på blod), somatisk (test på væv) eller frit cirkulerende tumor DNA. Fagudvalget finder det mest sandsynligt, at patienter vil testes for BRCA1/2-mutationer igennem både en germline og en somatisk test, iht. testning af BRCA1/2-mutationer inden for æggestokkekræft.

### Overvejelser omkring olaparibs placering i behandlingsalgoritmen:

Fagudvalget vurderer, at den bedste placering af olaparib i behandlingsalgoritmen vil være, efter at patienter har fået NHA og docetaxel. Dette skyldes, at der i PROfound primært indgik patienter med netop denne behandlingshistorik (ca. 70 % af patienterne var taxan-behandlede). På dette tidspunkt i behandlingsalgoritmen har de fleste patienter ofte fortsat en rimelig god almentilstand. Alternativt vurderer fagudvalget, at det også kan være til gavn for patienterne at anvende olaparib i en senere behandlingslinje, hvor patienter har modtaget behandling med både NHA, docetaxel og cabazitaxel. I denne patientpopulation som ikke har flere aktive behandlingsmuligheder er der fortsat en del patienter som er i god nok almentilstand til at modtage aktiv behandling, og som vil kunne have gavn af en targeteret behandling.

# 7. Relation til behandlingsvejledning

Der findes en RADS-behandlingsvejledning fra 2013, men denne inkluderer ikke patienter med BRCA1/2-muteret mCRPC og er af Medicinrådet vurderet forældet.

Fagudvalget vil tage stilling til eventuel indplacering af olaparib i forbindelse med udarbejdelse af Medicinrådets behandlingsvejledning vedr. metastatisk kastrationsresistent prostatakræft.

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# 9. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

**Medicinrådets fagudvalg vedrørende kræft i blærehalskirtlen**

| **Sammensætning af fagudvalg** | |
|---|---|
| **Formand** | **Indstillet af** |
| Joen Sveistrup<br>*Afdelingslæge* | Region Hovedstaden |
| **Medlemmer** | **Udpeget af** |
| Edo Koco<br>*Afdelingslæge* | Region Nordjylland |
| Jimmi Søndergaard<br>*Overlæge* | Region Nordjylland |
| *Deltager ikke med en speciallæge i urologi* | Region Midtjylland |
| Simon Buus<br>*Afdelingslæge* | Region Midtjylland |
| Steinbjørn Hansen<br>*Overlæge* | Region Syddanmark |
| Mads Hvid Aaberg Poulsen<br>Afdelingslæge | Region Syddanmark |
| Redas Trepiakas<br>*Overlæge* | Region Sjælland |
| Lisa Lindeborg<br>*Afdelingslæge* | Region Sjælland |
| Per Kongsted<br>*Afdelingslæge* | Region Hovedstaden |
| Rasmus Bisbjerg<br>*Overlæge* | Region Hovedstaden |
| Leif Otterstrøm<br>*Patient/patientrepræsentant* | Danske Patienter |

| | |
|---|---|
| Ole Jensen<br>*Patient/patientrepræsentant* | Danske Patienter |
| Stine Trolle Poulsen<br>*Farmaceut* | Dansk Selskab for Sygehusapoteksledelse |
| Jesper Hallas<br>*Professor, overlæge* | Dansk Selskab for Klinisk Farmakologi |
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# 10. Versionslog

| Versionslog | | |
|---|---|---|
| **Version** | **Dato** | **Ændring** |
| 1.0 | 24. november 2021 | Godkendt af Medicinrådet |

# 11. Bilag

## 11.1 Bilag 1: Cochrane – risiko for bias

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

**Tabel 7. Vurdering af risiko for bias i de Bono et al., 2020, PROfound, NCT02987543**

| Bias | Risiko for bias | Uddybning |
|---|---|---|
| Risiko for bias i randomiserings-processen | Lav | Allokering til interventions- eller kontrolarm var randomiseret i en ratio 2:1. Randomiseringen blev udført centralt via et interactive web or voice response system. |
| Effekt af tildeling til intervention | Forbehold | Allokering af behandling ikke blindet overfor patienterne (open label). Risikoen for bias i forbindelse med compliance vurderes at være lille. |
| Manglende data for effektmål | Lav | Effektivitetsanalyser blev udført på data fra ITT-populationen. Sikkerhedsanalyser er baseret på sikkerhedspopulationen bestående af alle patienter, der har modtaget mindst en dosis. |
| Risiko for bias ved indsamlingen af data | Lav | Intervention ikke blindet overfor patienterne, hvilket kan medføre bias i indsamlingen af data. 'Investigator' var blindet, hvilket reducerer risikoen for bias i forbindelse med vurdering af primært effektmål. |
| Risiko for bias ved udvælgelse af resultater, der rapporteres | Lav | Protokol er tilgængelig, og studiets primære effektmål er præsenteret. |
| Overordnet risiko for bias | Lav | |

**Tabel 8. Vurdering af risiko for bias de Witt et al., 2020, CARD, NCT0285691.**

| Bias | Risiko for bias | Uddybning |
|---|---|---|
| Risiko for bias i randomiserings-processen | **Lav** | Allokering til interventions- eller kontrolarm var randomiseret i en ratio 1:1. |
| Effekt af tildeling til intervention | **Forbehold** | Allokering af behandling ikke blindet overfor hverken patienter (open label) eller investigator. Risikoen for bias i forbindelse med compliance vurderes dog at være lille. |
| Manglende data for effektmål | **Lav** | Effektivitetsanalyser blev udført på data fra ITT-populationen. Sikkerhedsanalyser er baseret på sikkerhedspopulationen bestående af alle patienter, der har modtaget mindst en dosis. |
| Risiko for bias ved indsamlingen af data | **Forbehold** | Intervention ikke blindet overfor hverken patienter eller 'investigator', hvilket kan medføre bias i indsamlingen af data. Særligt kan den subjektive aflæsning af effektmål være forbundet med bias. |
| Risiko for bias ved udvælgelse af resultater, der rapporteres | **Lav** | Protokol er tilgængelig og studiets primære effektmål er præsenteret. |
| **Overordnet risiko for bias** | **Forbehold** | |

**Tabel 9. Vurdering af risiko for bias i Kwon et al.**

| Bias | Risiko for bias | Uddybning |
|---|---|---|
| Risiko for bias i randomiserings-processen | **Høj** | Studiet er ikke et randomiseret studie. |
| Effekt af tildeling til intervention | **Høj** | Ingen randomisering eller blinding, hvilket medfører en risiko for bias, i forhold til hvem der blev tildelt behandling. Yderligere er dosis ikke beskrevet. |
| Manglende data for effektmål | **Høj** | Studiet baseret på RWE-data. Beskrivelsen af frafald er uklar. |
| Risiko for bias ved indsamlingen af data | **Høj** | Ingen blinding eller randomisering, hvilket medfører en risiko for bias i indsamlingen af data. |
| Risiko for bias ved udvælgelse af resultater, der rapporteres | **Høj** | Ingen protokol tilgængelig. |
| **Overordnet risiko for bias** | **Høj** | |

## 11.2 Bilag 2: GRADE

**Klinisk spørgsmål 3: olaparib sammenlignet med NHA til behandling af BRCA1/2-muteret metastaserende kastrationsresistent prostatakræft**

**Tabel 10. GRADE evidensprofil for klinisk spørgsmål 3**

| Sikkerhedsvurdering | | | | | | | Antal patienter | | Effekt | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Antal studier | Studie-design | Risiko for bias | Inkonsistens | Indirekthed | Unøjagtighed | Andre overvejelser | Olaparib | NHA | Relativ (95 % CI) | Absolut (95 % CI) | Sikkerhed | Vigtighed |
| Samlet overlevelse (OS), median | | | | | | | | | | | | |
| 1 | RCT | Ikke alvorlig | Alvorlig[a] | Meget alvorlig[b] | Alvorlig[c] | Ingen | 102 | 58 | HR: 0,63 (0,39; 1,04) | 5,6 mdr. | ⨁◯◯◯ MEGET LAV | KRITISK |
| Samlet overlevelse (OS), rate ved 1 år | | | | | | | | | | | | |
| 1 | RCT | Ikke alvorlig | Alvorlig[a] | Meget alvorlig[b] | Alvorlig[c] | Ingen | 102 | 58 | | 17 %-point | ⨁◯◯◯ MEGET LAV | KRITISK |
| Progressionsfri overlevelse (PFS), median | | | | | | | | | | | | |
| 1 | RCT | Ikke alvorlig | Alvorlig[a] | Meget alvorlig[b] | Ikke alvorlig | Ingen | 102 | 58 | [redacted] | [redacted] | ⨁◯◯◯ MEGET LAV | VIGTIGT |
| Progressionsfri overlevelse (PFS), rate ved 1 år | | | | | | | | | | | | |
| 1 | RCT | Ikke alvorlig | Alvorlig[a] | Meget alvorlig[b] | Ikke alvorlig | Ingen | 102 | 58 | | [redacted] | ⨁◯◯◯ MEGET LAV | VIGTIGT |

| Sikkerhedsvurdering | | | | | | | Antal patienter | | Effekt | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Antal studier | Studie-design | Risiko for bias | Inkonsistens | Indirekthed | Unøjagtighed | Andre overvejelser | Olaparib | NHA | Relativ (95 % CI) | Absolut (95 % CI) | Sikkerhed | Vigtighed |
| Uønskede hændelser / bivirkninger | | | | | | | | | | | | |
| Kan ikke kategoriseres | | | | | | | | | | | | |
| Livskvalitet | | | | | | | | | | | | |
| Kan ikke kategoriseres | | | | | | | | | | | | |
| Kvalitet af den samlede evidens | | | MEGET LAV | | | | | | | | | |

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

[b] Der er nedgraderet to niveauer, da ikke alle patienterne i denne gruppe har modtaget både docetaxel og cabazitaxel, som var definitionen af populationen i protokollen. Yderligere afviger komparator også fra definitionen i protokollen.

[c] Der er nedgraderet et niveau, da konfidensintervallet er meget bredt.

# Application for the assessment of clinically added value of Lynparza (olaparib) as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and *BRCA1/2*-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent.

# Contents

# 1 Basic information

**Table 1**. Contact information

| Kontaktoplysninger | |
|---|---|
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| Titel | Sundhedsøkonom |
| Ansvarsområde | Onkologi |
| Telefonnummer | +46767988667 |
| E-mail | mattias.ekman@astrazeneca.com |

**Table 2**. Overview of the pharmaceutical

| | |
|---|---|
| Proprietary name | Lynparza |
| Generic name | Olaparib |
| Marketing authorization holder in Denmark | AstraZeneca AB |
| ATC code | L01XX46 |
| Pharmacotherapeutic group | poly [ADP-ribose] polymerase inhibitors (PARPi), |
| Active substance(s) | Olaparib |

| | |
|---|---|
| Pharmaceutical form(s) | Tablets 150 mg and 100 mg |
| Mechanism of action | Olaparib is an oral potent inhibitor of PARP1, PARP2, and PARP3. These PARP enzymes are required for the efficient repair of DNA single-strand breaks. During the repair process, after chromatin modification, PARP auto-modifies itself and dissociates from the DNA to facilitate access for base excision repair (BER) enzymes. Olaparib, when bound to the active site of DNA-associated PARP, prevents dissociation from DNA, blocking repair of the single-strand break |
| Dosage regimen | 2 tablets twice daily. |
| Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA) | Lynparza is indicated as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and *BRCA1/*2-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent. |
| Other approved therapeutic indications | **Ovarian cancer**:<br><br>**Tablets:**<br>Lynparza is indicated as monotherapy for the:<br>• maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2- mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.<br>• maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.<br><br>Lynparza in combination with bevacizumab is indicated for the:<br>• maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a BRCA1/2 mutation and/or genomic instability.<br><br>**Capsules:**<br>• Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy. |

| | |
|---|---|
| | **Breast cancer**:<br><br>• Monotherapy for the treatment of adult patients with germline *BRCA1/2*-mutations, who have HER2 negative locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments. Patients with hormone receptor (HR)-positive breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy. *(tablet formulation)*<br><br>**Adenocarcinoma of the pancreas:**<br><br>• Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with germline *BRCA1/2*-mutations who have metastatic adenocarcinoma of the pancreas and have not progressed after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen. *(tablet formulation)* |
| Will dispensing be restricted to hospitals? | Yes. Labelled BEGR |
| Combination therapy and/or co-medication | No |
| Packaging – types, sizes/number of units, and concentrations | 56 tablets |
| Orphan drug designation | No. Was orphan until March 2018 |

# 2 Abbreviations

| | |
|---|---|
| ADT | androgen deprivation therapy |
| AE | adverse event |
| BICR | blinded independent central review |
| BPI-SF | Brief Pain Inventory – Short Form |
| BRCA1 | breast cancer type 1 susceptibility protein |
| BRCA2 | breast cancer type 2 susceptibility protein |
| BRIP1 | BRCA1 interacting protein C-terminal helicase 1 |
| CDK12 | cyclin-dependent kinase 12 |
| CHEK1 | checkpoint kinase 1 |
| CHEK2 | checkpoint kinase 2 |
| CI | confidence interval |
| CRPC | castration-resistant prostate cancer |
| CSP | Clinical Study Protocol |
| CSR | Clinical Study Report |
| DCO | Data cut off |
| DHT | dihydrotestosterone |
| EAU | European Association of Urology |
| ECOG | Eastern Cooperative Oncology Group |
| EBRT | External Beam Radiation Therapy |
| EMA | European Medicines Agency |
| EQ-5D | EuroQol- 5 Dimension |
| FACT-P | Functional Assessment of Cancer Therapy – Prostate |
| FANCL | Fanconi anaemia, complementation group L |
| FAPSI-6 | 6-item Functional Assessment of Cancer Therapy Advanced Prostate Symptom Index |
| FDA | US Food and Drug Administration |
| gBRCA | genomisk BRCA mutation |
| HSPC | Hormone-sensitive prostate cancer |
| HR | hazard ratio |

| | |
|---|---|
| HRQoL | health-related quality of life |
| HRR | homologous recombination repair |
| HRRm | homologous recombination repair pathway gene mutation |
| ITT | intention to treat |
| MAIC | matched Indirect Comparison |
| mCRPC | metastatic castration-resistant prostate cancer |
| mHSPC | metastatic hormone-sensitive prostate cancer |
| NHA | new hormonal agent |
| OR | odds ratio |
| ORR | objective response rate |
| OS | overall survival |
| PARP | poly(adenosine diphosphate)-ribose polymerase |
| PCS | prostate cancer subscale |
| PFS | progression-free survival |
| PFS2 | second progression-free survival |
| PRO | patient-reported outcome |
| PS | performance status |
| PSA | prostate-specific antigen |
| RAD51B, RAD51C, RAD51D | RAD51 paralogues B, C and D |
| RAD54L | RAD54-like protein |
| rPFS | radiographic progression-free survival |
| RPSFTM | rank preserving structural failure time model |
| RR | relative risk |
| RT | radiotherapy |
| RWE | Real World Evidence (daglig klinisk praksis evidens) |
| SAE | serious adverse event |
| SD | standard deviation |
| SLR | Systematic Literature Review |
| SmPC | Summary of Product Characteristics |

| | |
|---|---|
| SOC | Standard of Care |
| SRE | skeletal-related event |
| SSB | single-strand break |
| SSRE | symptomatic skeletal-related event. |
| TTPP | time to pain progression |

# 3 Executive Summary (dansk)

## Sygdom og behandling:

Ved metastaserende kastrationsresistent prostatacancer (mCRPC) forstås PC med påviste metastaser typisk involverende enten knogler, lymfeknuder uden for det lille bækken eller parenkymatøse organer, der progredierer trods serum-testosteron i kastrationsniveau.

mCRPC definition :

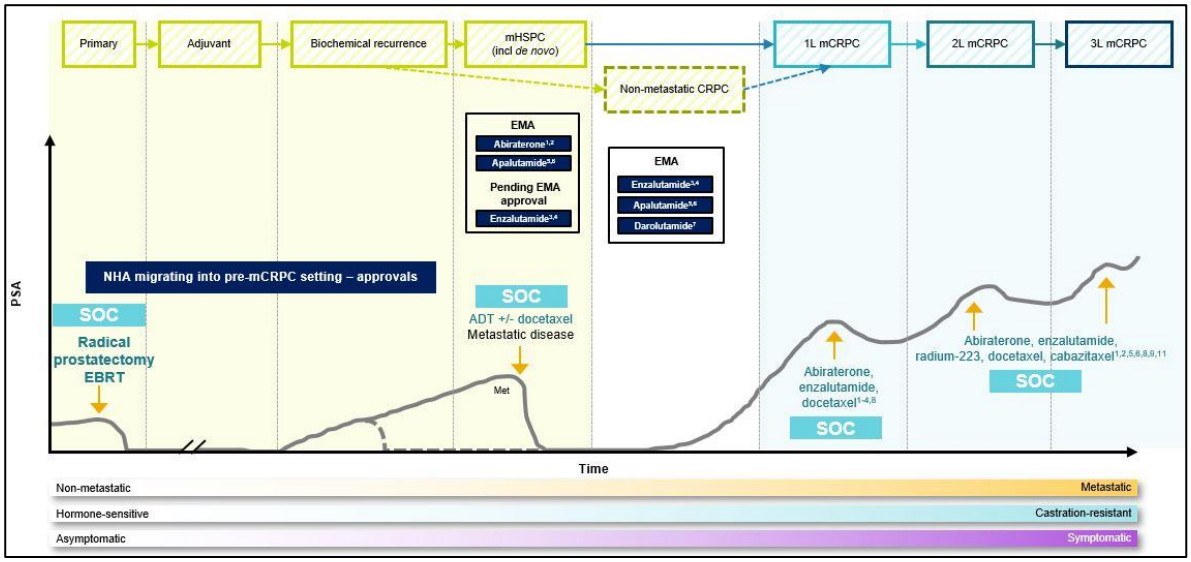
- **Serum Testosteron < 1,7 nmol/l (< 50 ng/dl) plus enten:**

    1. Biokemisk progression defineret som 3 konsekutive stigninger i PSA, målt med mindst 1 uges interval, resulterende i 50 % stigning i to målinger over nadir. PSA værdien bør være >2 ng/ml for at behandlingseffekten kan vurderes korrekt

eller

    2. Radiologisk progression med 2 eller flere knoglefoci på en knogleskintigrafi eller progression af bløddelslæsioner i henhold til Response Evaluation Criteria In Solid Tumors 1.1 (RECIST 1.1) [1].

**Figur 1**. De kliniske stadier af PC med udvikling i PSA og godkendte behandlingsmodaliteter




## Dansk klinisk praksis for behandling af mCRPC:

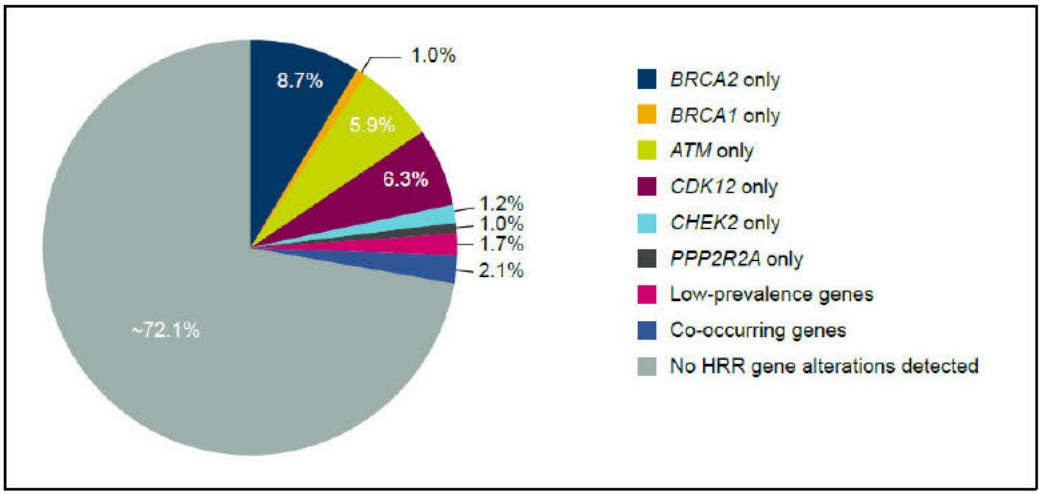
Incidensen af PC er ca. 4.500 og prævalensen ca. 42.000 i 2018. Heraf kan ca. 1/3 tilbydes potentiel helbredende behandling. De øvrige 2/3 overgår enten til observation, behandling med antiandrogen eller kastration (kirurgisk eller medicinsk). I forhold til prognose og behandling inddeles prostatakræft i tre kategorier: lokaliseret, lokalavanceret og metastaserende sygdom (se figur 1 for oversigt over sygdomsstadier og behandlingsmodaliteter). I den nuværende praksis skelnes herudover mellem høj- og lavvolumen metastatisk hormonsensitiv (mHSPC) sygdom (figur 1). Højvolumen sygdom er defineret ved visceral metastasering og/eller udbredt knoglemetastasering defineret som 4 eller flere knoglemetastaser, hvoraf mindst 1 findes uden for bækkenet/columna. Lavvolumen sygdom er defineret ved færre end 4 knoglemetastaser og ingen viscerale metastaser [2]. I dansk praksis behandles nydiagnosticeret højvolumen mHSPC fortrinsvis med ADT + tidlig docetaxel, mens en lille patientgruppe, der er uegnet til behandling med docetaxel, behandles med ADT + abirateron.  Incidensen af mCRPC kendes ikke med stor nøjagtighed, men anslås af Medicinrådets fagudvalg i protokollen for denne ansøgning til ca. 1.500 nydiagnosticerede patienter årligt.
En større andel af patienterne har en performance status (PS) der muliggør behandling i flere linjer. I de seneste år er flere lægemidler til behandling af mCRPC blevet tilgængelige og har vundet indpas i de nationale behandlings-rekommandationer. I dag anvendes docetaxel, cabazitaxel, abirateron (+ prednisolon), enzalutamid, og radium-223 diklorid til behandling af patienter med mCRPC. Generelt savnes stærk evidens for den optimale rækkefølge af de anbefalede behandlinger for mCRPC, men i dansk praksis anvises bl.a. følgende generelle principper: Docetaxel prioriteres i første linje til symptomatiske patienter og patienter med hurtig progression på ADT i HSPC-fasen. Cabazitaxel gives kun til patienter, der tidligere er behandlet med docetaxel (jvf. jevtana produktresumé). NHA (abirateron/enzalutamid) gives i første linje til asymptomatiske patienter og sekventiel behandling med NHA (enzalutamid efter abirateron, eller modsat) anbefales generelt ikke, men kan anvendes til et mindre antal patienter under visse forudsætninger.

Radium-223 bruges per indikation kun i 3. linje eller senere, men kan gives til et mindre antal patienter med symptomatiske knoglemetastaser (og uden viscerale metastaser), som er uegnede til behandling med docetaxel. Patienter gen-behandles ikke med samme stof [1-3]. Se figur 3 for oversigt over den danske behandlingsalgoritme/patientdynamik med anslåede cirka-estimater for patienter.

### HRR og BRCA1/2 mutationer:

Homolog rekombinationsreparation (HRR) er et vigtig element i raske cellers funktion. Det kræver funktionelle *BRCA1*- og *BRCA2*-gener, for at sikre korrekt reparation af DNA-strengbrud. Mutationer i gener i HRR kan medføre genomisk instabilitet og forstærke tumor vækst. De bedst undersøgte og veldefinerede mutationer i HRR er *BRCA1* og *BRCA2*. Mutationer i *BRCA1* eller *BRCA2* er vist at findes hos ca. 10 % af patienter med mCRPC (figur 2) [4].

Figur 2. prævalens af HRR mutationer i 2792 patienter med mCRPC (screenet til PROfound studiet).[5]




Source: de Bono *et al*, 2019 [5]

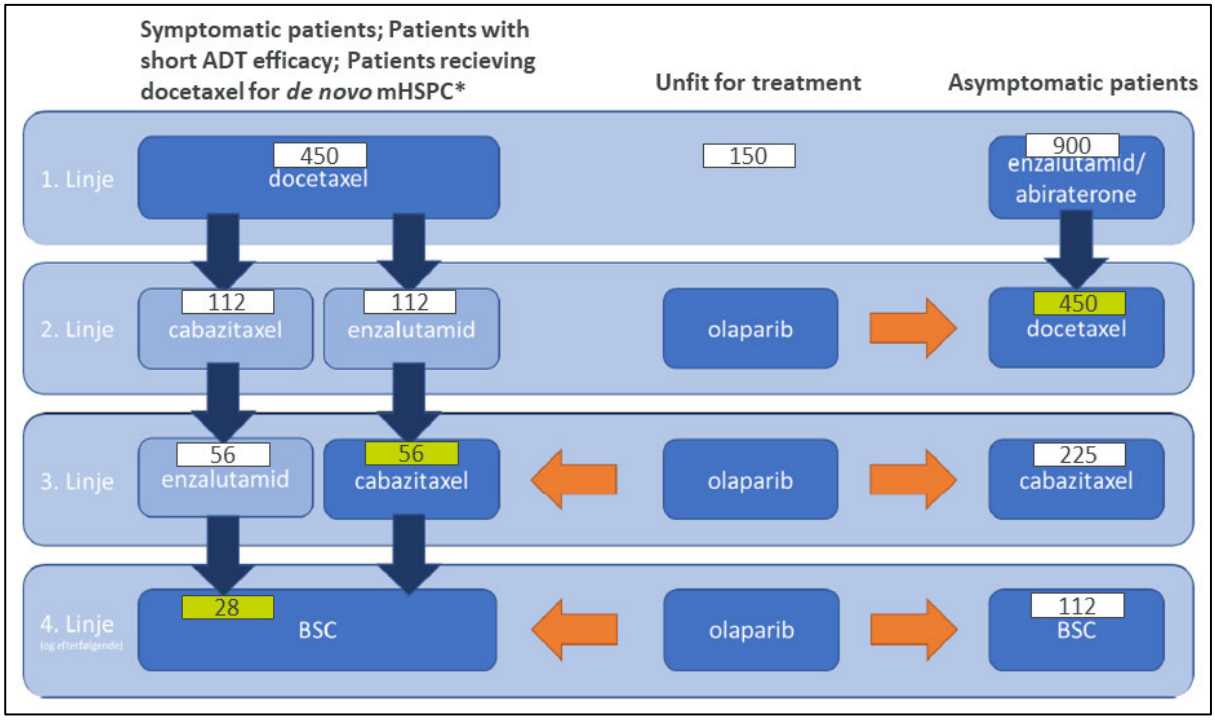
Prostatacancerpatienter med *BRCA2* mutationer har hyppigere mere aggressiv og avanceret sygdom på diagnosetidspunktet ift. patienter med BRCA1 mutationer, og progredierer hurtigere til metastatisk sygdom [6, 7]. Endvidere har et nyere studie, hvor patienternes mutations-status blev bestemt prospektivt, vist at patienter med *gBRCA2*-muteret mCRPC har markant nedsat overlevelse på de nuværende, godkendte standard-behandlinger (NHA eller taxan) end patienter uden *gBRCA2* mutationer (17.4 mdr. vs 33.2 mdr.) [8]. Patienter med *BRCA1/2* mutation er særligt sensitive for visse behandlinger bl.a. poly(ADP)-ribose polymerase inhibitorer (PARPi). Tabel 2 viser den øgede risiko for at udvikle PC hvis man er bærer af henholdsvis *BRCA1* og *BRCA2*.

**Tabel 2**. Forøget risiko for PC hos mandlige bærere af germline BRCA1 og BRCA2 mutationer.

| Gene | Relative risk vs non-carriers (95% CI) | Overall risk of developing prostate cancer (95% CI) |
|---|---|---|
| *BRCA1* | 3.75 (1.02–9.6) | 1.35 (1.03–1.76) |
| *BRCA2* | 2.5–8.6 | 2.64 (2.03–3.47) |

*Ref: [9-12]*

**Figur 3**. Patient dynamik og antal baseret på fagudvalgets protokol




Som estimat for det forventede antal patienter i forhold til indikation og de 3 kliniske spørgsmål er anvendt patientforløbet/algoritmen fra protokollen (figur 3). Omkring 1.500 patienter diagnosticeres årligt med mCRPC hvoraf ca. 10 % ikke har performance status til at kandidere til en af behandlingernenævnt i figuren[3]. Da algoritmen er simplificeret og ikke tager hensyn til tidligere behandling med docetaxel for *de novo* mHSPC, har AstraZeneca selv forsøgt at inkludere disse patienter i vores estimat i venstre kolonne af figur 3. Efterfølgende behandling for disse patienter, når de bliver kastrationsresistente er enzulatamid/abiratone eller cabazitaxel. På baggrund af dette, sammenholdt med antagelsen at ca. 50 % af patienterne ikke vil modtage næste behandling (2., 3 og 4. linje) [3, 13], er vi kommet frem at ca. 50 patienter (534 x 9.7%) patienter årligt vil kunne modtage olaparib under forudsætning af at alle patienter testes for *BRCA1/2*-mutation og at frekvensen af *BRCA1/2*-mutation er 9.7% [5] .

### Konklusion på de 3 kliniske spørgsmål.

På trods af forbedrede behandlingsmuligheder for mCRPC patienter findes der fortsat et stort udækket behov for nye, livsforlængende behandlinger med en adækvat bivirkningsprofil. Indenfor onkologien generelt, har målrettet behandling med udgangspunkt i patientens underliggende tumor-genetik vundet stadigt større indpas, men selvom *BRCA*-mutation hos mCRPC patienter synes associeret med dårligere prognose og ringere effekt af de nuværende, livsforlængende behandlinger, er 'præcisions-medicin' endnu ikke etableret indenfor mCRPC.

På baggrund af resultaterne fra PROfound studiet, har vi nu evidens for at en målrettet behandling med olaparib til mCRPC patienter med *BRCA1/2* mutation (somatisk eller germline), som har progredieret på tidligere behandling med NHA, resulterer i signifikant forbedret overlevelse sammenlignet med en anden

NHA. I denne ansøgning vil vi, gennem direkte og indirekte sammenligninger, således fremlægge evidens for at olaparib repræsenterer en ny og forbedret behandlingsmulighed specifikt til mCRPC patienter post-NHA med *BRCA1/2* mutation.

Protokollen fokuserer på mCRPC patienter med *BRCA1/2* mutation som tidligere har modtaget NHA behandling +/- tidligere taxan behandling. **Klinisk spørgsmål 1** omhandler en sammenligning af olaparib med docetaxel for taxan-naïve patienter. Der findes ingen publicerede direkte sammenlignende data for en post-NHA/*BRCAm* population for olaparib overfor docetaxel. Det har desuden ikke været muligt, at udarbejde en valid indirekte sammenligning, og vi har til besvarelse af **Klinisk spørgsmål 1** i stedet anvendt en naiv sammenligning på baggrund af RWE studier. Selvom data peger i retning af en klinisk merværdi til fordel for olaparib, kan der ikke konkluderes noget definitivt i forhold til de targets, som er fastsat af Medicinrådet specifikt angående klinisk merværdi.

I **Klinisk spørgsmål 2** har det været muligt at udarbejde en indirekte sammenligning med cabazitaxel via CARD studiet. Der er blevet spurgt specifikt til *BRCA*m patienter tidligere behandlet med docetaxel; men den gruppe er meget lille og resultaterne og de statistiske beregninger er usikre. Derfor er svarene baseret på patienter tidligere behandlet med et taxan-produkt. Resultaterne blev præsenteret fornylig i poster-format på ASCO 2021 og viser, at der er en trend til en OS gevinst for olaparib (HR 0.47 (0.12, 1.79)) og en signifikant rPFS (0.36 (0.20, 0.64)) fordel for olaparib i forhold til cabazitaxel. På bivirkningssiden er der en tendens til færre alvorlige bivirkninger på olaparib, men det lever ikke op til de mål der er sat fra Medicinrådet.

I **klinisk spørgsmål 3** har fagudvalget nævnt i protokollen, at sekventiel behandling med NHA (som anvendt i PROfound studiet) ikke er dansk standard, men at "fagudvalget alligevel ønsker at se data for det pågældende studie, fordi effekten af sekventiel behandling forventes at være lille og tilnærmelsesvis repræsentativ for *best supportive care*". Dette er et "frisk" estimat, men kan forsvares med den begrænsede effekt der ses for NHA i PROfound studiet. Besvarelsen af **Klinisk spørgsmål 3** er således baseret på den direkte sammenligning mellem olaparib og NHA i PROfound studiet, og på trods af at 69% af patienterne i kontrol-armen krydsede over til behandling med olaparib efter progression, viste data i *BRCA*m populationen en signifikant forbedring af mOS på 5.7 måneder (HR: 0.63(0.42-0.95)) vs komparator (NHA). Justeres der for overkrydsning fra olaparib til NHA, var OS-gevinsten på 9.15-10.16 måneder (HR: 0.27–0.40). Behandling med olaparib var også associeret med en betydelig og signifikant forbedring i rPFS på 6.8 måneder sammenlignet med NHA (HR 0.22 (0.15-0.32)). Bivirkninger af grad 3 eller mere i olaparib armen var forøget sammenholdt med NHA. Populationen i **Klinisk spørgsmål 3** er *BRCA*m patienter som tidligere har modtaget NHA og et taxan, og der besvares specifikt for denne gruppe angående behandlings-effekt.

Testning for *BRCA* mutationer er veletableret i Danmark, og vi forventer derfor ikke, at det vil medføre større udfordringer at indføre dette som en del af prostata cancer udredningen. Patient populationen for de 3 kliniske spørgsmål tilsammen er kun omkring 50 mænd årligt; men vi anser data fra PROfound som yderst relevante for at tilføre endnu en behandlingsmulighed til patienter med avanceret senstadie prostatakræft, enten til hele *BRCA*m post-NHA/taxan gruppen eller en subpopulation heraf.

# 4 Literature search

## 4.1 Relevant studies

**We received the following search guide from Medicinraadet:**

**For PubMed:**

**Table 3**. Search guide Medicinraadet PubMed

| # | Søgestreng | Kommentar |
|---|---|---|
| 1 | prostate[ti] AND (cancer[ti] OR carcinoma[ti] OR adenocarcinoma[ti]) | Population |
| 2 | castration resistant[ti] OR castrationresistant[ti] OR hormone-refractory[ti] OR hormone-resistant[ti] OR androgen-independent[ti] | |
| 3 | #1 AND #2 | |
| 4 | Prostatic Neoplasms, Castration-Resistant[mh] AND drug therapy[sh] | |
| 5 | CRPC[ti] | |
| 6 | #3 OR #4 OR #5 | |
| 7 | Neoplasm Metastasis[mh] | |
| 8 | metasta*[ti] | |
| 9 | #6 AND (#7 OR #8) | |
| 10 | mCRPC[ti] | |
| 11 | #9 OR #10 | |
| 12 | olaparib[nm] OR olaparib[tiab] OR Lynparza*[tiab] | Intervention og komparatorer |
| 13 | Docetaxel[mh] OR docetaxel[tiab] OR Taxotere*[tiab] | |
| 14 | cabazitaxel[nm] OR cabazitaxel[tiab] OR Jevtana*[tiab] | |

| | | |
|---|---|---|
| 15 | #12 OR #13 OR #14 | |
| 16 | #11 AND #15 | |
| 17 | abiraterone[tiab] OR enzalutamide[tiab] OR new hormonal agent*[tiab] OR novel hormonal agent*[tiab] OR second generation hormone therap*[tiab] OR second HT[tiab] | Krav til tidl. behandling |
| 18 | androgen receptor target*[tiab] OR androgen receptor-axis-target*[tiab] OR androgen-signaling-target*[tiab] OR ASTI*[tiab] OR ARAT*[tiab] | |
| 19 | #16 AND (#17 OR #18) | |
| 20 | english[la] AND hasabstract | Afgræsning til referencer på engelsk der har abstract |
| 21 | Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR Review[pt] OR Systematic Review[pt] OR case report[ti] | Eksklusions-kriterier |
| 22 | (#19 AND #20) NOT #21 | Endelig søgning |

## For Central:

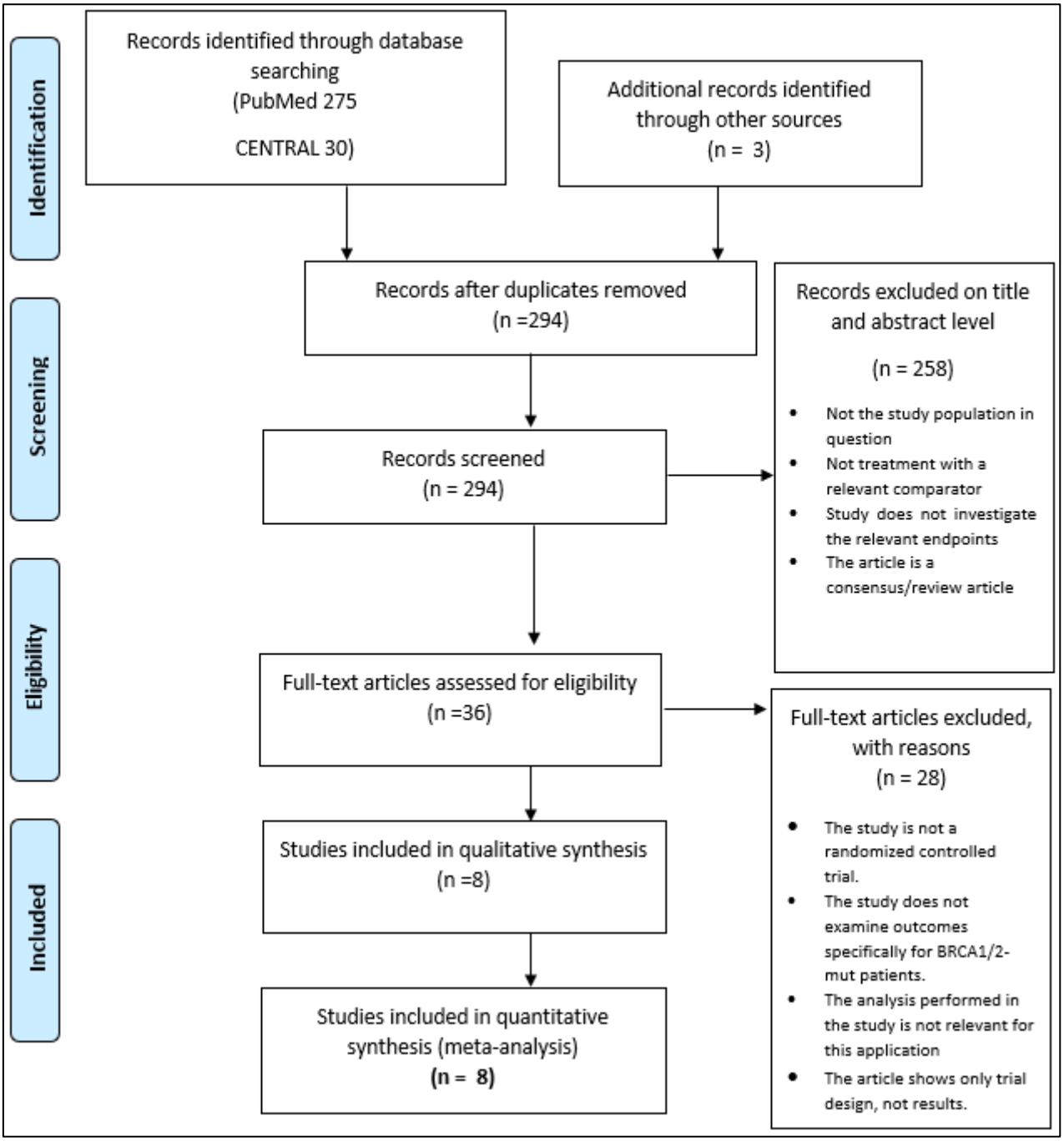
**Table 4**. Search guide Medicinraadet Central

| # | Søgestreng | Kommentar |
|---|---|---|
| #1 | (prostate near/2 (cancer or carcinoma or adenocarcinoma)):ti | Population |
| #2 | (castration next resistant or castrationresistant or (hormone next (refractory or resistant)) or androgen next independent):ti | |
| #3 | #1 and #2 | |
| #4 | castration resistant prostate cancer:kw | |
| #5 | CRPC:ti | |
| #6 | #3 or #4 or #5 | |
| #7 | metasta*:ti,kw | |
| #8 | #6 and #7 | |
| #9 | mCRPC:ti | |

| | | |
|---|---|---|
| #10 | #8 or #9 | |
| #11 | (olaparib or Lynparza*):ti,ab,kw | Intervention og komparator |
| #12 | (docetaxel or Taxotere*):ti,ab,kw | |
| #13 | (cabazitaxel or Jevtana*):ti,ab,kw | |
| #14 | #10 and (#11 or #12 or #13) | |
| #15 | (abiraterone or enzalutamide or ((new or novel) next hormonal next agent*) or "second generation hormone" next therap* or second next HT):ti,ab | Krav til tidl. behandling |
| #16 | (androgen near/3 target* or ASTI* or ARAT*):ti,ab | |
| #17 | #14 and (#15 or #16) | |
| #18 | ("conference abstract" or review):ti,pt | Eksklusions-kriterier |
| #19 | (clinicaltrials.gov or trialsearch):so | |
| #20 | (meeting or conference or proceedings):so | |
| #21 | nct*:au | |
| #22 | #18 or #19 or #20 or #21 | |
| #23 | #17 not #22 | |
| #24 | #23 not pubmed:an | Endelig søgning med eksklusion af referencer, der kommer fra Pubmed. Afgrænses til Trials. |

The literature search and included/excluded studies are described in details in a separate document enclosed with the application. The search revealed full publications that can be used in answering the clinical questions. The Prisma diagram is shown in figure 4.

**Figure 4**. Prisma diagram




The systematic literature search resulted in the identification of 7 peer-reviewed scientific articles as well as the docetaxel SmPC (see below table 5).

**Table 5**. References identified from SLR

| Reference (title, author, journal, year) | Trial name | NCT number | Dates of study (start and expected completion date) | Relevant for clinical question |
|---|---|---|---|---|
| 1) Kwon DH, Chou J, Yip SM, Reimers MA, Zhang L, Wright F, et al. Differential treatment outcomes in BRCA1/2-, CDK12-, and ATM-mutated metastatic castration-resistant prostate cancer. Cancer. 2021.<br><br>2) Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. The New England journal of medicine. 2004;351(15):1502-12.<br><br>3) Docetaxel SmPC | NA<br><br>TAX-327<br><br>NA | NA (RWE study)<br><br>NA<br><br>NA | Genomic, clinical, and demographic data were obtained from electronic medical records from January 1, 1988, to March 16, 2018.<br><br>Enrolment from March 2000 to June 2002. Study completed 2008.<br><br>NA | Clinical question #1.<br>Overall survival and AE grade 3 or more |
| 1) Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. The New England journal of medicine. 2019;381(26):2506-18.<br><br>2) Quality of life in patients with metastatic prostate cancer following treatment with cabazitaxel versus abiraterone or enzalutamide (CARD): an analysis of a randomised, multicentre, open-label, phase 4 study. The Lancet Oncology. 2020;21(11):1513-25.<br><br>3) Reason T, McCrea C, Hettle R, Ghate S, | CARD | NCT02485691 | Enrolment from November 2015. Study completed March 2021. | Clinical question #2.<br>Overall survival, progression free survival, AE grade 3 or more. |

| | | | | |
|---|---|---|---|---|
| Poehlein CH, Olmos D. Indirect treatment comparison of the efficacy of olaparib 300 mg tablets BID and cabazitaxel 25 mg/m2 every 3 weeks plus daily prednisolone and granulocyte colony-stimulating factor in the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC). Journal of Clinical Oncology. 2021;39(15_suppl):5051-(ASCO 2021 poster) | | | | |
| 1) Hussain M, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer. The New England journal of medicine. 2020;383(24):2345-57.<br><br>2) de Bono J, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. The New England journal of medicine. 2020;382(22):2091-102. | PROfound | NCT02987543 | Inclusion between July 2015 and September 2017 | Clinical question #1,2 and 3. Overall survival, progression free survival, AE grade 3 or more. |

The literature search did not identify any randomized controlled studies that directly allows for the comparison of olaparib with docetaxel for taxane-naïve *BRCA*m patients that have progressed on prior treatment with a NHA. Only the recent, retrospective, real-world study by Kwon et al [14] specifically examines the outcomes of HRR mutated patients (including *BRCA*m patients) on docetaxel after progression on a NHA. Consequently, in order to address clinical question #1, we utilize these data for an indirect comparison. In addition we will use data from the docetaxel SmPC for answering questions about AEs [15]. These data are derived from the TAX 327 study [16], so we will also refer to this study for questions on AEs for docetaxel.

For clinical question #2, the publications related to the CARD study can be used for an indirect comparison. Although the CARD study unfortunately does not examine outcomes for the *BRCA*m patients, it does compare cabazitaxel to a 2$^{nd}$ NHA, which is a similar control arm as in the PROfound study for a patient

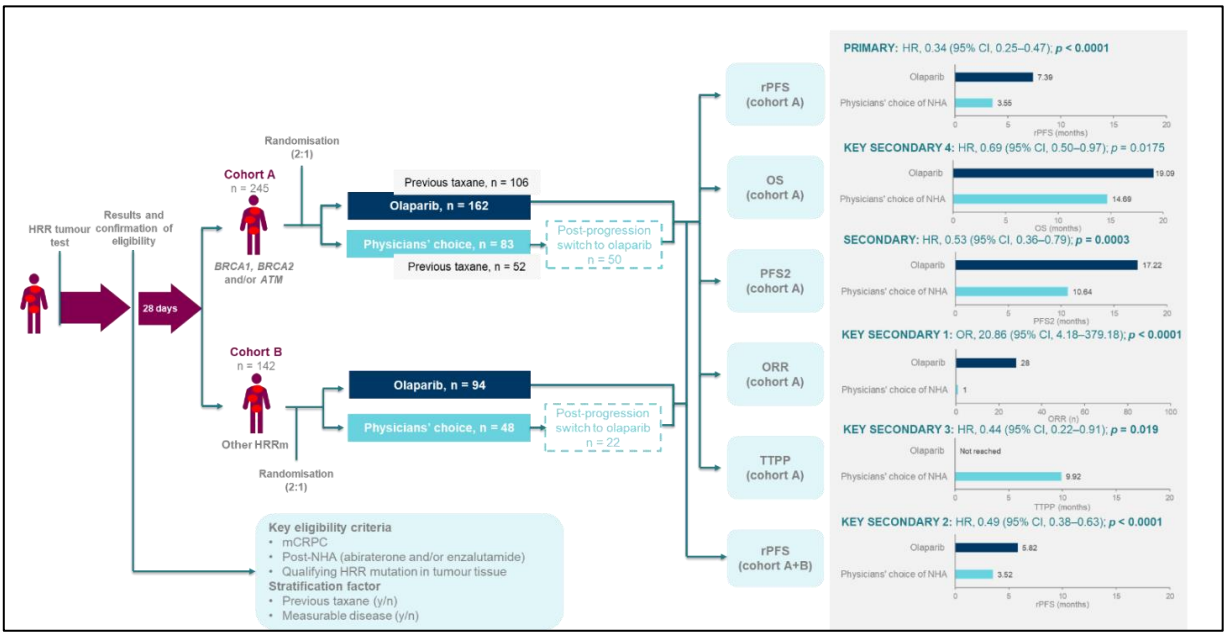
population which is comparable to that of PROfound. This indirect comparison was recently presented as a poster at ASCO 2021 [17]. As the number of prior docetaxel patients in the study are very low and unfit for a solid indirect comparison we have used data from the prior taxane group. This is also to align with the data from the poster.

For clinical question #3 we will use the PROfound data as suggested by Medicinrådets fagudvalg.

## 4.2 Main characteristics of included studies

### PROfound

**Figure 5**. An overview of the PROfound trial.




*[a]Alpha spend was 0.01 at the interim analysis; therefore, statistical significance was not reached.*
*Source: Clinical Study Report edition 1, 23 October 2019[18] and de Bono et al, 2020 [4]*

At EMA decision, olaparib was approved for the *BRCA*m 1/2 population only (excluding ATM from Cohort A). However the *BRCA*m population was a pre-specified subgroup in PROfound so the efficacy outcomes in the *BRCA*m population can be presented for most of the clinical questions from Medicinrådet often listed alongside those from Cohort A. 162 patients were randomized to Olaparib in Cohort A. 102 of these patients were *BRCA*m. In the control arm, 58 of 83 patients in Cohort A were *BRCA*m.

Patient characteristics for Cohort A and the *BRCA*m population are summarised in table A2 in the appendix. Patient demographics and baseline characteristics were broadly similar between Cohort A and the *BRCA*m population. There was a small imbalance between treatment arms in the *BRCA*m population: a slightly higher proportion of patients in the olaparib arm were Asian (26.5% vs 17.2%) or had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (50.0% vs 37.9%) than in the physicians' choice of NHA arm, and fewer patients had a Gleason score of 9 (38.2% vs 41.4%)[19]. Mutation status was

not a stratification factor for randomisation in the PROfound trial, which may explain any imbalances in baseline characteristics between the olaparib and physicians' choice of NHA arms of the *BRCA*m population. A total of 160 patients enrolled in the PROfound trial had a *BRCA1* and/or *BRCA2* mutation: 102 patients were in the olaparib arm and 58 in the physicians' choice of NHA arm[20]. At the second and final data cut-off (DCO2), 50 patients (31.3%) remained in the study of which 12 patients (7.5%) remained on treatment: 12 patients (11.8%) were in the olaparib arm and 0 (0.0%) were in the physicians' choice of NHA arm [20]. Radiographic progression and death were the most frequently reported reasons for treatment discontinuation and study termination, respectively. A full summary of reasons for treatment and study discontinuation is given in [20]

### DCO's

The primary analysis (DCO1) was performed when approximately 143 rPFS events (60% maturity) in cohort A had occurred based on the results of the BICR assessment. Analysis of secondary endpoints was performed at the time of the primary rPFS analysis including an interim analysis of OS. The final analysis (DCO2) of OS was performed following approximately 146 OS events (61% maturity) in cohort A.

### Efficacy PROfound *BRCA*m population

Primary and secondary efficacy results in cohort A (BRCA1/2 and ATM) are shown in figure 5. Outcomes were consistent between the *BRCA*m population and Cohort A, which is expected given that two-thirds of the population of Cohort A had a *BRCA1* and/or *BRCA2* mutation. Compared with physicians' choice of NHA, patients in the olaparib arm of the BRCAm population (excluding data from patients with ATM mutations) experienced:

- **81% reduction in BICR-assessed disease progression (6.8-month improvement in rPFS):** 9.8 (95% CI, 7.6–11.3) months versus 3.0 (95% CI, 1.8–3.6) months; HR, 0.22 (95% CI, 0.15–0.29)[21]
- **5.7-month improvement in OS** (despite approximately two-thirds of patients (69%) in the physicians' choice of NHA arm switching to the olaparib post-BICR-assessed progression): 20.1 months versus 14.4 months; HR, 0.63 (95% CI, 0.42–0.95) [21].
- **Increase in PFS2:** 16.8 (95% CI, 12.7–20.7) months versus 9.5 (95% CI, 7.6–11.2) months; HR, 0.48 (95% CI, 0.30–0.78)[22]
- **68% reduction in the risk of pain progression:** HR, 0.32 (95% CI, 0.12–0.82)[18]
- **36% reduction in the incidence of first SSRE:** 17.6% versus 20.7%; HR, 0.64 (95% CI, 0.31–1.39) [21].
- **Improvement in overall health-related quality of life** as measured by the FACT-P instrument, as well as in the domains related to **physical functioning and wellbeing**, **functional wellbeing**, **symptoms** and **prostate cancer-specific symptoms**.[23-28]

### CARD

In the CARD study, 255 patients with metastatic castration-resistant prostate cancer (mCRPC) who were previously treated with docetaxel and had progression within 12 months while receiving the alternative inhibitor (abiraterone or enzalutamide), were randomized in a 1:1 ratio to receive:

- Cabazitaxel: Cabazitaxel at a dose of 25 mg per square meter of body-surface area intravenously every 3 weeks, plus prednisone daily and granulocyte colony-stimulating factor

  OR

- Control group: Androgen-signaling–targeted inhibitor, either 1000 mg of abiraterone plus prednisone daily or 160 mg of enzalutamide daily. Abiraterone was given to patients who had previously received enzalutamide before trial entry, and enzalutamide was given to patients who had previously received abiraterone.

A treatment cycle was 3 weeks in both trial groups. Each patient was treated until the occurrence of imaging-based disease progression, the occurrence of unacceptable toxic effects, the start of a subsequent treatment, or a request by the patient to discontinue trial therapy. Of the 255 patients randomized, 250 were treated (126 with cabazitaxel and 124 with an androgen-signaling–targeted inhibitor). Of the 124 patients who received an androgen-signaling–targeted inhibitor, 58 received abiraterone and 66 received enzalutamide. The median follow-up (from randomization to the end of the trial) was 9.2 months.

The median age of the patients was 70 years, with 31.0% of the patients being 75 years of age or older. At randomization, 21 patients (8.2%) had PSA progression only, 39 patients (15.3%) had imaging-based progression, and 176 (69.0%) had pain progression. Metastases were present at diagnosis in 42.7% of the patients, and 44.3% of the patients had a duration of response to first androgen-deprivation therapy of less than 1 year.

At the cut-off date, imaging-based disease progression or death from any cause was reported in 196 patients, of whom 95 (73.6%) had been assigned to receive cabazitaxel and 101 (80.2%) had been assigned to receive an androgen-signaling– targeted inhibitor. The median imaging-based PFS was 8.0 months in the cabazitaxel group, as compared with 3.7 months in the control group (HR for imaging-based progression or death, 0.54; 95% CI, 0.40 to 0.73; P<0.001). 153 deaths were noted, with 70 deaths (54.3% of the patients) occurring in the cabazitaxel group and 83 (65.9%) in the control group. The median OS was 13.6 months in the cabazitaxel group, as compared with 11.0 months in the control group (HR for death, 0.64; 95% CI, 0.46 to 0.89; P=0.008). Progression was noted in 111 patients (86.0%) in the cabazitaxel group and in 115 (91.3%) in the control group. The median PFS was 4.4 months in the cabazitaxel group, as compared with 2.7 months in the control group (HR for progression or death, 0.52; 95% CI, 0.40 to 0.68; P<0.001).

Almost all the patients in both treatment groups had an adverse event of any grade (98.4% in the cabazitaxel group vs. 94.4% in the control group). The incidence of serious adverse events of any grade was similar in the cabazitaxel group (38.9%) and the control group (38.7%). Adverse events leading to treatment discontinuation occurred more frequently with cabazitaxel (19.8%) than with an androgen signaling–targeted inhibitor (8.9%).

### Kwon DH. RWE study

A multi-institutional, retrospective study of patients with mCRPC and DNA damage repair mutations (DDRm). Patient data, including systemic therapies and responses, were collected. The decline in prostate-specific antigen ≥ 50% from baseline (PSA50) and OS from the treatment start were compared by mutation and treatment type. A multivariable Cox proportional hazards model for OS was created that controlled for DDRm, first-line treatment received for mCRPC, and clinical factors.

Among 149 patient with mCRPC the most common DDRm were BRCA1/2 (44%), *CDK12* (32%), and *ATM* (15%). First-line treatment were dominated by abiraterone (40%) and enzalutamide (30%). The PSA50 rate with first-line abiraterone was lower for CDK12 (52%) than BRCA1/2 (89%; *P* = .02). After first-line abiraterone or enzalutamide, the median OS was longest with second-line carboplatin-chemotherapy (38 months) in comparison with abiraterone or enzalutamide (33 months), docetaxel (17 months), or cabazitaxel (11 months; *P* = .02). PSA50 responses to carboplatin-based chemotherapy were higher for BRCA1/2 (79%) than ATM (14%; *P* = .02) or CDK12 (38%; *P* = .08). In a multivariable analysis, neither the specific DDRm type nor the first-line treatment was associated with improved OS.

#### Methods:

A pooled retrospective analysis of patients with mCRPC and DDRm identified via somatic, germline, or circulating DNA next-generation sequencing (NGS) was conducted.

Genomic, clinical, and demographic data were obtained from electronic medical records from January 1, 1988, to March 16, 2018. The data cutoff was July 22, 2019. All sites obtained institutional review board approval, and deidentified patient data were shared among the institutions in a Health Insurance Portability and Accountability Act–compliant manner.

Only patients with the following pathogenic or likely pathogenic DDRm were included in the analysis: *ATM*, *ATR*, *BRCA1*, *BRCA2*, *BARD1*, *BRIP1*, *CDK12*, *CHEK2*, Fanconi anemia genes, MMR genes (*MSH1*, *MLH3*, *MSH2*, *MSH3*, *MSH6*, *PMS1*, and *PMS2*), *NBN*, *PALB2*, *RAD51*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*. Patients were categorized into 5 DDRm mutation groups: BRCA1/2, ATM, CDK12, MMR, and other.

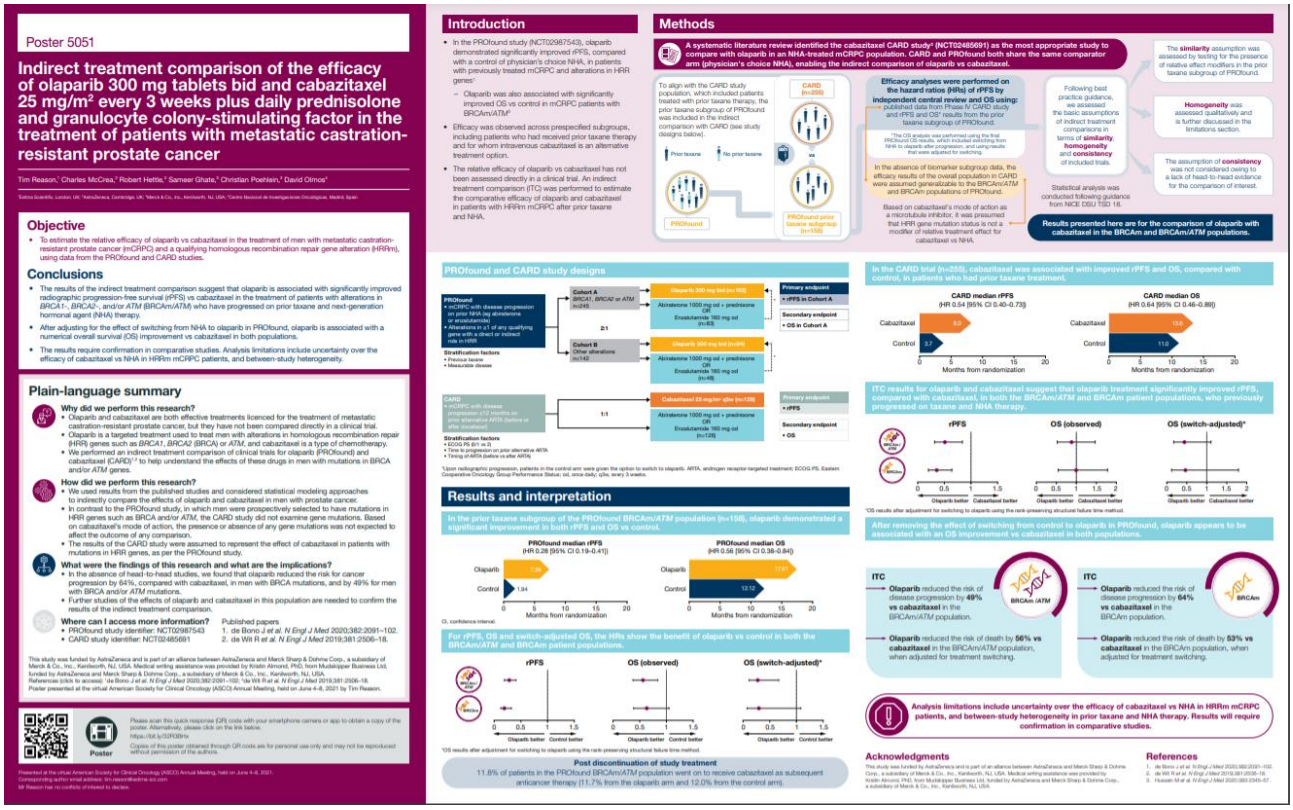
In addition to disease-related clinicopathologic data, data for systemic therapy initiated after the onset of mCRPC (defined as ≥2 consecutively rising serum prostate-specific antigen values and/or new radiographic metastases in the setting of suppressed testosterone levels) were obtained for patients with DDRm. For each systemic therapy, the treatment line, the decline in prostate-specific antigen ≥ 50% from baseline (PSA50), the time from treatment start to next treatment start (TNT), and the OS from the start of treatment were obtained. Concurrent taxane chemotherapy with carboplatin was categorized as carboplatin-based chemotherapy. Patients were followed until the date of death or last follow-up.

### Indirect comparison olaparib and cabazitaxel MAIC (not included in SLR/PRISMA)

MAICs can be used to establish the comparative efficacy of competing healthcare interventions that have been studied in clinical trials, but not directly, and are linked by a common comparator in the case of 'anchored' comparisons. The MAIC include results from the published studies and statistical modeling approaches to indirectly compare the effects of olaparib and cabazitaxel in men with mCRPC. The

PROfound study, prospectively selected patients based on mutations in HRR genes such as BRCA and/or ATM. In contrast, the CARD study did not examine gene mutations. Based on cabazitaxel's mode of action, the presence or absence of gene mutations were not expected to affect the outcome of this comparison and the results of the CARD study were assumed to represent the effect of cabazitaxel in patients with mutations in HRR genes. The comparison has been published as a poster during ASCO June 2021. The results in the poster reflect prior taxane (docetaxel and cabazitaxel) and not the specific group treated with prior docetaxel that is asked for in question 2, but as this group is very small any OS and PFS comparisons will be very uncertain and we have used prior taxane group to answer question 2.

**Figure 6**. Poster from ASCO 2021




*Source: [17]*

# 5 Olaparib vs docetaxel in BRCA 1/2

## 5.1 Olaparib vs docetaxel in BRCA 1/2. OS/OS 12 m

### 5.1.1 Presentation of relevant studies vs docetaxel in BRCA 1/2.

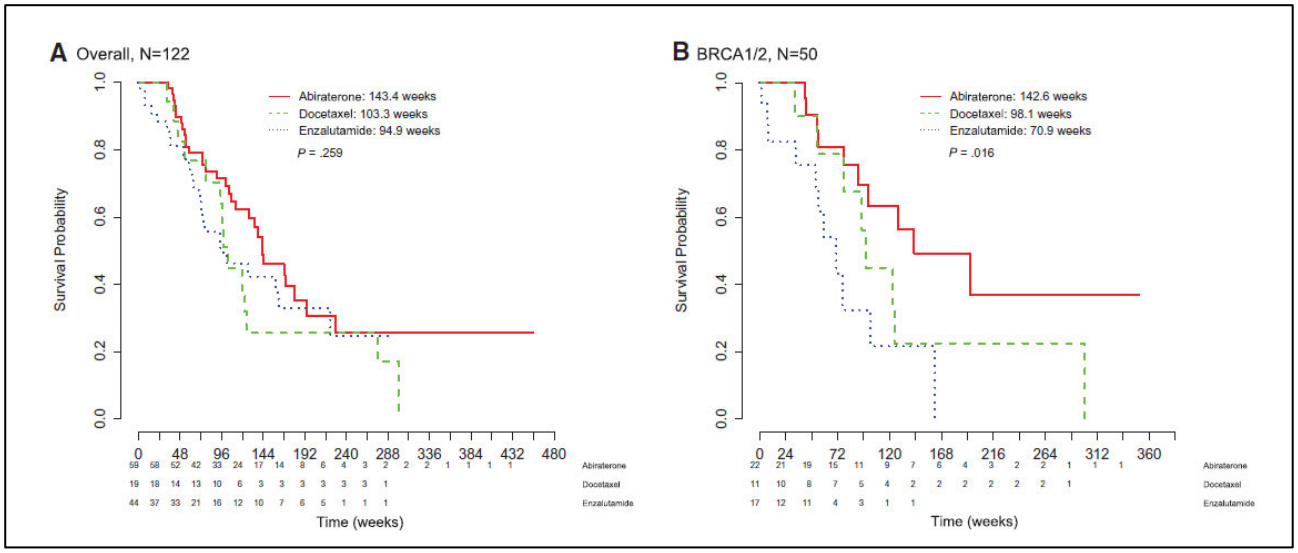
There are no randomized prospective clinical trials that allows for indirect comparison between olaparib and docetaxel in post-NHA mCRPC population, not for BRCA1/2-mut patients and nor for all comers. Available data for docetaxel in post-NHA mCRPC population are derived from retrospective real world evidence studies, the majority of which are for non-biomarker selected patients. Importantly, a prospective study previously demonstrated that germline BRCA2m patients do not respond similarly to current standard of cares, namely NHAs and taxanes [8]. We identified a very recent retrospective multi-center real world evidence study conducted in US that focused on several HRR mutations including BRCA1/2 and the outcomes of patients with different HRR mutations on current standard of cares [14]. Since this study presents data specifically for BRCA1/2-mut patients and separate the outcomes for second line post-NHA, we considered this study to be the most appropriate dataset relevant for this application. Although the study is limited by the small patient numbers, the data presented here is in line with the PROrepair-B data and confirm that BRCA1/2m and potentially other HRRm positive patients may not respond similarly to current stand of cares in mCRPC.

Kwon et al. included pooled retrospective analysis of patients from multiple institutions in the US with mCRPC and HRR mutations identified from somatic, germline or circulating tumor DNA by next generation sequencing. The HRR gene panel consisted of several different genes, but the patients were categorized into the five different groups ATM, BRCA1/2, CDK12, MMR and other mutations. The study reports clinical outcomes, such as PSA50 response rates, time to next treatment (TNT), and OS of systemic therapies received in the first-and second-line mCRPC settings and compared by therapy type and by mutation group. The study identified totally 149 mCRPC patients with HRR mutations, from which 60 had BRCA2 mutation and 5 BRCA1 mutation.

### 5.1.2 Results per study vs docetaxel in BRCA 1/2. OS/OS 12 m

From the 149 identified patients, 137 received systemic therapy. In the overall cohort(A) of the patients, there was no association between first-line treatment type and OS (figure 7A). However, the median OS for BRCA1/2m (B, n=50) was longest for those receiving abiraterone (33 months) versus docetaxel (23 months) or enzalutamide (16 months; figure 7B).

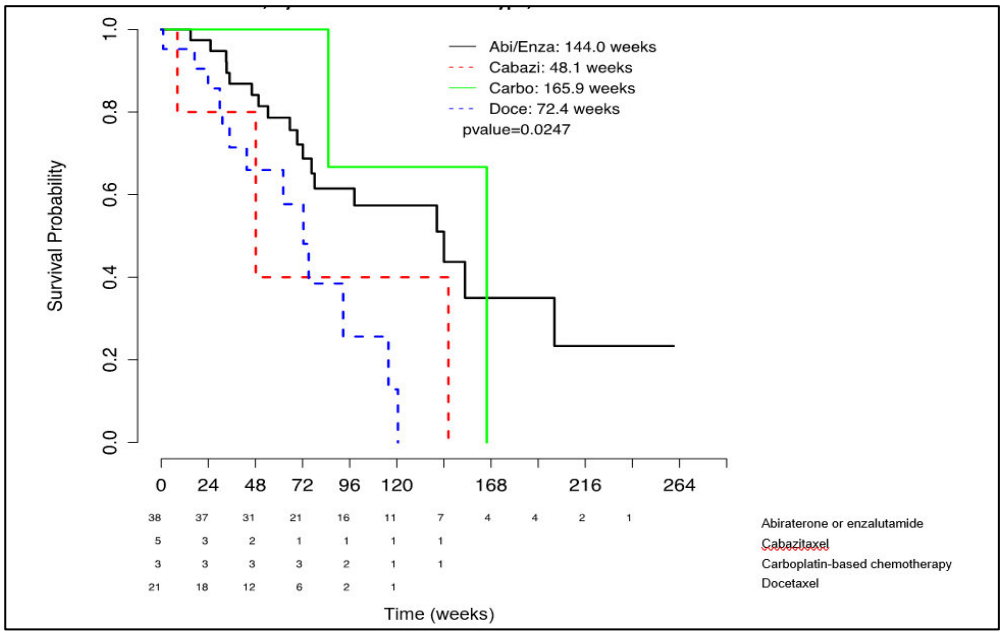
**Figure 7.** OS from the start of first-line treatment in A) total cohort and B) in BRCA1/2m patients




*Source: [14]*

There were 67 patients who received second line therapy after first-line NHA, namely abiraterone or enzalutamide. The OS analysis in this specific post-NHA and DDRm patient group showed that those who received another NHA had longer OS (33 months) than those who received docetaxel (17 months). The differences in OS across therapies were statistically significant indicating that this biomarker positive subgroup of mCRPC patients may not respond similarly to current standard of cares in mCRPC.

**Figure 8.** OS from start of 2L mCRPC therapy in patients with DDRm who received 1L ASI, by second-line treatment type




*Source: [14]*

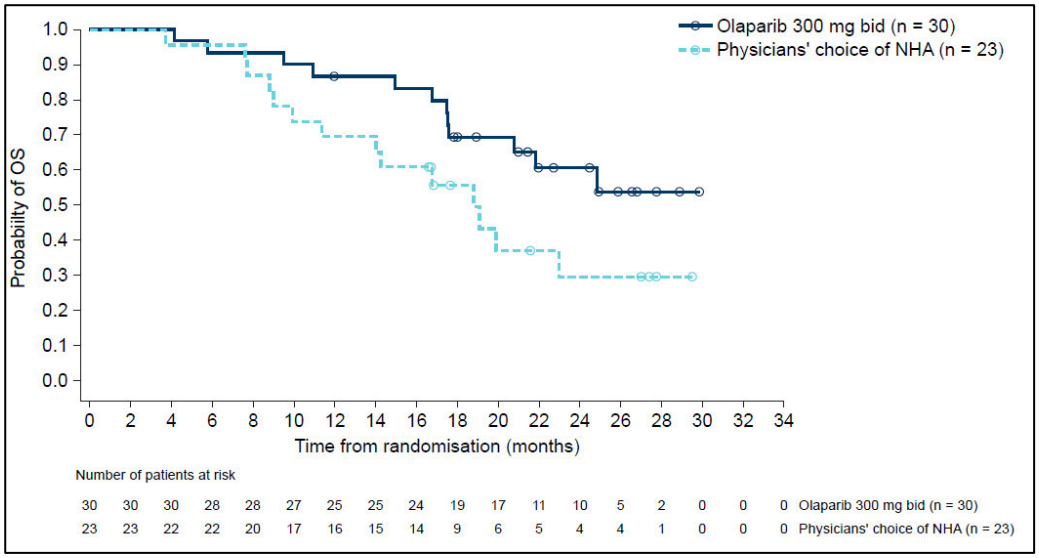
### 5.1.3 Comparative analyses vs docetaxel in BRCA 1/2. OS/OS 12 m

Although there are no RCT data available that allows for a direct comparison between docetaxel and olaparib for post-NHA BRCA1/2m mCRPC patients, a number of retrospective observational studies exist that compare docetaxel activity to NHA in a post-NHA mCRPC patient population [29-32]. These studies have analyzed outcomes for the general mCRPC post-NHA population without taking mutational status into consideration. One Japanese study show the NHA-Docetaxel sequence to result in significantly longer OS compared with the NHA-NHA sequence [30]. However, two other studies show no significant difference in OS between NHA-Docetaxel and NHA-NHA with trends each going in different directions [29, 31]. Finally, a recent real world evidence study by Swami et al showed the NHA-NHA treatment sequence to result in significantly superior OS compared with NHA-Docetaxel [32]. Results are thus inconsistent, pointing in different directions and there is no conclusive evidence that treatment with docetaxel as opposed to a second NHA (such as in the control arm of PROfound) leads to better outcomes for OS in a non-biomarker-selected patient population. Importantly, the recent study by Kwon et al examines outcomes specifically for patients with HRR mutations, of which BRCA-mutations, make up the largest group [14]. As mentioned above, this study showed that mHRR patients treated with docetaxel after 1L NHA had significantly poorer OS than those treated with NHA-NHA in sequence [14]. Hence, taken together it appears that OS outcomes from treatment with docetaxel in the post-NHA setting are on par with those of patients treated with a 2$^{nd}$ NHA for non-biomarker selected patients and likely inferior when examined specifically for the HRRm patient population. Indeed, when mOS estimates are examined in absolute terms from the three of the five retrospective studies where mOS estimates are provided from 2L treatment with docetaxel after previous NHA, the results range from 9.4 or 9.7 months [32], 17.5 months [30] to 16.7 months specifically for the HRRm patients [14]. It should be noted that an interesting retrospective study by Delanoy et al. has compared different sequencing of NHA, docetaxel, and cabazitaxel for mCRPC [33]. Here the authors report a mOS for the NHA-DOC-CAB sequence measured from 2L of 21.4 months. However, since this study only analyzed outcomes for patients who received all 3 lines of treatment, it has a certain inherent selection bias, which can explain why the reported mOS from 2L is higher for this study.

Considering that mOS for the control group of the no-prior-taxane BRCAm subgroup of the PROfound study was 18.79 months, we see no firm evidence to suggest that BRCAm patients treated with docetaxel instead of a 2$^{nd}$ NHA would have had superior outcomes to those in the control arm of the PROfound study. Indeed, as shown above, it's likely that outcomes would have been inferior had the BRCAm patients been treated with docetaxel, with the 16.7 months from the mHRR specific study by Kwon et al as the most appropriate estimate [14]. Using the data from the control arm of the PROfound study no-prior-taxane BRCAm subgroup in place of a docetaxel comparator arm thus likely provides a higher, conservative estimate of the mOS (18.79 months) for the comparator in this setting.

Hence, a substantial mOS benefit was seen for olaparib in the no-prior-taxane BRCAm subgroup with mOS not reached for olaparib compared with 18.79 months for NHA and a HR of 0.51 (CI 0.23-1.13) [34, 35]. See figure 9 for the KM plot.

**Figure 9**. Olaparib vs physicians choice for no-prior-taxane BRCAm subgroup




*Source: [34, 35].*

Since the study by Kwon et al does unfortunately not provide a hazard ratio for OS for docetaxel vs NHA from 2L for patients treated with NHA in 1L (only median OS is presented in the paper), we will for the health economic analysis for clinical question #1 instead use the hazard ratio reported by Swami et al for NHA vs docetaxel in 2L since to our knowledge, this study is the only study that included western patients and provides a hazard ratio for NHA vs docetaxel in 2L. The study by Swami does not take into account mutational status and since Kwon et al demonstrate that the mHRR patients have substantially poorer mOS when treated with docetaxel instead of NHA, the Swami study HR is thus likely a conservative estimate.

## 5.2 Olaparib vs docetaxel in BRCA 1/2. Grade 3 or more AE and Grade 5

### 5.2.1 Results per study vs docetaxel in BRCA 1/2. Grade 3 or more AE and Grade 5

The patient population in clinical question 1 is defined as mCRPC patients with BRCA 1/2 mutations (germline/somatic) who has progressed on NHA (enzalutamid or abirateron). In PROfound, a total of 78.5 % in the olaparib arm vs. 86.2 % in NHA had previously received either enzalutamid or abiraterone. There are no specific AE details available for the specific population defined in question 1 for PROfound. The publication by Hussein et al. do include a table of AEs and SAEs in the BRCA group but only for the Olaparib arm. We have used data from the overall population to answer the question as there likewise are no BRCAm data are available for docetaxel.

Due to the lack of direct comparator evidence for olaparib vs docetaxel, we will perform a naïve comparison of the AE data using the PROfound study data for olaparib and the SmPC for docetaxel (Taxotere).

### AEs for Olaparib based on PROfound:

In the PROfound study, 96.1% of patients treated with olaparib had an AE of any grade [36].

- Approximately one-half of patients (52.0%) in the olaparib arm experienced an AE of grade 3 or above (incl. grade 4 and 5). Same level was found in the BRCAm olaparib arm [36].
- Serious adverse events (SAEs) were reported for 36.7% in the olaparib arm in the PROfound study. The most frequently reported SAE was anaemia in the olaparib arm (9.0% of patients). Same level was found in the BRCAm Olaparib arm [36].
- Grade 5 AEs were reported in six patients (2.3%) in the olaparib arm. Discontinuations due to AEs was 18% in the olaparib arm [36].

### AEs for docetaxel based on data from SmPC:

Safety results for docetaxel (taxotere) included in the SmPC [37] were derived from the phase 3 TAX-327 study [16] which led to the first regulatory approval for mCRPC. Although the study was carried out prior to NHAs entering clinical practice for mCRPC, the safety profile for docetaxel is unlikely to differ substantially from the post NHA setting. The results are summarized in table 6 below:

**Table 6**. Safety profile of docetaxel in mCRPC

| MedDRA system organ classes | Very common adverse reactions | Common adverse reactions |
|---|---|---|
| Infections and infestations | Infection (G3/4: 3.3%) | |
| Blood and lymphatic system disorders | Neutropenia (G3/4: 32%);<br>Anaemia (G3/4: 4.9%) | Thrombocytopenia (G3/4: 0.6%);<br>Febrile neutropenia |
| Immune system disorders | | Hypersensitivity (G3/4: 0.6%) |
| Metabolism and nutrition disorders | Anorexia (G3/4: 0.6%) | |
| Nervous system disorders | Peripheral sensory neuropathy (G3/4: 1.2%);<br>Dysgeusia (G3/4: 0%) | Peripheral motor neuropathy (G3/4: 0%) |
| Eye disorders | | Lacrimation increased (G3/4: 0.6%) |
| Cardiac disorders | | Cardiac left ventricular function decrease (G3/4: 0.3%) |
| Respiratory, thoracic and mediastinal disorders | | Epistaxis (G3/4: 0%);<br>Dyspnoea (G3/4: 0.6%);<br>Cough (G3/4: 0%) |
| Gastrointestinal disorders | Nausea (G3/4: 2.4%);<br>Diarrhoea (G3/4: 1.2%);<br>Stomatitis/Pharyngitis (G3/4: 0.9%);<br>Vomiting (G3/4: 1.2%) | |
| Skin and subcutaneous tissue disorders | Alopecia;<br>Nail disorders (no severe) | Exfoliative rash (G3/4: 0.3%) |
| Musculoskeletal and connective bone disorders | | Arthralgia (G3/4: 0.3%);<br>Myalgia (G3/4: 0.3%) |
| General disorders and administration site conditions | Fatigue (G3/4: 3.9%);<br>Fluid retention (severe: 0.6%) | |

*Source: [16, 37]*

The frequency of grade 3/4 adverse events for docetaxel can be found by summing the frequencies in the above table: The proportion of patients experiencing a grade 3/4 adverse event with docetaxel was 55.8% [16, 37].

In the same study, 26% of patients experienced a serious adverse event attributed to docetaxel and 0.3% had a grade 5 AE [16].

### 5.2.2 Comparative analyses vs docetaxel in BRCA 1/2. Grade 3 or more AE and Grade 5

In conclusion, we find no clear difference between the frequency of grade 3/4 adverse events for olaparib (52%) and docetaxel (55.8%) in the overall populations. Similarly grade 5 adverse events were found in 2.3% of olaparib treated patients compared with 0.3% of patients treated with docetaxel. Hence, for both grade 3/4 and grade 5 AEs, the differences between olaparib and docetaxel fall below the threshold for the minimum clinical relevant difference of 10 %/5% of set by Medicinrådet.

## 5.3 Olaparib vs docetaxel in BRCA 1/2. PFS/PFS 12 m

The publication by Kwon et al does not include data on PFS

### 5.3.1 Results per study vs docetaxel in BRCA 1/2. PFS/PFS 12 m

The publication by Kwon et al does not include data on PFS

### 5.3.2 Comparative analyses vs docetaxel in BRCA 1/2. PFS/PFS 12 m

The publication by Kwon et al does not include data on PSF and olaparib cannot meet the target of 3 months/10% set by Medicinrådet due to lack of comparative date. For olaparib vs. BSC see section 8.

## 5.4 Olaparib vs docetaxel in BRCA 1/2. HQoL

### 5.4.1 Results per study vs docetaxel in BRCA 1/2. HQoL

We have not found studies that make it possible to compare HQoL outcomes for olaparib vs docetaxel in mCRPC in BRCAm or overall population.

### 5.4.2 Comparative analyses vs docetaxel in BRCA 1/2. HQoL

We cannot meet the target of 10 % set by Medicinraadet due to lack of comparative date. For olaparib vs. BSC see section 8.

# 6 Olaparib vs cabazitaxel in BRCA 1/2

## 6.1 Olaparib vs cabazitaxel in BRCA 1/2. OS/OS 12 m

### 6.1.1 Presentation of relevant studies vs cabazitaxel in BRCA 1/2.

In the absence of head-to-head trials comparing olaparib with other treatments than NHAs, an indirect treatment comparison was performed to inform the relative efficacy of the comparators not included in the PROfound trial.

A systematic literature review (SLR) was conducted to identify relevant comparative evidence. The systematic literature review was conducted in January 2020 and identified published clinical evidence on the use of health technologies in patients with mCRPC whose disease had progressed following treatment with an NHA, irrespective of HRR mutation status. The scope of the SLR was broader than that of the decision-problem, and did not restrict inclusion by patients with mCRPC who had HRR gene mutations, to capture all studies in a post-NHA setting that could inform indirect comparisons with existing drugs that are not targeted to HRR mutations.

Systematic literature review identified six publications that reported outcomes on cabazitaxel. Of these, only one study – the CARD trial [38] – was deemed relevant to inform relative efficacy to olaparib in the post-NHA setting. CARD is an ongoing Phase IV RCT that assessed the efficacy and safety of cabazitaxel compared with an NHA (enzalutamide or abiraterone plus prednisolone) in patients with mCRPC, who had received previous treatment with docetaxel and an NHA. As all patients enrolled in the CARD trial were required to have received previous docetaxel, the patient population is closely aligned with the prior-taxane subpopulation of the PROfound study, although not restricted to those patients who have mutations in HRR genes. As with PROfound, rPFS is the primary endpoint in the CARD trial (reported as imaging assessed PFS in both study publications) and OS is a secondary endpoint in both studies, allowing comparisons of comparative effectiveness and economic evaluation.

The remaining publications that reported outcomes in patients who received cabazitaxel were either small early phase or single-arm studies (often conducted in a single country or center) or cabazitaxel combination studies (with budesonide, prednisone, prednisolone, or abiraterone), or did not report on the outcomes of interest (split by those who had received a prior NHA, in case of a mixed population) and were therefore deemed unsuitable for inclusion in the evidence base for this application.

As the PROfound study is the first phase III study in patients with mCRPC and HRRm gene alterations, no other relevant biomarker studies were identified in the SLR that may have been included in an indirect comparison. The biomarker status of participants in the CARD trial is unknown and cannot be adjusted for in the analysis. PROfound is a prospective, multicentre, randomised, open-label, phase III trial evaluating the efficacy and safety of olaparib versus physician's choice of NHA in men with mCRPC, who have failed prior treatment with a new hormonal agent (NHA) and have a qualifying tumour mutation. PROfound included both patients who had been previously treated with a taxane and patients who were taxane naïve; prior treatment with a taxane was a stratification variable in the study. The PROfound study comprises two cohorts based on homologous recombination repair (HRR) gene mutation status:

**Cohort A:**

- BRCA1, BRCA2, ATM

**Cohort B:**

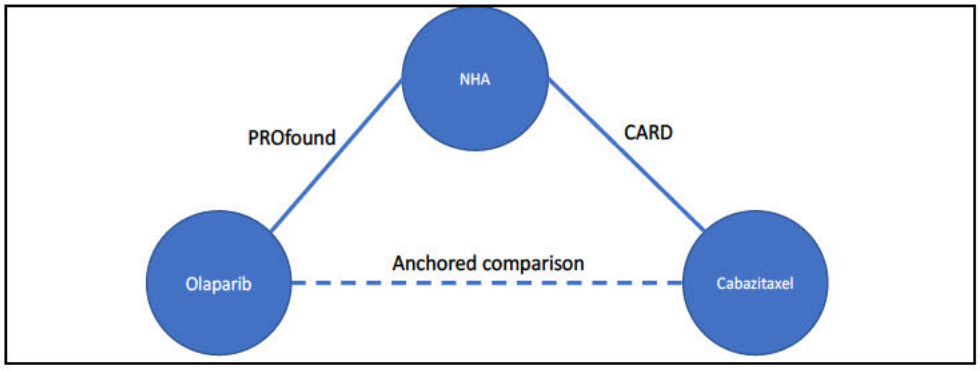
- BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D and RAD54L

Matching adjusted indirect comparison [39] (MAIC) is a technique widely used in oncology to establish the relative efficacy of two interventions for which individual patient data (IPD) is available for one trial/intervention but only aggregate data (AgD) is available for the other. MAIC is a method that has been used in multiple health technology assessment (HTA) submissions and is recommended by the National Institute for Health and Care Excellence (NICE) subject to appropriate application of the methods [40].

As with indirect treatment comparisons (ITCs), MAICs can be used to establish the comparative efficacy of competing healthcare interventions that have been studied in clinical trials, but not directly, and are linked by a common comparator in the case of 'anchored' comparisons.

The specific evidence networks for this analysis are shown in figure 10.

FIGURE 10: EVIDENCE NETWORKS FOR THIS ANALYSIS




As can be seen in figure 10, there is a common comparator (NHA) available to link olaparib to cabazitaxel in the PROfound and CARD studies and therefore following guidance from NICE DSU TSD 18 an anchored MAIC was conducted. Additionally, due to the potential additional uncertainty associated with conducting an MAIC using switching-adjusted OS data, an unanchored MAIC was conducted comparing olaparib and cabazitaxel in the BRCAm prior taxane subgroup. The outcomes of interest for this analysis were rPFS and OS.

The definitions of progression free survival for each study were as follows:

- PROfound: Time from randomisation until objective radiological disease progression (by RECIST 1.1 or prostate cancer working group 3 or death )

- CARD: Time from randomisation until objective tumour progression (RECIST 1.1 criteria), progression of bone lesions (according to prostate cancer working group 2 criteria [41]) or death

Following guidance from NICE DSU TSD 18, the analysis was conducted in the following steps:

1. An assessment of the effect modifiers was conducted as described in subsequent sections, in order to determine the variables to include for matching.

2. The following subgroups of the PROfound data were derived for the population of interest:

    - Cohort A prior taxanes only (cabazitaxel and/or docetaxel)
    - BRCAm prior taxanes only (cabazitaxel and/or docetaxel)
    - Cohort A prior docetaxel only (prior cabazitaxel monotherapy or in combination with docetaxel excluded)
    - BRCAm prior docetaxel only (prior cabazitaxel monotherapy or in combination with docetaxel excluded)

3. Weights for each patient in PROfound were calculated to match patients in the PROfound IPD to AgD in CARD.

4. A Bucher comparison was conducted using the matching-adjusted and unadjusted hazard ratios (HRs) vs. NHA.

5. Further analysis was conducted using adjusted and unadjusted HRs vs. NHA derived from counterfactual data from a rank preserving structural failure time (RPSFT) model, described elsewhere [42]. Analyses were conducted using recensored and non-recensored data. Please refer to the treatment-switching analysis technical report for further information.

All analyses were conducted using R® version 3.6.1 [43]. For the CARD study, curves of interest were digitized using the web application WebPlotDigitizer and pseudo-IPD recreated using the Guyot *et al.* algorithm [44]. Patients with missing values of any covariate were removed since standard MAIC procedures are not able to handle missing covariates. The MAIC was therefore technically a complete case analysis.

In addition to the efficacy analysis a simple Bucher comparison of safety endpoints was conducted using all patients in Cohort A and B. This was carried out separately for 'all grade' and 'grade 3-4' adverse events. Where adverse events were grouped together in CARD, these frequencies were also added in the

PROfound data to ensure that the AEs were comparable. The safety ITC was conducted using the Bucher method as described in NICE DSU TSD 4 [45].

### Matching variables

The following potential variables were evaluated for inclusion:

Variables:

- Neutrophil
- Alkaline phosphatase
- Haemoglobin
- LDH
- Enzalutamide
- Brief Pain Inventory
- Gleason score
- Age
- Visceral disease
- M1 disease
- ECOG
- PSA

The effect modifier analysis was conducted on the overall PROfound population (Cohort A+B) to achieve greater statistical power and be more inclusive of available data. If any survival outcome had a significant result, the variable was included in the analysis for all outcomes.

The results of the effect modifiers assessment for the rPFS and OS endpoints and the covariate imbalance analysis are presented in table 7 and table 8, respectively. As mentioned, table 7 and table 8 are based on Cohort A+B and equivalent statistics for statistical significance in of effect modifiers in the BRCAm populations are shown in Table 9. Age was the only variable identified as significant in the Cohort A+B population that was not identified as significant in the BRCAm population. Since age was identified as significant in the overall study population, it was included in the MAIC analysis for the BRCAm population too.

In all analyses, PROfound rPFS BICR data were from DCO1 (4th June 2019) as data were not collected beyond this cut-off; PROfound OS and safety data in all analyses are from DCO2 (20th March 2020).

**Table 7.** Assessment of effect modifiers - prior taxane subgroup (A+B)

| Variable | rPFS | OS- No RPSFT | OS- RPSFT- with re-censoring | OS- RPSFT- no re-censoring |
|---|---|---|---|---|
| Neutrophil | 1.000 (1.000, 1.000) | 1.000 (1.000, 1.000) | 1.000 (1.000, 1.000) | 1.000 (1.000, 1.000) |
| Alkaline phosphatase | 0.999 (0.998, 1.000) | **0.998 (0.997, 0.999)*** | **0.998 (0.997, 0.999)*** | **0.998 (0.997, 0.999)*** |
| Haemoglobin | 1.010 (0.996, 1.024) | 0.995 (0.980, 1.010) | 0.992 (0.977, 1.008) | 0.995 (0.980, 1.010) |
| LDH | 1.000 (0.999, 1.000) | 0.999 (0.999, 1.000) | 1.000 (0.999, 1.000) | 1.000 (0.999, 1.000) |
| Enzalutamide | 1.287 (0.824, 2.010) | 1.440 (0.903, 2.297) | **1.796 (1.100, 2.935)*** | 1.462 (0.918, 2.330) |
| Brief Pain Inventory | 1.323 (0.841, 2.081) | 1.499 (0.954, 2.357) | 1.416 (0.883, 2.271) | 1.457 (0.927, 2.291) |
| Gleason score | 0.825 (0.526, 1.292) | 1.296 (0.799, 2.102) | 0.976 (0.578, 1.647) | 1.207 (0.744, 1.958) |
| Age | **0.961 (0.933, 0.989)*** | 1.003 (0.974, 1.032) | 1.006 (0.976, 1.038) | 1.004 (0.976, 1.034) |
| Visceral disease | 0.808 (0.540, 1.210) | **1.750 (1.135, 2.696)*** | **1.664 (1.065, 2.600)*** | **1.630 (1.059, 2.510)*** |
| M1 disease | 0.915 (0.612, 1.369) | 0.786 (0.512, 1.206) | 0.854 (0.546, 1.335) | 0.708 (0.461, 1.086) |
| ECOG | 1.447 (0.629, 3.328) | 0.520 (0.236, 1.145) | 0.583 (0.264, 1.292) | 0.604 (0.274, 1.330) |
| PSA | 1.000 (1.000, 1.000) | 1.000 (1.000, 1.000) | 1.000 (1.000, 1.000) | 1.000 (1.000, 1.000) |

*Covariate was significant at 80% level

**Table 8.** Imbalance statistics for effect modifiers of interest.

| Variable | rPFS | OS- No RPSFT | OS- RPSFT- with re-censoring | OS- RPSFT- no re-censoring |
|---|---|---|---|---|
| Neutrophil | 1.000 | 1.000 | 1.000 | 1.000 |
| Alkaline phosphatase | 0.956 | 0.915 | 0.915 | 0.915 |
| Haemoglobin | 1.000 | 1.000 | 0.984 | 1.000 |
| LDH | 1.000 | 0.946 | 1.000 | 1.000 |
| Enzalutamide | 1.031 | 1.045 | 1.073 | 1.047 |
| Brief Pain Inventory | 1.013 | 1.019 | 1.016 | 1.017 |
| Gleason score | 1.025 | 0.967 | 1.003 | 0.976 |
| Age | 1.000 | 1.000 | 1.000 | 1.000 |
| Visceral disease | 1.049 | 0.882 | 0.892 | 0.896 |
| M1 disease | 1.017 | 1.046 | 1.030 | 1.067 |
| ECOG | 1.005 | 0.992 | 0.993 | 0.993 |
| PSA | 1.000 | 1.000 | 1.000 | 1.000 |

As can be seen in table 7, most variables were found not to be effect modifiers with the exception of alkaline phosphatase levels at baseline, age (rPFS only), ECOG (non-RPSFT OS only) and visceral disease (RPSFT and non-RPSFT data). This indicates that for the prior taxane subgroup, an MAIC may not be required since the majority of variables are not considered to be effect modifiers for the outcomes of interest. It can also be seen in table 8 and 9 that the majority of variables, with the exception of alkaline phosphatase and visceral disease, did not appear to be imbalanced and therefore adjusting for the majority of variables is unlikely to reduce the bias in the estimate of treatment effect relative to a standard unadjusted Bucher comparison.

**Table 9.** Assessment of effect modifiers – BRCAm prior taxane subgroup.

| Variable | rPFS | OS- No RPSFT | OS- RPSFT- with re-censoring | OS- RPSFT- no re-censoring |
|---|---|---|---|---|
| **Neutrophil** | 1.000 (1.000, 1.000) | 1.000 (1.000, 1.000) | 1.000 (1.000, 1.000) | 1.000 (1.000, 1.000) |
| **Alkaline phosphatase** | **0.998 (0.998, 0.999)** | 0.999 (0.998, 1.000) | 0.999 (0.998, 1.000) | 0.999 (0.998, 1.000) |
| **Haemoglobin** | 0.993 (0.978, 1.007) | 1.015 (0.986, 1.045) | 0.999 (0.971, 1.028) | 1.011 (0.983, 1.039) |
| **LDH** | 1.000 (0.999, 1.000) | 0.999 (0.998, 1.000) | 0.999 (0.998, 1.000) | 0.999 (0.998, 1.000) |
| **Enzalutamide** | 1.448 (0.909, 2.308) | 1.590 (0.768, 3.295) | 1.674 (0.774, 3.618) | 1.613 (0.777, 3.347) |
| **Brief Pain Inventory** | 1.306 (0.831, 2.052) | 1.542 (0.765, 3.106) | 1.658 (0.795, 3.457) | 1.549 (0.772, 3.106) |
| **Gleason score** | 1.132 (0.697, 1.839) | 0.721 (0.332, 1.567) | 0.525 (0.221, 1.248) | 0.715 (0.330, 1.549) |
| **Age** | 1.003 (0.974, 1.033) | 1.031 (0.983, 1.082) | 1.044 (0.992, 1.098) | 1.037 (0.987, 1.089) |
| **Visceral disease** | **1.776* (1.153, 2.737)** | 1.925 (0.984, 3.765) | 1.840 (0.918, 3.688) | 1.688 (0.867, 3.286) |
| **M1 disease** | 0.829 (0.540, 1.271) | 0.810 (0.413, 1.588) | 0.883 (0.438, 1.779) | 0.616 (0.312, 1.214) |
| **ECOG (0-1)** | 0.482 (0.218, 1.064) | 0.386 (0.147, 1.012) | **0.351* (0.132, 0.936)** | 0.450 (0.173, 1.170) |
| **PSA** | 1.000 (1.000, 1.000) | 1.000 (1.000, 1.000) | 1.000 (1.000, 1.001) | 1.000 (1.000, 1.000) |

*Covariate was significant at 80% level

The final list of matching variables for both rPFS and OS is shown in table 10:

**Table 10**: Unweighted and reweighted baseline characteristics

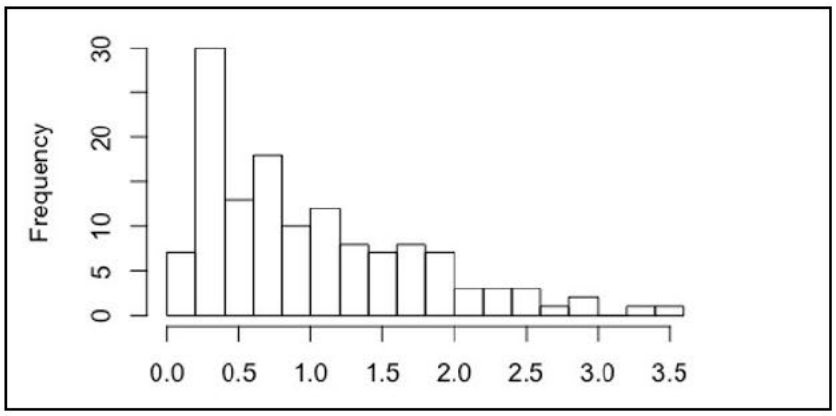
| Covariate | PROfound (prior taxane) | CARD | PROfound (reweighted to CARD) |
|---|---|---|---|
| Age (mean) | 67.0 | 70.0 | 69.99 |
| Visceral disease (%) | 38.8 | 16.3 | 16.3 |
| Alkaline phosphatase (IU/L) | 192 | 226.6 | 226.6 |
| Eco 0-1 (%) | 94.0 | 95.3 | 95.29 |

As can be seen in table 10, the weighting procedures produced weights that generated identical or similar baseline characteristics at the aggregate level to comparator studies. This indicates that the procedure of weighting patients in PROfound so that their baseline characteristics at the aggregate level match those of CARD has been successful.

## Validity of weights and effective sample size

In line with NICE DSU TSD 18, a histogram of the rescaled weights was produced in order to check for extreme values. This is shown in figure 11.

**Figure 11.** Histogram of re-scaled weights for prior taxane subgroup




*Source: [46]*

It can be seen from figure 11 that there were some high outlying values for weights, indicating that some patients were contributing much more to the analysis and therefore the results of the adjusted analysis

may be sensitive to inclusion of those patients. The effective sample size for the MAIC for the prior taxane subgroup was 86 patients (olaparib: 63; NHA: 23), which is approximately 54% of the original sample size. In the prior taxane group, less than 7 % of patients were weighted to 0 in the MAIC(figure 11).

This loss of sample size is implicitly associated with a loss of precision and should be considered when interpreting the results.

### Adjusted PROfound data and CARD data

In order to make indirect comparisons versus the CARD trial, the MAIC weights were used to calculate new rPFS and OS HRs for olaparib versus NHA in PROfound. These HRs represent the treatment effect that would have been observed if patients in PROfound had equivalent characteristics to those in CARD. These HRs were used to compare directly to rPFS and OS HRs from CARD, which were sourced directly from the study publication. The HRs for rPFS and OS from the CARD study were 0.54 (95% CI: 0.40 to 0.73) and 0.64 (95% CI: 0.46 to 0.89), respectively.

The prior taxane group is both described in the report and the poster from ASCO 2021(figure 6) [17].

### Proportional hazards

It is important to assess the validity of the proportional hazards (PH) assumption in order to verify the appropriateness of using the Cox model for analysis. Violation of the PH assumption may mean that analyses that allow for the HR to vary over time may be more appropriate. The PH assumption in the PROfound (pre and post matching) and CARD studies was assessed by visual inspection of the log-cumulative hazards plots and the Schoenfeld plots, and conducting Schoenfeld individual tests.

### RPSFTM estimates

A RPSFTM estimates the causal effect of treatment using a counterfactual framework, where counterfactual survival times are those that would have been observed if treatment switching had not occurred. Counterfactual survival times ($Ui$ ) were estimated using Equation 1.

Equation1 Counterfactual survival model:

$$U_i = T_{A_i} + e^{\psi} T_{B_i}$$

Where:

- $T_{A_i}$ is the time spent on investigators choice of NHA
- $T_{B_i}$ is the time spent on olaparib
- $e^{\psi}$is the acceleration factor, which is the degree to which being on olaparib increases survival; $e^{-\psi}$ is the degree to which survival times need to be decreased by

$T_{A_i}$ and $T_{B_i}$ are known values and taken directly from the PROfound trial. The acceleration factor $e^{\psi}$ is unknown and estimated through g-estimation. With g-estimation, a value for $\psi$ is selected from a range of

values, and input into the counterfactual survival model (Equation 1) for every patient in the trial (both control and experimental arms) to work out an untreated survival time ($U_i$) for every patient. The average untreated survival times between the randomised groups are then compared. The final value of $\psi$ is that for which the untreated survival times between the randomised groups are equal. This counterfactual survival data is then used for the treatment switchers in the investigators choice of NHA arm.

For g-estimation, the R package 'rpsftm' was used[54] The grid-search algorithm used to estimate the acceleration factor is the interval bisection method [54]. The rpsftm() function in this package allows the user to specify:

- the test used for estimating the equation, available tests are log rank, cox proportional hazards and Weibull
- the range of values selected from for estimating $\psi$ (default -1 to 1)
- whether or not the analysis should be recensored

For patients in the investigators choice of NHA arm who switch to olaparib, the counterfactual survival model involves shrinking both survival and censoring times. The amount by which they shrink depends on the size of the treatment effect and the time from starting olaparib to censoring Counterfactual censoring times may be prone to informative censoring if treatment switching decisions are related to prognostic factors and/or duration of treatment is related to prognostic factors[55]. This possible bias may be avoided by breaking the dependence between censoring time and treatment by recensoring. If $C_i$ is the potential censoring time for patient i, then a participant is then recensored at the minimum possible censoring time:

Equation 2 incorporating recensoring:

$$D_i^*(\psi) = \min(C_i, C_i e^{\psi})$$

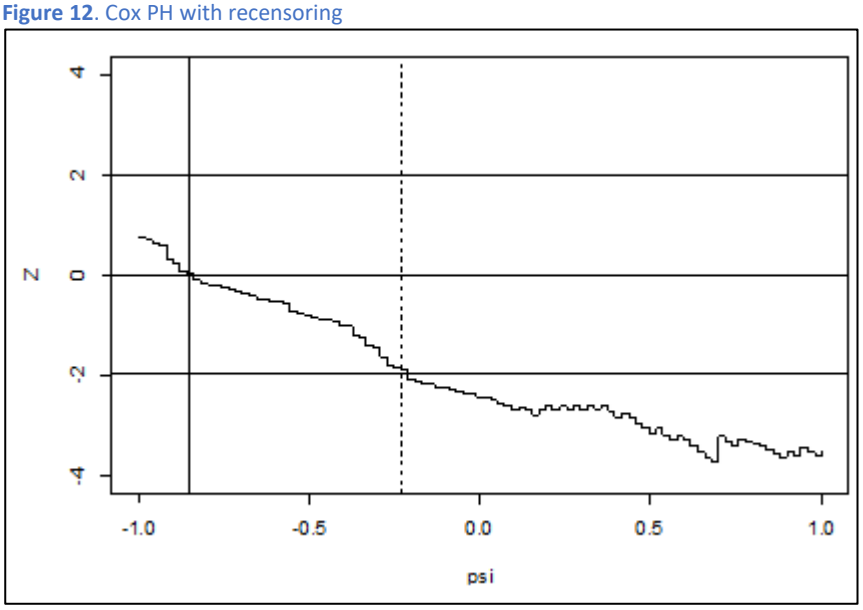
If $D_i^*(\psi) < U_i(\psi)$, then $U_i$ is replaced by $D_i^*$ and the censoring indicator is replaced by 0.

This involves a loss of information as the data are artificially censored earlier than the trial follow-up. Comparing the counterfactual survival times for the investigators choice of NHA arm to the olaparib arm is based on shorter-term data for the investigators choice of NHA arm, which is visible in a comparison of recensored KM OS curves to non-recensored KM OS curves. If the treatment effect changes over time, recensoring can lead to a biased estimate of the average treatment effect because longer term data are discarded. Therefore, both recensored and non-recensored results are compared, as whilst recensoring can help avoid informative censoring bias, it can result in missing information bias when the treatment effect changes over time, or when long-term trends in hazards are not established in the short term.

The analysis was performed using all three methods and the default range for estimating $\psi$ (-1 to 1). The analysis includes inspection of a plot of $Z(\psi)$ against $\psi$ to check that the model finds a root (i.e., a unique value for $\psi$).

The diagnostic plot of *Z(ψ)* against $\psi$ below(figure 12) is for the Cox PH with recensoring, i.e. the base case RPSFTM analysis:

**Figure 12**. Cox PH with recensoring

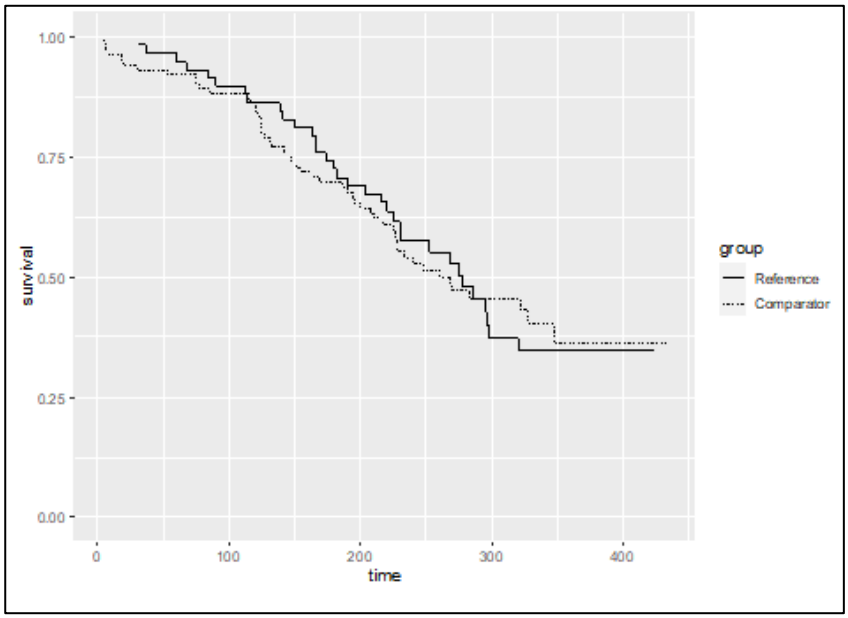



*Source: AstraZeneca. MAIC to assess the efficacy of olaparib vs cabazitaxel. Version 1. 29 Sep. 2020 [46]*

The plots confirms that unique roots were found and that the search interval for ψ was sufficiently wide.

The KM plots of the counterfactual times(figure 13) were also inspected to check that the distributions are the same at $\psi$.

**Figure 13**: KM plots of the counterfactual times for Cox PH with recensoring:




*Source: AstraZeneca. MAIC to assess the efficacy of olaparib vs cabazitaxel. Version 1. 29 Sep. 2020 [46]*

Comparison of the counterfactual survival times for the reference and comparator arms confirm that their distributions are similar at ψ, which suggests that the RPSFTM has worked

For the confidence intervals, the method retains the P value from the unadjusted analysis by design. The calculation of the standard error for the analysis involved taking the log of the RPSFTM-adjusted HR estimate, and dividing by the z-score from the unadjusted results.

In the olaparib arm, 102 patients had a BRCA mutation vs. 58 patients in the NHA arm. For patients with a BRCA mutation, the unadjusted hazard ratio for OS for olaparib vs. investigators choice of NHA arm is 0.60 (0.40, 0.91). Median survival is 20.1 months in the olaparib arm and 14.5 months (unadjusted) in the investigators choice of NHA arm.

Results of the RPSFTM switching adjustment:

- The first step was to calculate the acceleration factor. Acceleration factors shorten the survival time by ~0.43-0.50

**Table 11**. Acceleration factors with different methods

| Acceleration factor | w/o recensoring | w recensoring |
|---|---|---|
| Log rank test | 0.47 | 0.43 |
| Cox proportional hazards | 0.45 | 0.43 |
| Weibull | 0.50 | 0.43 |

*Source: AstraZeneca. MAIC to assess the efficacy of olaparib vs cabazitaxel. Version 1. 29 Sep. 2020 [46]*

- The second step was to apply the acceleration factor to data and recalculate survival. Variation in the point estimate is due primarily to the impact of recensoring with estimates being consistent across models selected for g-estimation (0.43 for models with recensoring versus 0.47-0.50 for models without).

**Table 12**. Treatment-switching adjusted hazard ratios

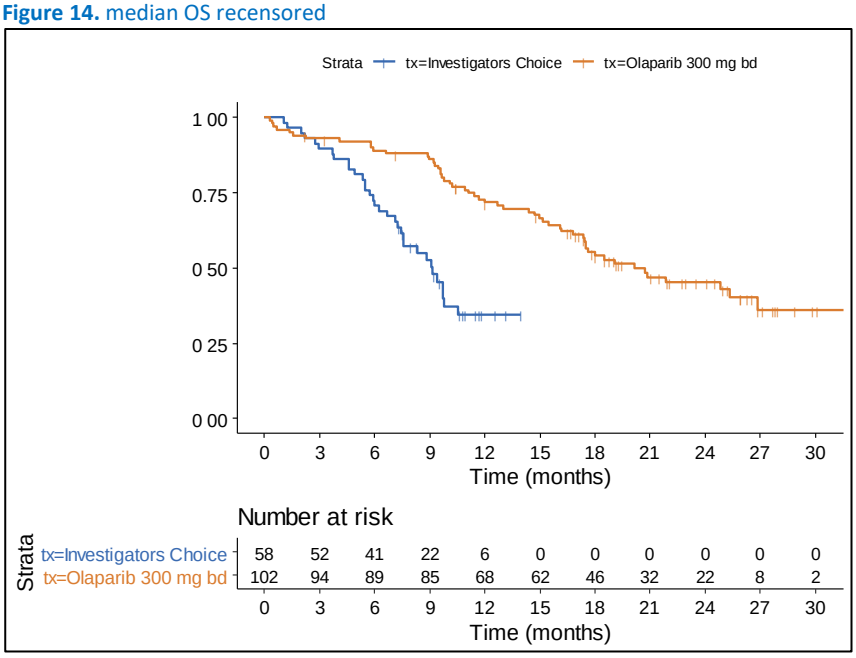
| HR (olaparib vs. investigators choice of NHA) | Without recensoring | With recensoring |
|---|---|---|
| Log rank test | 0.40 (0.18, 0.9) | 0.29 (0.1, 0.86) |
| Cox proportional hazards | 0.37 (0.16, 0.83) | 0.28 (0.1, 0.79) |
| Weibull | 0.39 (0.18, 0.84) | 0.27 (0.09, 0.78) |

*Source: AstraZeneca. MAIC to assess the efficacy of olaparib vs cabazitaxel. Version 1. 29 Sep. 2020 [46]*

- There are wide confidence intervals around the central HR estimates: the method retains the P value from the ITT analysis, thus, in situations when the point estimate of the HR is reduced, the CI widens
- The results with recensoring are used for the base case estimates to avoid informative censoring bias
- This is consistent with the method used in publications of these results[17]

Cox proportional hazards, with recensoring, median OS for investigator choice is 9.15 months(see figure and table 18):

**Figure 14.** median OS recensored




*Source: AstraZeneca. MAIC to assess the efficacy of olaparib vs cabazitaxel. Version 1. 29 Sep. 2020 [46]*

PROfound includes a sequence of treatments with different starting points. Only subsequent PARP inhibitor use was included in the cross-over adjustment for PROfound, because it is not yet established as standard therapy. There were not compensate for other differences in subsequent therapies, as these reflect current clinical practice. Both cabazitaxel and NHAs are standard therapies in mCRPC. OS in the CARD trial also represents a sequence of treatments with different starting points – cabazitaxel or NHA (22.3% CABA → NHA, 33.3% NHA → CABA). Hence, cross-over adjustment of CARD OS hazard ratio should not be needed. In addition, no access to individual patient data from the CARD study makes it difficult to perform a rigorous cross-over adjustment with standard methods.

### 6.1.2 Results per study vs cabazitaxel in BRCA 1/2. OS/OS 12 months

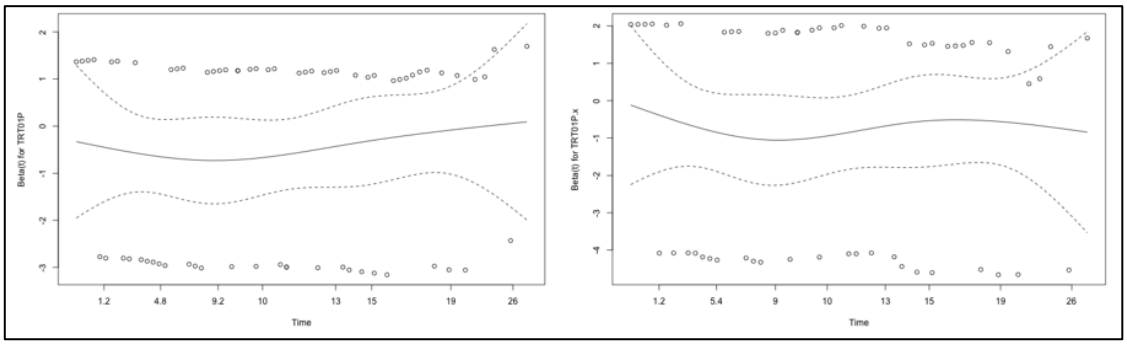
#### Non-RPSFT OS

Schoenfeld residual plots and log-cumulative hazard plots for the non-RPSFT OS endpoint of the PROfound study are presented in figure 15 and figure 16, respectively.

Visual inspection of the log-cumulative hazards plots for non-RPSFT OS indicates that there was not substantial departure from the PH assumption. This is further confirmed by the Schoenfeld individual tests, which resulted p-values of 0.48 and 0.82 in the unadjusted and adjusted analyses, respectively, in

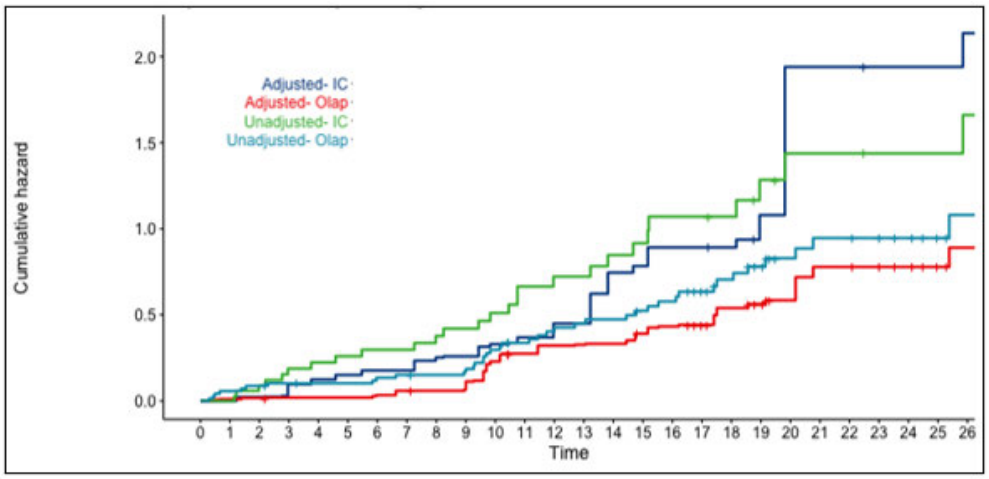
PROfound and 0.94 in the CARD study, indicating that there was no evidence against the null hypothesis of proportional hazards at 5% significance.

**Figure 15**. PROfound non-RPSFT OS: Schoenfeld plots for unadjusted (left) and adjusted (right) analyses



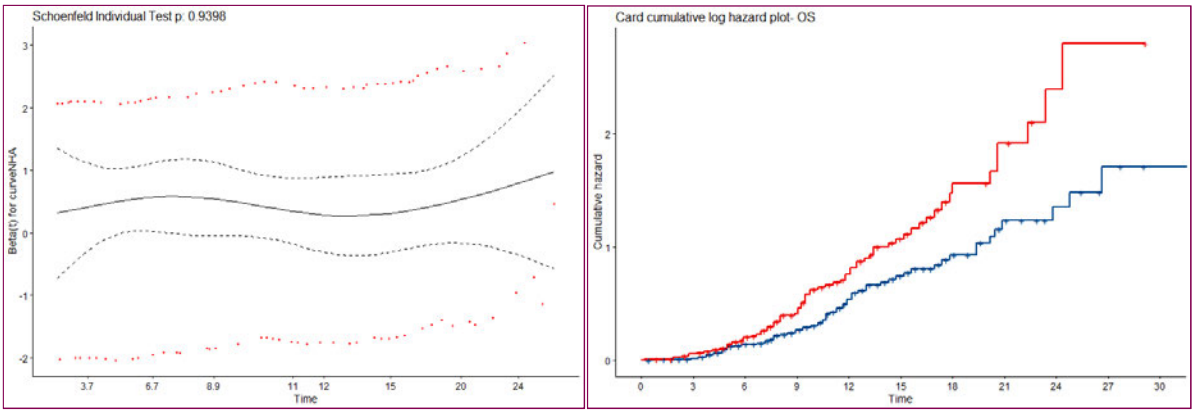

*Source: AstraZeneca. MAIC to assess the efficacy of olaparib vs cabazitaxel. Version 1. 29 Sep. 2020 [46]*

**Figure 16**: Unadjusted and adjusted log-cumulative hazard plots from PROfound study




*Source: AstraZeneca. MAIC to assess the efficacy of olaparib vs cabazitaxel. Version 1. 29 Sep. 2020 [46]*

**Figure 17**: CARD OS: Schoenfeld (left) and log-cumulative hazards (right) plots

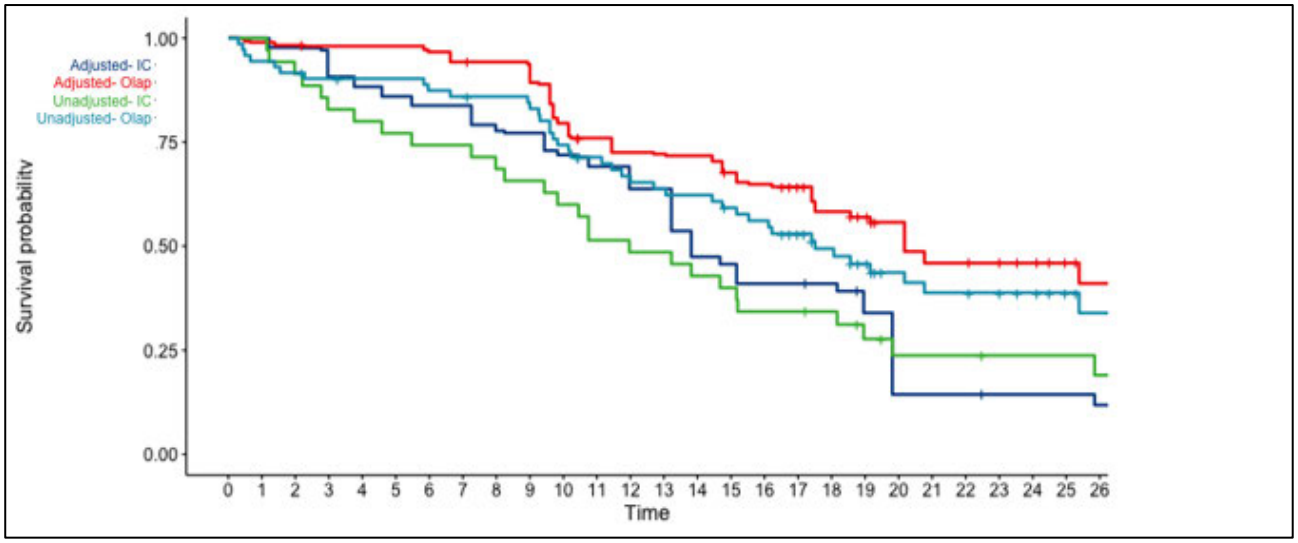



*Source: AstraZeneca. MAIC to assess the efficacy of olaparib vs cabazitaxel. Version 1. 29 Sep. 2020 [46]*

Since there was not substantial departure from the PH assumption across both the PROfound and CARD trials(figure 15, 17), the Bucher method using the MAIC-adjusted and unadjusted HRs was considered appropriate.

The MAIC-unadjusted and adjusted hazard ratios for olaparib versus NHA were 0.63 (95 % CI: 0.39, 1.04) and 0.49 (95 % CI: 0.27, 0.89), respectively (Figure ); the corresponding MAIC-unadjusted and adjusted ITC results for olaparib versus cabazitaxel were 0.99 (95 % CI: 0.55, 1.78) and 0.77 (95 % CI: 0.39, 1.51), respectively (table 13).

**Figure 18**: Adjusted and unadjusted non-RPSFT OS Kaplan-Meier plots for olaparib and NHA (anchored analysis)




*Source: AstraZeneca. MAIC to assess the efficacy of olaparib vs cabazitaxel. Version 1. 29 Sep. 2020 [46]*

**Table 13**: Comparative non-RPSFT OS HRs generated by MAIC

| Analysis | Olaparib vs. NHA HR (95% CI) (PROfound) | Olaparib vs. cabazitaxel HR (95% CI) | Cabazitaxel vs. NHA HR (95% CI) (CARD study) |
|---|---|---|---|
| **Adjusted (n*=56)** | 0.49 (0.27, 0.89) | 0.77 (0.39, 1.51) | 0.64 (0.46 to 0.89) |
| Non-adjusted (n=107) | 0.63 (0.39, 1.04) | 0.99 (0.55, 1.78) | |

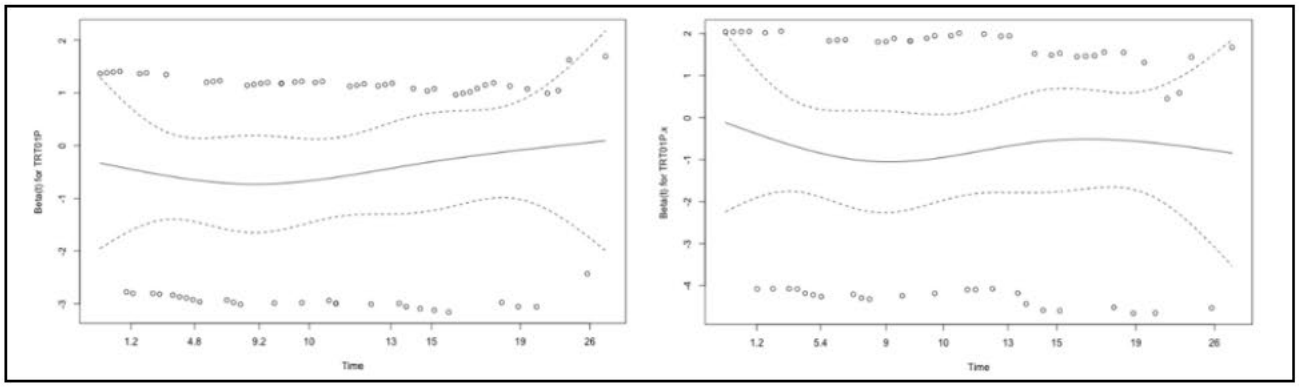
*Effective sample size. *Source: AstraZeneca. MAIC to assess the efficacy of olaparib vs cabazitaxel. Version 1. 29 Sep. 2020 [46]*

## RPSFT OS with re-censoring

Schoenfeld residual plots and log-cumulative hazard plots for the RPSFT OS with re-censoring endpoint of the PROfound study are presented in and figure 19 and figure 20, respectively.

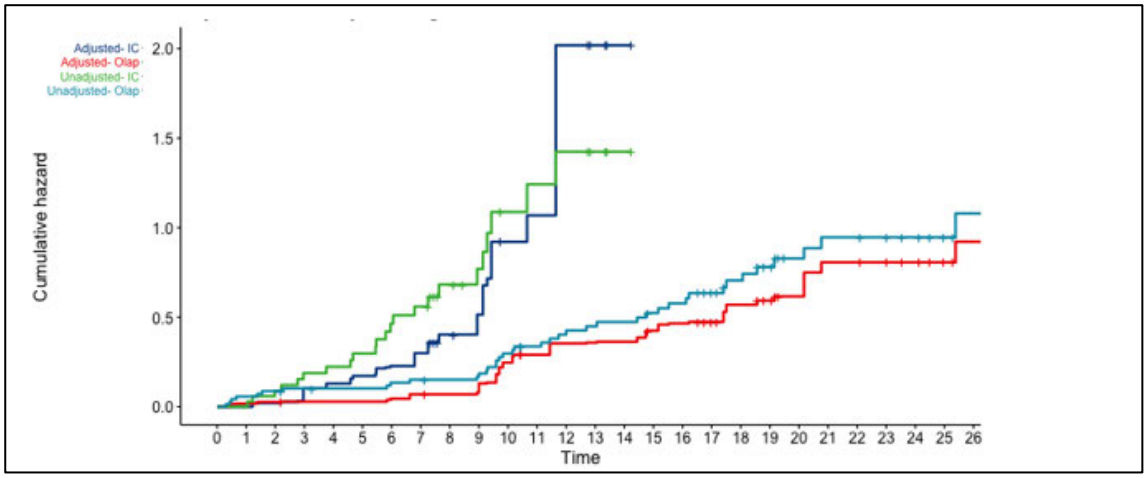
Visual inspection of the log-cumulative hazards plots for RPSFT OS with re-censoring indicates that there was not substantial departure from the PH assumption. This is further confirmed by the Schoenfeld individual tests, which resulted in p-values of 0.93 and 0.83 in the unadjusted and adjusted analyses, respectively, in PROfound, indicating that there was no evidence against the null hypothesis of proportional hazards at 5% significance.

**Figure 19**: PROfound RPSFT OS with re-censoring: Schoenfeld plots for unadjusted (left) and adjusted (right) analyses




*Source: AstraZeneca. MAIC to assess the efficacy of olaparib vs cabazitaxel. Version 1. 29 Sep. 2020 [46]*

**Figure 20**: Unadjusted and adjusted log-cumulative hazard plots from PROfound study




*Source: AstraZeneca. MAIC to assess the efficacy of olaparib vs cabazitaxel. Version 1. 29 Sep. 2020 [46]*

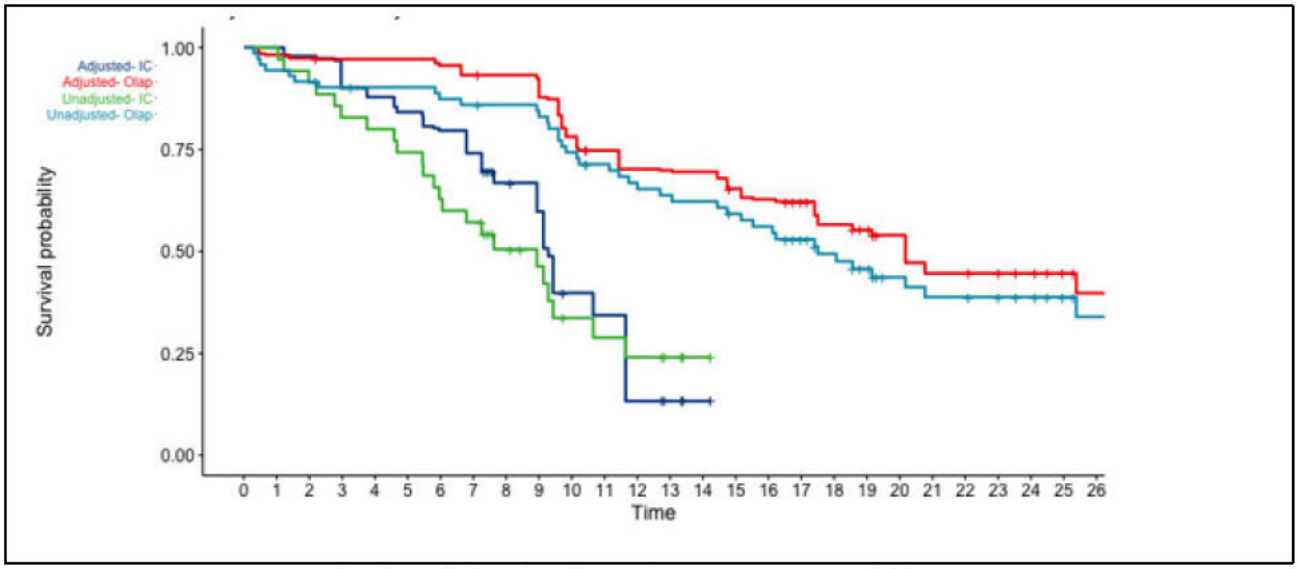
Since there was not substantial departure from the PH assumption across both the PROfound and CARD trials, the Bucher method using the MAIC-adjusted and unadjusted HRs was considered appropriate.

The MAIC-unadjusted and adjusted hazard ratios for olaparib versus NHA were 0.301 (95 % CI: 0.168, 0.539) and 0.216 (95 % CI: 0.108, 0.433), respectively (figure 21); the corresponding MAIC-unadjusted and adjusted ITC results for olaparib versus cabazitaxel were 0.470 (95 % CI: 0.241, 0.919) and 0.338 (95 % CI: 0.156, 0.729), respectively (table 14).

The unadjusted hazard ratios for olaparib versus NHA, generated by Visible Analytics who conducted the treatment switching analyses, are also provided in table 14. These 95% confidence intervals are preferred for the prior taxane subgroup, since the 95% confidence intervals for the RPSFTM data were generated by retaining the ITT p-value by design. Please refer to the treatment switching analysis report for further information.

An ITC analysis using the HR and 95% confidence intervals generated in the Visible Analytics analysis and the CARD data was also conducted and is presented in table 9.The HR is consistent with the non-adjusted analyses presented; however, the confidence intervals differ due to the methods of the RPSFTM approach (as described above).

**Figure 21**: Adjusted and unadjusted RPSFT OS with re-censoring KM plots for olaparib and NHA (anchored analysis)




*Source: AstraZeneca. MAIC to assess the efficacy of olaparib vs cabazitaxel. Version 1. 29 Sep. 2020 [46]*

**Table 14**: Comparative RPSFT OS with re-censoring HRs generated by MAIC

| Analysis | Olaparib vs. NHA HR (95% CI) (PROfound) | Olaparib vs. cabazitaxel HR (95% CI) | Cabazitaxel vs. NHA HR (95% CI) (CARD) |
|---|---|---|---|
| **Adjusted (n*=56)** | 0.216 (0.108, 0.433) | 0.338 (0.156, 0.729) | 0.64 (0.46 to 0.89) |
| Non-adjusted (n=107) | 0.301 (0.168, 0.539) | 0.470 (0.241, 0.919) | |
| Treatment switching analysis (RPSFTM Cox proportional hazards conducted by Visible analytics) | 0.30 (0.08, 1.08) | 0.47 (0.12, 1.79) | |

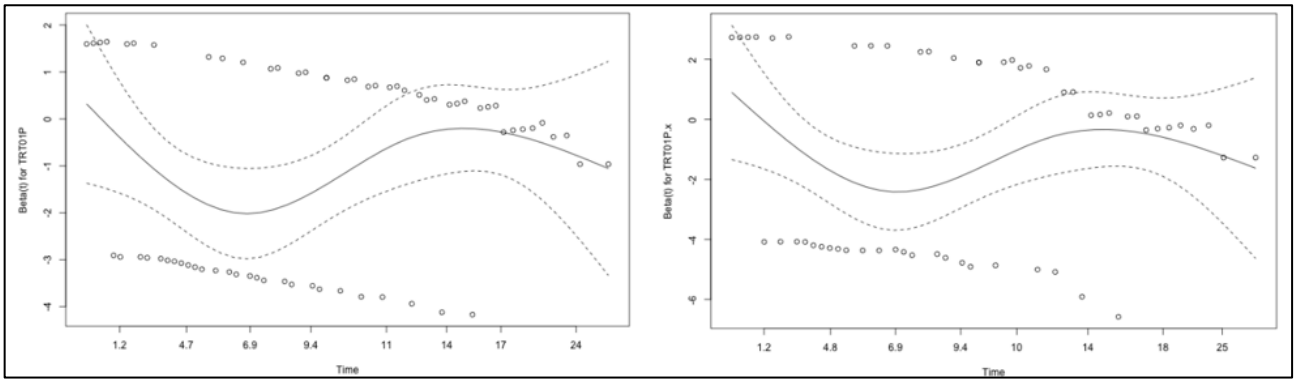
*Effective sample size; *Source: AstraZeneca. MAIC to assess the efficacy of olaparib vs cabazitaxel. Version 1. 29 Sep. 2020 [46]. ASCO 2021 poster [17]*

### RPSFT OS without re-censoring

Schoenfeld residual plots and log-cumulative hazard plots for the RPSFT OS without re-censoring endpoint of the PROfound study are presented in figure 22 and figure 23, respectively.

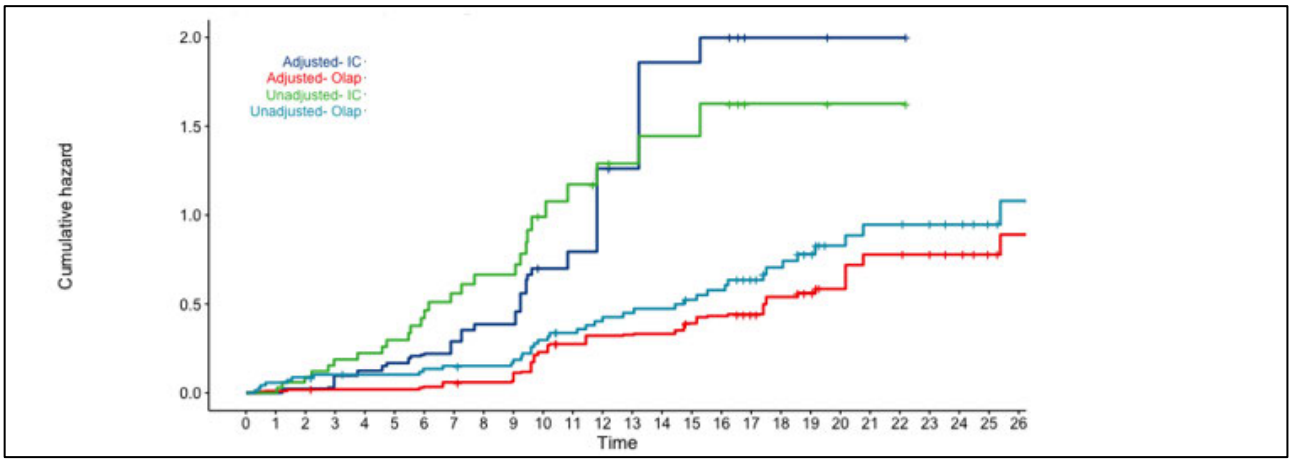
Visual inspection of the log-cumulative hazards plots for non-RPSFT OS indicates that there was not substantial departure from the PH assumption. This is further confirmed by the Schoenfeld individual tests, which resulted in p-values of 0.84 and 0.33 in the unadjusted and adjusted analyses, respectively, in PROfound, indicating that there was no evidence against the null hypothesis of proportional hazards at 5% significance.

**Figure 22**: PROfound non-RPSFT OS: Schoenfeld plots for unadjusted (left) and adjusted (right) analyses




*Source: AstraZeneca. MAIC to assess the efficacy of olaparib vs cabazitaxel. Version 1. 29 Sep. 2020 [46]*

**Figure 23**: Unadjusted and adjusted log-cumulative hazard plots from PROfound study




*Source: AstraZeneca. MAIC to assess the efficacy of olaparib vs cabazitaxel. Version 1. 29 Sep. 2020 [46]*

Since there was not substantial departure from the PH assumption across both the PROfound and CARD trials, the Bucher method using the MAIC-adjusted and unadjusted HRs was considered appropriate.

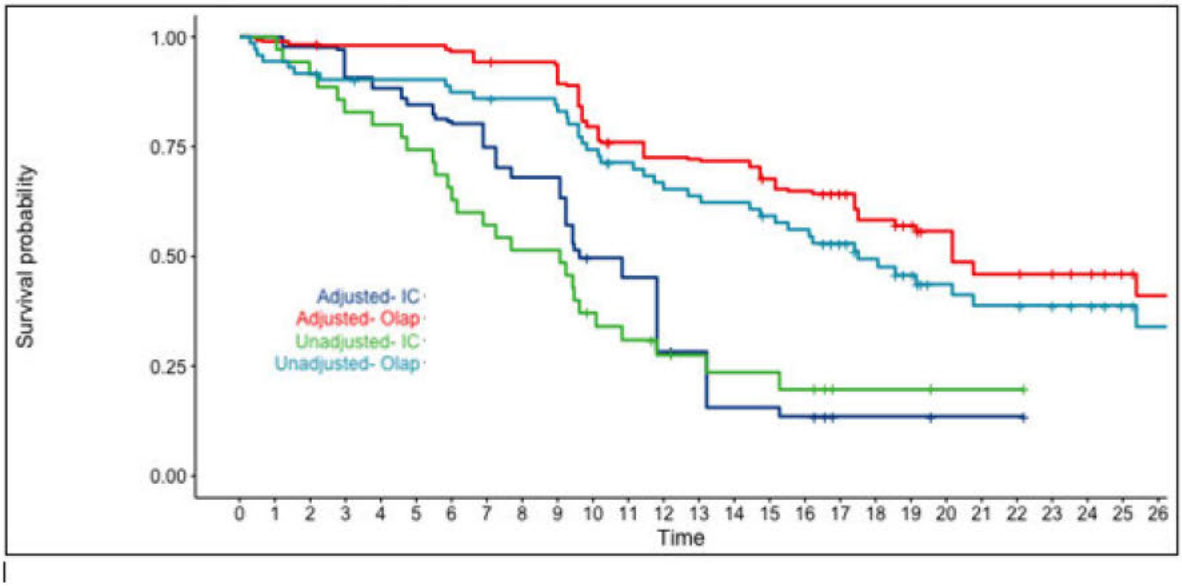
The MAIC-unadjusted and adjusted hazard ratios for olaparib versus NHA were 0.381 (95 % CI: 0.229, 0.634) and 0.281 (95 % CI: 0.146, 0.542), respectively (figure 24); the corresponding MAIC-unadjusted and adjusted ITC results for olaparib versus cabazitaxel were 0.596 (95 % CI: 0.325, 1.092) and 0.439 (95 % CI: 0.210, 0.916), respectively (table 15).

The unadjusted hazard ratios for olaparib versus NHA, generated by Visible Analytics who conducted the treatment switching analyses, are also provided in table 9. These 95% confidence intervals are preferred for the prior taxane subgroup, since the 95% confidence intervals for the RPSFTM data were generated by retaining the ITT p-value by design. Please refer to the treatment switching analysis report for further information.

An ITC analysis using the HR and 95% confidence intervals generated in the Visible Analytics analysis and the CARD data was also conducted and is presented in table 10. The HR is consistent with the non-adjusted

analyses presented; however, the confidence intervals differ due to the methods of the RPSFTM approach (as described above).

**Figure 24**: Adjusted and unadjusted RPSFT OS without re-censoring KM plots for olaparib and NHA (anchored analysis)




*Source: AstraZeneca. MAIC to assess the efficacy of olaparib vs cabazitaxel. Version 1. 29 Sep. 2020 [46]*

**Table 15**: Comparative RPSFT OS without re-censoring HRs generated by MAIC

| Analysis | Olaparib vs. NHA HR (95% CI) (PROfound) | Olaparib vs. cabazitaxel HR (95% CI) | Cabazitaxel vs. NHA HR (95% CI) (CARD) |
|---|---|---|---|
| **Adjusted (n*=56)** | 0.281 (0.146, 0.542) | 0.439 (0.210, 0.916) | 0.64 (0.46 to 0.89) |
| Non-adjusted (n=107) | 0.381 (0.229, 0.634) | 0.596 (0.325, 1.092) | |
| Treatment switching analysis (RPSFTM Cox proportional hazards conducted by Visible analytics) | 0.38 (0.13, 1.07) | 0.59 (0.20, 1.79) | |

*Effective sample size. *Source: AstraZeneca. MAIC to assess the efficacy of olaparib vs cabazitaxel. Version 1. 29 Sep. 2020 [46]*

### 6.1.3 Comparative analyses vs cabazitaxel in BRCA 1/2. OS/OS 12 m

#### Anchored BRCAm analysis

The purpose of this analysis was to estimate the relative efficacy of olaparib versus cabazitaxel with IPD from the PROfound study and AgD from the CARD study. The comparison was made using the prior taxane (docetaxel and/or cabazitaxel) from the BRCAm subgroup of the PROfound study.

In the prior taxane group after removing the effect of switching from control to olaparib in PROfound, olaparib appears to be associated with an OS improvement vs cabazitaxel in the prior taxane (docetaxel or cabazitaxel) BRCAm population. Olaparib reduced the risk of death by 53% vs cabazitaxel in the BRCAm population, when adjusted for treatment switching but the difference is not significant [17, 46].

## 6.2 Olaparib vs cabazitaxel in BRCA 1/2. Grade 3 or more AE and Grade 5

### 6.2.1 Results per study vs cabazitaxel in BRCA 1/2. Grade 3 or more AE and Grade 5

The patient population in clinical question 2 is defined as mCRPC patients with BRCA 1/2 mutations (germline/somatic) who have progressed on NHA (enzalutamid or abirateron) and docetaxel. In PROfound, a total of 78.5 % in the olaparib arm vs. 86.2 % in NHA had previously received either enzalutamid or abiraterone and 70.6 % of patient in the olaparib arm received a prior taxane vs. 60.3 % in the NHA arm. The are no specific AE details for the group defined by question 2, Cohort A or the BRCAm population and we have used data from the overall PROfound population to answer this question. The CARD trial do also not have information around the specific population in question 2.

#### CARD vs PROfound naïve comparison

Grade 5 is listed as AE and not treatment related grade 5 AEs

#### PROfound:

- Almost all the patients in both treatment groups had an **AE of any grade** (96.1% in the olaparib group vs. 88.5 % in the androgen-signaling–targeted inhibitor group) [36].

- Approximately one-half of patients (52.0%) in the olaparib arm experienced an **AE of grade 3** or above compared with 40.0% of patients in the physicians' choice of NHA arm [36].

- Serious adverse events **(SAEs)** were reported more often in the olaparib arm than in the physicians' choice of NHA arm (36.7% vs 30.0%); however, exposure to olaparib was approximately twice as long as that of the physicians' choice of NHA (230 days vs 120 days). The most frequently reported

SAE was anaemia in the olaparib arm (9.0% of patients) and urinary tract infection in the physicians' choice of NHA arm (3.1%) [36].

- **Grade 5 AEs** were reported in six patients (2.3%) in the olaparib arm and in three patients (2.3%) in the physicians' choice of NHA arm [36].

- AEs leading to death was similar with 10(4 %) in the Olaparib arm and 6(5%) in the NHA group(DCO2).

- 13 AE-related deaths (3.4% of the study population; olaparib arm, 6 patients [2.3%]; physicians' choice of NHA arm, 7 patients [5.3%]) (DCO1)

- **Discontinuations** due to AEs was higher in the Olaparib arm, 18 % vs. 8 % in the comparator group [36].

CARD:

- Almost all the patients in both treatment groups had an **AE of any grade** (98.4% in the cabazitaxel group vs. 94.4% in the HNA arm) [38].

- **AEs of grade 3** or higher occurred in 56.3% of patients receiving cabazitaxel and in 52.4% of those receiving an androgen-signaling–targeted inhibitor [38].

- The incidence of **SAE** of any grade was similar in the cabazitaxel group (38.9%) and the comparator group (38.7%) [38].

  **Grade 5** AEs in the cabazitaxel group: infection (2 patients), bronchial aspiration (1), general health deterioration due to progressive disease (2), spinal cord compression (1), and head injury (1) vs. infection (2), pulmonary thromboembolism (1), cardiac disorder (2), cerebral bleeding associated with hyperfibrinolysis (1), renal failure (2), and general health deterioration due to progressive disease (6) [38]. The grade 5 AEs that were reported in the NHA group were related to infection (2), pulmonary thromboembolism (1), cardiac disorder (2), cerebral bleeding associated with hyperfibrinolysis (1), renal failure (2), and general health deterioration due to progressive disease (6), which in one patient was associated with upper gastrointestinal bleeding, hypertensive crisis, and cardiac failure.

- AE leading to death during the assessment period from randomization to 30 days after the last treatment administration occurred less frequently with cabazitaxel (7 patients [5.6%]) than with an androgen-signaling–targeted inhibitor (14 patients [11.3%])

- AEs leading to treatment **discontinuation** occurred more frequently with cabazitaxel (19.8%) than HNA (8.9%) [38].

Table 16. PROfound vs CARD naïve comparison. Safety

| Study | AE any Grade % | AE Grade 3 or more % | SAE % | AE Grade 5 % | AEs and deaths % | Discontinuations % |
|---|---|---|---|---|---|---|
| **Olaparib vs NHA [36]** | 96.1 vs. 88.5 | 52.0 vs. 40.0 | 36.7 vs. 30.0 | 2.3 vs. 2.3 | 4 vs. 4 | 18.0 vs. 8.0 |
| **Cabazitaxel vs NHA [38]** | 98.4 vs 94.4 | 56.3 vs. 52.4 | 38.9 vs. 38.7 | 5.4 vs. 11.1 | 5.6 vs. 11.3 | 19.8 vs. 8.9 |

## MAIC

The results of the safety ITC for Cohort A and B from PROfound vs. cabazitaxel are shown in table 17. Data are reported as odds ratios for olaparib compared with cabazitaxel for any grade and grade 3-4 events; 95% confidence intervals are provided in brackets. 17 vs 14 endpoints are in favor of olaparib but none of the observations are significant.

Table 17: Safety ITC for olaparib vs. cabazitaxel

| Endpoint | Any grade | Grade 3-4 |
|---|---|---|
| **Renal disorder** | 1.627 (0.563 , 4.706) | 3.071 (0.569 , 16.578) |
| **Cardiac disorder** | 1.783 (0.456 , 6.967) | 6.458 (0.503 , 82.851) |
| **Arthralgia** | 2.047 (0.666 , 6.290) | 2.073 (0.017 , 254.912) |
| **Dyspnoea** | 1.242 (0.230 , 6.724) | 6.317 (0.048 , 829.953) |
| **Alopecia** | 0.105 (0.003 , 4.129) | 0.515 (0.002 , 132.931) |
| **Spinal cord or nerve root disorder** | 0.793 (0.014 , 46.334) | 0.873 (0.013 , 57.423) |
| **Psychiatric disorder** | 4.226 (1.227 , 14.554) | 0.255 (0.003 , 25.582) |
| **Hypertensive disorder** | 1.516 (0.344 , 6.677) | 0.510 (0.052 , 5.024) |
| **Weight loss** | 2.273 (0.523 , 9.888) | 1.032 (0.006 , 186.337) |
| **Febrile neutropenia** | 0.062 (0.001 , 3.600) | 0.062 (0.001 , 3.600) |
| **Bone fracture** | 1.243 (0.019 , 79.649) | 1.039 (0.010 , 104.180) |
| **Anemia** | 1.691 (0.307 , 9.315) | 3.036 (0.807 , 11.422) |
| **Leukopenia** | 1.185 (0.063 , 22.176) | 0.018 (0.000 , 1.172) |
| **Neutropenia** | 0.662 (0.035 , 12.453) | 0.453 (0.022 , 9.451) |
| **Thrombocytopenia** | 1.702 (0.350 , 8.264) | 4.719 (0.169 , 132.039) |
| **Aspartate aminotransferase increased** | 1.216 (0.256 , 5.777) | 0.031 (0.000 , 2.814) |
| **Alanine aminotransferase increased** | 0.349 (0.068 , 1.791) | 0.256 (0.003 , 20.745) |
| **Hypokalemia** | 0.778 (0.206 , 2.937) | 0.512 (0.017 , 15.508) |
| **Asthenia or fatigue** | 0.657 (0.337 , 1.281) | 0.340 (0.057 , 2.028) |
| **Infection** | 0.551 (0.046 , 6.572) | 0.229 (0.007 , 7.805) |

| | | |
|---|---|---|
| **Musculoskeletal pain** | 2.763 (0.930 , 8.207) | 7.565 (0.231 , 248.095) |
| **Nausea or vomiting** | 2.850 (1.379 , 5.889) | 21.577 (0.516 , 902.265) |
| **Peripheral neuropathy** | 0.207 (0.030 , 1.449) | 0.063 (0.000 , 8.497) |
| **Constipation** | 0.912 (0.353 , 2.358) | 0.515 (0.002 , 132.931) |
| **Hematuria** | 0.133 (0.037 , 0.479) | 2.081 (0.069 , 63.031) |
| **Decreased appetite** | 2.329 (0.971 , 5.589) | 6.346 (0.267 , 150.670) |
| **Dysgeusia** | 1.627 (0.265 , 9.979) | 0.515 (0.002 , 132.931) |
| **Bladder or urethral symptom** | 0.422 (0.008 , 23.592) | 0.515 (0.002 , 132.931) |
| **Abdominal pain** | 0.748 (0.099 , 5.640) | 2.073 (0.032 , 134.206) |
| **Stomatitis** | 0.651 (0.076 , 5.602) | 0.515 (0.002 , 132.931) |
| **Peripheral edema** | 2.075 (0.650 , 6.624) | 1.034 (0.006 , 186.730) |

< 1 favours olaparib. *Source: AstraZeneca. MAIC to assess the efficacy of olaparib vs cabazitaxel. Version 1. 29 Sep. 2020 [46]*

Medicinrådet has asked for RR instead of OR. We have not be able to recalculated it due do difficulties in defining ACR but do not expect that that overall result will change and further this table cannot fully answer the question and target for this endpoint (effektmål).

### 6.2.2 Comparative analyses vs cabazitaxel in BRCA 1/2. Grade 3 or more AE and Grade 5

The target from Medicinrådet is 10 % difference in Grade 3 and 4 AEs. For grade 5 it is 5 %. The naïve comparison show a difference 4.3 % (Grade 3 or more) and 3.1 % (Grade 5) but the comparison is of low evidence as the AE reporting in the comparator NHA arm also is somewhat higher also in CARD vs PROfound. The MAIC comparison show a favor of olaparib in 17 out of 31 observations but again this cannot answer the AE question. There is a trend for a numerical lower AE incidence and severity in favor of olaparib but is cannot document a 10 % and 5 % absolute difference.

## 6.3 Olaparib vs cabazitaxel in BRCA 1/2. PFS/PFS rate 12 m

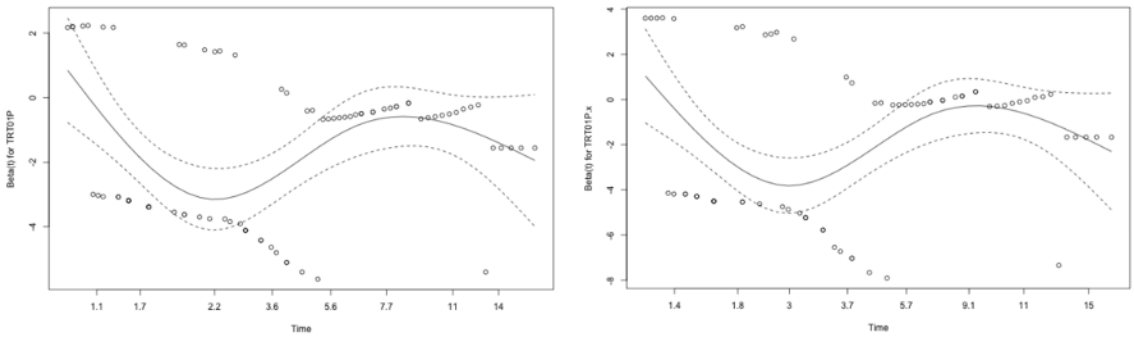
### 6.3.1 Results per study vs cabazitaxel in BRCA 1/2. PFS/PFS 12 m

Schoenfeld residual plots and log-cumulative hazard plots for the rPFS endpoint of the PROfound study are presented in figure 22 and figure 23, respectively; equivalent plots for the CARD study are presented in figure 24.

Visual inspection of the log-cumulative hazards plots for rPFS indicates that there was not substantial departure from the PH assumption. This is further confirmed by the Schoenfeld individual tests, which resulted p-values of 0.66 and 0.30 in the unadjusted and adjusted analyses, respectively, in PROfound and

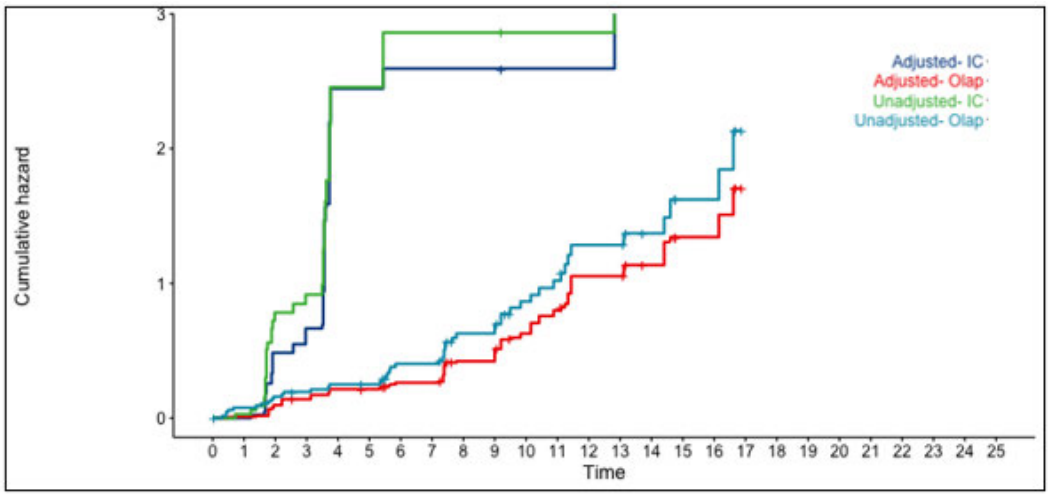
0.75 in the CARD study, indicating that there was no evidence against the null hypothesis of proportional hazards at 5% significance.

**Figure 22**: PROfound rPFS: Schoenfeld plots for unadjusted (left) and adjusted (right) analyses



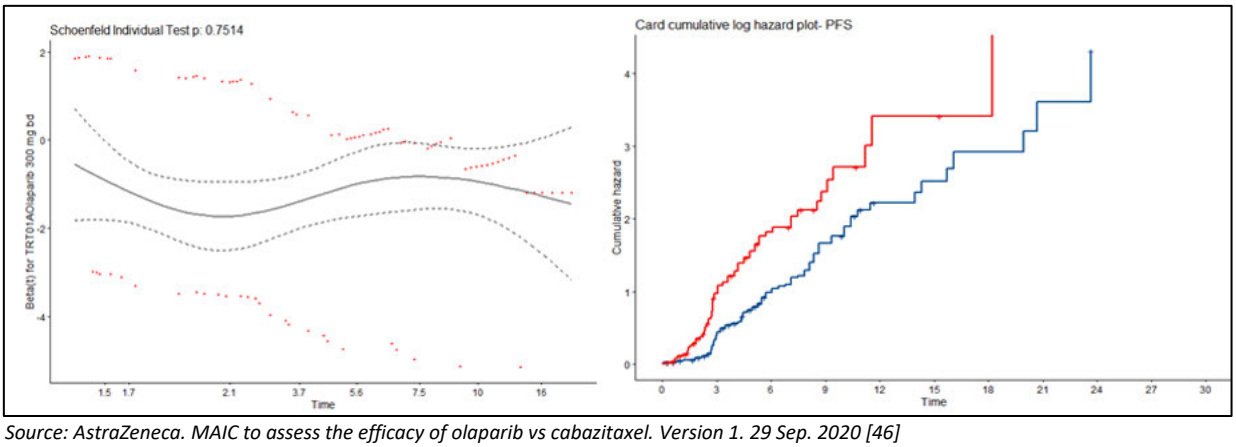

*Source: AstraZeneca. MAIC to assess the efficacy of olaparib vs cabazitaxel. Version 1. 29 Sep. 2020 [46]*

**Figure 23**: Unadjusted and adjusted log-cumulative hazard plots from PROfound study (anchored analysis)




*Source: AstraZeneca. MAIC to assess the efficacy of olaparib vs cabazitaxel. Version 1. 29 Sep. 2020*

**Figure 24**: CARD rPFS: Schoenfeld (left) and log-cumulative hazards (right) plots

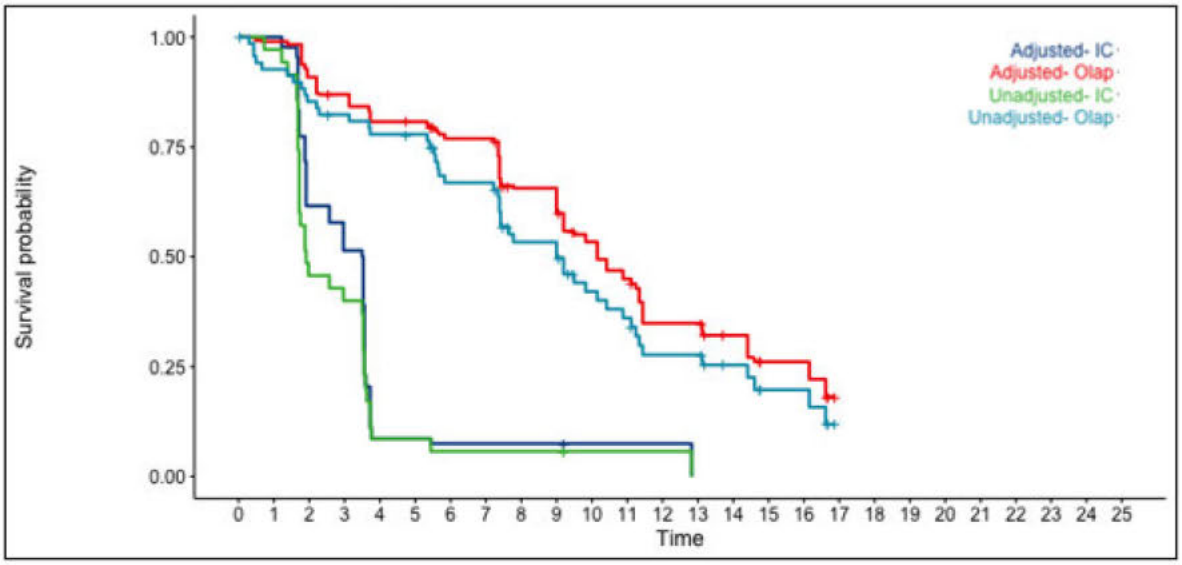



*Source: AstraZeneca. MAIC to assess the efficacy of olaparib vs cabazitaxel. Version 1. 29 Sep. 2020 [46]*

Since there was not substantial departure from the PH assumption across both the PROfound and CARD trials, the Bucher method using the MAIC-adjusted and unadjusted HRs was considered appropriate.

The MAIC-unadjusted and adjusted hazard ratios for olaparib versus NHA were 0.19 (95 % CI: 0.12, 0.32) and 0.18 (95 % CI: 0.04, 0.75), respectively (figure 25); the corresponding MAIC-unadjusted and adjusted ITC results for olaparib versus cabazitaxel were 0.36 (95 % CI: 0.20, 0.64) and 0.33 (95 % CI: 0.07, 1.43), respectively (table 18).

**Figure 25**: Adjusted and unadjusted rPFS KM plots for olaparib and NHA (anchored analysis)




*Source: AstraZeneca. MAIC to assess the efficacy of olaparib vs cabazitaxel. Version 1. 29 Sep. 2020 [46]*

**Table 18**: Comparative rPFS HRs generated by MAIC

| Analysis | Olaparib vs. NHA HR (95% CI) (PROfound) | Olaparib vs. cabazitaxel HR (95% CI) | Cabazitaxel vs. NHA HR (95% CI) (CARD study) |
|---|---|---|---|
| **Adjusted (n*=56)** | 0.18 (0.04, 0.75) | 0.33 (0.07, 1.43) | 0.54 (0.40 to 0.73) |
| **Non-adjusted (n=107)** | 0.19 (0.12, 0.32) | 0.36 (0.20, 0.64) | |

*Effective sample size

A summary of all results is shown in table 19.

**Table 19**: Results summary prior taxane

| Prior taxanes | RPSFT data | OS/PFS | Adjusted olaparib vs NHA HR (95% CI) | Adjusted olaparib vs cabazitaxel HR (95% CI) | Unadjusted olaparib vs NHA HR (95% CI) | Unadjusted olaparib vs cabazitaxel HR (95% CI) |
|---|---|---|---|---|---|---|
| Prior cabazitaxel or docetaxel | No | PFS | 0.18 (0.04, 0.75) | 0.33 (0.07, 1.43) | 0.19 (0.12, 0.32) | 0.36 (0.20, 0.64) |
| Prior cabazitaxel or docetaxel | No | OS | 0.49 (0.27, 0.89) | 0.77 (0.39, 1.51) | 0.63 (0.39, 1.04) | 0.99 (0.55, 1.78) |
| Prior cabazitaxel or docetaxel | Yes- with re-censoring | OS | 0.216 (0.108, 0.433) | 0.338 (0.156, 0.729) | 0.301 (0.168, 0.539) | 0.470 (0.241, 0.919) |
| Prior cabazitaxel or docetaxel | Yes- without re-censoring | OS | 0.281 (0.146, 0.542) | 0.439 (0.210, 0.916) | 0.381 (0.229, 0.634) | 0.596 (0.325, 1.092) |

Naïve:

Investigator rPFS at 12 month in PROfound is 41.3 % vs 0 % for NHA (see table 21). rPFS is not published in the CARD article. Read of the curve show 27 % rPFS at 12 months vs 7 % for NHA. Absolute difference in median iPFS(investigator) CARD was 4.3 months and in PROfound ( BRCAm investigator) 7.9 months.

### 6.3.2 Comparative analyses vs cabazitaxel in BRCA 1/2. PFS/PFS 12 m

PFS at 12 month is not part of the MAIC. For PFS vs. cabazitaxel, olaparib reduced the risk of disease progression by 64% (0.2, 0.64) in the BRCAm population who previously progressed on taxane(docetaxel/cabazitaxel) and NHA therapy [17, 46]. In a naïve comparison there was an absolute difference of approximately 14 % in favor of olaparib and 3.6 months in median iPFS (investigator). The targets from Medicinrådet were 10 % and 3 months. Olaparib met the targets set by Medicinrådet in the prior taxane population.

## 6.4 Olaparib vs cabazitaxel in BRCA 1/2. HQoL

### 6.4.1 Results per study vs cabazitaxel in BRCA 1/2. HQoL

Data between PROfound and CARD cannot be compared and the data required in the protocol (patients with at least 10 % improvement from baseline) are not available

#### CARD

A separate publication from CARD [47] showed that an improvement in total FACT-P score from baseline was reported by 27 (25.0%) patients vs 26 (22.8%) for cabazitaxel vs NHA. FACT-P score was maintained or improved for 81 (75.0%) patients with cabazitaxel and 86 (75.4%) patients with NHA. A deterioration in FACT-P from baseline was reported by 22.2% with cabazitaxel vs 24.6% with NHA. Median time to FACT-P deterioration was 14.8 months for cabazitaxel vs 8.9 months for NHA (HR 0.72; 95% CI 0.44–1.20; p = 0.2072). Overall cabazitaxel was associated with a greater pain response and delayed pain progression vs NHA [47]. Cabazitaxel and NHA were associated with similar outcomes in HRQL

#### PROfound

In the BRCAm population, olaparib was associated with a clinically meaningful difference in six domains of the FACT-P instrument compared with physicians' choice of NHA, including FACT-P total score and the three domains that relate specifically to prostate cancer. In the overall population (Cohort of PROfound the time to deterioration in FACT-P total and TOI, FAPSI-6, PWB and PCS scores favored olaparib but were not statistically significant, with hazard ratios ranging from 0.68 to 0.94 [23-28, 36].

### 6.4.2 Comparative analyses vs cabazitaxel in BRCA 1/2. HQoL

Data between PROfound and CARD cannot be compared in an indirect comparison. However olaparib show a clinically meaningful difference vs NHA while the outcomes were similar in the CARD trial. The 10 % target from Medicinrådet cannot be met.

# 7 Clinical question olaparib vs. BSC in BRCA 1/2

## 7.1 Olaparib vs BSC in BRCA 1/2. PFS/PFS 12 m

### 7.1.1 Presentation of relevant studies olaparib vs. BSC

The data for this question is derived directly from the PROfound study. Medicinraadet has decided that the comparator arm NHA at this stage of the disease is to be considered equal to BSC. However, while we acknowledge that the 1$^{st}$ NHA- 2$^{nd}$ NHA treatment sequence is not recommended for most patients in Denmark, recent real-world evidence from countries with comparable health systems such as Sweden has

shown that a substantial fraction of patients have received such a treatment sequence [48]. A recent prospective, randomized cross-over trial showed that PSA responses can be achieved in 36% of patients when the optimal sequencing of NHA-NHA is utilized (Abiraterone followed by Enzalutamide) [49]. Hence, although we recognize that the control arm is not standard practice according to Danish guidelines, we believe that equating the 2nd NHA treatment to BSC diminishes the value of the 2nd NHA since real outcomes on just BSC are likely inferior to those of the patients in the control arm of PROfound. We urge Medicinraadet to take this into consideration when evaluating our answer to this question.

The patient population in clinical question 3 is defined as mCRPC patients with BRCA 1/2 mutations (germline/somatic) who has progressed on NHA (enzalutamid or abirateron) and docetaxel/cabazitaxel. In the BRCAm subgroup of patient in the PROfound study 70.6 % of patient in the olaparib arm received a prior taxane vs. 60.3 % in the NHA arm. A total of 78.5 % in the olaparib arm vs. 86.2 % in NHA had previously received either enzalutamid or abiraterone.

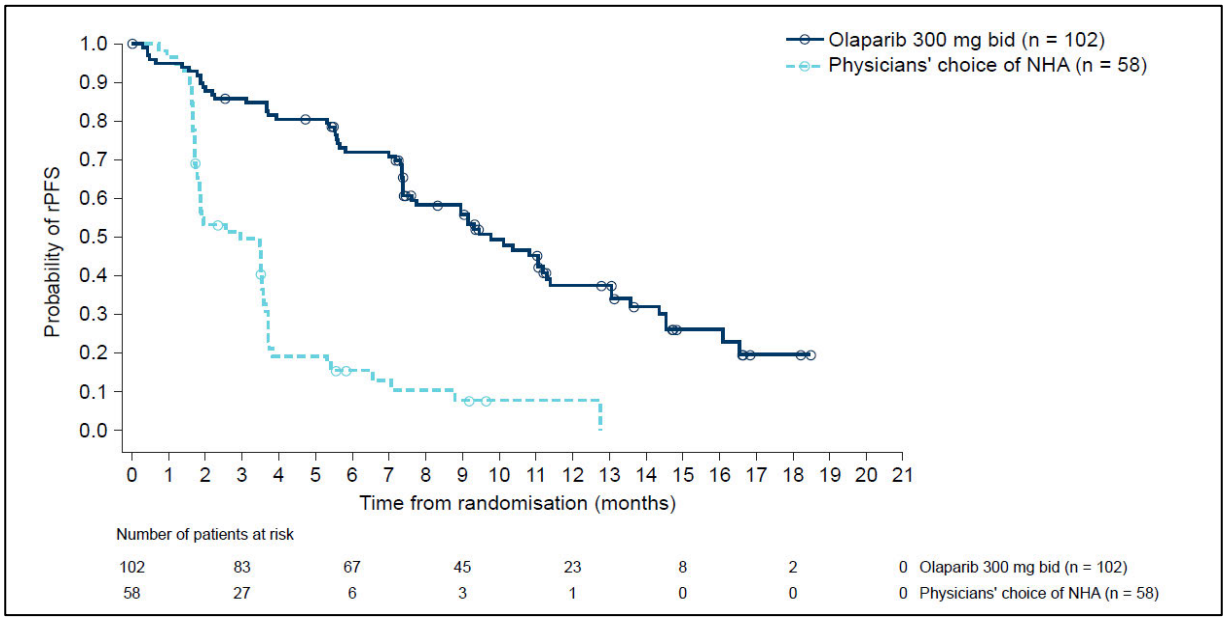
To assess the consistency of the treatment effect across patients with different baseline characteristics, an analysis of BICR-assessed rPFS in the BRCAm population of PROfound was performed for eight pre-specified subgroups (figure 26). Outcomes were consistent across all predefined subgroups, and broadly similar to the equivalent outcomes in Cohort A . A clinically meaningful reduction in the risk of radiological disease progression or death in patients who received olaparib compared with those in the physicians' choice of NHA arm was observed. The study was not powered to assess the relative efficacy of olaparib compared with physicians' choice of NHA owing to multiple testing, and overall there was no differential treatment effect in the eight pre-specified subgroups.

We cannot present exact data covering the requested BRCAm, prior NHA and taxane population for all the endpoints in question 3 but can show absolute and relative differences for rPFS and OS and AE in the olaparib arm from the BRCAm population.

### 7.1.2 Results per study olaparib vs BSC in BRCA 1/2. PFS/PFS 12 m

In the BRCAm population (figure 27), olaparib was associated with a clinically meaningful 78% reduction in the risk of BICR-assessed rPFS, corresponding to a survival advantage of 6.8 months with olaparib compared with physicians' choice of NHA (9.8 [95% CI, 7.6–11.3] months vs 3.0 [95% CI, 1.8–3.6] months; HR, 0.22 [95% CI, 0.15–0.32]) [15, 21, 50]. These results are consistent with Cohort A: olaparib was associated with a statistically significant and clinically meaningful 66% reduction in the risk of BICR-assessed rPFS, corresponding to an advantage of 3.8 months compared with physicians' choice of NHA (7.4 months vs 3.6 months; HR, 0.34 [95% CI, 0.25–0.47]; $p < 0.0001$; (table 20)[18].

**Figure 27**. KM plot of BICR-assessed rPFS in BRCAm population (*BRCA1* and/or *BRCA2* mutations).




*Source: [4, 21, 36]*

**Table 20**. rPFS assessed by BICR Cohort A and BRCAm

| | Cohort A | | BRCAm population | |
|---|---|---|---|---|
| **BICR-assessed rPFS[a]** | **Olaparib 300 mg bid (n = 162)** | **Physicians' choice of NHA (n = 83)** | **Olaparib 300 mg bid (n = 102)** | **Physicians' choice of NHA (n = 58)** |
| Events, n (%) | 106 (65.4) | 68 (81.9) | 62 (60.8) | 51 (87.9) |
| Median rPFS, months (95% CI) | 7.39 (6.24–9.33) | 3.55 (1.91–3.71) | 9.79 (7.62–11.30) | 2.96 (1.81–3.55) |
| HR (95% CI) | 0.34 (0.25–0.47); $p < 0.0001$ | | 0.22 (0.15–0.32) | |

[a]Disease progression, as assessed by BICR and defined by RECIST version 1.1 and/or PCWG3 or death (by any cause in the absence of progression) regardless of whether the patient withdrew from randomised therapy or received another anti-cancer therapy before progression. *Source: Clinical Study Report PROfound Version 1, 23 October 2019,[18] de Bono et al, 2020 [4], wave2a_v1_e_final [21] and SmPC.[15]*

A sensitivity analysis of investigator-assessed rPFS in the BRCAm population confirmed the robustness of the BICR-assessed rPFS analysis. Olaparib was associated with a 7.9-month increase in investigator-assessed rPFS compared with physicians' choice of NHA (9.8 [95% CI, 8.6–12.7] months vs 1.9 [95% CI, 1.7–3.6] months; HR, 0.17 [95% CI, 0.11–0.27]; Table 21).[18]

These results are consistent with the sensitivity analysis of Cohort A: olaparib was associated with a clinically meaningful increase in investigator-assessed rPFS of 6.2 months compared with physicians' choice of NHA (9.8 months vs 3.6 months; HR, 0.24 [95% CI, 0.17–0.34]; $p < 0.0001$, table 21) [4, 18].

**Table 21.** Sensitivity analysis of rPFS: investigator-assessed rPFS.

| **Sensitivity analysis: investigator-assessed rPFS[a]** | Cohort A | | BRCAm population | |
|---|---|---|---|---|
| | **Olaparib 300 mg bid (n = 162)** | **Physicians' choice of NHA (n = 83)** | **Olaparib 300 mg bid (n = 102)** | **Physicians' choice of NHA (n = 58)** |
| Event, n (%) | 95 (58.6) | 66 (79.5) | 61 (59.8) | 49 (84.5) |
| Median rPFS, months (95% CI) | 9.79 (8.74–12.65) | 3.55 (1.87–3.71) | 9.79 (8.57–12.65) | 1.91 (1.74–3.61) |
| HR (95% CI) | 0.24 (0.17–0.34); $p < 0.0001$ | | 0.172 (0.111–0.267) | |
| rPFS at 6 months, % | 70.49 | 24.49 | 73.36 | 18.85 |
| rPFS at 12 months, % | 42.39 | 2.76 | 41.33 | 0.00 |

[a]Disease progression, as assessed by BICR defined by RECIST version 1.1 and/or PCWG3 or death (by any cause in the absence of progression) regardless of whether the patient withdrew from randomised therapy or received another anti-cancer therapy before progression.
*Source: Clinical Study Report PROfound Version 1, 23 October 2019,[18] de Bono et al, 2020 [4] and iemt2590.[18]*

### Prior taxane group

[redacted]

[redacted]

*Source [18]*

## 7.1.3 Comparative analyses Olaparib vs. BSC BRCAm . PFS/PFS 12 m

**In the overall BRCAm group olaparib was associated with a 7.9-month increase in investigator-assessed (6.8 months BICR) rPFS compared with physicians' choice of NHA (9.8 [95% CI, 8.6–12.7] months vs 1.9 (1.7–3.6) months; HR, 0.17 (0.11–0.27). This was confirmed by the investigator assessed rPFS analysis olaparib vs. NHA in BRCA 1/2 OS/OS rate.**

**PFS rate is available at 12 months in the investigator assessed analysis and show a difference of 41.33% in favour of the overall BRCAm group .**

[redacted]

**Olaparib met the target for 3 months absolute difference for median rPFS(investigator and BICR) in the BRCAm overall group and in the prior taxane subgroup the target of a 10 % difference at 12 months was seen for rPFS**

## 7.2 Olaparib vs BSC in BRCA 1/2. OS/OS 12 m

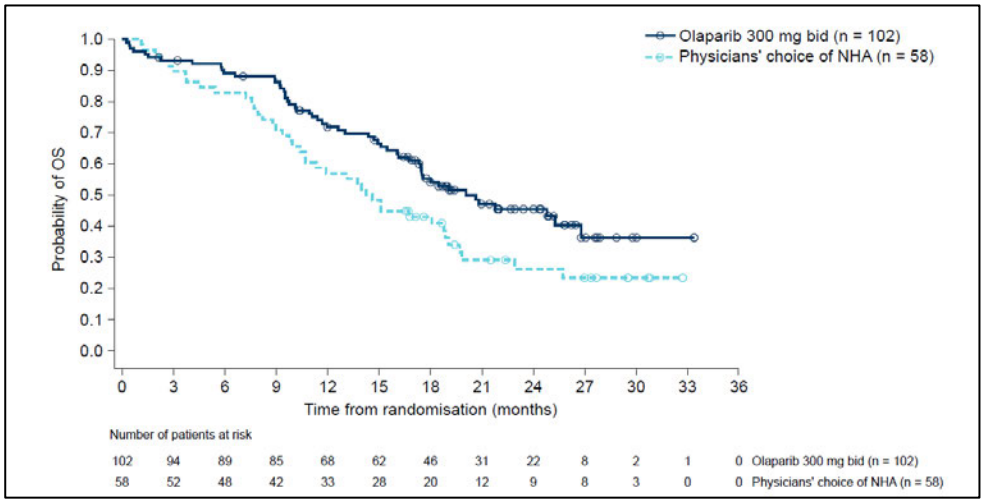
### 7.2.1 Results per study Olaparib vs. ADT in BRCA 1/2. OS/OS 12 m

In the overall *BRCA*m population(figure 29), olaparib was associated with 5.7-month increase in OS benefit compared with physicians' choice of NHA despite approximately two-thirds of patients (69%)[50] in the physicians' choice of NHA arm switching to the olaparib arm post-BICR-assessed (DCO1) or investigator-assessed (DCO2) progression: 20.1 (17.4–26.8) months vs 14.4 (10.7–18.9) months; HR =0.63 (0.42–0.95) [21].

At DCO1, in the prior taxane, BRCAm population, 41 events (56.9%) had occurred in the olaparib arm and 27 (77.1%) in the physicians' choice of NHA arm. Olaparib was associated with an OS benefit of 5.5 months compared with NHA 17.5 (13.0–25.3) months vs 11.9 (8.2–15.2)) months; HR = 0.63 (0.39–1.04)(figure 30).

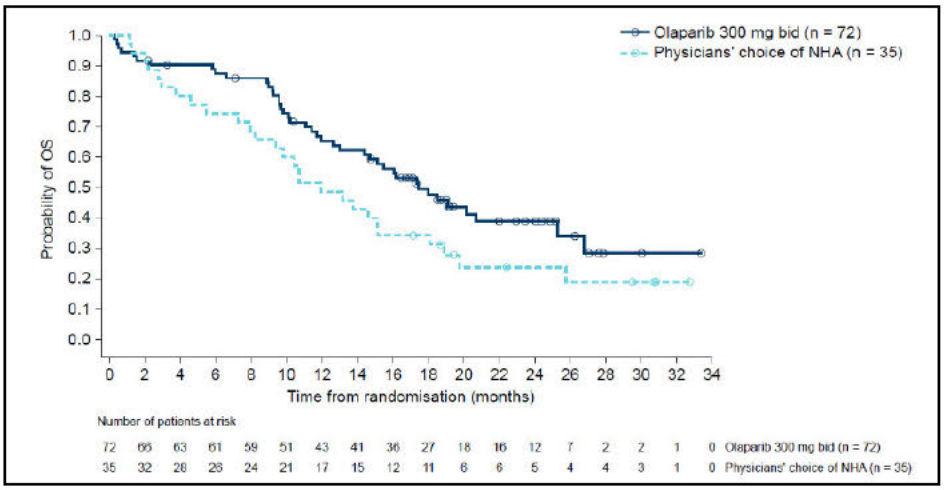
The data for the prior taxane group are consistent with the outcome for the overall BRCAm popuation and the final analysis for Cohort A. In Cohort A, olaparib was associated with a statistically significant and clinically meaningful increase in OS benefit of 4.4 months compared with the physicians' choice of NHA arm despite two-thirds of patients (68%)[50] in the physicians' choice of NHA arm switching to the olaparib arm post-BICR-assessed (DCO1) or investigator-assessed (DCO2) progression:19.1 months vs 14.7 months; HR =0.69 (0.50–0.97); *p* = 0.0175;[36] [28]

**Figure 29.** KM plot of BICR-assessed **OS** in overall **BRCAm** population.




*Source: Clinical Study Report PROfound edition 1, 23 October 2019,[18] Clinical Study Report PROfound addendum Version 1, 23 July 2020,[36] de Bono et al, 2020 [4]*

**Figure 30 .** KM plot of BICR-assessed **OS** in prior taxane, **BRCAm** population .




*Source: Clinical Study Report PROfound edition 1, 23 October 2019,[18] Clinical Study Report PROfound addendum Version 1, 23 July 2020,[36], [28]*

The effect outcomes are summarized in table 22

**Table 22.** Final OS in BRCAm and BRCAm prior taxane population

| Final OS | BRCAm, prior taxane | | BRCAm population | |
|---|---|---|---|---|
| | Olaparib 300 mg bid (n = 72) | Physicians' choice of NHA (n = 35) | Olaparib 300 mg bid (n = 102) | Physicians' choice of NHA (n = 58) |
| Events, n (%) | 41 (56.9) | 27 (77.1) | 53 (52.0) | 41 (70.7) |
| Median OS, months | 17.45 (13.01–25.30) | 11.93 (8.21–15.15) | 20.1 (17.4–26.8) | 14.4 (10.7–18.9) |
| HR (95% CI) | 0.63 (0.39–1.04) | | 0.63 (0.42–0.95) | |

*Source: Clinical Study Report PROfound edition 1, 23 October 2019,[18] Clinical Study Report PROfound addendum Version 1, 23 July 2020,[36] de Bono et al, 2020 [4], and SmPC.[15], Hussein [28]*

OS at 12 months is not published in the publication of PROfound but a read of the curve in the overall BRCAm population show OS at 12 months was approximately 73 % for olaparib vs. 57 % for NHA. In the BRCAm, prior taxane group it is approximately 67 % vs. 50 %.

A treatment-switching adjustment was performed to account for patients randomised to the physicians' choice of NHA arm who switched to the olaparib arm after disease progression. Of 58 patients in the physicians' choice of NHA arm of the BRCAm population, 40 (69%) switched to olaparib. The median OS for patients in the BRCAm population who received physicians' choice following adjustment for treatment switching ranged from 9.15 months to 10.16 months depending on the test and on the use of recensoring (HR for OS olaparib vs physicians' choice of NHA:0.27–0.40)[51].

The choice of model used to calculate the acceleration factor for the rank-preserving structural failure time model (RPSFTM) was based on the plausibility of the assumptions in each model and the preference of the analyst. The acceleration factor was consistent across each model; the Cox proportional hazards model

with recensoring was preferred for the base case because a plateau in OS for the physicians' choice of NHA arm was observed without recensoring, which was considered clinically implausible[50]. The Cox proportional hazards model without recensoring is thus presented as a scenario analysis (table 23).

**Table 23**. Median OS and HR adjusted for treatment switching using RPSFTM.

| Test | Recensoring | Median OS NHA adjusted for switching, months | Difference in OS NHA adjusted for switching and olaparib (observed), months | OS HR (95% CI) for olaparib vs NHA |
|---|---|---|---|---|
| **BRCAm population** | | | | |
| **Log rank** | Without | 9.80 | 10.3 | 0.40 (0.18–0.9) |
| | With | 9.25 | 10.9 | 0.29 (0.1–0.86) |
| **Cox proportional hazards** | Without | 9.57 | 10.5 | 0.37 (0.16–0.83) |
| | With | 9.15 | 11.0 | 0.28 (0.1–0.79) |
| **Weibull** | Without | 10.16 | 9.9 | 0.39 (0.18–0.84) |
| | With | 9.15 | 11.0 | 0.27 (0.09–0.78) |

*Source: Lynparza in metastatic prostate cancer: adjusting for treatment switching. Version 3.0. 6 November 2020.[50]*

### 7.2.2 Comparative analyses Olaparib vs. BSC in BRCA 1/2. OS/OS 12 m

In the overall *BRCA*m population, olaparib was associated with 5.7-month increase in OS benefit compared with physicians' choice of NHA despite approximately two-thirds of patients (69%)[50] in the physicians' choice of NHA arm switching to the olaparib arm post-BICR-assessed (DCO1) or investigator-assessed (DCO2) progression 20.1 months (17.4–26.8) months vs 14.4 months (10.7–18.9); HR = 0.63 (0.42–0.95). In the BRCAm prior taxane group olaparib was associated with an OS benefit of 5.5 months compared with physicians' choice of NHA with HR = 0.63 and CI just crossing the upper limit 0.39–1.04. OS at 12 months show approximately 16 % and 17 % difference in favor of olaparib vs. NHA in the two subgroups. The targets from Medicinrådet were 3 months absolute difference and/or 5 % at 12 months. Olaparib met the targets for OS vs. BSC.

## 7.3 Olaparib vs. BSC in BRCA 1/2 Grade 5 and Grade 3 or more

### 7.3.1 Results per study BRCA 1/2 Grade 5 and Grade 3 or more

**The patient population in clinical question 3 is defined as mCRPC patients with BRCA 1/2 mutations (germline/somatic) who has progressed on NHA (enzalutamid or abirateron) and docetaxel/cabazitaxel. In PROfound, a total of 78.5 % in the olaparib arm vs. 86.2 % in NHA had previously received either enzalutamid or abiraterone and 70.6 % of patient in the olaparib arm received a prior taxane vs. 60.3 % in the NHA arm. The are no specific AE details for the patient population defined for question 3, the overall BRCAm population vs. NHA or Cohort A and the safety analysis comprised all patients who received at least one dose of randomised study treatment in either cohort A or cohort B. Data presented are from the safety update at DCO2(table 24). In the supplementary appendix to the OS publication by Hussain et al there is an AE table for BRCAm but only for the Olaparib arm. Grade 5 event are listed as AE and not treatment related AEs**

**Table 24.** Most frequently reported AEs occurring in at least 5% of patients. PROfound study (safety analysis set).

| AE | Number of patients (%) | |
|---|---|---|
| | Olaparib 300 mg bid (n = 256) | Physicians' choice of NHA (n = 130) |
| Any AE | 246 (96.1) | 115 (88.5) |
| Anaemia | 126 (49.2) | 20 (15.4) |
| Nausea | 110 (43.0) | 27 (20.8) |
| Decreased appetite | 80 (31.3) | 24 (18.5) |
| Fatigue | 69 (27.0) | 28 (21.5) |
| Constipation | 49 (19.1) | 19 (14.6) |
| Vomiting | 51 (19.9) | 17 (13.1) |
| Diarrhoea | 55 (21.5) | 9 (6.9) |
| Asthenia | 40 (15.6) | 19 (14.6) |
| Back pain | 36 (14.1) | 18 (13.8) |
| Peripheral oedema | 34 (13.3) | 10 (7.7) |
| Arthralgia | 26 (10.2) | 14 (10.8) |
| Urinary tract infection | 21 (8.2) | 15 (11.5) |
| Cough | 29 (11.3) | 3 (2.3) |
| Dyspnoea | 27 (10.5) | 5 (3.8) |
| Weight decreased | 21 (8.2) | 7 (5.4) |
| Musculoskeletal pain | 18 (7.0) | 6 (4.6) |
| Thrombocytopenia | 22 (8.6) | 2 (1.5) |
| Dizziness | 18 (7.0) | 5 (3.8) |
| Dyspepsia | 20 (7.8) | 3 (2.3) |
| Pyrexia | 17 (6.6) | 6 (4.6) |
| Musculoskeletal chest pain | 16 (6.3) | 6 (4.6) |
| Dysgeusia | 18 (7.0) | 2 (1.5) |
| Haematuria | 9 (3.5) | 11 (8.5) |
| Pain in extremity | 14 (5.5) | 6 (4.6) |

*Source [18] de Bono et al, 2020 [4]*

The largest differences in incidence between the 2 arms were for the AEs of anaemia and nausea: anaemia occurred at an incidence of 46.1% in the olaparib arm vs an incidence of 15.4% in the NHA arm ; nausea occurred at an incidence of 41.4% in the olaparib arm vs an incidence of 19.2% in the NHA arm.

Other observations:

- Most AEs of nausea were CTCAE Grade ≤2 (only 3 [1.2%] olaparib-treated patients had AEs of nausea that were CTCAE Grade 3);
- 55 (21.5%) olaparib treated patients had AEs of anaemia that were CTCAE Grade ≥3, compared with 7 (5.4%) patients in the investigators choice of NHA arm.
- Pulmonary embolism was reported in 11 (4.3%) patients in the olaparib arm and 1 (0.8%) patient in the investigators choice NHA arm. Six (2.3%) patients in the olaparib arm and 1 (0.8%) patient in the investigators choice of NHA arm reported pulmonary embolism Grade ≥3.
- The time to onset of the events ranged between 6 and 337 days
- For all AEs the first AE occurred within the first 3 months of treatment.

Approximately one-half of patients (52.0%) in the olaparib arm experienced an AE of grade 3 or above compared with 40.0% of patients in the physicians' choice of NHA arm (table 19). In the olaparib BRCAm arm the Grade 3 or more was also 52 %. Anaemia was the only AE of grade 3 or higher reported by 5% or more of patients. Grade 4 AEs were reported by six patients (2.3%) in the olaparib arm compared with six patients (4.6%) in the physicians' choice of NHA arm [36].

A total of eight patients in the olaparib arm had grade 4 AEs: anaemia and pulmonary embolism (both in one patient), platelet count decreased (one patient), pneumonia and septic shock (both in one patient), respiratory failure and sepsis (both in one patient), and thrombocytopenia (four patients). In the physicians' choice of NHA arm, six patients experienced grade 4 AEs: increased ALT (one patient), duodenal ulcer perforation (one patient), hypocalcaemia (one patient), neutrophil count decreased (one patient) and sepsis (two patients). Two patients who experienced grade 4 AEs also reported grade 5 AEs [36].

Grade 5 AEs were reported in six patients (2.3%) in the olaparib arm and in three patients (2.3%) in the physicians' choice of NHA arm. In both treatment arms, most deaths occurred at least 30 days following the last dose of study treatment and were related to mCRPC. AEs with an outcome of death(DCO2) were reported for 16 patients in the overall population, 10 (4%) in the olaparib arm and 6 (5%) in the NHA. One patient in the olaparib arm had a grade 4 adverse event that was classified at the time of the primary analysis as lung infection, but was reclassified in the present final OS analysis as pneumonia and was not considered by the investigator to be causally related to olaparib. Three patients who crossed over to olaparib from the control arm had an adverse event with an outcome of death however none were considered causally related. The 10 AEs/deaths with time from first and last dose is described in the EMA assessment report)[36] [15].

In the protocol the request is for Grade 3 and 4 AEs. The listed Grade 5 events should in practice be deducted from the 133 and 52 events but as the incidence of Grade 5 is equal and low(2,3%) in both arms we have not done this. The reporting is in line with the SMPC.Below in table 25 are listed AEs of grade ≥ 3. The AE incidence is also reported in the supplementary appendix of the OS publication by Hussein et al and the also report and incidence of 52% BRCAm arm (split between gBRCA and sBRCAm group[28].

**Table 25.** AEs grade ≥ 3 reported in more than two patients in either treatment arm of the PROfound study (safety analysis set).

| AEs grade ≥ 3 | Number of patients (%) | |
|---|---|---|
| | Olaparib 300 mg bid (n = 256) | Physicians' choice of NHA (n = 130) |
| **Patients with any AE grade ≥ 3** | **133 (52.0)** | **52 (40.0)** |
| **Blood and lymphatic system disorders** | **71 (27.7)** | **9 (6.9)** |
| Anaemia | 58 (22.7) | 7 (5.4) |
| Neutropenia | 10 (3.9) | 0 |
| Thrombocytopenia | 9 (3.5) | 0 |
| Lymphopenia | 3 (1.2) | 1 (0.8) |
| **Infections and infestations** | **20 (7.8)** | **11 (8.5)** |
| Pneumonia | 8 (3.1) | 3 (2.3) |
| Urinary tract infection | 5 (2.0) | 5 (3.8) |
| Sepsis | 3 (1.2) | 3 (2.3) |
| **Respiratory, thoracic and mediastinal disorders** | **19 (7.4)** | **2 (1.5)** |
| Pulmonary embolism | 7 (2.7) | 1 (0.8) |
| Dyspnoea | 6 (2.3) | 0 |
| Pneumonia aspiration | 3 (1.2) | 0 |
| **Gastrointestinal disorders** | **16 (6.3)** | **5 (3.8)** |
| Vomiting | 6 (2.3) | 1 (0.8) |
| Nausea | 4 (1.6) | 0 |
| **Investigations** | 17 (6.6) | 4 (3.1) |
| Decreased neutrophil count | 4 (1.6) | 1 (0.8) |
| Decreased white blood cell count | 4 (1.6) | 0 |
| Decreased platelet count | 5 (2.0) | 0 |
| **Musculoskeletal and connective tissue disorders** | **12 (4.7)** | **6 (4.6)** |
| Muscle weakness | 3 (1.2) | 1 (0.8) |
| **General disorders and administration site conditions** | **11 (4.3)** | **11 (8.5)** |
| Asthenia | 4 (1.6) | 4 (3.1) |
| Fatigue | 4 (1.6) | 3 (2.3) |
| **Metabolism and nutrition disorders** | **11 (4.3)** | **8 (6.2)** |
| Decreased appetite | 4 (1.6) | 1 (0.8) |
| **Nervous system disorders** | **8 (3.1)** | **5 (3.8)** |
| Cerebrovascular accident | 3 (1.2) | 0 |
| **Vascular disorders** | **6 (2.3)** | **5 (3.8)** |
| Hypertension | 3 (1.2) | 3 (2.3) |
| **Injury, poisoning and procedural complications** | 10 (3.9) | 3 (2.3) |
| Femur fracture | 3 (1.2) | 0 |

*Source [18] de Bono et al, 2020 [4]*

### 7.3.2 Comparative analyses Grade 5 and Grade 3 or more

**In absolute values, 12 % points more patients had Grade ≥ 3 AE in the olaparib arm. Grade 5 AEs were reported in six patients (2.3%) in the olaparib arm and in three patients (2.3%) in the physicians' choice of NHA arm. Olaparib does not meet the target of 10 % and 5 % difference, respectively.**

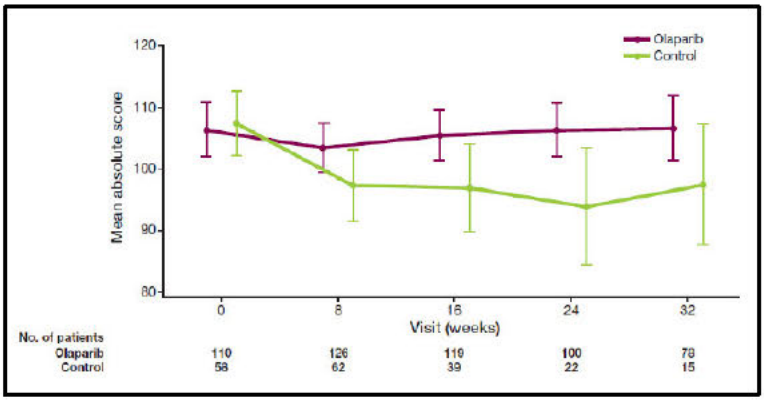
## 7.4 Olaparib vs. BSC in BRCA 1/2 HQoL

### 7.4.1 Results per study Olaparib vs. BSC in BRCA 1/2 HQoL

**While the requested analysis from Medicinrådets fagudvalg of the fraction of patients who experience >= 10 points reduction in FACT-P from baseline is not accessible to us at present, we will provide the relevant HRQoL data that is available to us for the BRCAm subgroup as well as Cohort A.**

**For Cohort A, of which the BRCAm subgroup comprised the majority of patients, the mean FACT-P total score over time can be seen in figure 31. Although the analysis clearly shows a favorable trend with better preservation of quality of life in the olaparib arm, the differences in mean FACT-P score are not statistically significant.**

**Figure 31**. Mean FACT-P total score over time for Cohort A.



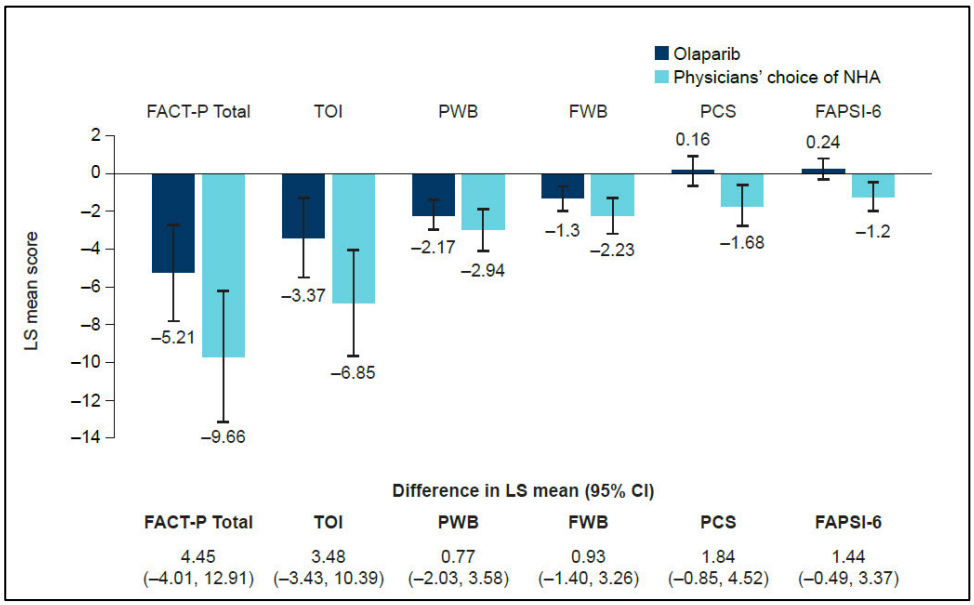

*Source: [53]*

**In the BRCAm population, olaparib was associated with a clinically meaningful difference in six domains of the FACT-P instrument compared with physicians' choice of NHA, including FACT-P total score and the three domains that relate specifically to prostate cancer (table 26) :**

- FACT-P total score, olaparib, –5.2 (standard deviation [SD], 2.6) versus physicians' choice of NHA, –9.7 (SD, 3.5)[23]
- Trial Outcome Index (TOI), –3.4 (SD, 2.1) versus –6.9 (SD, 2.8)[24]
- physical wellbeing (PWB) score, –2.2 (SD, 0.9) versus –2.9 (SD, 1.2)[27]
- functional wellbeing (FWB) score, –1.3 (SD, 0.7) versus –2.2 (SD, 1.0)[26]
- prostate cancer subscale (PCS) score, 0.2 (SD, 0.8) versus –1.7 (SD, 1.1)[28]

- 6-item Functional Assessment of Cancer Therapy – Advanced Prostate Symptom Index (FAPSI-6), 0.2 (SD, 0.6) versus –1.2 (SD, 0.8).[25]

**Table 26**. Overall adjusted mean change from baseline in FACT-P total score and subscales in the BRCAm population .




Notes

- *For FACT-P total, a change in LS mean score of ≥ 6 points was required to be considered clinically meaningful.*
- *For FACT-G total, a change in LS mean score of ≥ 3 points was required to be considered clinically meaningful.*
- *For TOI, a change in LS mean score of ≥ 5 points was required to be considered clinically meaningful.*
- *For PWB, FWB, PCS and FAPSI-6, a change in LS mean score of ≥ 2 points was required to be considered clinically meaningful.*

*Lower scores indicate higher deterioration in HRQoL. Source: Clinical Study Report PROfound Version 1, 23 October 2019[18] and iemt2503c–h.[23-27]*

### 7.4.2 Comparative analyses Olaparib vs. BSC. BRCA 1/2 HQoL.

For Cohort A, of which the majority of patients were BRCAm, there was a clear trend in favor of better preserved quality of life of time as measured by mean FACT-P total score. However the differences in mean FACT-P total score were not statistically significant.

In the BRCAm population, olaparib was associated with a clinically meaningful difference in six domains of the FACT-P instrument compared with physicians' choice of NHA, including FACT-P total score and the three domains that relate specifically to prostate cancer. However a 10 % difference short and long term(more than 6 months) cannot be shown vs BSC.

# 8 AEs Olaparib quantitative overview

The AE profile of Olaparib has been described in both question 2 and 3 but below we include more information on AE of special interest.

## AEs of special interest, DCO2

No myelodysplastic syndrome or acute myeloid leukaemia events occurred in either treatment arm while therapy was ongoing or during or after the 30-day safety follow-up period. Five incidences of benign, malignant or unspecified neoplasms occurred in the olaparib arm at DCO2 and four in the physicians' choice of NHA arm: one incidence of glioma was reported in the olaparib arm (0.4%), and one incidence of gastric cancer and transitional cell carcinoma (1.5%) in the physicians' choice of NHA arm.

## SAEs, DCO2

SAEs were reported more often in the olaparib arm than in the physicians' choice of NHA arm (36.7% vs 30.0%; however, exposure to olaparib was approximately twice as long as that of the physicians' choice of NHA (230 days vs 120 days). The most frequently reported SAE was anaemia in the olaparib arm (9.0% of patients) and urinary tract infection in the physicians' choice of NHA arm (3.1%)(table 27) [18] .

**Table 27**. SAEs reported by at least two patients in the treatment arms of the PROfound study (safety analysis set).

| | Number of patients (%)[a] | |
|---|---|---|
| SAE | Olaparib 300 mg bid (n = 256) | Physicians' choice of NHA (n = 130) |
| **Patients with any SAE** | **94 (36.7)** | **39 (30.0)** |
| **Blood and lymphatic system disorders** | **29 (11.3)** | **1 (0.8)** |
| Anaemia | 23 (9.0) | 0 |
| Thrombocytopenia | 4 (1.6) | 0 |
| Neutropenia | 3 (1.2) | 0 |
| **Infections and infestations** | **24 (9.4)** | **12 (9.2)** |
| Pneumonia | 11 (4.3) | 3 (2.3) |
| Urinary tract infection | 5 (2.0) | 4 (3.1) |
| Sepsis | 3 (1.2) | 3 (2.3) |
| **Respiratory, thoracic and mediastinal disorders** | **17 (6.6)** | **3 (2.3)** |
| Pulmonary embolism | 5 (2.0) | 1 (0.8) |
| Dyspnoea | 4 (1.6) | 1 (0.8) |
| Pneumonia aspiration | 3 (1.2) | 0 |
| Pneumothorax | 2 (0.8) | 0 |
| **Gastrointestinal disorders** | **13 (5.1)** | **5 (3.8)** |
| Vomiting | 4 (1.6) | 1 (0.8) |
| Nausea | 2 (0.8) | 2 (1.5) |
| **General disorders and administration site conditions** | **11 (4.3)** | **5 (3.8)** |
| Asthenia | 4 (1.6) | 1 (0.8) |
| Pyrexia | 3 (1.2) | 2 (1.5) |
| Fatigue | 2 (0.8) | 0 |

| | | |
|---|---|---|
| **Injury, poisoning and procedural complications** | **11 (4.3)** | **3 (2.3)** |
| Femur fracture | 3 (1.2) | 0 |
| Fall | 1 (0.4) | 2 (1.5) |
| **Renal and urinary disorders** | **10 (3.9)** | **6 (4.6)** |
| Haematuria | 3 (1.2) | 1 (0.8) |
| Urinary retention | 2 (0.8) | 0 |
| Acute kidney injury | 1 (0.4) | 2 (1.5) |
| Urinary tract obstruction | 0 | 2 (1.5) |
| **Metabolism and nutrition disorders** | **6 (2.3)** | **3 (2.3)** |
| Decreased appetite | 2 (0.8) | 0 |
| Hyponatraemia | 2 (0.8) | 0 |
| Dehydration | 0 | 3 (2.3) |
| **Nervous system disorders** | **7 (2.7)** | **2 (1.5)** |
| Cerebrovascular accident | 3 (1.2) | 0 |
| **Cardiovascular disorders** | **8 (3.1)** | **4 (3.1)** |
| Cardiopulmonary failure | 2 (0.8) | 0 |
| Angina pectoris | 1 (0.4) | 2 (1.5) |
| **Musculoskeletal and connective tissue disorders** | **10 (3.9)** | **1 (0.8)** |
| Bone pain | 2 (0.8) | 0 |
| Muscular weakness | 2 (0.8) | 0 |
| Musculoskeletal chest pain | 2 (0.8) | 0 |

[a]Patients with multiple SAEs were counted once for each system organ class/preferred term.
*Source: [18]*

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# 10 Appendices

## 10.1 Main characteristics of included studies

**AstraZeneca has rights to use tables from the PROfound and CARD study. We have not done a table A2 for the study by Kwon as it is a RWE study. The study is described in section 6.**

| Table A2 PROfound Olaparib for Metastatic Castration-Resistant Prostate Cancer. De Bono et al. 2020. N Engl J Med 2020 | |
|---|---|
| **Trial name** | PROfound |
| **NCT number** | NCT02987543 |
| **Objective** | To evaluate the efficacy and safety of olaparib versus investigators choice of either enzalutamide or abiraterone in patients with mCRPC with qualifying mutations in HRR genes, who have failed prior treatment with an NHA. |
| **Publications – title, author, journal, year** | Olaparib for Metastatic Castration-Resistant Prostate Cancer. De Bono et al. 2020. N Engl J Med 2020<br><br>Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer. Hussain et al. N Engl J Med. 2020 |
| **Study type and design** | A prospective, multicenter, open-label randomized phase 3 trial. Enrolled patients were randomly assigned 2:1 via an interactive voice response system to either olaparib or physicians choice of NHA (enzalutamide or abiraterone). Crossover to olaparib was allowed for patients who had experienced radiological progression in the control arm. |
| **Follow-up time** | Median follow up for OS: 21.91 months for the olaparib arm ; 21.04 for the NHA arm. |

**Table A2 PROfound Olaparib for Metastatic Castration-Resistant Prostate Cancer. De Bono et al. 2020. N Engl J Med 2020**

**Population (inclusion and exclusion criteria)**

| Inclusion criteria | Exclusion criteria |
|---|---|
| • Men aged ≥ 18 years with a histologically confirmed diagnosis of prostate cancer, ECOG PS score of 0–2, serum testosterone levels of ≤ 50 ng/dL for ≤ 28 days before randomisation, normal organ and bone marrow function measured ≤ 28 days prior to administration of study treatment and life expectancy ≥ 16 weeks | • Previous treatment with a PARP inhibitor, receipt of any systematic anti-cancer therapy (except radiotherapy) within 3 weeks before study treatment or DNA-damaging cytotoxic chemotherapy, except if given for a non-prostate cancer indication and last dose > 5 years before randomisation. Previous estramustine is allowed. |
| • A qualifying HRRm in the tumour tissue | • Metastatic disease limited to regional pelvic lymph nodes of local recurrence (e.g. bladder, rectum), spinal cord compression unless considered to have received definitive treatment and with evidence of clinically stable disease for 28 days |
| • Eligible for enzalutamide or abiraterone treatment with documented current evidence of mCRPC and metastatic disease defined by at least one metastatic lesion diagnosed by either bone scan or CT/MRI scan | • Patients with MDS or AML or other malignancy (including MDS and MGUS) within the last 5 years except adequately treated non-melanoma skin cancer or other solid tumours including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for ≥ 5 years |
| • Progression as per local investigator following an NHA (e.g. abiraterone and/or enzalutamide) for the treatment of metastatic prostate cancer and/or CRPC | • Patients incligible for bone and soft tissue progression must have a super scan showing intense symmetrical activity in the bones and no soft tissue lesion (measurable or non-measurable) that can be evaluated using RECIST. |
| • Patients without previous surgical castration must be currently taking and willing to continue taking an LHRH analogue (agonist or antagonist) therapy for the duration of the study treatment | • Resting ECG indicating uncontrolled, potentially reversible cardiac conditions, as judged by the investigator, or patients with long QT syndrome |
| • Radiographic disease progression as per local assessment at study entry while receiving ADT | |

**Intervention**

Dosing information for the investigational product and comparators

| Study treatment | | Formulation | Dosing information | Permitted dose reductions |
|---|---|---|---|---|
| Olaparib | Olaparib | 100 mg tablets<br>150 mg tablets | 300 mg (2 x 150 mg tablets) orally bid | Step 1: 250 mg bid<br>Step 2: 200 mg bid<br>No further dose reductions are permitted. Once the dose is reduced, escalation is not permitted |
| Physicians' choice of NHA | Abiraterone | 250 mg tablets<br>500 mg tablets | 1000 mg (4 x 250 mg or 2 x 500 mg tablets) orally od combined with prednisone 5 mg orally bid | Reduction to 250 mg od in patients with moderate hepatic impairment at baseline<br>Following treatment-induced hepatotoxicity, interrupt treatment until AST, ALT and total bilirubin levels return to baseline values. Treatment may be restarted at the discretion of the investigator at a reduced dose of 750 mg (step 1) or 500 mg (step 2). No further dose reductions are permitted |
| | Enzalutamide | 40 mg capsules or tablets | 160 mg (4 x 40 mg capsules/tablets) orally od | For grade ≥ 3 AEs or intolerable side effects, interrupt treatment for 1 week or until symptoms improve to grade ≤ 2, then resume at the same or reduced dose (120 mg or 80 mg) at the discretion of the investigator |

**Baseline characteristics**

| Baseline characteristics. Overall population | Olaparib 300 mg bid (n = 256) | NHA (n = 131) | Total (N = 387) |
|---|---|---|---|
| **Age, years** | | | |
| Mean (SD) | 68.5 (8.4) | 68.9 (7.6) | 68.6 (8 2) |
| Median (range) | 69.0 (47–91) | 69 0 (49–87) | 69 0 (47–91) |
| < 65, n (%) | 82 (32 0) | 34 (26.0) | 116 (30.0) |
| ≥ 65, n (%) | 174 (68.0) | 97 (74.0) | 271 (70.0) |
| **Race, n (%)** | | | |
| White | 163 (63.7) | 85 (64.9) | 248 (64.1) |
| Black or African American | 7 (2.7) | 1 (0.8) | 8 (2.1) |
| Asian | 69 (27 0) | 36 (27.5) | 105 (27.1) |
| Other | 2 (0.8) | 1 (0.8) | 3 (0.8) |
| Missing | 15 (5.9) | 8 (6.1) | 23 (5.9) |
| **Ethnic group, n (%)** | | | |
| Hispanic or Latino | 17 (6.6) | 12 (9.2) | 29 (7.5) |
| Not Hispanic or Latino | 228 (89.1) | 112 (85 5) | 340 (87.9) |
| Missing | 15 (5.9) | 8 (6.1) | 23 (5.9) |
| **Sites of disease at baseline, n (%)[a]** | | | |
| Prostate | 41 (16 0) | 21 (16.0) | 62 (16 0) |
| Locoregional lymph nodes | 54 (21.1) | 31 (23.7) | 85 (22 0) |
| Distant lymph nodes | 99 (38.7) | 51 (38.9) | 150 (38.8) |
| Bone | 218 (85.2) | 113 (86 3) | 331 (85.5) |
| Respiratory | 43 (16 8) | 15 (11.5) | 58 (15 0) |
| Liver | 25 (9.8) | 18 (13.7) | 43 (11.1) |
| Other distant metastases | 57 (22 3) | 31 (23.7) | 88 (22.7) |
| Bone only | 65 (25.4) | 36 (27.5) | 101 (26.1) |
| Lymph node only | 18 (7.0) | 9 (6.9) | 27 (7.0) |
| Bone and lymph node only | 46 (18 0) | 19 (14.5) | 65 (16 8) |
| **ECOG performance status at baseline, n (%)** | | | |
| 0 | 131 (51.2) | 55 (42.0) | 186 (48.1) |
| 1 | 112 (43.8) | 74 (54.2) | 183 (47.3) |
| 2 | 13 (5.1) | 4 (3.1) | 17 (4.4) |
| **Total Gleason index at baseline, n (%)** | | | |
| 2 | 1 (0.4) | 0 | 1 (0.3) |
| 3 | 0 | 0 | 0 |
| 4 | 2 (0.8) | 0 | 2 (0.5) |
| 5 | 2 (0.8) | 1 (0.8) | 3 (0.8) |

| | | | |
|---|---|---|---|
| 6 | 6 (2.3) | 4 (3.1) | 10 (2.6) |
| 7 | 57 (22 3) | 27 (20.6) | 84 (21.7) |
| 8 | 61 (23 8) | 28 (21.4) | 89 (23 0) |
| 9 | 101 (39.5) | 56 (42.7) | 157 (40.6) |
| 10 | 21 (8.2) | 11 (8.4) | 32 (8.3) |
| Missing | 5 (2.0) | 4 (3.1) | 9 (2.3) |
| **Baseline pain score (BPI-SF worst pain [item 3]), n (%)** | | | |
| 0–< 2 | 125 (48.8) | 57 (43.5) | 182 (47.0) |
| 2–3 | 31 (12.1) | 13 (9.9) | 44 (11.4) |
| > 3 | 93 (36 3) | 56 (42.7) | 149 (38.5) |
| Missing | 7 (2.7) | 5 (3.8) | 12 (3.1) |
| **Baseline PSA level (µg/L), n (%)** | | | |
| Median, (range) | 68.2 (0.2–7240.7) | 106.5 (1.9–7115.0) | 81.9 (0.2–7240.7) |
| **Measurable disease at baseline, n (%)[b]** | | | |
| Yes | 149 (58.2) | 72 (55.0) | 221 (57.1) |
| No | 107 (41.8) | 59 (45.0) | 166 (42.9) |
| **Previous taxane therapy, n (%)** | | | |
| Yes | 170 (66.4) | 84 (64.1) | 254 (65.6) |
| No | 86 (33.6) | 47 (35.9) | 133 (34.4) |
| Previous docetaxel | 95 (37.1) | 48 (36.6) | 143 (37.0) |
| Previous cabazitaxel | 13 (5.1) | 2 (1.5) | 15 (3.9) |
| Previous docetaxel and cabazitaxel | 39 (15 2) | 23 (17.6) | 62 (16 0) |
| **Previous NHA use, n (%)** | | | |
| Enzalutamide | 103 (40.2) | 54 (41.2) | 157 (40.6) |
| Abiraterone | 97 (37 9) | 54 (41.2) | 151 (39.0) |
| Enzalutamide and abiraterone | 51 (19 9) | 23 (17.6) | 74 (19.1) |

Baseline characteristics BRCAm population

| **Baseline characteristic** | **BRCAm** | |
|---|---|---|
| | **Olaparib 300 mg bid (n = 102)** | **Physicians' choice of NHA (n = 58)** |
| **Age, years** | | |
| Mean (SD) | 67.0 | 67.1 |
| Median (range) | 68.0 (47–86) | 67 0 (49–86) |
| < 65, n (%) | 33 (32.4) | 21 (36.2) |
| ≥ 65, n (%) | 69 (67.6) | 37 (63.8) |
| **Race, n (%)** | | |

| | | |
|---|---|---|
| White | 67 (65.7) | 41 (70.7) |
| Black or African American | 2 (2 0) | 0 (0) |
| Asian | 27 (26.5) | 10 (17.2) |
| Other | 0 | 1 (1.7) |
| Missing | 6 (5 9) | 6 (10.3) |
| **Ethnic group, n (%)** | | |
| Hispanic or Latino | 7 (6 9) | 4 (6.9) |
| Not Hispanic or Latino | 91 (89.2) | 49 (84.5) |
| Missing | 4 (3 9) | 5 (8.6) |
| **Mutation status, n (%)** | | |
| *BRCA1* | 8 (7 8) | 5 (4.9) |
| *BRCA2* | 81 (79.4) | 47 (46.1) |
| *ATM* | 0 | 0 |
| *BRCA1* and *ATM* | 1 (1 0) | 0 |
| *BRCA1* and other HRRm[a] | 1 (1 0) | 0 |
| *BRCA2* and *ATM* | 2 (2 0) | 0 |
| *BRCA2* and other HRRm[a] | 9 (8 8) | 6 (5.9) |
| *ATM* and other HRRm[a] | 0 | 0 |
| **Sites of disease at baseline,[b] n (%)** | | |
| Bone | NR (89.0) | NR (86.0) |
| Respiratory tract | NR (23.0) | NR (16.0) |
| Liver | NR (12.0) | NR (17.0) |
| Bone only | NR (89.0) | NR (86.0) |
| Lymph node only | NR (62.0) | NR (71.0) |
| **ECOG PS at baseline, n (%)** | | |
| 0 | 51 (50.0) | 22 (37.9) |
| 1 | 43 (42.2) | 33 (56.9) |
| 2 | 8 (7 8) | 3 (5.2) |
| **Total Gleason score at baseline** | | |
| 2 | 1 (1 0) | 0 |
| 3 | 0 | 0 |
| 4 | 0 | 0 |
| 5 | 1 (1 0) | 0 |
| 6 | 5 (4 9) | 3 (5.2) |
| 7 | 25 (24.5) | 17 (29.3) |
| 8 | 20 (19.6) | 8 (13.8) |
| 9 | 39 (38.2) | 24 (41.4) |
| 10 | 7 (6 9) | 5 (8.6) |
| Missing | 4 (3 9) | 1 (1.7) |
| **Baseline pain score (BPI-SF worst pain [item 3])** | | |
| 0–< 2 | 53 (52.0) | 26 (44.8) |
| 2–3 | 10 (9.8) | 4 (6.9) |
| > 3 | 35 (34.3) | 26 (44.8) |
| Missing | 4 (3 9) | 2 (3.4) |
| **Baseline PSA level, µg/L** | | |
| Median (range) | 57.5 (0.22–7240.74) | 104.0 (1.85–7115.00) |
| **Measurable disease at baseline[c]** | | |
| Yes | NR (58.0) | NR (55.0) |
| No | NR (42.0) | NR (45.0) |
| **Previous taxane treatment, n (%)** | | |
| Yes | 72 (70.6) | 35 (60.3) |

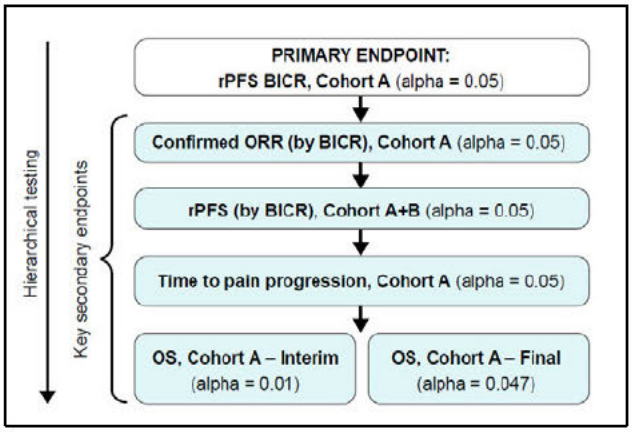
**Table A2 PROfound Olaparib for Metastatic Castration-Resistant Prostate Cancer. De Bono et al. 2020. N Engl J Med 2020**

| | | |
|---|---|---|
| No | 30 (29.4) | 23 (39.7) |
| Previous docetaxel for mCRPC | 41 (40.2) | 18 (31.0) |
| Previous cabazitaxel for mCRPC | 2 (2 0) | 1 (1.7) |
| Previous docetaxel and cabazitaxel for mCRPC | 18 (17.6) | 10 (17.2) |
| **Previous NHA use, n (%)** | | |
| Enzalutamide | 42 (41.2) | 29 (50.0) |
| Abiraterone | 38 (37.3) | 21 (36.2) |
| Enzalutamide and abiraterone | 20 (19.6) | 8 (13.8) |

Baseline characteristics BRCAm population by prior taxane use

| Baseline characteristics | BRCAm Prior taxane population | | BRCAm no prior taxane population | |
|---|---|---|---|---|
| | Olaparib 300 mg bid (n = 72) | Physicians' choice of NHA (n = 35) | Olaparib 300 mg bid (n = 30) | Physicians' choice of NHA (n = 23) |
| **Age, years** | | | | |
| ≥ 65, n (%) | 47 (65.3) | 20 (57.1) | 8 (26.7) | 6 (26.1) |
| **Sites of disease at baseline, n (%)** | | | | |
| Bone only | 22 (30.6) | 8 (22.9) | 9 (30.0) | 8 (34.8) |
| **ECOG PS at baseline, n (%)** | | | | |
| 0 | 34 (47.2) | 10 (28.6) | 17 (56.7) | 12 (52.2) |
| 1 | 31 (43.1) | 22 (62.9) | 12 (40.0) | 11 (47.8) |
| 2 | 7 (9.7) | 3 (8.6) | 1 (3.3) | 0 |
| **Measurable disease at baseline, n (%)** | | | | |
| Yes | 46 (63.9) | 23 (65.7) | 19 (63.3) | 13 (56.5) |
| No | 26 (36.1) | 12 (34.3) | 11 (36.7) | 10 (43.5) |

| Table A2 PROfound Olaparib for Metastatic Castration-Resistant Prostate Cancer. De Bono et al. 2020. N Engl J Med 2020 | |
|---|---|
| **Primary and secondary endpoints** | **Primary endpoint**<br>• rPFS by BICR The time from randomisation until the date of objective radiological disease progression or death (by any cause in the absence of disease progression) regardless of whether the patient withdrew from randomised therapy or received another anticancer therapy prior to disease progression. Objective progression is assessed according to RECIST v1.1 in soft tissue and PCWG-3 in bone.<br>**Secondary endpoints**<br>• ORR by BICR: Number of patients with a CR and PR according to the BICR assessed by RECIST 1.1 and PCWG-3 divided by the number of patients in the treatment group with measurable disease at baseline.<br>• TTPP: based on BPI-SF worst pain and opiate analgesic use Time from the date of randomisation to the time point at which worsening in pain was observed for asymptomatic patients and symptomatic patients (at baseline)<br>• OS: Time from the date of randomisation until death due to any cause. Assessment report EMA/541236/2020 Page 104/162<br>• PFS2: Time from the date of randomisation to the earliest of the investigator-assessed progression events (subsequent to that used for the primary variable of rPFS) or death Database lock 04 June 2019 and final OS analysis 20 March |

| Table A2 PROfound Olaparib for Metastatic Castration-Resistant Prostate Cancer. De Bono et al. 2020. N Engl J Med 2020 | |
|---|---|
| **Method of analysis and DCOs** | The PROfound study had 95% power to detect a statistically significant difference in the primary endpoint at a two-sided alpha level of 5% based on 143 rPFS events (60% maturity) occurring in 240 patients in cohort A who were randomised 2:1 to receive olaparib or physicians' choice of NHA, assuming the true treatment effect had an HR of 0.53. This correlates to a 4.5-month improvement in rPFS in the olaparib arm over an assumed 5-month median rPFS in the physicians' choice of NHA arm, assuming exponential distribution. The smallest treatment difference that would be statistically significant at the final analysis was an HR of 0.71.<br><br>Hierarchical testing procedure used in the PROfound trial.<br><br>  <br><br>The first data cut-off (DCO1) was performed on 4 June 2019 when 174 rPFS events had occurred (71% data maturity) in patients with a mutation in *BRCA1*, *BRCA2* or *ATM* (cohort A). These data are used in the final analysis of the primary endpoint, rPFS, and key secondary endpoints, ORR, TTPP and PFS2, as well as an interim analysis of OS and safety. A second and final data cut-off (DCO2) was performed on 20 March 2020, following 146 OS events (60% maturity) in cohort A, and was used in the final OS analysis and an updated safety analysis. |
| **Subgroup analyses** | The important subgroups for this application are:<br><br>Taxane chemotherapy naïve patients vs patients with prior taxane treatment.<br><br>BRCAm patients (Patients with germline and/or somatic mutations in BRCA1 and/or BRCA2.<br><br>All subgroups were pre-defined. |

| Table A2 CARD Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. De Wit et al. N Engl J Med. 2019 | |
|---|---|
| **Trial name** | CARD |
| **NCT number** | NCT02485691 |
| **Objective** | To compare the radiographic progression-free survival (rPFS) [using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 for tumor lesions and Prostate Cancer Working Group 2 (PCWG2) criteria for bone scan lesions or death due to any cause] with chemotherapy (cabazitaxel plus prednisone, Arm A) versus Androgen Receptor (AR)-targeted therapy (enzalutamide or abiraterone acetate plus prednisone, Arm B) in mCRPC patients who have been treated with docetaxel and who had disease progression while receiving AR-targeted therapy within 12 months of AR treatment initiation (≤12 months, either before or after docetaxel). |
| **Publications – title, author, journal, year** | Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. De Wit et al. N Engl J Med. 2019<br><br>Quality of life in patients with metastatic prostate cancer following treatment with cabazitaxel versus abiraterone or enzalutamide (CARD): an analysis of a randomised, multicentre, open-label, phase 4 study. Fizazi et al. Lancet Onc. 2020 |

| Table A2 CARD Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. De Wit et al. N Engl J Med. 2019 | |
|---|---|
| **Study type and design** | A prospective, multicenter, open-label randomized phase 4 study. Enrolled patients were randomly assigned 1:1 via an interactive voice response system to either cabazitaxel or an NHA (enzalutamide or abiraterone). |
| **Follow-up time** | Median follow up was 9.2 months. |
| **Population (inclusion and exclusion criteria)** | **Inclusion criteria:**<br>• Histologically confirmed prostate adenocarcinoma<br>• Metastatic disease<br>• Effective castration with serum testosterone levels <0.5 ng/mL. If the patient has been treated with LHRH agonists or antagonist (i.e., without orchiectomy), then this therapy should be continued.<br>• Progressive disease defined by at least one of the following:<br>• Progression in measurable disease (Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 criteria).<br>• Appearance of 2 or more new bone lesions (Prostate Cancer Working Group 2 [PCWG2]).<br>• Rising Prostate Specific Antigen (PSA) (PCWG2).<br>• Having received prior docetaxel for at least 3 cycles (before or after an Androgen Receptor (AR)-targeted therapy). Docetaxel administration in combination with androgen deprivation therapy (ADT) in metastatic hormone-sensitive disease is considered a prior exposure. Docetaxel rechallenge is allowed.<br>• Having progressive disease (PD) while receiving AR-targeted therapy with abiraterone acetate or |

| Table A2 CARD Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. De Wit et al. N Engl J Med. 2019 | |
|---|---|
| | enzalutamide within 12 months of AR treatment initiation (≤12 months), even if treatment duration is longer than 12 months. Patients treated with Abiraterone Acetate + ADT in metastatic hormone-sensitive setting are eligible in the study if they have progressed within 12 months with the AR-targeted agent. Patients having PSA progression only (as per PCWG2) within 12 months are eligible.<br>• A PSA value of at least 2 ng/mL is required at study entry.<br>• Prior AR-targeted therapy (abiraterone acetate or enzalutamide) must be stopped at least 2 weeks before study treatment.<br>• Signed informed consent<br>**Exclusion criteria:**<br>• Prior chemotherapy other than docetaxel for prostate cancer, except estramustine and except adjuvant/neoadjuvant treatment completed >3 years ago.<br>• Less than 28 days elapsed from prior treatment with chemotherapy, immunotherapy, radiotherapy, or surgery to the time of randomization.<br>• Adverse events (excluding alopecia and those listed in the specific exclusion criteria) from any prior anticancer therapy of Grade >1 (National Cancer Institute Common Terminology Criteria [NCI CTCAE] v4.0) at the time of randomization.<br>• Eastern Cooperative Oncology Group performance status (ECOG PS) >2 (ECOG 2 must be related to prostate cancer, not to other comorbidities). |

| Table A2 CARD Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. De Wit et al. N Engl J Med. 2019 | |
|---|---|
| | • Prior malignancy. Adequately treated basal cell or squamous cell skin or superficial (pTis, pTa, and pT1) bladder cancer are allowed, as well as any other cancer for which treatment has been completed ≥5 years ago and from which the patient has been disease-free for ≥5 years.<br>• Participation in another clinical trial and any concurrent treatment with any investigational drug within 30 days prior to randomization.<br>• Acquired immunodeficiency syndrome (AIDS-related illnesses) or known human immunodeficiency virus (HIV) disease requiring antiretroviral treatment.<br>• Patients with reproductive potential who do not agree, in conjunction with their partner, to use accepted and effective method of contraception during the study treatment period and up to 6 months after the last administered dose. The definition of "effective method of contraception" described hereafter: oral contraceptives, combined hormonal intravaginal, transdermal, intra uterine device or condoms will be based on respective study treatment labelling and country-specific regulatory requirements, and are documented in the Informed Consent Form.<br>• Known allergies, hypersensitivity or intolerance to prednisone or excipients of abiraterone acetate, enzalutamide, docetaxel, or polysorbate 80.<br>• Known history of mineralocorticoid excess or deficiency.<br>• History of seizure, underlying brain injury with loss of consciousness, transient ischemic attack within the past 12 months, cerebral vascular accident, brain arteriovenous malformation, brain metastases, or the |

| Table A2 CARD Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. De Wit et al. N Engl J Med. 2019 | |
|---|---|
| | use of concomitant medications that may lower the seizure threshold.<br>• Unable to swallow a whole tablet or capsule.<br>• Inadequate organ and bone marrow function as evidenced by:<br>• Hemoglobin <10.0 g/dL;<br>• Absolute neutrophil count <1.5 × 10^9/L;<br>• Platelet count <100 × 10^9/L;<br>• Aspartate aminotransferase/serum glutamic oxaloacetic transaminase and/or alanine aminotransferase/serum glutamic pyruvic transaminase >1.5 × the upper limit of normal (ULN);<br>• Total bilirubin >1.0 × ULN;<br>• Potassium <3.5 mmol/L;<br>• Child-Pugh Class C.<br>• Contraindications to the use of corticosteroid treatment.<br>• Symptomatic peripheral neuropathy Grade ≥2 (NCI CTCAE v4.0).<br>• Uncontrolled severe illness or medical condition including uncontrolled diabetes mellitus, history of cardiovascular disease (uncontrolled hypertension, arterial thrombotic events in the past 6 months, congestive heart failure, severe or unstable angina pectoris, recent myocardial infarction within the last 6 months, or uncontrolled cardiac arrhythmia).<br>• Concomitant vaccination with yellow fever vaccine. |

| Table A2 CARD Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. De Wit et al. N Engl J Med. 2019 | |
|---|---|
| | For the full list of inclusion/exclusion criteria, see https://www.nejm.org/doi/suppl/10.1056/NEJMoa1911206/suppl_file/nejmoa1911206_protocol.pdf |
| **Intervention** | Cabazitaxel (129 patients):<br>• Cabazitaxel 25 mg/m^2 intravenously in 1 hour every 3 weeks + prednisone 10 mg orally given daily + Primary prophylactic G-CSF<br>NHA (126 patients):<br>• Abiraterone acetate oral 1000 mg once daily continuously + prednisone 5 mg orally given twice daily OR enzalutamide oral 160 mg once daily continuously. |
| **Baseline characteristics** | **Patient characteristics for the CARD study** |

**Table A2 CARD Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. De Wit et al. N Engl J Med. 2019**

Table 1. Characteristics of the Patients at Baseline.*

| Characteristic | Cabazitaxel (N=129) | Androgen-Signaling–Targeted Inhibitor (N=126) |
|---|---|---|
| Age | | |
| Median (range) — yr | 70.0 (46–85) | 71.0 (45–88) |
| ≥75 yr — no. (%) | 45 (34.9) | 34 (27.0) |
| ECOG performance-status score — no. (%)† | | |
| 0 or 1 | 123 (95.3) | 119 (94.4) |
| 2 | 6 (4.7) | 7 (5.6) |
| Liver or lung metastases — no. (%) | 21 (16.3) | 25 (19.8) |
| PSA — ng/ml | | |
| Mean | 264.4±1352.5 | 232.9±453.8 |
| Median (range) | 62.0 (1.1–15,000.0) | 60.5 (1.5–2868.0) |
| Neutrophil count per mm³ | | |
| Mean | 5000±2000 | 4700±1700 |
| Median (range) | 4500 (2000–11,000) | 4500 (2000–9000) |
| Hemoglobin — g/liter | | |
| Mean | 122.0±14.1 | 121.2±14.1 |
| Median (range) | 121.0 (91–170) | 122.0 (82–162) |
| Alkaline phosphatase — IU/liter | | |
| Mean | 226.6±322.2 | 235.3±306.8 |
| Median (range) | 132.5 (41–2275) | 122.0 (35–1980) |
| Lactate dehydrogenase — IU/liter | | |
| Mean | 331.0±276.3 | 348.5±348.3 |
| Median (range) | 248.0 (135–2753) | 251.0 (50–3374) |
| Type of progression at trial entry — no. (%) | | |
| PSA only | 11 (8.5) | 10 (7.9) |
| Imaging-based, with or without PSA progression | 23 (17.8) | 16 (12.7) |
| Pain, with or without PSA or imaging-based progression | 86 (66.7) | 90 (71.4) |
| Missing data | 9 (7.0) | 10 (7.9) |
| **Disease history** | | |
| M1 disease at diagnosis — no. (%)‡ | 49 (38.0) | 60 (47.6) |
| Gleason score 8–10 at diagnosis — no. (%)§ | 73 (56.6) | 81 (64.3) |
| First androgen-deprivation therapy | | |
| Median duration (range) — mo | 13.7 (2–114) | 12.6 (3–179) |
| Duration <12 mo — no. (%) | 56 (43.4) | 57 (45.2) |
| Previous androgen-signaling–targeted inhibitor — no. (%) | | |
| Abiraterone | 56 (43.4) | 67 (53.2) |
| Enzalutamide | 72 (55.8) | 59 (46.8) |
| Missing data | 1 (0.8) | 0 |
| Timing of previous androgen-signaling–targeted inhibitor — no. (%) | | |
| Before docetaxel | 50 (38.8) | 49 (38.9) |
| After docetaxel | 79 (61.2) | 77 (61.1) |
| Time from initiation of previous androgen-signaling–targeted inhibitor to progression ≤6 mo — no. (%) | 65 (50.4) | 62 (49.2) |

* Plus–minus values are means ±SD. Patients in the androgen-signaling–targeted inhibitor group received either abiraterone or enzalutamide. PSA denotes prostate-specific antigen.
† Eastern Cooperative Oncology Group (ECOG) performance-status scores are on a 5-point scale, with higher numbers indicating greater disability.
‡ M1 disease was defined as metastatic disease (distant metastases).
§ Gleason scores range from 2 to 10, with scores of 8 to 10 indicating a high-grade cancer.

Source: De Wit et al. N Engl J Med. 2019

| Table A2 CARD Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. De Wit et al. N Engl J Med. 2019 | |
|---|---|
| **Primary and secondary endpoints** | **Primary endpoint**<br>• rPFS defined as the time from randomization to the occurrence of radiological tumor progressions using RECIST 1.1 and progression of bone lesions using Prostate Cancer Working Group 2 (PCWG2) criteria<br>**Secondary endpoints**<br>• PSA response rate<br>• Time to PSA progression (TTPP)<br>• Progression-free survival<br>• Objective tumor response (RECIST1.1 criteria in patients with measurable disease)<br>• Duration of tumor response - Pain intensity palliation<br>• Time to pain progression.<br>• Symptomatic Skeletal Events (SSEs) rate<br>• Time to occurrence of Symptomatic Skeletal Events (SSEs)<br>• OS<br>• Health status/utility (EQ-5D-5L)<br>• To evaluate the correlation of a signature of resistance to AR targeted agents with clinical outcomes, via the analysis of Circulating Tumor Cells (CTCs) phenotypes as well as expression and localization of proteins including AR isoforms in CTCs.<br>• Evaluate safety in the 2 treatments arms |
| **Method of analysis** | The analyses of the primary efficacy endpoint were performed on the ITT population. The trial was designed to have 80% power to detect a hazard ratio of 0.67 (cabazitaxel vs. |

| Table A2 CARD Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. De Wit et al. N Engl J Med. 2019 | |
|---|---|
| | androgen-signaling–targeted inhibitor) in the analysis of imaging-based progression-free survival, with the use of a stratified log-rank test at a two-sided alpha level of 5%. |
| **Subgroup analyses** | A number of subgroups were pre-specified for the purpose of stratification such as: Eastern Cooperative Oncology Group performance-status score (0 or 1 vs. 2), time to disease progression (≤6 months vs. >6 to 12 months), and timing of the previous alternative androgen-signaling–targeted inhibitor (before vs. after docetaxel). |

| Table A2 Differential Treatment Outcomes in *BRCA1/2-*, *CDK12-*, and *ATM*-Mutated Metastatic Castration-Resistant Prostate Cancer. Kwon et al. Cancer 2021 | |
|---|---|
| **Trial name** | NA |
| **NCT number** | NA |
| **Objective** | To compare clinical outcomes in a multicenter cohort of patients with mCRPC and DDRm on the basis of therapy and DDRm type. |
| **Publications – title, author, journal, year** | Differential Treatment Outcomes in *BRCA1/2-*, *CDK12-*, and *ATM*-Mutated Metastatic Castration-Resistant Prostate Cancer, Kwon et al, Cancer, 2021. |

| Table A2 Differential Treatment Outcomes in *BRCA1/2-*, *CDK12-*, and *ATM*-Mutated Metastatic Castration-Resistant Prostate Cancer. Kwon et al. Cancer 2021 | |
|---|---|
| **Study type and design** | A retrospective, multicenter, study. Genomic, clinical, and demographic data were obtained from electronic medical records from January 1, 1988, to March 16, 2018, for UBC and UM; the data cutoff for UCSF was July 22, 2019. The tumor mutational status was determined by Next Generation Sequencing (NGS) of tumor biopsies and/or plasma circulating tumor DNA. Only patients with the following pathogenic or likely pathogenic DDRm were included in the analysis: *ATM*, *ATR*, *BRCA1*, *BRCA2*, *BARD1*, *BRIP1*, *CDK12*, *CHEK2*, Fanconi anemia genes, MMR genes (*MSH1*, *MLH3*, *MSH2*, *MSH3*, *MSH6*, *PMS1*, and *PMS2*), *NBN*, *PALB2*, *RAD51*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*. Patients were categorized into 5 DDRm mutation groups: BRCA1/2, ATM, CDK12, MMR, and other. |
| **Follow-up time** | The median follow-up from the start of the first mCRPC treatment was 22.2 months. |
| **Population (inclusion and exclusion criteria)** | Patient data from electronic medical records was included for patients with **mCRPC and a qualifying mutation** in the following genes: *ATM*, *ATR*, *BRCA1*, *BRCA2*, *BARD1*, *BRIP1*, *CDK12*, *CHEK2*, Fanconi anemia genes, MMR genes (*MSH1*, *MLH3*, *MSH2*, *MSH3*, *MSH6*, *PMS1*, and *PMS2*), *NBN*, *PALB2*, *RAD51*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*. |
| **Intervention** | Data from patients receiving the following treatments was included in the analysis:<br>• Abiraterone |

| Table A2 Differential Treatment Outcomes in *BRCA1/2-*, *CDK12-*, and *ATM*-Mutated Metastatic Castration-Resistant Prostate Cancer. Kwon et al. Cancer 2021 | |
|---|---|
| | • Enzalutamide<br>• Docetaxel<br>• Cabazitaxel<br>• Carboplatin-based treatment<br>• Olaparib<br>• Pembrolizumab<br>• Other check-point inhibitor (Ipilimumab, Nivolumab or "unknown"). |
| **Baseline characteristics** | Patient characteristics for the whole cohort (DDRm) as well as the BRCA1/2 mutated patients below: |

| Characteristic | Overall (n = 149) | BRCA1/2 (n = 65) |
|---|---|---|
| Age at diagnosis, median (range), y | 63 (34-87) | 61 (34-86) |
| Ethnicity, No. (%) | | |
| White | 101 (68) | 42 (65) |
| Asian | 12 (8) | 7 (11) |
| African American | 7 (5) | 1 (2) |
| Hispanic | 2 (1) | 0 |
| Other | 10 (7) | 2 (3) |
| Missing | 17 (11) | 13 (20) |
| Stage at diagnosis, No. (%) | | |
| Localized | 66 (44) | 31 (48) |
| Regional lymph nodes | 18 (12) | 7 (11) |
| Metastatic | 63 (42) | 27 (42) |
| Missing | 2 (1) | 0 |
| Visceral disease at time of metastasis or CRPC, No. (%) | | |
| Yes | 17 (11) | 8 (12) |
| No | 123 (83) | 51 (78) |
| Missing | 9 (6) | 6 (9) |
| PSA at diagnosis, median (range), ng/mL | 18 (2-5000) | 18 (4-5000) |
| Gleason score at diagnosis, No. (%) | | |
| <8 | 28 (19) | 17 (26) |
| ≥8 | 108 (72) | 43 (66) |
| Missing | 13 (9) | 5 (8) |
| Definitive local therapy, No. (%) | | |
| Surgery | 45 (30) | 20 (31) |
| Radiation therapy | 36 (24) | 18 (28) |
| None | 65 (44) | 27 (42) |
| Missing | 3 (2) | 0 |
| Source of tissue, No. (%) | | |
| Prostate | 20 (13) | 7 (11) |
| Lymph node | 5 (3) | 2 (3) |
| Blood (ctDNA or cfDNA) | 64 (43) | 38 (58) |
| Germline | 8 (5) | 2 (3) |
| Liver | 7 (5) | 2 (3) |
| Bone | 2 (1) | 0 |
| Other soft tissue[b] | 8 (5) | 5 (8) |
| Unknown metastasis | 34 (23) | 9 (14) |
| Missing | 1 (1) | 0 |
| Lines of therapy received in mCRPC setting, No. (%) | | |
| 0 | 5 (3) | 3 (5) |
| 1 or 2 | 67 (45) | 36 (55) |
| ≥3 | 72 (48) | 24 (37) |
| Missing | 5 (3) | 2 (3) |

| Table A2 Differential Treatment Outcomes in *BRCA1/2-*, *CDK12-*, and *ATM*-Mutated Metastatic Castration-Resistant Prostate Cancer. Kwon et al. Cancer 2021 | |
|---|---|
| **Primary and secondary endpoints** | The following endpoints were investigated in the study:<br>• PSA50 response<br>• Time to Next Treatment (TNT)<br>• Overall Survival (OS) |
| **Method of analysis** | Clinical and demographic characteristics were summarized by mutation group in contingency tables. The PSA50 response rates, TNT, and OS of systemic therapies received in the first-and second-line mCRPC settings were compared by therapy type and by mutation group with the Fisher exact test, the Wilcoxon rank sum test, and the log-rank test, respectively. A multivariable Cox proportional hazards model of OS was used to account for age, stage, and prostate-specific antigen at diagnosis; ethnicity; presence of visceral metastases at the time of mCRPC or metastasis; type of first-line treatment received; and mutation group. $P <$ .05 was considered significant for statistical testing. No multiple testing adjustments were performed. Analyses were performed with R statistical computing software. |
| **Subgroup analyses** | The patients were categorized into five sub-groups based on their mutation status: BRCA1/2, ATM, CDK12, MMR, and "other".<br>In addition, sub-group analyses were performed on the basis of the type of treatment the patients received. |

## 10.2 Results per study

| Table A3a PROfound Olaparib for Metastatic Castration-Resistant Prostate Cancer. De Bono et al. 2020. N Engl J Med 2020 | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Trial name: | PROfound<br>Olaparib for Metastatic Castration-Resistant Prostate Cancer. De Bono et al. 2020. N Engl J Med 2020 | | | | | | | | | |
| NCT number: | NCT02987543 | | | | | | | | | |
| | | | | **Estimated absolute difference in effect** | | | **Estimated relative difference in effect** | | | **Description of methods used for estimation** |
| **Outcome** | **Study arm** | **N** | **Result (CI)** | **Difference** | **95% CI** | ***P* value** | **Difference** | **95% CI** | ***P* value** | |
| rPFS (BICR) | Olaparib | 162 | 7.39 (6.24–9.33) months | 3.84 | 1.84-5.84 | NA | HR: 0.34 | 0.25–0.47 | $p < 0.0001$ | Primary analysis using a log rank test stratified by previous taxane treatment (yes/no) and measurable disease (yes/no), and the corresponding *p* value calculated. The HR and CI were estimated using a Cox |

| Table A3a PROfound Olaparib for Metastatic Castration-Resistant Prostate Cancer. De Bono et al. 2020. N Engl J Med 2020 | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Cohort A | NHA | 83 | 3.55 (1.91–3.71) months | | | | | | | Proportional hazards model (with ties=Efron and the stratification variables as covariates) and the two-sided CI was calculated using a profile likelihood approach. In the presence of non-proportionality, the HR was interpreted as an average HR over the observed extent of follow-up. The primary analysis was based on the BICR assessment of rPFS using all scans regardless of whether they were scheduled or not. Estimated rPFS rates at 6 and 12 months were summarised using the K–M plot<br>95% CI for absolute value is calculated by AstraZeneca |
| rPFS (BICR) BRCAm | Olaparib | 102 | 9.79 (7.62–11.30) months | 6.83 | 4.39-9.28 | NA | HR: 0.22 | 0.15–0.32 | NA | 95% CI for absolute value is calculated by AstraZeneca |
| | NHA | 58 | 2.96 (1.81–3.55) months | | | | | | | |
| [redacted] | | | | | | | | | | 95% CI for absolute value is calculated by AstraZeneca |
| [redacted] | | | | | | | | | | 95% CI for absolute value is calculated by AstraZeneca |

| Table A3a PROfound Olaparib for Metastatic Castration-Resistant Prostate Cancer. De Bono et al. 2020. N Engl J Med 2020 | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| OS Cohort A | Olaparib | 162 | 19.09 (17.35–23.43) months | 4.4 | 1.05-9.38 | NA | HR: 0.69 | 0.50–0.97 | $p$ = 0.0175 | Interim OS was analysed at the time of the primary rPFS analysis with approximately 49% maturity in cohort A (approximately 117 events). Testing of the OS endpoint utilised the alpha level recycled from the rPFS primary endpoint and the secondary endpoints ORR (cohort A), rPFS (cohort A+B) and TTPP (cohort A) using a two-sided 5% alpha spend. Using an O'Brien–Fleming spending function, the interim analysis used an approximately 0.012 alpha level with 80% information fraction and the final OS analysis will use an alpha level of 0 021 with approximately 146 events (61% maturity) estimated to occur approximately 48 months following randomisation of the first patient in the trial. The $p$ value will be based on the stratified log rank test using previous taxane treatment and measurable disease as strata. HR and 95% CI will be based on the Cox model<br>95% CI for absolute value is calculated by AstraZeneca |
| | NHA | 83 | 14.69 (11.93–18.79) months | | | | | | | |
| OS BRCAm | Olaparib | 102 | 20.1 (17.4–26.8) months | 5.7 | 1.11-10.28 | NA | HR: 0.63 | 0.42–0.95 | NA | |
| | NHA | 58 | 14.4 (10.7–18.9) months | | | | | | | |
| OS BRCAm Prior Taxane | Olaparib | 72 | 17.45 (13.01–25.30) months | 5.5 | -0.28-11.31 | NA | HR: 0.63 | 0.39–1.04 | NA | 95% CI for absolute value is calculated by AstraZeneca |
| | NHA | 35 | 11.93 (8.21–15.15) months | | | | | | | |
| OS BRCAm No prior Taxane | Olaparib | 30 | NC (NC–NC) | NA | NA | NA | HR: 0.51 | 0.23–1.13 | NA | |
| | NHA | 23 | 18.79 (11.33–NC) months | | | | | | | |

| Table A3a PROfound Olaparib for Metastatic Castration-Resistant Prostate Cancer. De Bono et al. 2020. N Engl J Med 2020 | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| PFS2 Cohort A | Olaparib | 162 | 17.22 (12.71–18.30) months | 6.58 | 1.82-11.35 | NA | HR: 0.53 | 0.36–0.79 | $p$ = 0.0003 | Time from randomisation to the earliest investigator-assessed progression event subsequent to that used for the primary variable or death PFS2 was analysed using the methods employed for analysis of the rPFS primary endpoint. The HR and corresponding 95% CI were based on the Cox model using previous taxane treatment and measurable disease as strata |
| | NHA | 83 | 10.64 (9.13–11.24) months | | | | | | | |
| PFS2 BRCAm | Olaparib | 102 | 16.79 (12.65–20.70) months | 7.26 | 2.69-11.84 | NA | HR: 0.482 | 0.301–0.776 | NA | Time from randomisation to the earliest investigator-assessed progression event subsequent to that used for the primary variable or death PFS2 was analysed using the methods employed for analysis of the rPFS primary endpoint. The HR and corresponding 95% CI were based on the Cox model using previous taxane treatment and measurable disease as strata |
| | NHA | 58 | 9.53 (7.59–11.24) months | | | | | | | |
| TTPP Cohort A | Olaparib | 162 | NR | NA | NA | NA | HR: 0.44 | 0.22–0.91 | $p$ = 0.0192 | TTPP was analysed at the time of the primary rPFS analysis using the methods employed in the rPFS analysis. The $p$ value was based on the stratified log rank test using previous taxane treatment and measurable disease as strata, and HR and 95% CI were based on the Cox model. A two-sided 5% alpha level was used to test TTPP based on the multiplicity strategy |
| | NHA | 83 | 9.92 months | | | | | | | |
| TTPP BRCAm | Olaparib | 102 | NR | NA | NA | NA | HR: 0.32 | 0.12–0.81 | NA | Time from randomisation to first SSRE as defined by the use of radiation therapy to prevent or relieve symptoms, occurrence of new radiologically confirmed symptomatic pathological bone fractures (vertebral or non-vertebral) or spinal compression, or surgical intervention for bone metastasis |
| | NHA | 58 | NR | | | | | | | |
| | Olaparib | 162 | NR | NA | NA | NA | HR: 0.37 | 0.20–0.70 | $p$ = 0.0013 | |

| Table A3a PROfound Olaparib for Metastatic Castration-Resistant Prostate Cancer. De Bono et al. 2020. N Engl J Med 2020 | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Time to first SSRE Cohort A | NHA | 83 | NR | | | | | | | |
| Time to first SSRE Cohort A | Olaparib | 162 | NR | NA | NA | NA | HR: 0.37 | 0.20–0.70 | $p = 0.0013$ | |
| | NHA | 83 | NR | | | | | | | |
| PRO FACT-P total score, overall adjusted mean change from baseline<br>Cohort A | Olaparib | 102 | -6.23 (mean change from baseline) | 6.21 | 0.12-12.30 | NA | NA | NA | $p = 0.0456$ | FACT-P is multidimensional, self-report instrument designed to assess HRQoL in patients with prostate cancer. It comprises 27 core items across four domains: Physical, Social/family, Emotional and Functional wellbeing, and supplemented by 12 site-specific items relating to prostate-related symptoms. Higher scores represent better HRQoL[52]<br>Continuous PRO endpoints were summarised using mean, SD, median and range by treatment group for each visit until fewer than one-third of patients have evaluable data. Absolute and change from baseline scores for each time point were calculated for each treatment group.<br>The proportion of patients with the best responses of improve, no change and worsened on FACT-P and subscale scores including TOI were compared between treatments using logistic regression employing the methods and covariates used for analysis of ORR |
| | NHA | 58 | -12.44 (mean change from baseline) | | | | | | | |
| PRO FACT-P total score, overall adjusted mean change from baseline<br>BRCAm | Olaparib | 102 | -5.21 (mean change from baseline) | 4.45 | -4.01 -12.91 | NA | NA | NA | NA | FACT-P is multidimensional, self-report instrument designed to assess HRQoL in patients with prostate cancer. It comprises 27 core items across four domains: Physical, Social/family, Emotional and Functional wellbeing, and supplemented by 12 site-specific items relating to prostate-related symptoms. Higher scores represent better HRQoL[52]<br>Continuous PRO endpoints were summarised using mean, SD, median and range by treatment group for each visit until fewer than one-third of patients have evaluable data. Absolute and change from baseline scores for each time point were calculated for each treatment group.The proportion of patients with the best responses of improve, no change and worsened on FACT-P and subscale scores including TOI were compared between treatments using logistic regression employing the methods and covariates used for analysis of ORR |
| | NHA | 58 | -9.66 (mean change from baseline) | | | | | | | |
| | Olaparib | 256 | 133(52%) | 12 % | 0.9 – 22.9 | NA | RR= 1.27 | 1.00-1.61 | NA | 95% CI for absolute value is calculated by AstraZeneca |

| Table A3a PROfound Olaparib for Metastatic Castration-Resistant Prostate Cancer. De Bono et al. 2020. N Engl J Med 2020 | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Treatment related AE Grade 3 or more | NHA | 130 | 53(40%) | | | | | | | RR is calculated by AstraZeneca |
| SAE | Olaparib | 256 | 94 (36,7%) | 6,7 % | -3.7 – 30.0 | NA | RR =1.22 | 0.9-1.66 | NA | 95% CI for absolute value is calculated by AstraZeneca.<br>RR is calculated by AstraZeneca |
| | NHA | 130 | 39 (30%) | | | | | | | |
| Grade 5 | Olaparib | 256 | 6 (2,34%) | 0.3% | -3.17 – 3.17 | NA | RR = 1.02 | 0.26-4.00 | NA | 95% CI for absolute value is calculated by AstraZeneca<br>RR is calculated by AstraZeneca |
| | NHA | 130 | 3 (2,31%) | | | | | | | |

| Table A3b CARD Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. De Wit et al. N Engl J Med. 2019 | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Trial name: | CARD | | | | | | | | | | |
| NCT number: | NCT02485691 | | | | | | | | | | |
| | | | | **Estimated absolute difference in effect** | | | **Estimated relative difference in effect** | | | **Description of methods used for estimation** | **References** |
| **Outcome** | **Study arm** | **N** | **Result (CI)** | **Difference** | **95% CI** | ***P* value** | **Difference** | **95% CI** | ***P* value** | | |

| Table A3b CARD Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. De Wit et al. N Engl J Med. 2019 | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| imaging based PFS | Cabazitaxel | 129 | 8.0 (5.7-9.2) months | 4.3 | (1.83 ; 6.77) | NA | HR: 0.54 | 0.40–0.73 | P<0.001 | The median survival is based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm.<br>rPFS defined as the time from randomization to the occurrence of one of the following:<br>• Progression of measurable lesions using RECIST 1.1<br>• Progression of bone lesions using PCWG2 criteria<br>• Death due to any cause<br>95% CI for absolute value is calculated by AstraZeneca | |
| | NHA | 126 | 3.7 (2.8–5.1) months | | | | | | | | |
| OS | Cabazitaxel | 129 | 13.6 (11.5-17.5) months | 2.6 | (-0.16 ; 5.37) | NA | HR: 0.64 | 0.46-0.89 | 0.008 | OS: defined as the time interval from the date of randomization to the date of death due to any cause<br>95% CI for absolute value is calculated by AstraZeneca | |
| | NHA | 126 | 11.0 (9.2–12.9) months | | | | | | | | |
| Time to first symptomatic skeletal event | Cabazitaxel | 129 | NE (20.0-NE) months | NA | NA | NA | HR: 0.59 | 0.35-1.01 | P=0.05 | Time to SSE is defined as the time interval between the date of randomization and the date of the occurrence of the first event defining a SSE, whichever is earlier. For each patient, SSE will be assessed at baseline, every 3 weeks during study treatment, at the end of treatment visit and every 12 weeks during follow-up until occurrence of first SSE or study cut off, whichever comes first. | |
| | NHA | 126 | 16.7 (10.8–NE) months | | | | | | | | |
| TTPP | Cabazitaxel | 111 | NE (NE-NE) months | NA | NA | NA | HR: 0.55 | 0.32-0.97 | P=0.035 | Time to pain progression is defined as the time interval between the date of randomization and the date of either first documented pain progression. Pain | |

| Table A3b CARD Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. De Wit et al. N Engl J Med. 2019 | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | NHA | 109 | 8.5 (4.9–NE) months | | | | | | progression, in patients with no pain or stable pain at baseline, is defined as:<br>• an increase by ≥30% from baseline in the BPI-SF pain intensity score observed at 2 consecutive evaluations ≥3 weeks apart without decrease in analgesic usage score OR increase in analgesic usage score ≥ 30%. | |
| AE Grade 3 or more | Cabazitaxel | 126 | 56.3 % | 3.9 % | NA | NA | RR = 1.08 | 0.77 - 1.50 | NA | Treatment Emergent Adverse Events (TEAE): Type according to MedDRA (Medical Dictionary for Regulatory Activities), frequency, severity according to NCI CTCAE V4.0, seriousness, and relationship of study treatment will be assessed. Laboratory abnormalities will be assessed according to the NCI CTCAE v.4.0<br>RR calculated by AstraZeneca | |
| | NHA | 124 | 52.4 % | | | | | | | | |
| SAE any Grade | Cabazitaxel | 126 | 38.9 % | 0.2 % | NA | NA | RR = 1.01 | 0.68 - 1.50 | NA | RR calculated by AstraZeneca | |
| | NHA | 124 | 38.7 % | | | | | | | | |
| PRO FACT-P total score mean change from baseline | Cabazitaxel | 129 | -6.33 (SE 2.81) | 4.58 | -1.36-10.52 | P=0.13 | NA | NA | NA | Health status/utility (EQ-5D-5L) evaluation at baseline (within 3 days prior the first study treatment), at each visit before drug administration, at end of treatment visit and every 12 weeks during the follow-up period | |
| | NHA | 126 | -10.91 (SE 3.13) | | | | | | | | |

## 10.3 Results per PICO (clinical question)

Table A4 for clinical question 1 is of limited use due to the RWE design of the Kwon study. Very few data are available and the OS data used from PROfound are included in table A4 related to question 3

| Table A4 Results referring to Clinical Question 1 Olaparib vs. docetaxel | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Results per outcome: | | | | | | | | |
| | | Absolute difference in effect | | | Relative difference in effect | | | Methods used for quantitative synthesis |
| | Studies included in the analysis | Difference | CI | *P* value | Difference | CI | *P* value | |
| Treatment related AE Grade 3 or more | PROfound<br>Kwon et al | 3.8 % | NA | NA | NA | NA | | |
| AE Grade 5 | PROfound<br>Kwon et al | 2.0 % | NA | NA | NA | NA | | |
| SAE any Grade | PROfound<br>Kwon et al | 10.7 % | NA | NA | NA | NA | | |

| Table A4 Results referring to Clinical Question 2. Olaparib vs. Cabazitaxel | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Results per outcome: | | Absolute difference in effect | | | Relative difference in effect | | | Methods used for quantitative synthesis |
| | Studies included in the analysis | Difference | CI | *P* value | Difference | CI | *P* value | |
| OS BRCAm vs. cabazitaxel prior taxane<br>Adjusted for switching | MAIC(ASCO Poster), CARD, PROfound | NA | NA | NA | HR=0.47 | 0.12-1.79 | NA | (MAIC) is a technique widely used in oncology to establish the relative efficacy of two interventions for which individual patient data (IPD) is available for one trial/intervention but only aggregate data (AgD) is available for the other. MAICs can be used to establish the comparative efficacy of competing nterventions that have been studied in clinical trials, but not directly, and are linked by a common comparator in the case of anchored comparisons. |
| rPFS BRCAm vs. cabazitaxel. prior Taxane | MAIC (ASCO Poster), CARD, PROfound | NA | NA | NA | HR=0.36 | (0.2, 0.64) | | (MAIC) is a technique widely used in oncology to establish the relative efficacy of two interventions for which individual patient data (IPD) is available for one trial/intervention but only aggregate data (AgD) is available for the other. MAICs can be used to establish the comparative efficacy of competing nterventions that have been studied in clinical trials, but not directly, and are linked by a common comparator in the case of anchored comparisons. |
| rPFS<br>naive | PROfound<br>CARD | 3.6 months | NA | NA | NA | NA | NA | |
| rPFS at 12 months | PROfound<br>CARD | 14 % | NA | NA | NA | NA | NA | From CARD the 12 months rPFS is a read of the curve in the publication |
| PRO FACT-P | PROfound<br>CARD | NA | NA | NA | NA | NA | NA | Absolute and change from baseline scores in FACT-P total score, TOI, FAPSI-6, PCS, PWB and FWB subscales |

| Table A4 Results referring to Clinical Question 2. Olaparib vs. Cabazitaxel | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Treatment related AE Grade 3 or more | PROfound<br>CARD<br>Naive | 4.3 % | NA | NA | NA | NA | NA | |
| AE Grade 5 | PROfound<br>CARD<br>Naive | 3.1 % | NA | NA | NA | NA | NA | |

| Table A4 Results referring to Clinical Question 3 Olaparib vs. BSC (NHA) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Results per outcome: | | | | | | | | |
| | | **Absolute difference in effect** | | | **Relative difference in effect** | | | **Methods used for quantitative synthesis** |
| | **Studies included in the analysis** | **Difference** | **CI** | ***P* value** | **Difference** | **CI** | ***P* value** | |
| OS BRCAm | PROfound | 5.7 | 1.11-10.28 | NA | HR=0.63 | 0.42–0.95 | NA | 95% CI for absolute value is calculated by AstraZeneca |
| OS BRCAm vs. NHS no prior Taxane | PROfound | NA | NA | NA | HR=0.51 | 0.23–1.13 | NA | |

| Table A4 Results referring to Clinical Question 3 Olaparib vs. BSC (NHA) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| OS BRCAm vs. NHS prior Taxane | PROfound | 5.5 | -0.28-11.31 | NA | HR=0.63 | 0.39–1.04 | NA | 95% CI for absolute value is calculated by AstraZeneca |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 95% CI for absolute value is calculated by AstraZeneca |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | Time from randomisation until the date of objective disease progression (as assessed by BICR using RECIST version 1.1 or PCWG3) or death (by any cause in the absence of progression) regardless of whether the subject withdrew from randomised therapy or received another anti-cancer therapy prior to disease progression.<br>95% CI for absolute value is calculated by AstraZeneca |
| PRO FACT-P total score, overall adjusted mean change from baseline<br>BRCAm | PROfound | 4.45 | -4.01 -12.91 | NA | NA | NA | NA | Absolute and change from baseline scores in FACT-P total score, TOI, FAPSI-6, PCS, PWB and FWB subscales |
| Treatment related AE Grade 3 or more | PROfound | 12 % | 0.9 – 22.9 | NA | RR = 1,27 | 1.00-1.61 | NA | 95% CI for absolute value is calculated by AstraZeneca.<br>RR calculated by AstraZeneca |
| AE Grade 5 | PROfound | 0.3 % | -3,17 – 3,17 | NA | RR = 1.02 | 0.26-4.00 | NA | CI calculated by AstraZeneca<br>RR calculated by AstraZeneca |

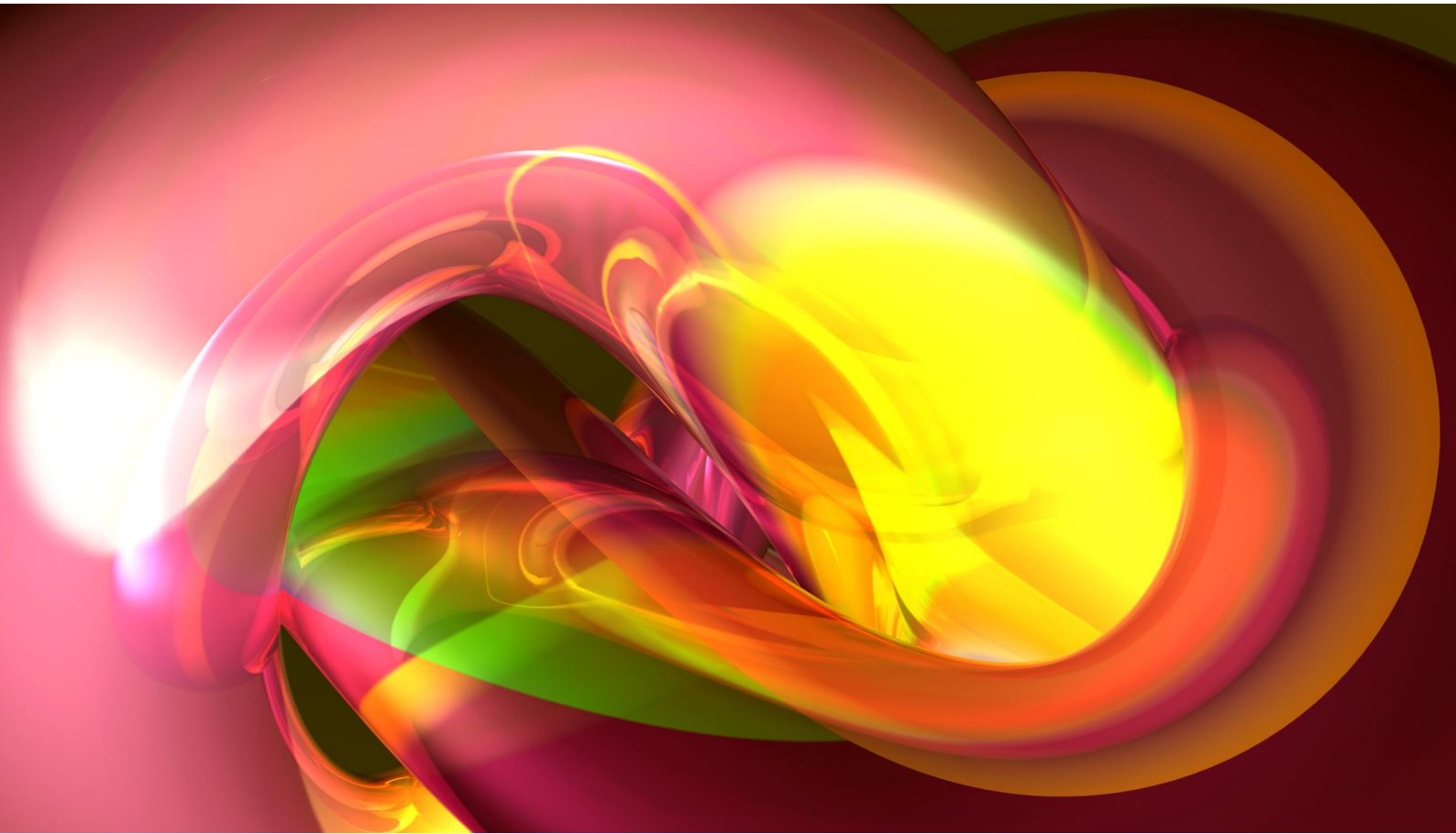
| Table A4 Results referring to Clinical Question 3 Olaparib vs. BSC (NHA) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| SAE any Grade | PROfound | 6,7 % | -3.7 – 30.0 | NA | RR = 1.22 | 0.9-1.66 | NA | Exposure to olaparib was approximately twice as long as that of the physicians' choice of NHA (230 days vs 120 days) |

# Lynparza® (olaparib) for patients with metastatic castration resistant prostate cancer

Cost Analysis

2021-06-18

Updated 2021-07-16, 2021-08-09 & 2021-08-19



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# Executive summary

## Background

Olaparib (Lynparza™) was recently approved by the European Commission as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) and BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent. The approved maintenance monotherapy dose for olaparib tablets is 300 mg twice daily, which equates to taking 4 tablets per day (twice, 2 x 150 mg tablets taken 12 hours apart) (EMA 2020). It is estimated that around 52 new patients per year will be eligible for treatment with olaparib in the mCRPC indication from 2021 to 2025 in Denmark.

## Analysis

In the cost analysis olaparib is compared to docetaxel, cabazitaxel or best supportive care (BSC) depending on where in the treatment pathway olaparib would be used. In addition to acquisition costs for these treatments, the analyses also include a possibility for subsequent therapy use in later lines. However, subsequent therapy plays much less of a role here compared previous appraisal of first-line olaparib monotherapy in BRCAm positive ovarian cancer.

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

## Results

In the base case, the results on average cost per patient showed that for patients treated with olaparib, the discounted costs over 10 years were DKK 574 840, compared with DKK 102 382 for docetaxel, DKK 268 933 for cabazitaxel and DKK 102 894 for best supportive care. The difference in cost over 10 years was DKK 472 458 vs docetaxel, DKK 305 907 vs. cabazitaxel and DKK 471 946 vs BSC. The drug acquisition constitutes the major part of the costs for olaparib (78% of the total cost), and therefore results were most sensitive to changes in drug acquisition costs for olaparib, and relatively insensitive to most other variables.

The yearly budget impact of treatment with olaparib compared with docetaxel, cabazitaxel and BSC in the overall BRCAm patient population increased from DKK 2.6 million in 2021 to DKK 14.5 million in 2025.

## Conclusion

The cost per patient and budget impact for olaparib in mCRPC varied in a predictable way depending on scenario and comparator. The scenario analysis indicated that the cost results were stable for most variables. The total budget impact of olaparib in mCRPC is relatively low in absolute terms, with an estimated budget impact of around DKK 14.5 million at peak year sales.

# Glossary of terms

| Acronym | Definition | Acronym | Definition |
|---|---|---|---|
| ADT | Androgen deprivation therapy | MRU | Medical resource use |
| AE | Adverse event | NCCN | National Comprehensive Cancer Network |
| AF | Acceleration factor | NHA | New hormonal agent |
| AIC | Akaike information criterion | NICE | National Institute for Health and Care Excellence |
| AUC | Area under the curve | NMA | Network meta-analyses |
| AUP | Public Price inclusive VAT | ORR | Objective response rate |
| BRCA | Breast cancer antigen | OS | Overall survival |
| DSU | Decision Support Unit | PARP | Poly adenosine diphosphate-ribose polymerase |
| ECOG | Eastern Cooperative Oncology Group | PD | Progressed disease |
| EMA | European Medicines Agency | PF | Progression free |
| ENZ | Enzalutamide | PFS | Progression-free survival |
| ESMO | European Society for Medical Oncology | PRE | Prednisone |
| FACT-P | Functional Assessment of Cancer Therapy- | PSA | Prostate-specific antigen |
| FDA | Food and Drug Administration | qd | once daily |
| gBRCAm | Germline breast cancer mutated | RECIST | Response Evaluation Criteria in Solid Tumors |
| G-CSF | Granulocyte-colony stimulating factor | rPFS | Radiographic progression-free survival |
| HR | Hazard ratio | RPSFTM | Rank preserving structural failure time model |
| HRR | Homologous recombination repair | SC | Subcutaneous |
| HRRm | Homologous recombination repair mutation | SLR | Systematic Literature Review |
| HTA | Health technology assessment | SmPC | Summary of product characteristics |
| icNHA | Investigator's choice of new hormonal agent | SOL | Solution |
| INV | Investigator | SRE | Skeletal-related events |
| IPCW | Inverse Probability Censoring Weighted | TA | Technology appraisal |
| ITC | Indirect treatment comparison | TAB | Tablet |
| ITT | Intent-to-treat | TSD | Technical Support Document |
| IV | Intravenous | TTD | Time to treatment discontinuation |
| KM | Kaplan-Meier | Tx | Treatment |
| LHRH | Luteinizing hormone-releasing hormone | UK | United Kingdom |
| LY | Life-years | US | United States |
| LYG | Life years gained | UTI | Urinary tract infection |
| mCRPC | Metastatic castrate-resistant prostate cancer | | |
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# Contents

# Cost-effectiveness of olaparib in BRCAm mCRPC

## 1 Indication

Lynparza is indicated as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) and *BRCA1/2* mutation (germline and/or somatic) who have progressed following a prior new hormonal agent (NHA, e.g. abiraterone and enzalutamide).

## 2 Target patient population

This application focuses on the BRCA mutated subgroup in the PROfound trial (de Bono 2020, Hussain 2020). This subpopulation includes patients with mCRPC and confirmed alterations in BRCA1 and BRCA2 mutations and who have progressed following a prior NHA. The targeted patient population aligns with the indication.

Patient characteristics used in the model are based on Cohort A in the PROfound study and are presented in Table 1. Patient characteristics in Cohort A closely match those in the BRCAm population (Appendix A).

*Table 1 Baseline patient characteristics (Cohort A)*

| Patient characteristics | Overall |
|---|---|
| Mean age at baseline, years | 68.1 |
| Weight (kg) | 80 |
| Body surface area ($m^2$) | 1.91 |
| Source: Clinical study report (CSN), Cohort A<br>Abbreviations: [a] Body surface area has been calculated using the Mosteller formula (Height [cm] × weight [kg]/3600)$^{1/2}$, sourced from Sacco et al. (2) as not available in PROfound. | |

## 3 Treatment options considered in the economic evaluation

### 3.1 Intervention

The intervention of interest is olaparib tablets 300 mg BID (600 mg).

### 3.2 Comparator

The comparators considered in the model were informed by the protocol from Medicinrådet.

Based on the protocol, three treatments were identified as relevant comparators.

- Docetaxel for patients who are taxane- chemotherapy-naïve;
- Cabazitaxel for patients who have previously received at least one taxane-based chemotherapy;
- Best supportive care for patients who have progressed after treatment with NHA, docetaxel and cabazitaxel and who do not have other treatment opportunities.
- For all comparators, the population consists of patients with confirmed alternations in BRCA1 and BRCA2 mutations (BRCAm overall population);

In order to compare olaparib with the most relevant taxane (docetaxel or cabazitaxel), the BRCAm patient population was split into two subgroups:

- BRCAm no prior taxane subgroup (patients who are chemotherapy-naïve at baseline) to enable a comparison to docetaxel.
- BRCAm prior taxane subgroup (patients who had previously received at least one prior taxane-based treatment) to enable a comparison to cabazitaxel.

It needs to be highlighted that the clinical benefit of olaparib over NHA in the BRCAm patient population was observed irrespective of previous taxane exposure. Hence, splitting the BRCAm patient population into subgroups based on previous taxane exposure was performed to allow the comparison between olaparib and the most relevant taxane rather than to identify a subgroup with the highest clinical benefit.

More detailed description of comparators in the above mentioned patient populations are presented below.

## BRCAm overall population

### Best supportive care (BSC):

- While the PROfound trial used either abiraterone acetate or enzalutamide (new hormonal therapies, NHA), the present cost analysis compares with BSC as retreatment with NHAs is not recommended in guidelines, except in a selected population.
- As BSC was not used in the PROfound trial, the data on olaparib vs abiraterone acetate or enzalutamide is used a proxy for BSC. In terms of efficacy, this is conservative as retreatment with NHA could be expected to have higher efficacy than BSC. Possibly also more side effects, but as will be shown later, the side effects (adverse events) are in general associated with relatively limited costs. Using NHA as proxy for BSC could potentially overestimate costs for BSC, but patients with BSC also receive a number of treatments and are regularly monitored.

## BRCAm no prior taxane subgroup in PROfound

### Docetaxel

Docetaxel in combination with prednisolone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer. The dosing schedule included in the model, in line with SmPC, was 75 mg/m$^2$ administered as 1-hour IV infusion every 3 weeks in combination with prednisolone 5mg orally bd (SmPC docetaxel).

## BRCA prior taxane subgroup in PROfound

### Cabazitaxel

Cabazitaxel in combination with prednisolone is indicated for the treatment of adult patients with mCRPC previously treated with a docetaxel-containing regimen. The dose regimen considered in the model was based on the recommended dose by the Danish clinical guidelines and clinical praxis: 20 mg/m$^2$ administered as one-hour intravenous (IV) infusion every 3 weeks in combination with oral prednisolone 10 mg daily (SmPC cabazitaxel). Although this dosing regimen does not align with the

treatment dosing schedule in the CARD study (i.e. a dose of 25 mg/m$^2$ administered IV over a period of 1 hour every 3 weeks (de Wit 2019) with oral prednisone at a dose of 10 mg daily) which was used in the indirect treatment comparison of olaparib and cabazitaxel, equal efficacy between 20 mg/m$^2$ and 25 mg/m$^2$ is assumed.

# 4 Objective

To assess the cost per patient and budget impact of olaparib (Lynparza®) as a treatment for patients with metastatic castration-resistant prostate cancer and *BRCA1/2* mutations who have progressed following a prior new hormonal agent compared with NHA and relevant taxane-based chemotherapy (docetaxel or cabazitaxel) depending on previous taxane exposure.

# 5 Perspective

In the base case scenario for the cost per patient analysis, the model takes a limited societal perspective including patient time costs and transportation costs in addition to health care costs. The budget impact analysis takes a health care payer perspective. The health care payer perspective includes disease management costs and treatment-related costs (acquisition, administration, monitoring, terminal care, and adverse events). The limited societal perspective and the health care perspective can be justified based on the assumption that the patient population was not employed due to the severity of advanced stage III or IV prostate cancer; therefore, it is not expected that the treatment of mCRPC will induce extra loss of productivity beyond that caused by the underlying disease. In addition, a majority of the patient population is above the retirement age. Consequently, excluding indirect costs is not anticipated to affect the cost-effectiveness results very much. The direct non-medical costs associated with such items as travelling and time use have been included in the cost per patient analysis.

# 6 Time horizon

In the base case analysis, the time horizon is 10 years. This is considered to be long enough to cover the life expectancy of patients with mCRPC and fully capture all the downstream costs and health benefits associated with olaparib therapy after previous use of an NHA. Shorter and longer time horizons (5 and 15 years) are tested in sensitivity analyses.

# 7 Cycle length and half-cycle correction

A cycle length of one calendar month (30.44 days) was used in the model. This was chosen as it is short enough to accurately capture differences in cost between cycles and matches the data collection cycle in the PROfound trial.

A half-cycle correction was applied to prevent under- or over-estimation of costs. A half-cycle correction was not applied to medication acquisition and administration costs, since treatments are administered at the start of each cycle and costs would, therefore, be incurred at the start of each cycle regardless of the patient's movement thereafter. Half-cycle correction was not applied for those costs that were assumed to occur as one-off events (e.g. adverse events, skeletal-related events).

## 8 Discounting

As per recommendation by the Danish Finance Ministry, costs were discounted by 3.5% over the duration of the model time horizon. The discount rate was varied between 0% and 5% in sensitivity analysis. No discounting was applied in the budget impact analysis.

## 9 Software

The model has been developed in Microsoft Excel®, a flexible and user-friendly platform. The model is run through Visual Basic macros.

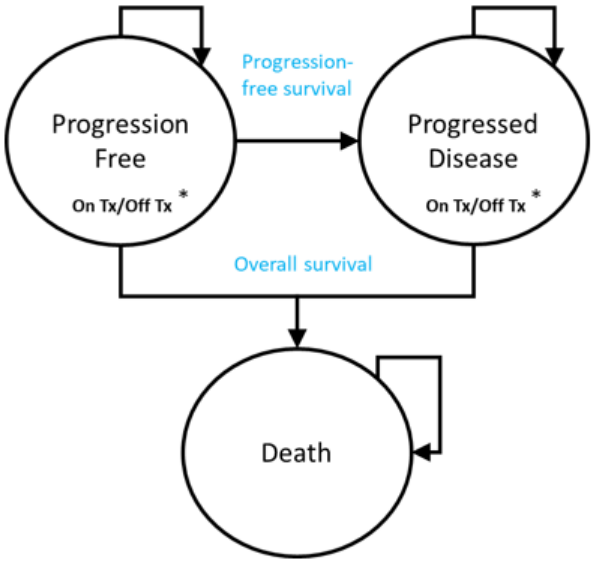
Please note that you need to re-run the model analysis whenever the model settings or model inputs have been changed. Otherwise the results will not be updated.

## 10 Health economic model and its structure

A three-state cohort partitioned survival (or 'area-under the curve') model was developed in Excel to evaluate the cost of olaparib versus BSC or a taxane in the mCRPC setting. The model uses survival curves (radiological progression-free survival [rPFS] and overall survival [OS]) to calculate the proportion of simulated patients at a given time point in each health state.

The model structure was designed to accurately reflect the natural disease progression and capture the benefits of olaparib in delaying disease progression and subsequent lines of therapy. This type of model was used to make full use of the available clinical trial data, and it includes the most commonly used health states in economic models of advanced cancer. The structure of the current model is displayed in Figure 1.

*Figure 1 Three health-state cost-effectiveness model structure*



Note: Health state transitions are not explicitly modelled in the partitioned survival analysis. The direction of transition in the model is provided as an illustration. *On treatment (i.e. On Tx) and off treatment (i.e. Off Tx) are not a part of the health states for efficacy estimation, but only included to track patients for the purpose of treatment-related cost assignment.
Abbreviations: TX = treatment

The course of disease is reflected with three mutually exclusive and fully exhaustive (patients must occupy one of the states at any given time) health states:

Progression free (PF): PF state includes patients who are alive with no progression of the disease. At the end of each cycle, patients in the PF state can remain in the PF state, progress to progressed disease (PD), or die.

Progressed disease (PD) : PD state includes patients who are alive and with progressed disease. Those in this state can either remain in PD or die.

Death: Death state includes patients who transition into this state from PF and PD when they die, from any cause. Once in this state, they remain in this state for the remaining time horizon.

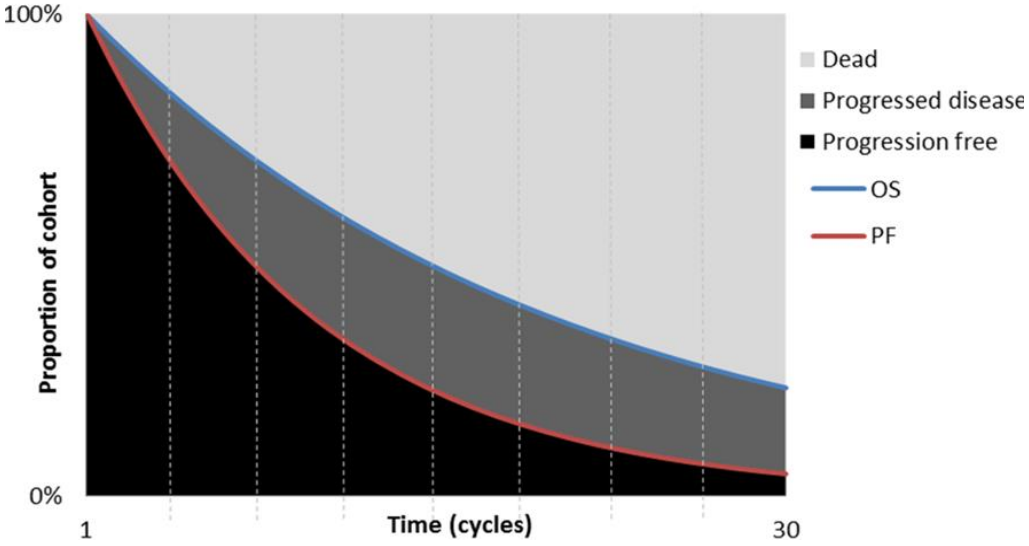
The simulated cohort of patients start each treatment when they enter the PF health state.

## 10.1 Modeling efficacy

### 10.1.1 Partitioned survival model

Treatment-specific rPFS and OS curves are used in the model to partition patients in the PF, PD, and death health states over time. The rPFS curve dictates what percentage of patients remain in the PF state, and the OS curve dictates the percentage of patients alive. The remaining patients (i.e. alive minus progression-free) occupy the PD state as illustrated in Figure 2. Costs and utilities are assigned to each health state.

*Figure 2 Illustration of the partitioned survival calculation*




Abbreviations: OS, overall survival; PFS, progression-free survival.

Progression is defined according to the PROfound trial, where rPFS was a primary endpoint, defined as the time from randomization until the date of objective radiological disease progression (assessed using Response Evaluation Criteria in Solid Tumors [RECIST 1.1, soft tissue] and Prostate Cancer Working Group 3 [PCWG3, bone] criteria) or death (by any cause in the absence of progression). In the base case analysis rPFS BICR is used to model progression.

### 10.1.2 Cross-over and treatment switching adjustment

In the PROfound trial protocol, treatment switching can occur when patients in the NHA arm meet the criteria to receive subsequent olaparib during study follow-up. At DCO2, 86 out of 131 patients randomized to NHA in Cohort A+B switched to olaparib on progression. Given that olaparib is not currently reimbursed in this treatment setting in Denmark (i.e. after disease progression on two lines of NHA), the OS estimations based on intent-to-treat (ITT) analysis may not be reflective of the current clinical practice and may underestimate the "true" OS difference for olaparib compared with NHA. Therefore, exploratory analyses of OS adjusting for impact of subsequent PARP inhibitor treatments were performed. Multiple naïve and sophisticated adjustment methods were explored for the treatment switching analysis. The sophisticated adjustment methods included were:

- Rank Preserving Structural Failure Time Model (RPSFTM);
- Inverse Probability of Censoring Weights (IPCW);
- Two-stage estimation (TSE).

The treatment switching analyses were performed using R (R Foundation). Detailed methodological considerations for the choice of adjustment method are provided in the technical report provided separately. Of the aforementioned methods, the TSE approach was excluded, as an appropriate secondary baseline could not be identified, with the method considered to provide biased results. IPCW and RPSFTM methods were compared, with the RPSFTM approach deemed the most appropriate on the basis that it is not dependent on data, particularly time-varying data, to predict switching. The RPSFTM approach also utilizes all data for switchers and non-switchers, compared with the IPCW approach, which involve analysis on reduced sample sizes. This issue of reduced sample size is particularly important in the case of the PROfound data, due to the relatively small sample size of the investigators' choice of NHA arm when divided into switchers/non-switchers.

The choice of model used to calculate the acceleration factor for the RPSFTM is based on the plausibility of the assumptions each model makes and the analyst's preferences. The Cox proportional hazard model with recensoring was the preferred model for the cost-effectiveness analysis and was also the method used for cross-over adjustment in the PROfound publication.

### 10.1.3 Subsequent therapies

The model design does not explicitly capture efficacy of subsequent treatments after discontinuation from initial therapy. The proportion of patients receiving subsequent treatments and the duration is sourced from the PROfound trial and were applied to patients upon disease progression. However, the survival benefit attributable to subsequent treatments is implicitly captured in the treatment-specific OS estimates.

### 10.1.4 Approach to parametric fitting

The PROfound patient-level trial data were analyzed to capture key disease outcomes (rPFS and OS) of olaparib and NHA. Parametric survival analysis is the common approach for extrapolation of time-to-event outcomes and is recommended by the NICE Decision Support Unit (DSU) for the analysis of survival outcomes for economic evaluations alongside clinical trials (NICE-DSU 2013). This approach formally accounts for censored observations and uses statistical distributions that can account for the typically skewed distributions of time-to-event variables. Following the algorithm, the following steps of statistical analyses were conducted for each endpoint:

Step 1: Kaplan-Meier (KM) curves were generated for various clinical outcomes using the arm-specific patient-level data. If the KM curves cross, the proportional hazards assumption is violated, and Step 2 could be skipped.

Step 2: Residual plots were generated to evaluate the proportional hazards assumption.

Step 3: Parametric distributions were fitted to the KM curves. Conventional parametric distributions were considered following the NICE DSU recommendation: Exponential, Weibull, Gompertz, Log-logistic, Lognormal, and Generalised Gamma.

Step 4: For each endpoint and subgroup, the distributions for the base-case and scenario analyses were selected following the model selection process proposed by the NICE TSD 14, consultations with medical advisors and available clinical evidence (NICE DSU TSD 14, 2013).The model selection process included the following considerations:

- Visual inspection of the fit of the distributions to the KM curves ;
- Comparison of the AIC and BIC statistics from the different distributions;
- Feedback from AZ medical experts to assess the plausibility of the long-term extrapolations;
- Validation against external and other published data sources.

### 10.1.5 Approach to estimate relative efficacy

In the absence of head-to-head trials comparing olaparib with other treatments than NHAs, an indirect treatment comparison was performed to inform the relative efficacy of the comparators not included in the PROfound trial.

A systematic literature review (SLR) was conducted to identify relevant comparative evidence. The systematic literature review was conducted in January 2020 and identified published clinical evidence on the use of health technologies in patients with mCRPC whose disease had progressed following treatment with an NHA, irrespective of HRR mutation status. The scope of the SLR was broader than that of the decision-problem, and did not restrict inclusion by patients with mCRPC who had HRR gene mutations, to capture all studies in a post-NHA setting that could inform indirect comparisons with existing drugs that are not targeted to HRR mutations. More detailed description of the SLR methodology and results are provided in Appendix B and in a separately provided report.

#### 10.1.5.1 Cabazitaxel

Systematic literature review identified six publications that reported outcomes on cabazitaxel. Of these, only one study – the CARD trial (de Wit 2019) – was deemed relevant to inform relative efficacy to olaparib in the post-NHA setting. CARD is an ongoing Phase IV RCT that assessed the efficacy and safety of cabazitaxel compared with an NHA (enzalutamide or abiraterone plus prednisolone) in patients with mCRPC, who had received previous treatment with docetaxel and an NHA. As all patients enrolled in the CARD trial were required to have received previous docetaxel, the patient population is closely aligned with the prior-taxane subpopulation of the PROfound study, although not restricted to those patients who have mutations in HRR genes. As with PROfound, rPFS is the primary endpoint in the CARD trial (reported as imaging assessed PFS in both study publications) and OS is a secondary endpoint in both studies, allowing comparisons of comparative effectiveness and economic evaluation.

The remaining publications that reported outcomes in patients who received cabazitaxel were either small early phase or single-arm studies (often conducted in a single country or center) or cabazitaxel combination studies (with budesonide, prednisone, prednisolone, or abiraterone), or did not report on the outcomes of interest (split by those who had received a prior NHA, in case of a mixed population) and were therefore deemed unsuitable for inclusion in the evidence base for this appraisal. More details are provided in Appendix B.

#### 10.1.5.2 Docetaxel

Although the SLR identified eight publications that included docetaxel, none of these studies were relevant to the decision-problem, since they:

1) either did not include docetaxel as a monotherapy arm (three publications) (Lewis 2018, Oudard 2005, Petrioli 2015), or

2) did not include patients based on progression on prior NHA therapy (a pre-requisite for randomization in the PROfound study; two publications) (Castellano 2017, Pili 2010), or

3) did not report appropriate data on the key survival outcomes of OS and rPFS results (three publications) (de Bono 2017, Puente 2018, Sugiyama 2018).

#### 10.1.5.3 Other treatments

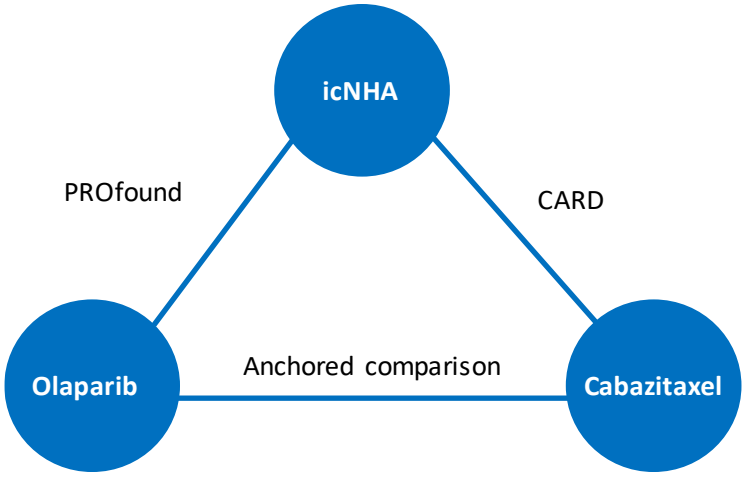
No common comparators were either found in radium-223 clinical trials.

### 10.1.6 Evidence Networks for indirect treatment comparison

#### 10.1.6.1 Cabazitaxel (comparator in a prior-taxane subgroup)

The evidence network for the analysis comparing olaparib and cabazitaxel is shown in Figure 3. As can be seen in the figure, there is a common comparator (NHA) available to link olaparib to cabazitaxel in the PROfound and the CARD studies (de Wit 2019). Relative efficacy (summarized as HR for PFS and OS) for cabazitaxel vs. NHA was taken from the CARD study and applied directly to the baseline (NHA) survival curves to inform PFS and OS curves for cabazitaxel.

*Figure 3 Evidence network for relative efficacy including cabazitaxel*




Abbreviation: icNHA – investigator's choice of new hormonal agent

#### 10.1.6.2 Docetaxel (comparator in a no prior taxane subgroup)

As no relevant docetaxel RCTs were identified in the clinical SLR eligible for comparison with PROfound, observational data were used to inform the modelling of PFS and OS.

Flatiron data (Swami 2020) published at ASCO 2020, assessed docetaxel compared with NHA in patients with metastatic prostate cancer previously treated with an NHA at centers in the United States. These data are considered the best available to inform the comparative effectiveness of docetaxel compared with NHA in the taxane-naïve and post-NHA mCRPC setting. As for the cabazitaxel comparison, HRs (NHA vs. docetaxel) reported in the RWE study were applied to the baseline survival curves for NHA in order to derive extrapolated survival curves for docetaxel. A more detailed description of the study is presented in Appendix B.

## 10.2 Time on treatment

Time on treatment is modeled based on the assumption that treatment duration is equal to time spent in the PF disease state (i.e. treatment discontinuation occurs when patients progress). This reflects the expected clinical practice in Denmark as treatment until progression is in line with treatment duration in other tumour types (ovarian, breast) and is indicated in the SmPC for olaparib.

## 10.3 Costs and outcomes evaluated

Health outcomes are measured by life-years (LY) and QALYs accrued in PF and PD health states. QALYs are calculated from the health state utility values (HSUVs), as well as disutility associated with AE, SRE and time to death. Costs that are evaluated include medication costs (acquisition and administration costs), subsequent treatment and concomitant medication costs, AE costs, SRE costs, and disease management and terminal care costs. Incremental clinical benefits and incremental costs are calculated based on the health and cost outcomes for olaparib and each comparator.

## 10.4 Uncertainty analysis

The model explored structural and parameter uncertainty in a variety of ways:

- Scenario and sensitivity analyses were conducted to assess the impact of changes in key model parameters on the results. Examples include changing the time horizon, discount rates and using different efficacy assumptions.
- Probabilistic sensitivity analysis (PSA) was also performed to account for statistical uncertainties of multiple key parameters. The PSA simultaneously varied all parameters with uncertainty in the model, sampling various input parameters from the appropriate probability distributions.

## 10.5 Model validation

A review of the model was performed by an internal peer reviewer not involved with the original programming. The review included:

- Detailed review of the mathematical formulas and sequence of calculations;
- Checking the functionality of any built-in VBA macros and subroutines;
- Extreme-value testing to identify and correct potential inconsistencies in model behaviour which could have been the result of programming or typing errors;
- Checking the intermediate calculations for references (e.g. whether they are linked to correct cells) and implementation (e.g. whether correct signs for the parameters were used);

- Checking data inputs against references and sources;
- Evaluation of the face validity of predicted results.

Following the validation, any identified errors were corrected before the model was finalized.

# 11 Model inputs and data sources

## 11.1 Clinical inputs

### Relative efficacy for the comparison against NHA

The clinical inputs required for the cost analysis (rPFS, OS, AEs, and SREs) were derived from the patient-level data from PROfound sourced from data cut-off 1 (DCO1: 4 June 2019), when 113 rPFS events had occurred in patients with a BRCA1/ BRCA2 mutations (71% data maturity), except for final OS and safety data that are presented from data cut-off 2 (DCO2; 20 March 2020) following 94 deaths in BRCAm cohort (59% data maturity) (EMA Lynparza EPAR). As the PROfound data are still limited, parametric curves were fitted to the rPFS and OS data to estimate long-term outcomes beyond the duration of the clinical data.

### Relative efficacy for the comparison against taxanes

The relative efficacy (rPFS and OS) among interventions was derived from different sources, including the CARD study for olaparib versus cabazitaxel (comparator in a prior taxane use subgroup) and the observational study for olaparib versus docetaxel (comparator in a no prior taxane subgroup). Previous clinical trials and NICE submissions were used to inform AEs for cabazitaxel and docetaxel. Details of the clinical inputs and the approach to select base case are described in the next sections.

## 11.2 Estimating rPFS and OS for olaparib and NHA

This section describes the standard process for selecting rPFS and OS projections for olaparib and NHA based on PROfound patient-level trial data. The curve fitting details below are provided for the following patient populations:

- BRCAm overall population
- BRCAm no prior taxane subgroup
- BRCAm prior taxane subgroup

### 11.2.1 Estimating rPFS

The survival curves for the rPFS were fitted to the patient-level data from PROfound. In line with the primary endpoint of the PROfound trial, rPFS BICR is selected as the base case measure of progression.

It must be noted that in the model, rPFS is capped by OS such that risk of progression or death of patients is less than or equal to the mortality risk.

#### 11.2.1.1 Non-parametric data

Non-parametric data for rPFS for all three populations are presented in Table 2. KM curves are presented in Figure 4.

*Table 2 Total number of events and median time-to-event for rPFS in BRCAm (overall, no prior taxane, and prior taxane) groups.*

| | NHA | Olaparib | Difference (olaparib-NHA) |
|---|---|---|---|
| **BRCAm overall population** | | | |
| Number of patients | 58 | 102 | |
| Total number of events | 51 | 62 | 11 |
| Median time to event (95% CI), months | 2.96 (1.81-3.55) | 9.79 (7.62-11.30) | 6.83 (5.82-7.75) |
| **HR = 0.22 (95% CI: 0.15-0.32)** | | | |
| **BRCA no prior taxane subgroup** | | | |
| Number of patients | 23 | 30 | |
| Total number of events | 17 | 14 | 3 |
| Median time to event (95% CI), months | 3.71 (1.84-6.57) | 13.60 (7.39-NA) | 9.89 (5.55-NA) |
| **HR = 0.17 (95% CI: 0.08-0.36)** | | | |
| **BRCAm prior taxane subgroup** | | | |
| Number of patients | 35 | 72 | |
| Total number of events | 34 | 48 | 14 |
| Median time to event (95% CI), months | 1.91 (1.71-3.52) | 8.97 (7.36-10.84) | 7.06 (5.65-7.32) |
| **HR = 0.19 (95% CI: 0.12-0.32)** | | | |

#### 11.2.1.2 Parametric models

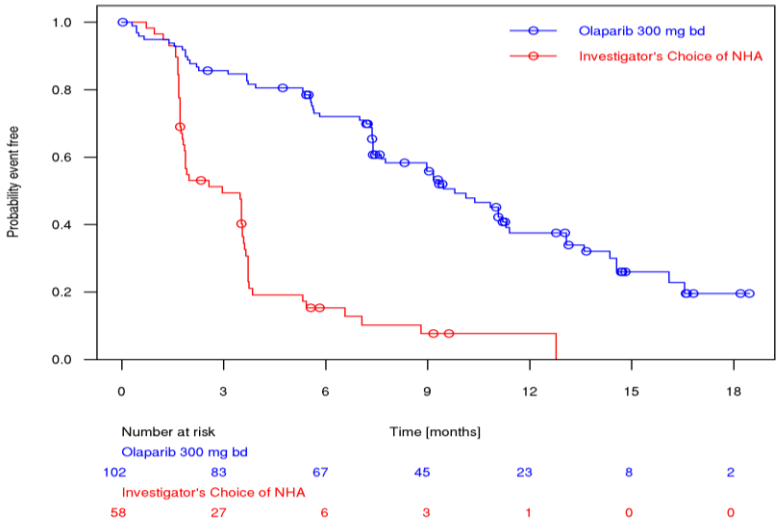
The first step to identifying the most appropriate survival curves for rPFS (BICR) is to compare the KM curves for olaparib and NHA to determine whether they overlap. An overlap between the KM curves would mean that relative hazards change over time and thus the proportional hazards assumption is violated. The rPFS BICR KM curves for olaparib vs. NHA presented in Figure 4 show a clear separation between the rPFS BICR for olaparib and NHA in all three groups.

Next, proportionality between the olaparib and NHA rPFS BICR curves was assessed to determine if individual parametric curves should be fitted for olaparib and NHA, or if the same distribution should be used across treatments. This assessment was done using the Schoenfeld residuals plot for rPFS BICR (Figure 5). A relatively flat line in the Schoenfeld residuals plot (locally estimated scatterplot smoothing [LOESS] solid line in Figure 5) would indicate proportionality between the two curves.

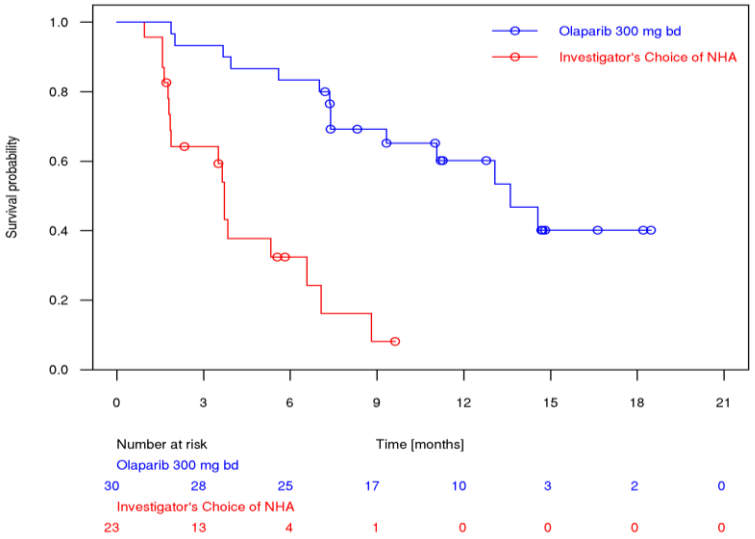
Inspection of the Schoenfeld residual plots for rPFS suggests that treatment effect is likely to vary over time (particularly in BRCAm overall and prior taxane subgroup). This indicates a potential violation of proportional hazards and therefore, individual curves for olaparib and NHA were modelled. In the no prior taxane subgroup, the LOESS line is more flat than in the other groups which may suggest proportional hazard. Yet, for the sake of consistency across all three populations, individual curves for treatment and control were modelled for all subgroups. Separate parametric models of the same type were fitted to each arm as recommended in the NICE DSU technical support document for survival analysis (NICE DSU-TSD 14, 2013).

*Figure 4 A Kaplan Meier curve per arm for rPFS (BICR) in A: BRCAm overall population; B: BRCAm no prior taxane subgroup; C: BRCAm prior taxane subgroup; olaparib vs. NHA*

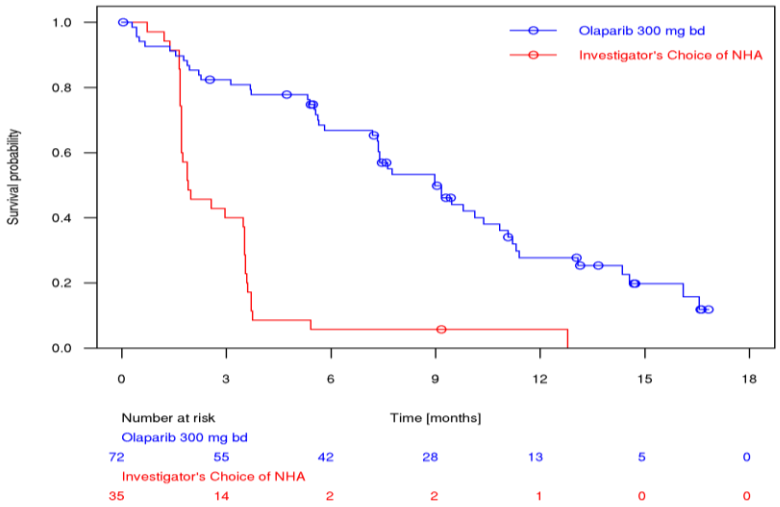
A




B

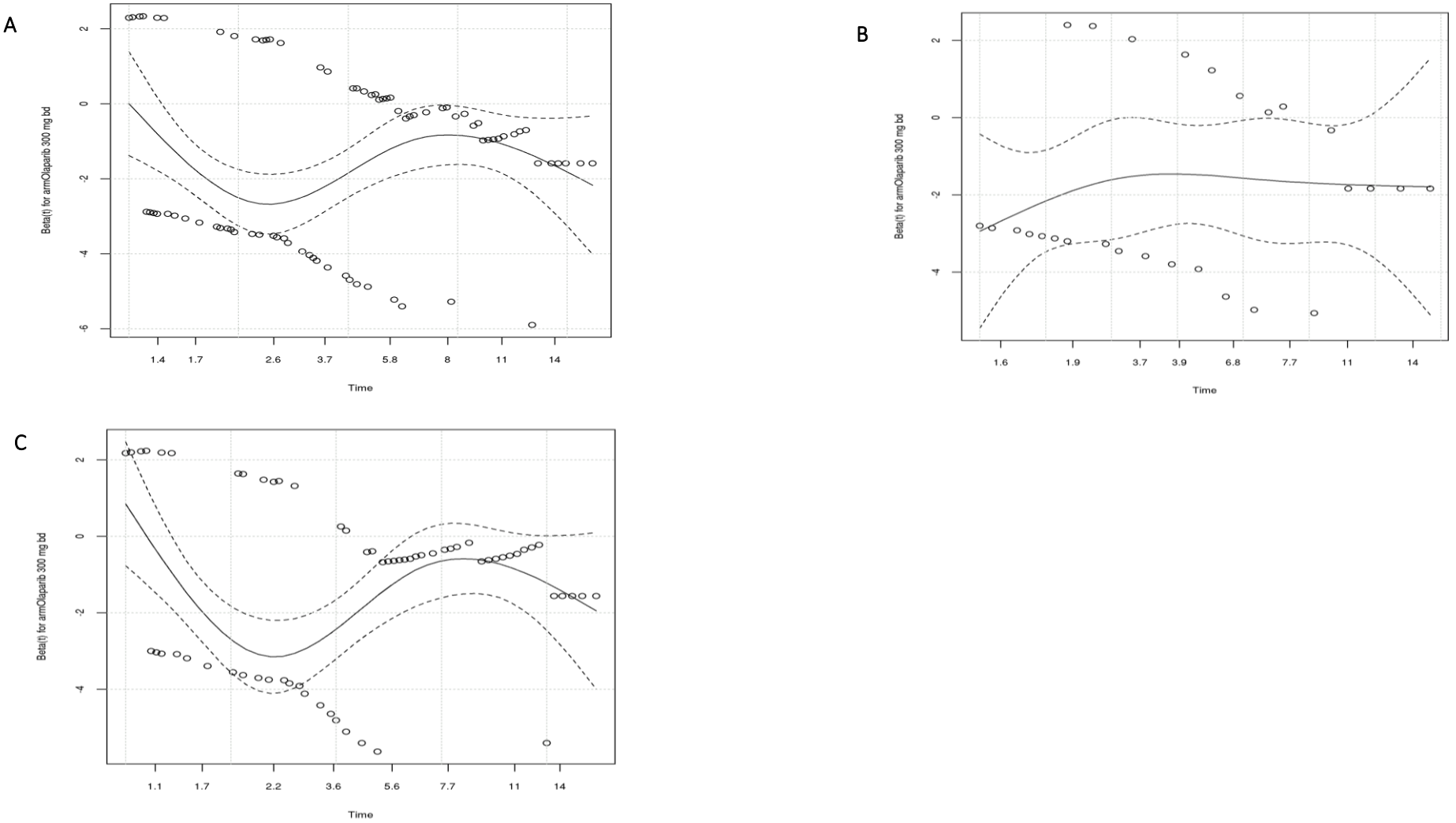



C




Abbreviations: BICR = blinded independent central review; NHA = new hormonal agent; KM = Kaplan-Meier; rPFS = radiographic progression-free survival
Reference: AstraZeneca data on file 2020.

*Figure 5 rPFS BICR Schoenfeld residuals plot in A: BRCAm overall population; B: BRCAm no prior taxane subgroup; C: BRCAm prior taxane subgroup; olaparib vs. NHA*




Abbreviations: BICR = blinded independent central review; NHA = i new hormonal agent; KM = Kaplan-Meier; rPFS = radiographic progression-free survival
Reference: AstraZeneca data on file 2020

The AIC and BIC values for each parametric fitting model for both olaparib and NHA arms for all three groups are shown in Table 3.

*Table 3 Goodness-of-Fit (AIC and BIC) of rPFS BICR for BRCAm (overall, no prior taxane and prior taxane) groups*

| | Olaparib | | NHA | |
|---|---|---|---|---|
| **BRCAm overall population** | | | | |
| **Model** | **AIC** | **BIC** | **AIC** | **BIC** |
| Exponential | 448.99 | 451.61 | 238.89 | 240.95 |
| Weibull | **444.67** | **449.92** | 228.93 | 233.05 |
| Lognormal | 456.52 | 461.77 | **213.17** | **217.29** |
| Log-logistic | 450.75 | 456.00 | **213.86** | **217.98** |
| Gompertz | **442.53** | **447.78** | 238.63 | 242.75 |
| Generalized Gamma | **444.60** | **452.47** | **209.85** | **216.03** |
| **BRCA no prior taxane subgroup** | | | | |
| Exponential | 116.02 | 117.42 | 91.82 | 92.95 |
| Weibull | **114.81** | **117.62** | 89.26 | 91.53 |
| Lognormal | **114.61** | **117.41** | **86.75** | **89.02** |
| Log-logistic | **114.72** | **117.52** | **87.96** | **90.23** |
| Gompertz | 115.87 | 118.67 | 91.57 | 93.84 |
| Generalized Gamma | 116.54 | 120.75 | **88.13** | **91.54** |
| **BRCA prior taxane subgroup** | | | | |
| Exponential | 329.73 | 332.00 | 145.76 | 147.31 |
| Weibull | **327.27** | **331.82** | 139.03 | 142.14 |
| Lognormal | 338.61 | 343.16 | **124.58** | **127.69** |
| Log-logistic | 334.53 | 339.08 | **122.71** | **125.82** |
| Gompertz | **324.04** | **328.59** | 146.86 | 149.97 |
| Generalized Gamma | **325.98** | **332.81** | **122.74** | **127.40** |

The best three fits based on statistical goodness-of-fit are:

### BRCAm overall population

Olaparib: Gompertz, Generalized gamma, Weibull
NHA: Generalized gamma, Lognormal, Log-logistic

### BRCAm no prior taxane subgroup

Olaparib: Lognormal, Log-logistic, Weibull
NHA: Lognormal, Log-logistic, Generalized gamma

### BRCAm prior taxane subgroup

Olaparib: Gompertz, Generalized gamma, Weibull
NHA: Log-logistic, Generalized gamma, Lognormal

The fitted curves along with KM data for BRCAm overall, no prior taxane and prior taxane subgroup are shown in Figure 6, Figure 10, and Figure 14, respectively.

### 11.2.1.3 BRCAm overall population

*Figure 6 Parametric models plotted with the KM data in BRCAm overall population*

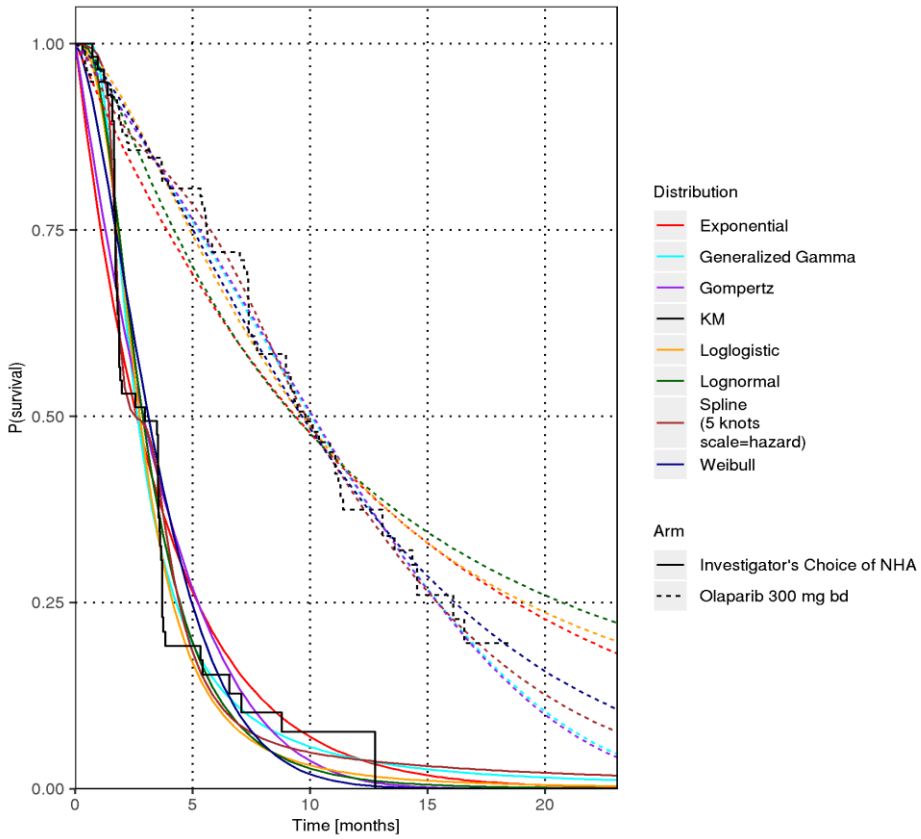
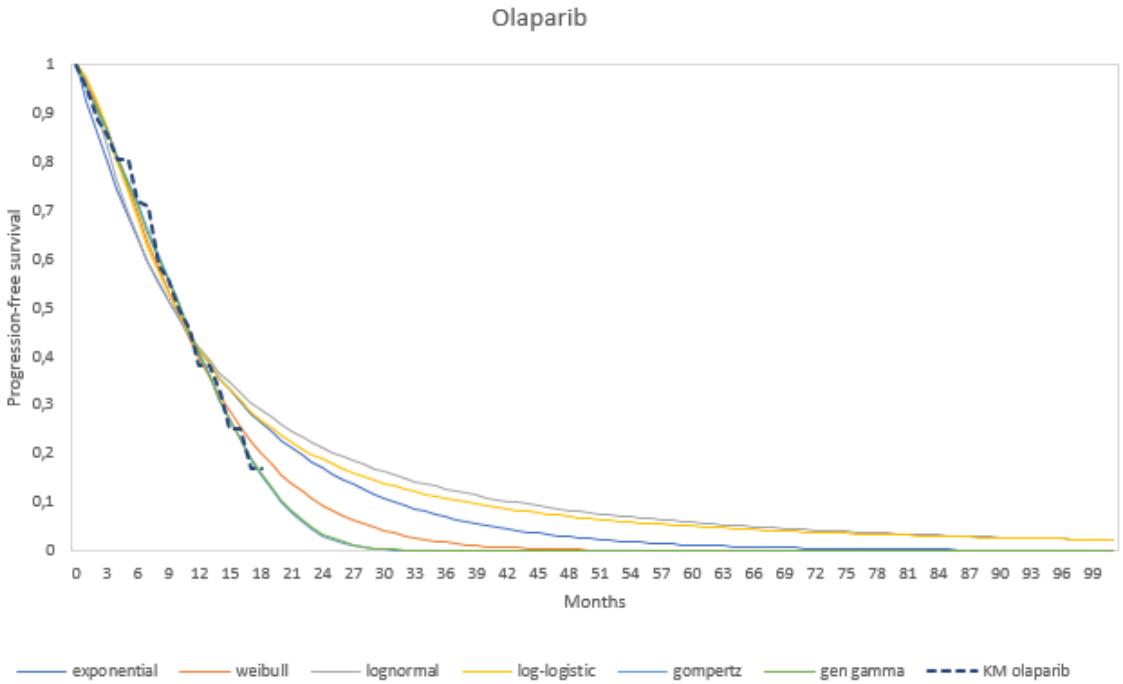
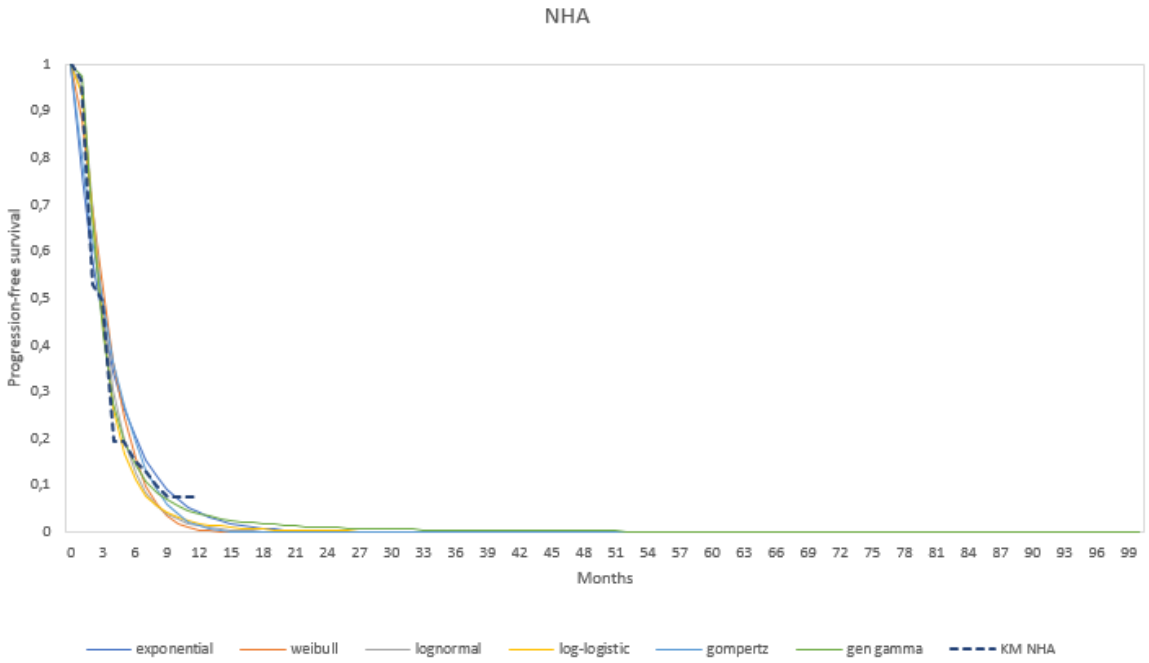



*Figure 7 Long-term projections of rPFS BICR for olaparib in BRCAm overall population*




Abbreviations: BICR = blinded independent central review; NHA = new hormonal agent; KM = Kaplan-Meier; rPFS = radiographic progression-free survival

*Figure 8 Long-term projections of rPFS BICR for NHA in BRCAm overall population*




Abbreviations: BICR = blinded independent central review; NHA = new hormonal agent; KM = Kaplan-Meier; rPFS = radiographic progression-free survival

Based on visual inspection of how well the parametric models fit the plotted KM curves from the trial (Figure 6), Weibull, Gompertz, and Generalized gamma seem to provide the best fit to the KM for olaparib. For NHA, most of the parametric models showed a relatively good data fit.

Based on the inspection of the long-term trends estimated by the parametric models (Figure 7 and Figure 8Figure ), Loglogistic, Lognormal, and Exponential functions seem to overpredict the long-term PFS in the olaparib arm. Based on consultation with AZ's medical advisors, such a long time in a progression-free state is not expected in the mCRPC setting.

Although Generalized gamma function seem to provide a good statistical fit to the KM data in both arms, this function is prone to extreme parameterizations and instability of convergence and tend to produce unrealistic tails (as illustrated in Figure 8 for the NHA arm). For this reason, the Generalized gamma function was not used in the base case analysis. Although Gompertz function did not show the best statistical fit in the NHA arm, it was deemed to provide clinically plausible long-term extrapolations. As discussed above, parametric models of the same type were chosen for both arms.

**Based on visual inspection, assessment of statistical fits and clinical expectations regarding long term progression risk for patients on NHA, a Gompertz distribution is selected for both olaparib and NHA rPFS in the base case.**

Alternative parametric functions are explored in scenario analyses. The Gompertz distribution fitted to the KM data in the trial is presented in Figure 9. Parameters for the Gompertz distribution used in the base case is presented in Table 4.

*Figure 9 Best fitting function (Gompertz) for PFS vs. KM data in BRCAm overall population*

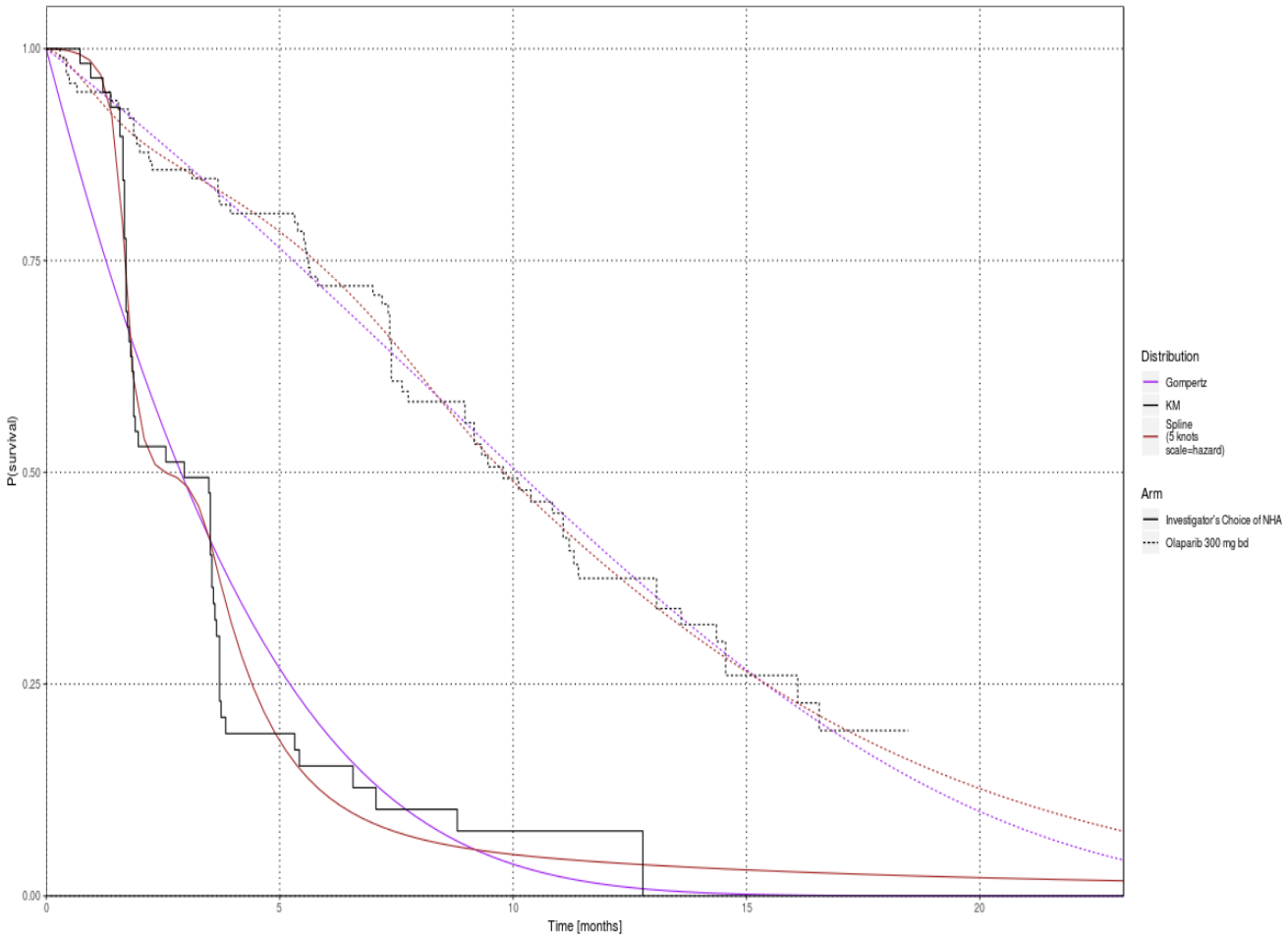



*Table 4 Parameters for the Gompertz distribution fitted to PFS in BRCAm overall population*

| Variable | Estimate | L95% | U95% |
|---|---|---|---|
| **NHA** | | | |
| shape | 0.080559 | -0.019564 | 0.18068 |
| rate | 0.21373 | 0.14215 | 0.32135 |
| **Olaparib** | | | |
| shape | 0.086762 | 0.029827 | 0.1437 |
| rate | 0.04285 | 0.026692 | 0.068789 |

### 11.2.1.4 BRCAm no prior taxane subgroup

*Figure 10 Parametric models plotted with the KM data in BRCAm no prior taxane subgroup*

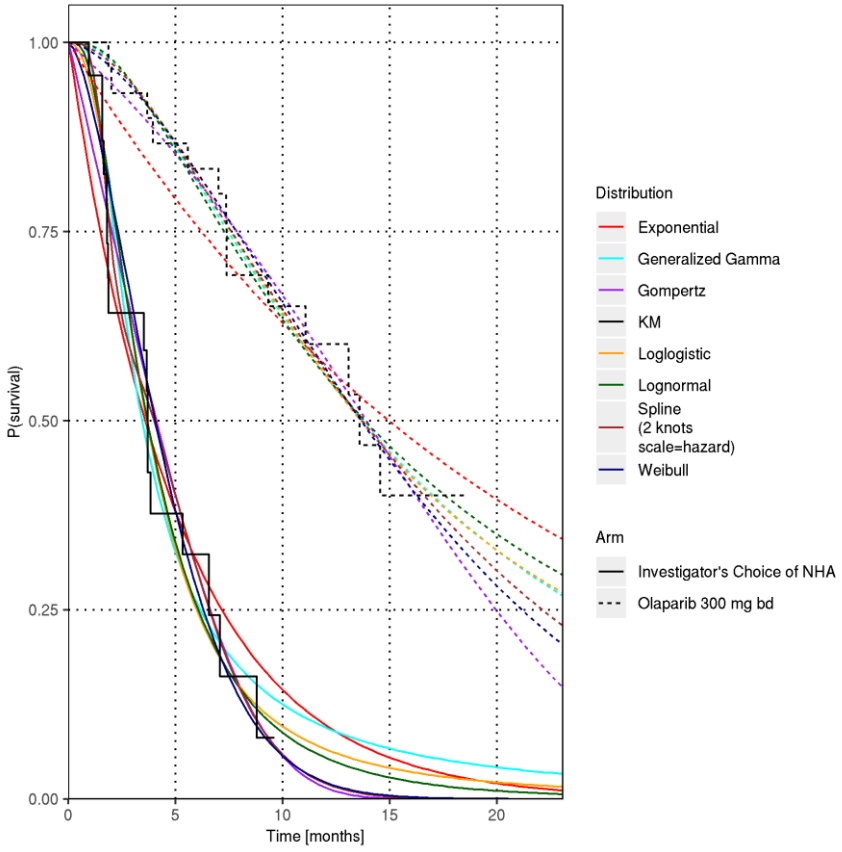
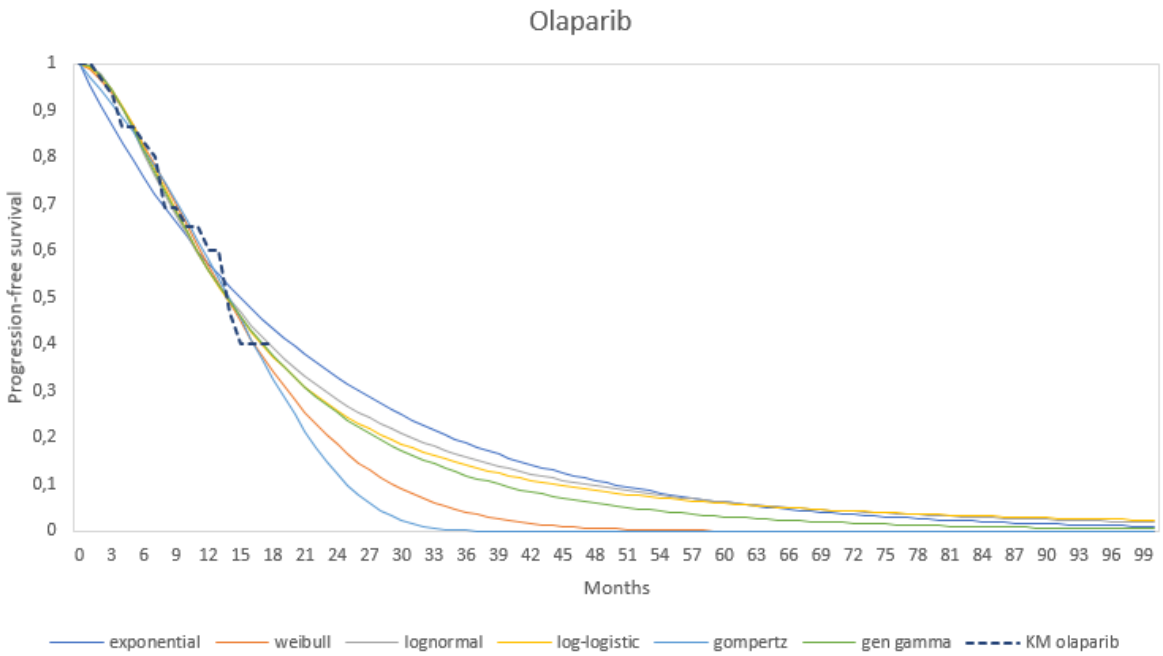
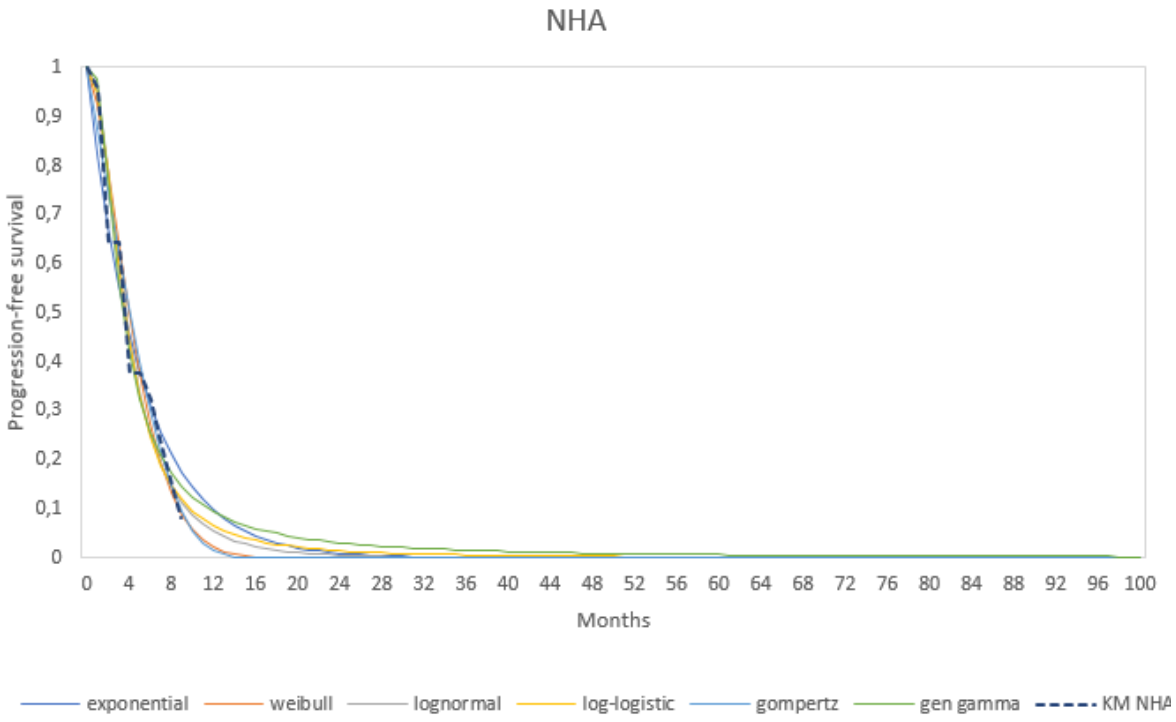



*Figure 11 Long-term projections of rPFS BICR for olaparib in BRCAm no prior taxane subgroup*




Abbreviations: BICR = blinded independent central review; NHA = new hormonal agent; KM = Kaplan-Meier; rPFS = radiographic progression-free survival

*Figure 12 Long-term projections of rPFS BICR for NHA in BRCAm no prior taxane subgroup*




Abbreviations: BICR = blinded independent central review; NHA = new hormonal agent; KM = Kaplan-Meier; rPFS = radiographic progression-free survival

Based on visual inspection of the parametric models plotted with the KM data (Figure 10), Weibull and Gompertz are the best fit to the KM for both olaparib and NHA.

Based on the inspection of the long-term trends estimated by the parametric models (Figure 11 and Figure 12) both Weibull and Gompertz provided reasonable PFS estimates and reflected the shape of the KM curves in both arms.

**Based on visual inspection, assessment of statistical fits and clinical expectations regarding long term progression risk for patients on NHA, a Gompertz distribution is selected for both olaparib and NHA rPFS in the base case.**

Alternative parametric functions are explored in scenario analyses. The Gompertz distribution fitted to the KM data in the trial is presented in Figure 13. Parameters for the Gompertz distribution used in the base case is presented in Table 5.

*Figure 13 Best fitting function (Gompertz) for PFS vs. KM data in BRCAm no prior taxane subgroup*

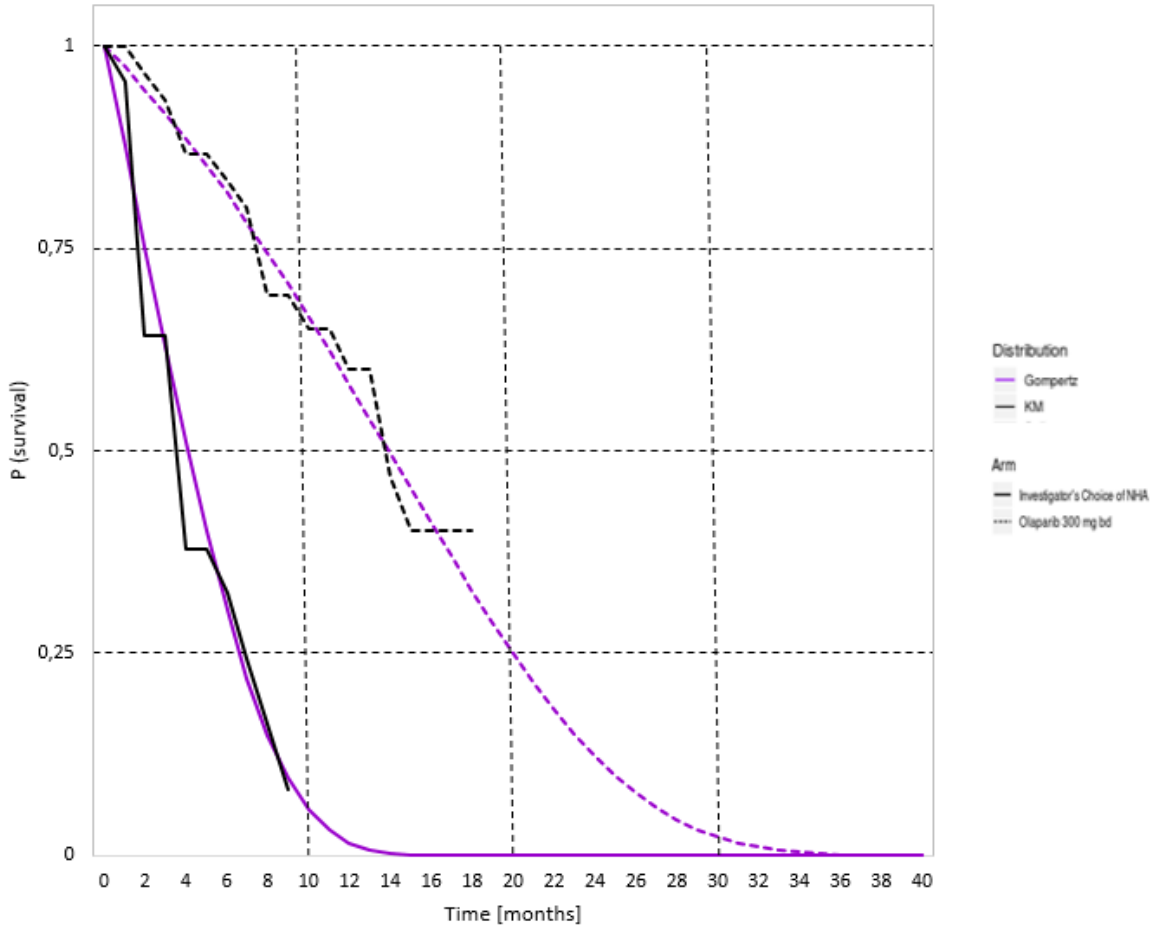



*Table 5 Parameters for the Gompertz distribution fitted to PFS in BRCAm no prior taxane subgroup*

| Variable | Estimate | L95% | U95% |
|---|---|---|---|
| NHA | | | |
| shape | 0.15324 | -0.038757 | 0.34523 |
| rate | 0.12131 | 0.053393 | 0.27563 |
| **Olaparib** | | | |
| shape | 0.088323 | -0.026953 | 0.2036 |
| rate | 0.025333 | 0.0090341 | 0.071037 |

### 11.2.1.5 BRCAm prior taxane subgroup

*Figure 14 Parametric models plotted with the KM data in BRCAm prior taxane subgroup*

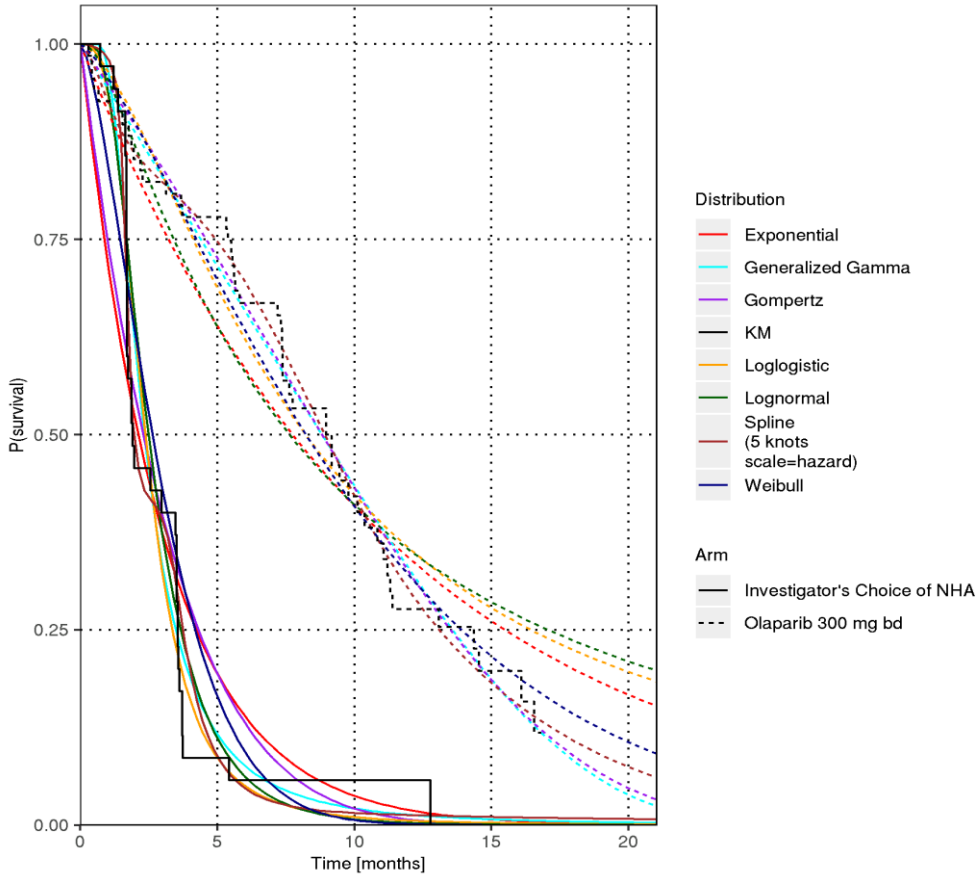
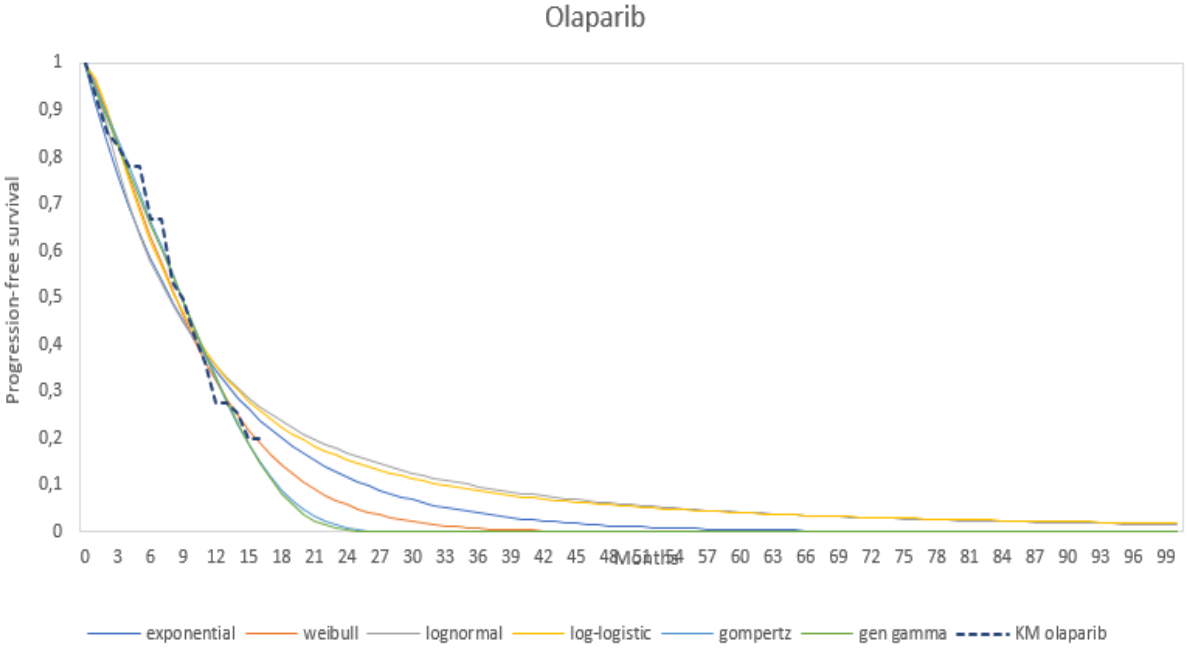
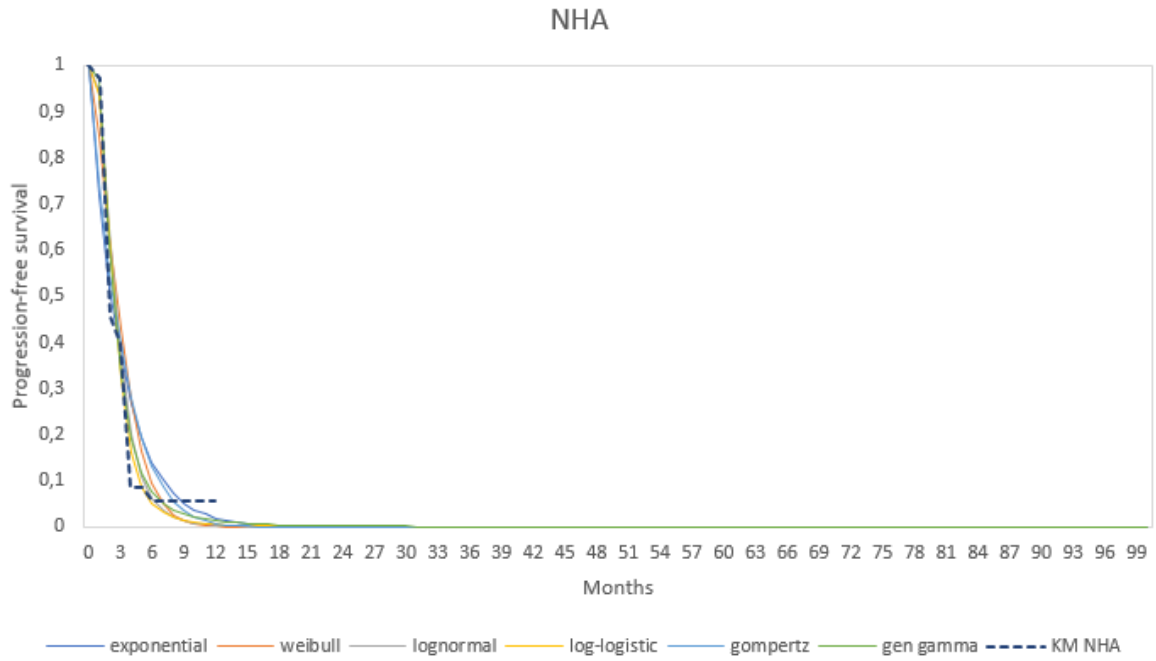



*Figure 15 Long-term projections of rPFS BICR for olaparib in BRCAm prior taxane subgroup*




Abbreviations: BICR = blinded independent central review; NHA = new hormonal agent; KM = Kaplan-Meier; rPFS = radiographic progression-free survival

*Figure 16 Long-term projections of rPFS BICR for NHA in BRCAm prior taxane subgroup*




Abbreviations: BICR = blinded independent central review; NHA = new hormonal agent; KM = Kaplan-Meier; rPFS = radiographic progression-free survival

Based on visual inspection of the parametric models plotted with the KM data (Figure 14), Weibull, Gompertz, and Generalized gamma are the best fit to the KM for both olaparib. For NHA, Loglogistic, Lognormal, and Generalized gamma seem to provide the best visual fit to the KM data.

Based on the inspection of the long-term projections (Figure 15) Weibull, Gompertz, and Generalized gamma provided reasonable PFS estimates and depicted a trend observed in the KM data in the olaparib arm. In the NHA arm (Figure 16), all parametric models showed a relatively good visual fit.

**Based on visual inspection, assessment of statistical fits and clinical expectations regarding long term progression risk for patients on NHA, a Gompertz distribution is selected for both olaparib and NHA rPFS in the base case.**

Alternative parametric functions are explored in scenario analyses. The Gompertz distribution fitted to the KM data in the trial is presented in Figure 17. Parameters for the Gompertz distribution used in the base case is presented in Table 6.

*Figure 17 Best fitting function (Gompertz) for PFS vs KM data in BRCAm prior taxane subgroup*

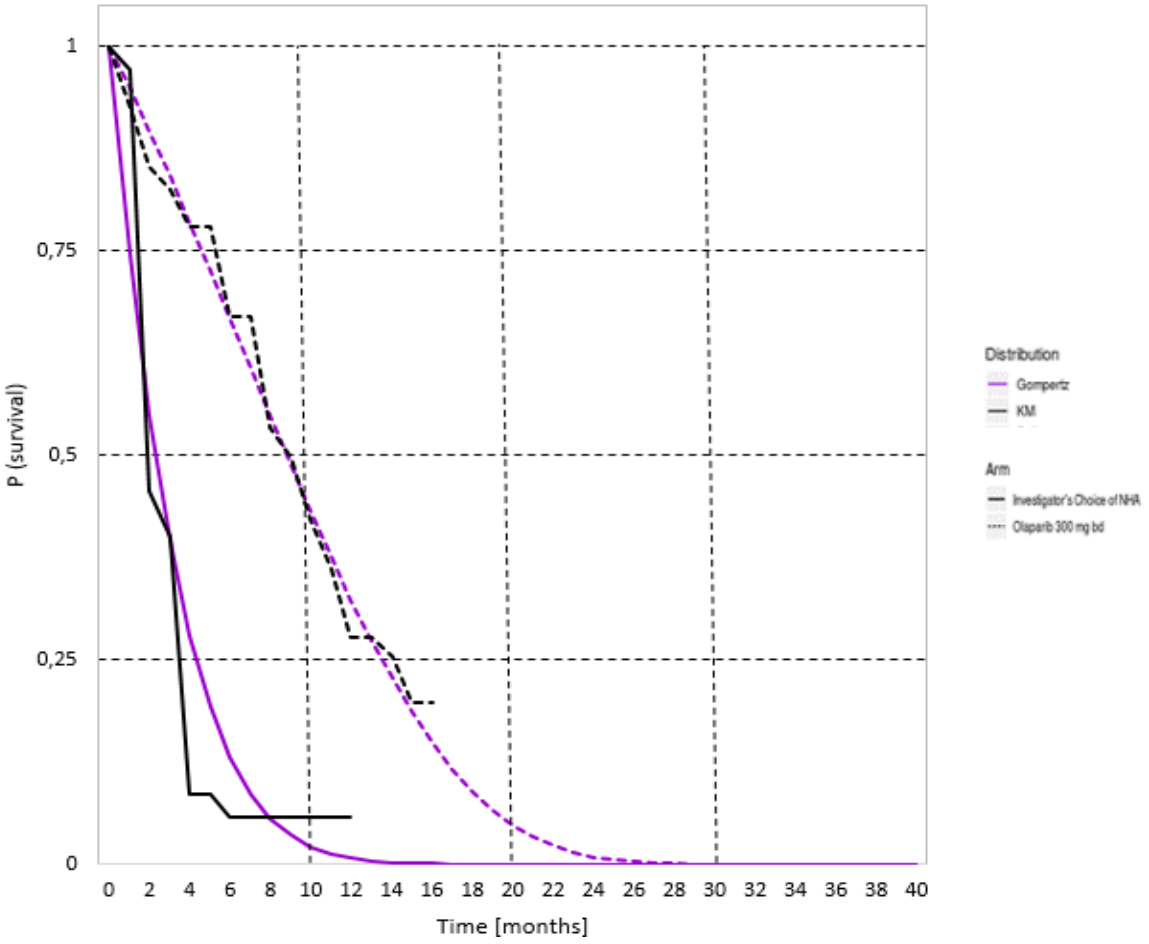



*Table 6 Parameters for the Gompertz distribution fitted to PFS in BRCAm prior taxane subgroup*

| Variable | Estimate | L95% | U95% |
|---|---|---|---|
| NHA | | | |
| shape | 0.058859 | -0.057201 | 0.17492 |
| rate | 0.28243 | 0.17728 | 0.44995 |
| **Olaparib** | | | |
| shape | 0.096727 | 0.030287 | 0.16317 |
| rate | 0.049797 | 0.029079 | 0.085273 |

### 11.2.2 Estimating OS

As discussed earlier, in the PROfound trial, a substantial share of patients in the NHA has crossed-over to olaparib. Given that the OS estimations based on the unadjusted OS would underestimate the "true" OS difference for olaparib compared with NHA, and in order to align with line with clinical practice, the switching adjusted OS option is selected for the base case analysis. This section describes details of the parametric fits for RPSFTM switching adjusted OS. It must be noted that to keep the mortality risk of the eligible patients equivalent to or greater than the general population in all model cycles, OS was capped by general mortality using Danish life tables (Statistics Denmark, 2017).

#### 11.2.2.1 Non-parametric data

Non-parametric data for OS (RPSFTM switching adjusted) for all three populations are presented in Table 7. KM curves are presented in Figure 4.

*Table 7 Total number of events and median time-to-event for OS (RPSFTM switching adjusted) in BRCAm (overall, no prior taxane, and prior taxane) groups*

| | NHA | Olaparib | Difference (olaparib - NHA) |
|---|---|---|---|
| **BRCAm overall population** | | | |
| Number of patients | 58 | 102 | |
| Total number of events | 33 | 53 | 20 |
| Median time to event (95% CI), months | 9.15 (7.56-NA) | 20.11 (17.45-NA) | 10.96 (9.89-NA) |
| **HR = 0.28 (95% CI: 0.1, 0.79)** | | | |
| **BRCA no prior taxane subgroup** | | | |
| Number of patients | 23 | 30 | |
| Total number of events | 10 | 12 | 2 |
| Median time to event (95% CI), months | 8.46 (7.59-NA) | NA (20.83-NA) | NA (13.24-NA) |
| **HR = 0.13 (95% CI: 0.01,1.18)** | | | |
| **BRCAm prior taxane subgroup** | | | |
| Number of patients | 35 | 72 | |
| Total number of events | 23 | 41 | 18 |
| Median time to event (95% CI), months | 8.91 (5.94-11.60) | 17.45 (14.69-26.81) | 8.54 (8.75-15.21) |
| **HR = 0.30 (95% CI: 0.08; 1.08)** | | | |

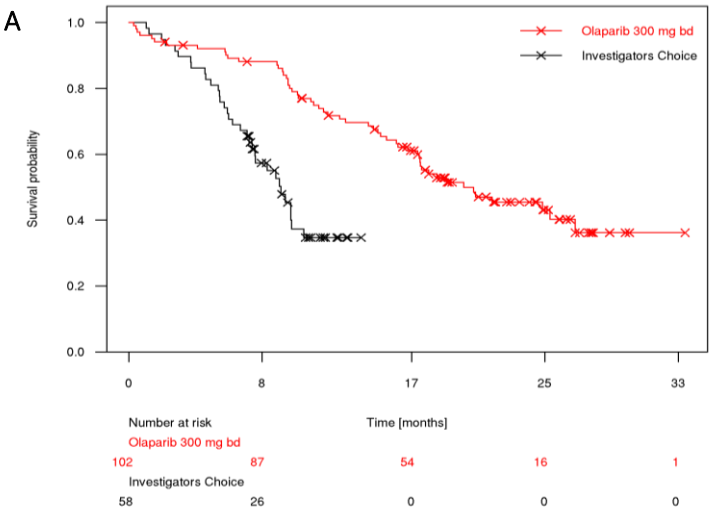
#### 11.2.2.2 Parametric models

Figure 18 compares the RPSFTM switching adjusted OS KM curves for olaparib vs. NHA for BRCA mutated population from PROfound DCO2 (final OS). As shown in the Figure 18, the KM curves clearly show a separation between olaparib and NHA in all three groups, indicating potential long-term survival gains for olaparib.

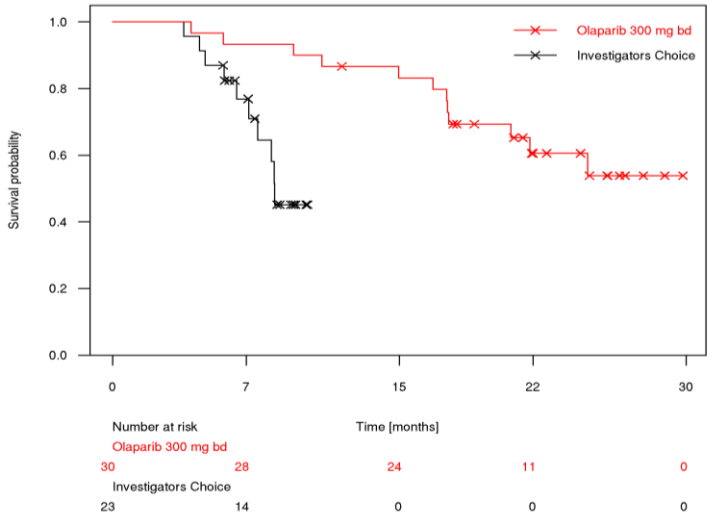
The Schoenfeld residuals plots for the RPSFTM switching adjusted OS in all three groups are presented in Figure 19. The plots indicate that the proportional hazards assumption does not hold as the Schoenfeld residuals plot (LOESS solid line in Figure 19) is not consistently horizontal across the groups. Therefore, individual curves for olaparib and NHA were modelled. As for rPFS, separate parametric models of the same type are fitted to each arm as recommended in the NICE DSU technical support document for survival analysis

*Figure 18 Kaplan-Meier curves of RPSFTM switching adjusted OS in A: BRCAm overall population; B: no prior taxane subgroup; C: prior taxane subgroup; olaparib vs. NHA*

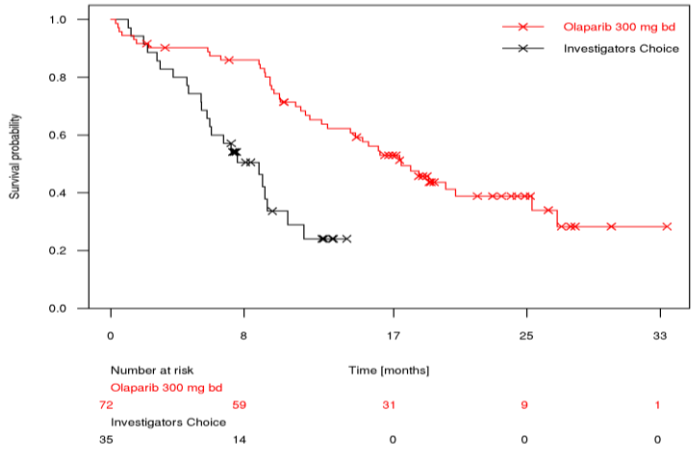
A




B




C




Reference: AstraZeneca data on file 2020.

*Figure 19 RPSFTM switching adjusted OS Schoenfeld residuals plot ; A: BRCAm overall population; B: no prior taxane subgroup; C: prior taxane subgroup: olaparib vs. NHA*

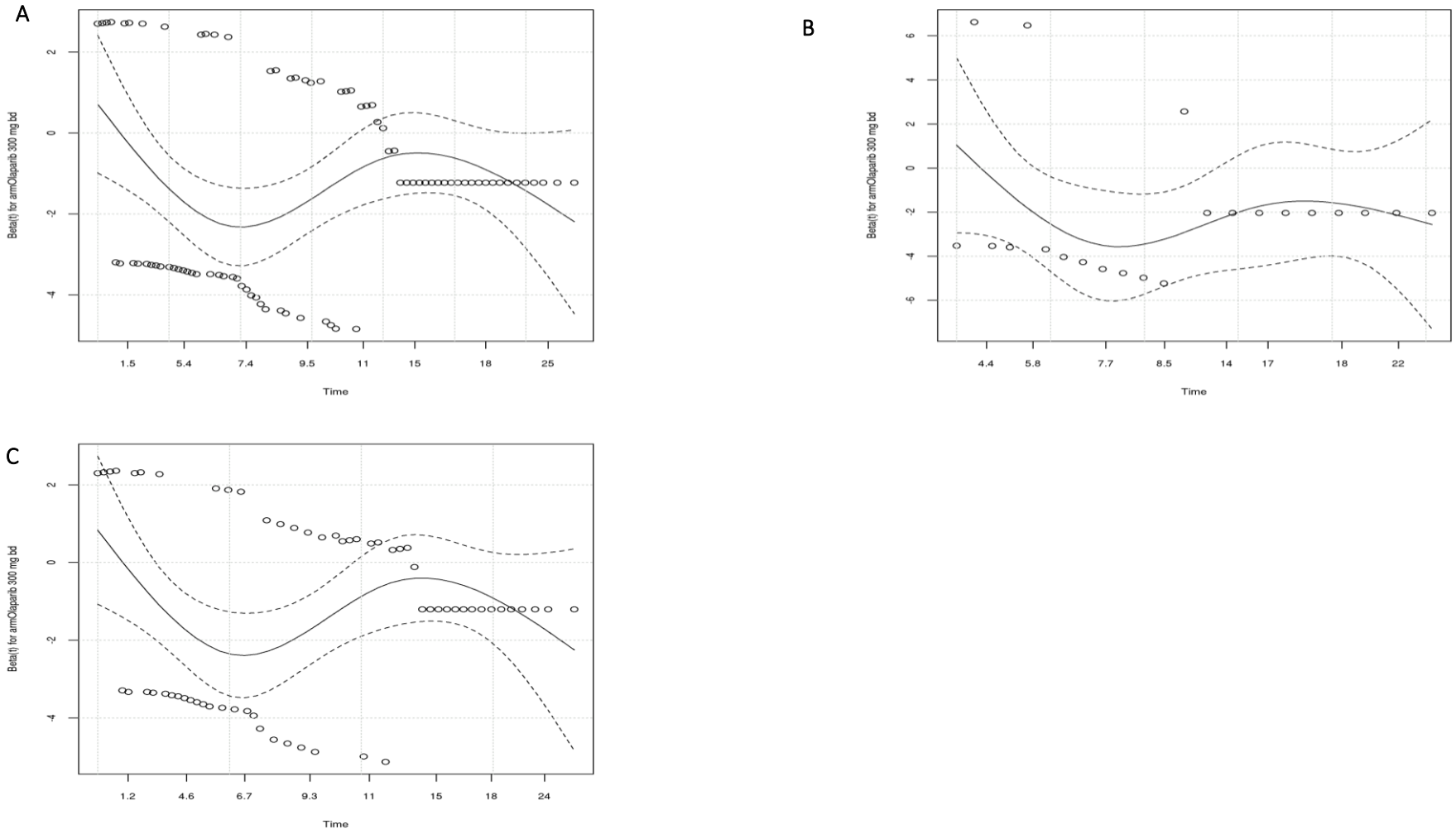


Table 8 presents the AIC/BIC of each parametric fitting model for OS (RPSFTM switching adjusted) for both olaparib and NHA in the BRCAm overall, no prior taxane and prior taxane subgroups.

*Table 8 Goodness-of-Fit (AIC and BIC) of OS (RPSFTM) for BRCAm overall, no prior taxane and prior taxane subgroups*

| | Olaparib | | NHA | |
|---|---|---|---|---|
| **BRCAm overall population** | | | | |
| **Model** | **AIC** | **BIC** | **AIC** | **BIC** |
| Exponential | 474.00 | 476.63 | 240.90 | 242.96 |
| Weibull | **472.86** | **478.11** | **231.59** | **235.71** |
| Lognormal | 484.77 | 490.02 | **232.43** | **236.55** |
| Log-logistic | 476.19 | 481.44 | **231.12** | **235.24** |
| Gompertz | **471.17** | **476.42** | 234.86 | 238.98 |
| Generalized Gamma | **473.5** | **481.38** | 233.29 | 239.48 |
| **BRCA no prior taxane subgroup** | | | | |
| Exponential | 119.84 | 121.24 | 78.67 | 79.80 |
| Weibull | **116.93** | **119.74** | **68.04** | **70.31** |
| Lognormal | **117.14** | **119.94** | **67.34** | **69.61** |
| Log-logistic | **116.90** | **119.71** | **67.63** | **69.9** |
| Gompertz | 117.87 | 120.67 | 69.64 | 71.91 |
| Generalized Gamma | 118.89 | 123.1 | 69.31 | 72.72 |
| **BRCA prior taxane subgroup** | | | | |
| Exponential | **351.90** | **354.17** | 158.88 | 160.44 |
| Weibull | **352.57** | **357.12** | **155.43** | **158.54** |
| Lognormal | 362.09 | 366.64 | **155.66** | **158.77** |
| Log-logistic | 356.02 | 360.57 | **155.39** | **158.5** |
| Gompertz | **351.17** | **355.73** | 157.29 | 160.4 |
| Generalized Gamma | 353.20 | 360.03 | 157.15 | 161.81 |

The best three fits based on statistical goodness-of-fit are:

### BRCAm overall population

Olaparib: Gompertz, Weibull, Generalized gamma
NHA: Log-logistic, Weibull, Lognormal

### BRCAm no prior taxane subgroup

Olaparib: Log-logistic, Weibull, Lognormal
NHA: Lognormal, Log-logistic, Weibull

### BRCAm prior taxane subgroup

Olaparib: Gompertz, Exponential, Weibull
NHA: Log-logistic, Weibull, Lognormal

The fitted curves along with KM data for BRCAm overall, no prior taxane and prior taxane subgroup are shown in Figure 20, Figure 24, and Figure 28, respectively. Long-term projections of (RPSFTM) switching adjusted overall survival for olaparib and NHA are presented in Figure 21-22 for BRCAm overall population, Figures 25-26 for BRCAm no prior taxane subgroup, and Figure 29-30 for BRCAm prior taxane subgroup.

### 11.2.2.3 BRCAm overall population

*Figure 20 Parametric models plotted with the KM data in BRCAm overall population for OS (RPSFTM)*

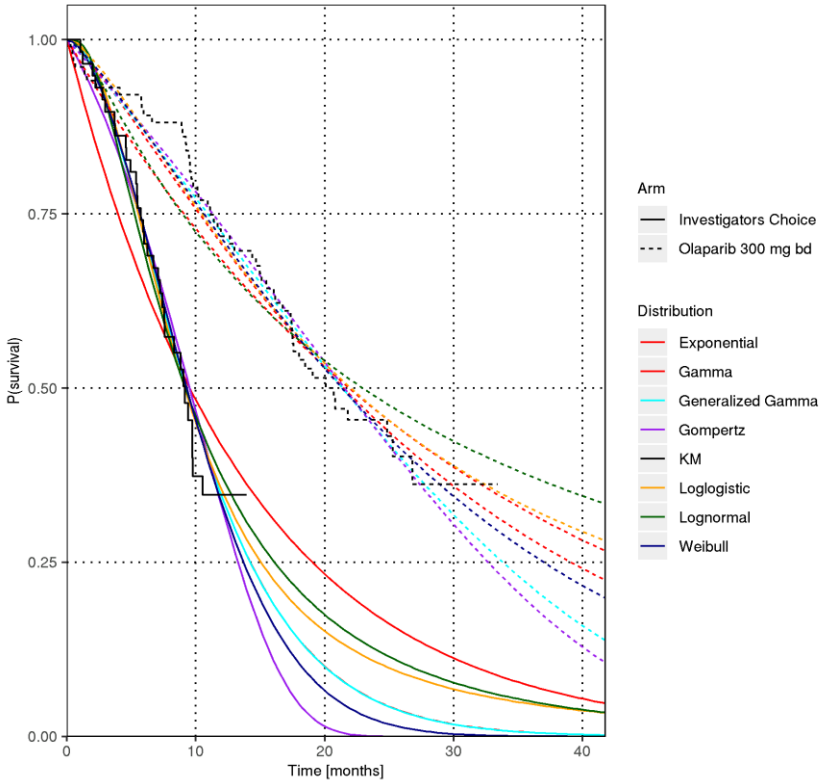
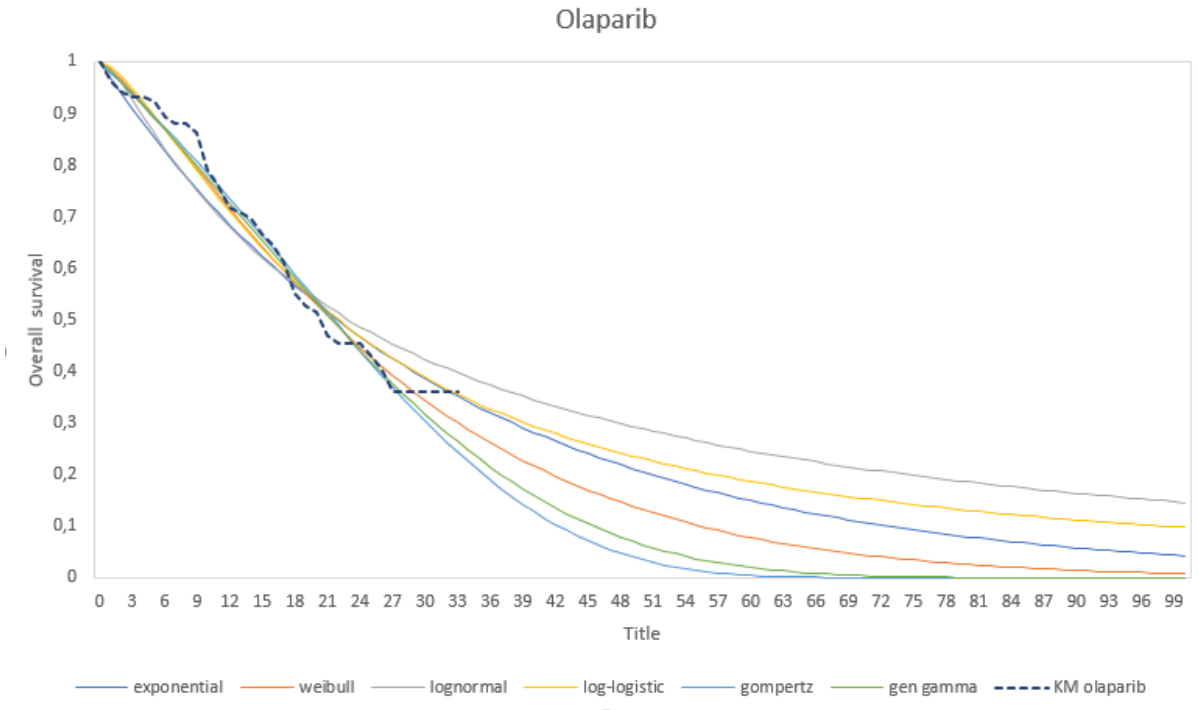
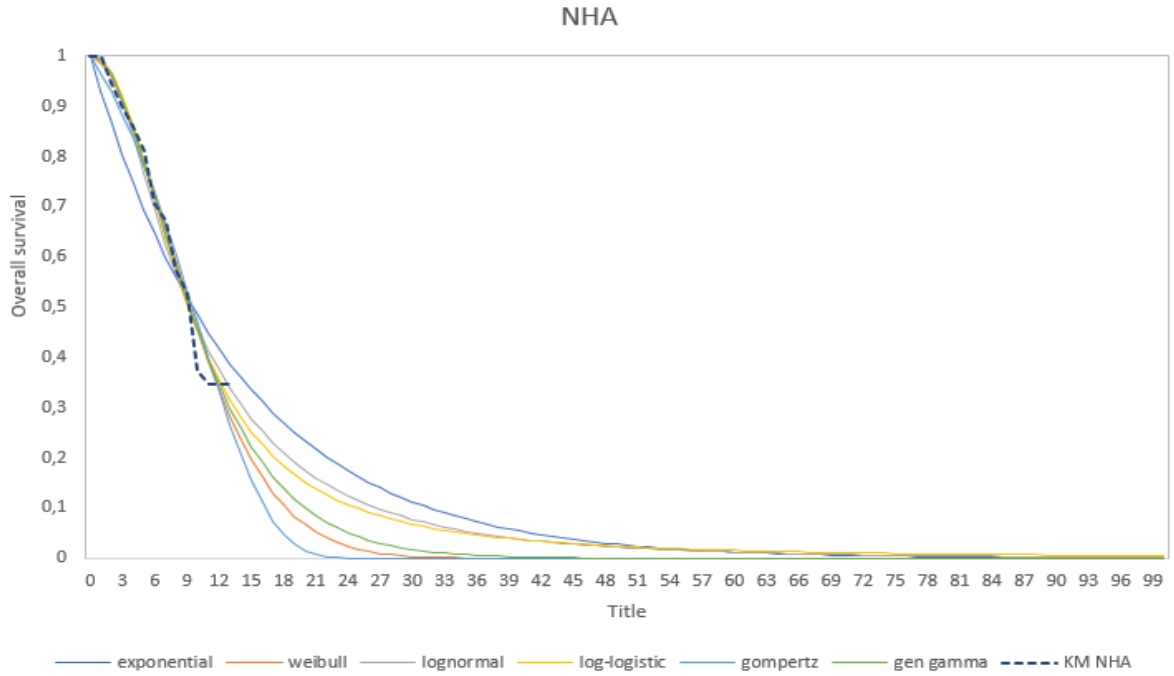



*Figure 21 Long-term projections of OS (RPSFTM switching adjusted) for olaparib in BRCA overall population*




Abbreviations: KM = Kaplan-Meier; OS = overall survival; RPSFTM = rank preserving structural failure time model

*Figure 22 Long-term projections of OS (RPSFTM switching adjusted) for NHA in BRCA overall population*




Abbreviations: NHA = new hormonal agent; KM = Kaplan-Meier; OS = overall survival; RPSFTM = rank preserving structural failure time model

Based on visual inspection, Generalized gamma, Gompertz, and Weibull show best match to the KM data for both olaparib and NHA (Figure 20). Based on the inspection of the long-term projections, Weibull, Gompertz, and Generalized gamma provided clinically reasonable OS estimates for both olaparib (Figure 21) and NHA (Figure 22).

Since Weibull parametric model provides good statistical fit, matches the KM data in both olaparib and NHA arms as well as provides clinically reasonable long-term projections, it is selected to inform the OS in the BRCAm overall population.

**Switching adjusted OS is modelled using a Weibull distribution as it provides reasonable long-term projections, shows a good match to the KM data, and provides good statistical fit.**

Alternative parametric functions are explored in scenario analyses. The Weibull function for OS overlaid with KM data in the is presented in Figure 23. Parameters for the Weibull distribution chosen for the base case is presented in Table 9.

*Figure 23 Best fitting function (Weibull) for OS vs KM data in BRCAm overall population*

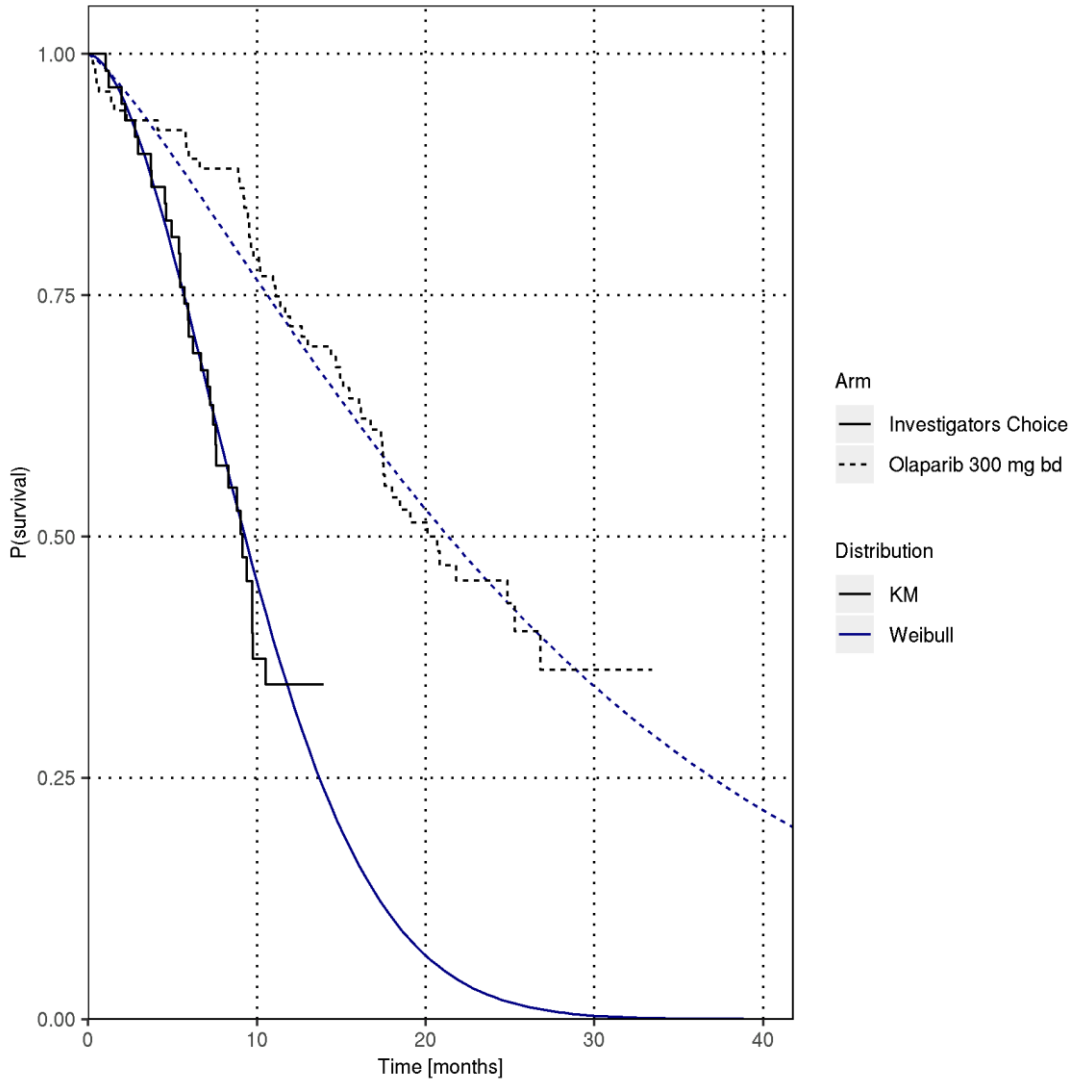



*Table 9 Parameters for the Weibull distribution fitted to OS in BRCAm overall population*

| Variable | Estimate | L95% | U95% |
|---|---|---|---|
| NHA | | | |
| shape | 1.7804 | 1.32 | 2.4014 |
| scale | 11.403 | 9.3324 | 13.934 |
| **Olaparib** | | | |
| shape | 1.2594 | 0.98707 | 1.6068 |
| scale | 28.546 | 22.632 | 36.005 |

### 11.2.2.4 BRCAm no prior taxane subgroup

*Figure 24 Parametric models plotted with the KM data in BRCAm no prior taxane subgroup for OS (RPSFTM switching adjusted)*

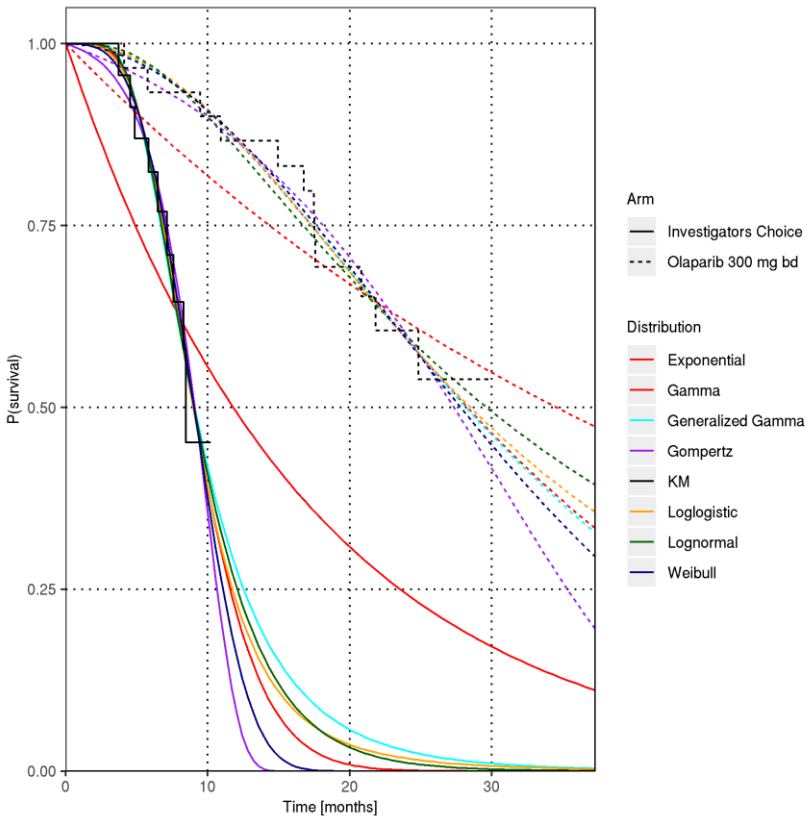
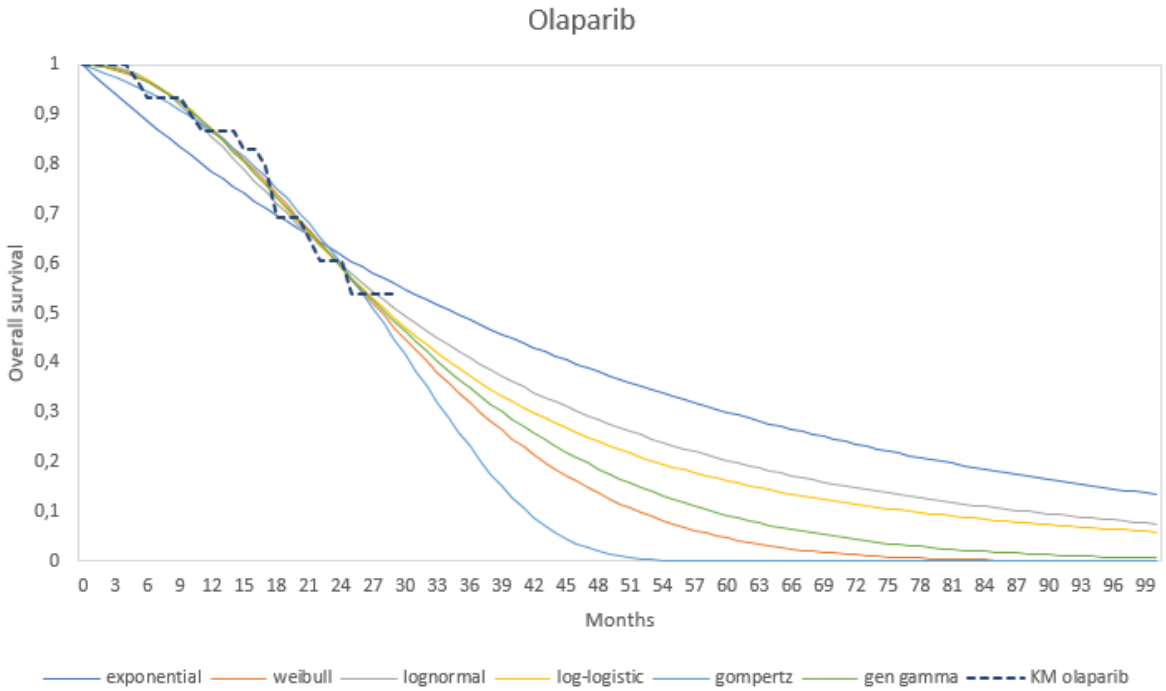
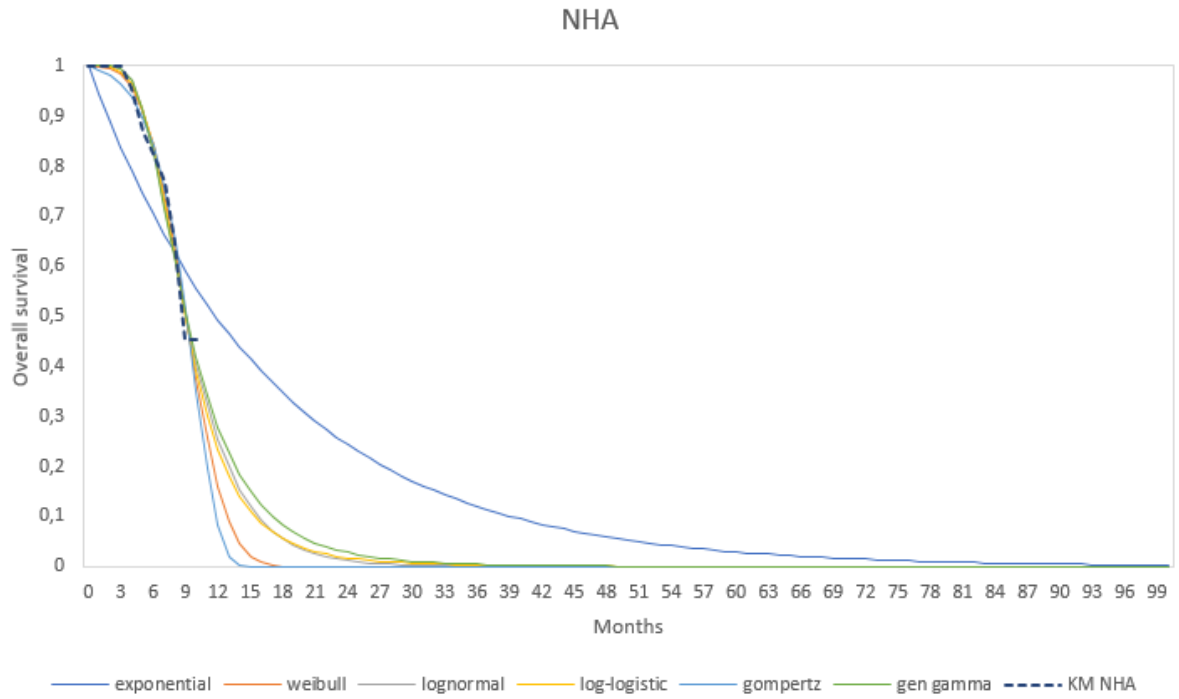



*Figure 25 Long-term projections of OS (RPSFTM switching adjusted) for olaparib in BRCA no prior taxane subgroup*




Abbreviations: KM = Kaplan-Meier; OS = overall survival; RPSFTM = rank preserving structural failure time model

*Figure 26 Long-term projections of OS (RPSFTM switching adjusted) for NHA in BRCA no prior taxane subgroup*




Abbreviations: NHA = new hormonal agent; KM = Kaplan-Meier; OS = overall survival; RPSFTM = rank preserving structural failure time model

Based on visual inspection of parametric models fitted with the KM data (Figure 24), all parametric functions, except exponential, fit the KM data in the trial. Based on the inspection of the long-term projections Weibull, Gompertz, and Generalized gamma parametric models provided clinically reasonable OS estimates for both olaparib (Figure 25) and NHA (Figure 26) arms.

Since Weibull parametric model provides good statistical fit, matches the KM data in both olaparib and NHA arms as well as provides clinically reasonable long-term projections, it is selected to inform OS in the BRCAm no prior taxane subgroup.

**Switching adjusted OS is modelled using a Weibull distribution as it provides reasonable long-term projections, shows a good match to the KM data, and provides good statistical fit.**

Alternative parametric functions are explored in scenario analyses. The Weibull function for OS overlaid with KM data in the is presented in Figure 27. Parameters for the Weibull distribution chosen for the base case is presented in Table 10.

*Figure 27 Best fitting function (Weibull) for OS vs KM data in BRCAm no prior taxane subgroup*

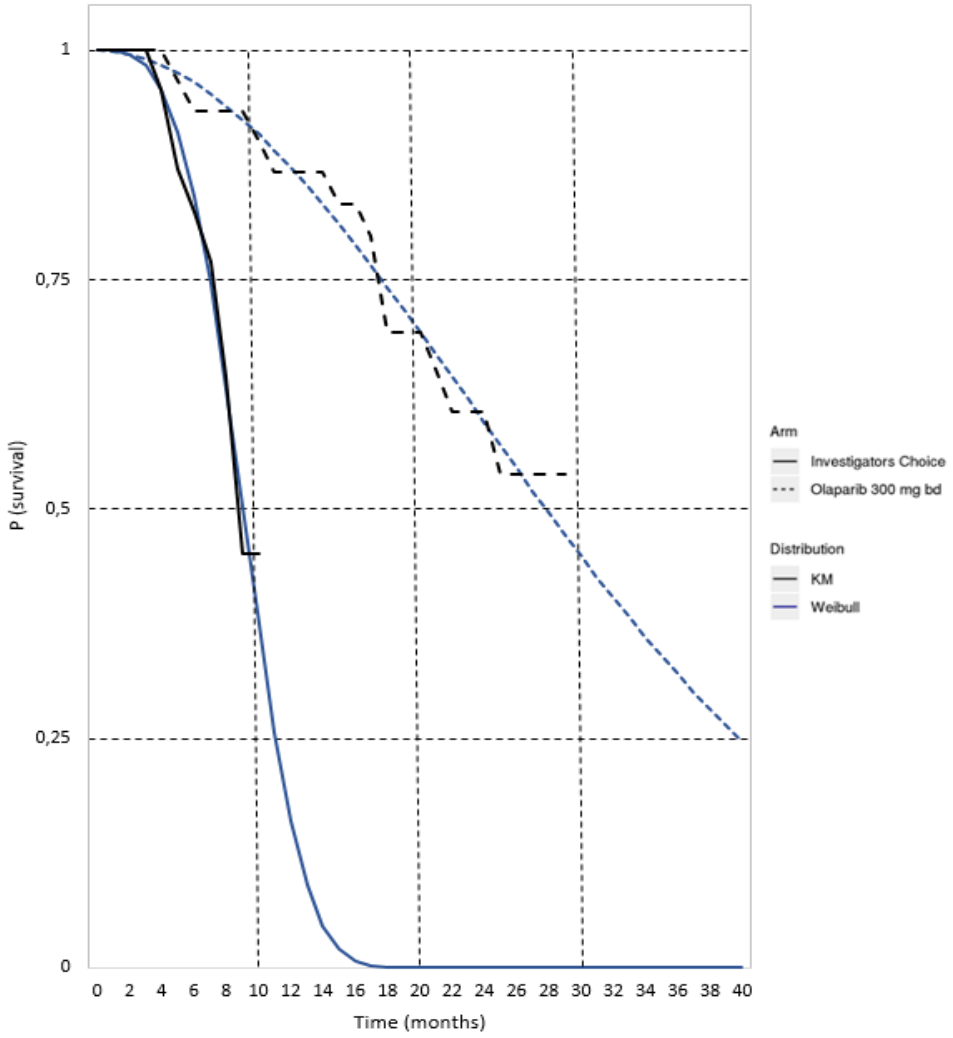



*Table 10 Parameters for the Weibull distribution fitted to OS in BRCAm no prior taxane subgroup*

| Variable | Estimate | L95% | U95% |
|---|---|---|---|
| NHA | | | |
| shape | 3.3981 | 2.0023 | 5.7668 |
| scale | 10.049 | 8.196 | 12.32 |
| **Olaparib** | | | |
| shape | 1.9313 | 1.1537 | 3.233 |
| scale | 33.629 | 23.551 | 48.018 |

### 11.2.2.5 BRCAm prior taxane subgroup

*Figure 28 Parametric models plotted with the KM data in BRCAm prior taxane subgroup for OS (RPSFTM switching adjusted)*

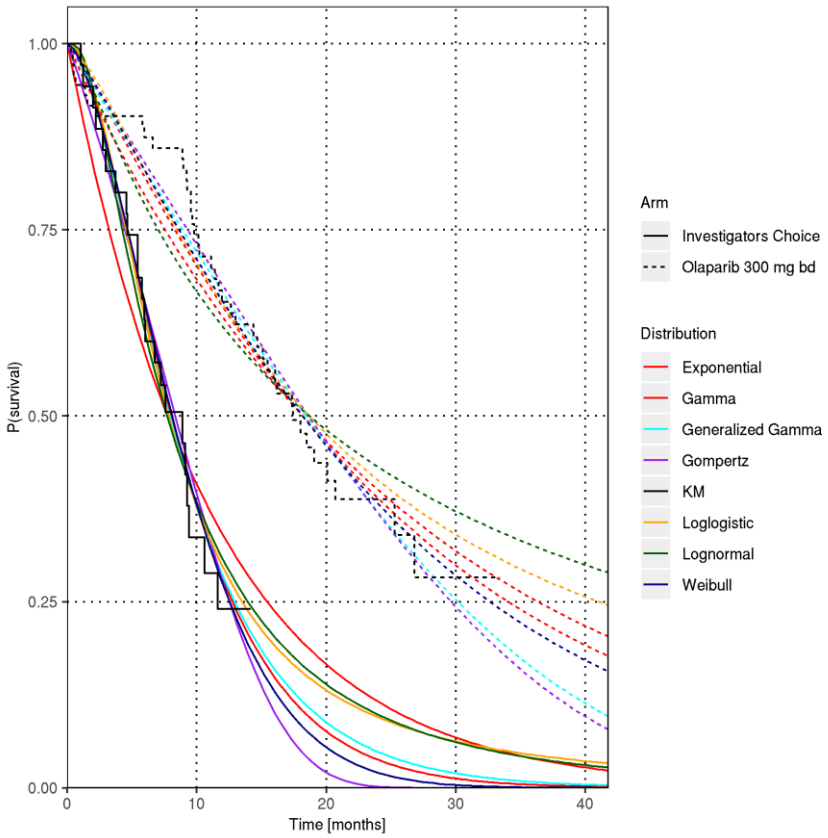
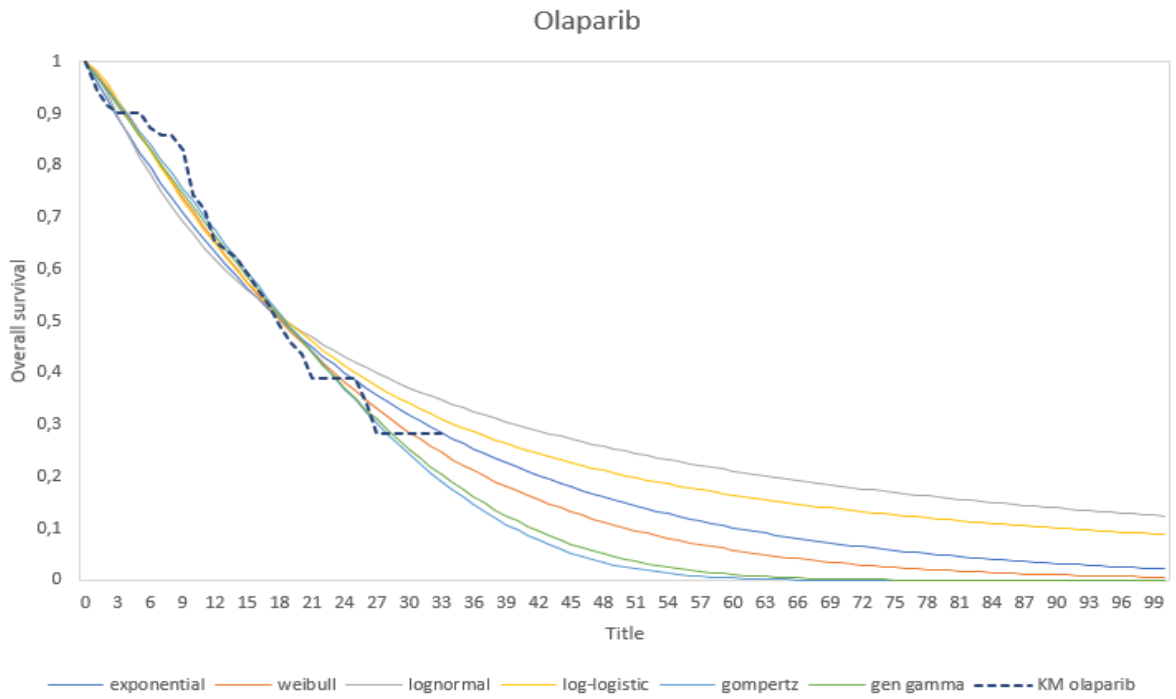
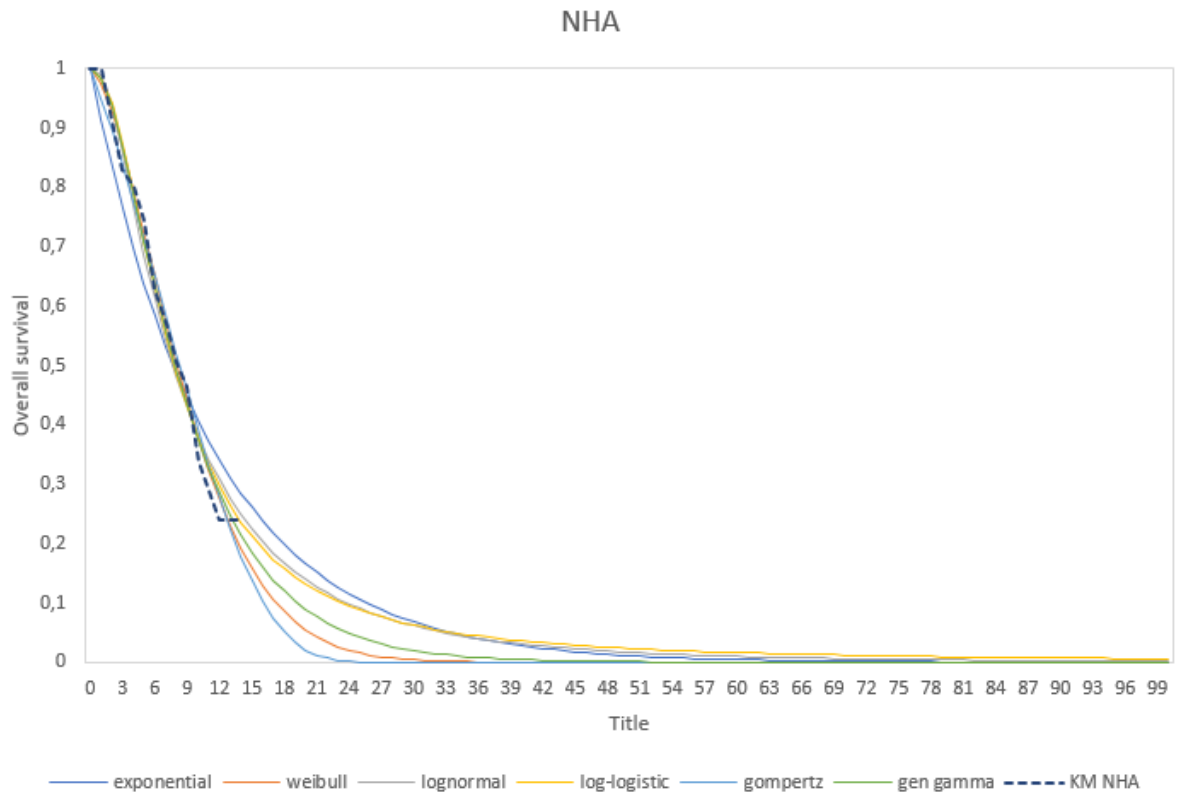



*Figure 29 Long-term projections of OS (RPSFTM switching adjusted) for olaparib in BRCA prior taxane subgroup*




Abbreviations: KM = Kaplan-Meier; OS = overall survival; RPSFTM = rank preserving structural failure time model

*Figure 30 Long-term projections of OS (RPSFTM switching adjusted) for NHA in BRCA prior taxane subgroup*




Abbreviations: NHA = new hormonal agent; KM = Kaplan-Meier; OS = overall survival; RPSFTM = rank preserving structural failure time model

Similar to the other subgroups, Gompertz, Weibull, and Generalized gamma matched the KM data for both olaparib and NHA (Figure 28). These models also provide the most clinically plausible OS estimates for both olaparib (Figure 29) and NHA (Figure 30). Based on the inspection of the long-term projections Weibull, Gompertz, and Generalized gamma provided clinically reasonable OS estimates for both olaparib (Figure 21) and NHA (Figure 22) arms.

Since Weibull parametric model provides good statistical fit, matches the KM data in both olaparib and NHA arms as well as provides clinically reasonable long-term projections, it is selected to inform OS in the BRCAm no prior taxane subgroup.

**Switching adjusted OS is modelled using a Weibull distribution as it provides reasonable long-term projections, shows a good match to the KM data, and provides good statistical fit.**

Alternative parametric functions are explored in scenario analyses. The Weibull function for OS overlaid with KM data in the is presented in Figure 31. Parameters for the Weibull distribution chosen for the base case is presented in Table 11.

*Figure 31 Best fitting function (Weibull) for OS vs KM data in BRCAm prior taxane subgroup*

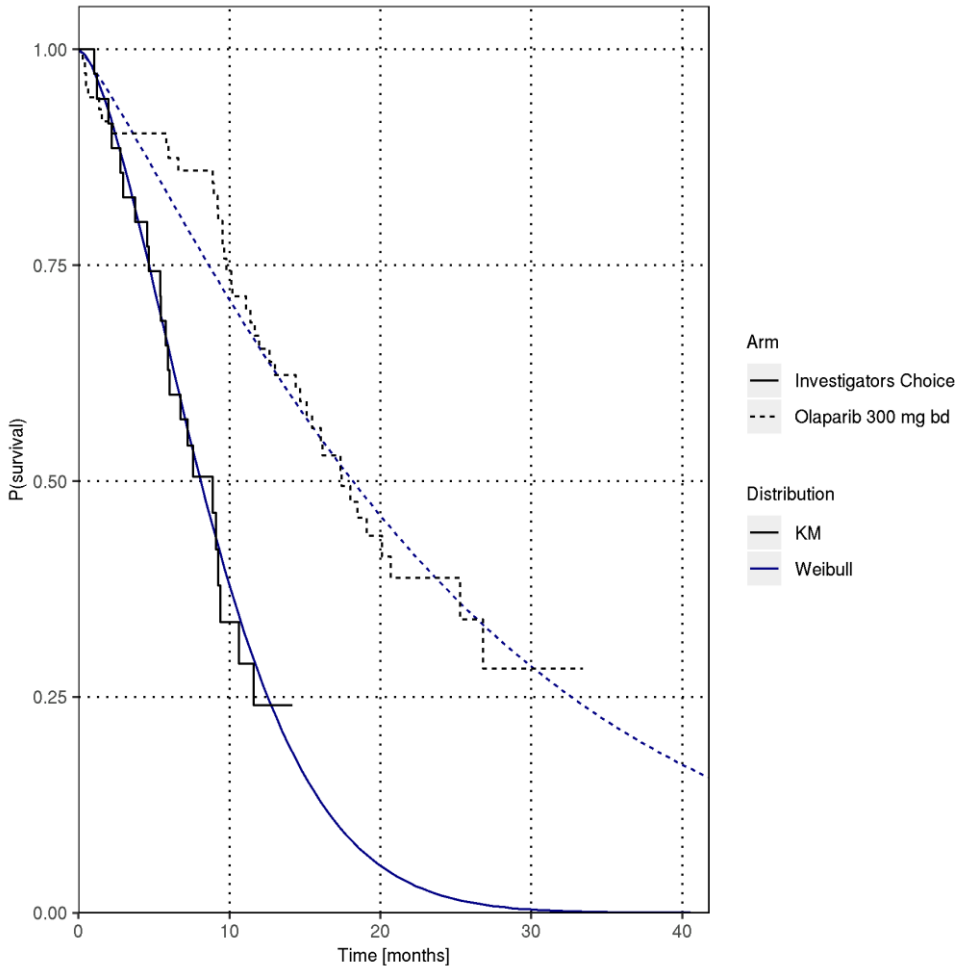



*Table 11 Parameters for the Weibull distribution fitted to OS in BRCAm prior taxane subgroup*

| Variable | Estimate | L95% | U95% |
|---|---|---|---|
| NHA | | | |
| shape | 1.5851 | 1.1157 | 2.2521 |
| scale | 10.198 | 7.8598 | 13.232 |
| **Olaparib** | | | |
| shape | 1.1813 | 0.89792 | 1.5542 |
| scale | 24.771 | 18.875 | 32.508 |

## 11.3 Relative Efficacy (rPFS & OS) for comparators outside the PROfound trial

The relative efficacy for comparators outside of the PROfound trial (docetaxel and cabazitaxel) is established by applying a hazard ratio (HR) to a baseline survival curve for a common comparator. As outlined previously, NHA was a common comparator between the PROfound trial and the observational study (Swami 2020) for the docetaxel comparison and between PROfound and the CARD study (de Wit 2019) for the cabazitaxel comparison.

This approach of informing PFS and OS requires an assumption of proportional hazards between NHA and docetaxel/cabazitaxel. Therefore, a hypothesis of proportional hazards between NHA and cabazitaxel in the CARD study was tested by inspecting the log-cumulative hazards and Schoenfeld plots and conducting Schoenfeld individual tests for both PFS (Figure 32) and OS (Figure 33).

*Figure 32 CARD rPFS: Schoenfeld (left) and log-cumulative hazards (right) plots*

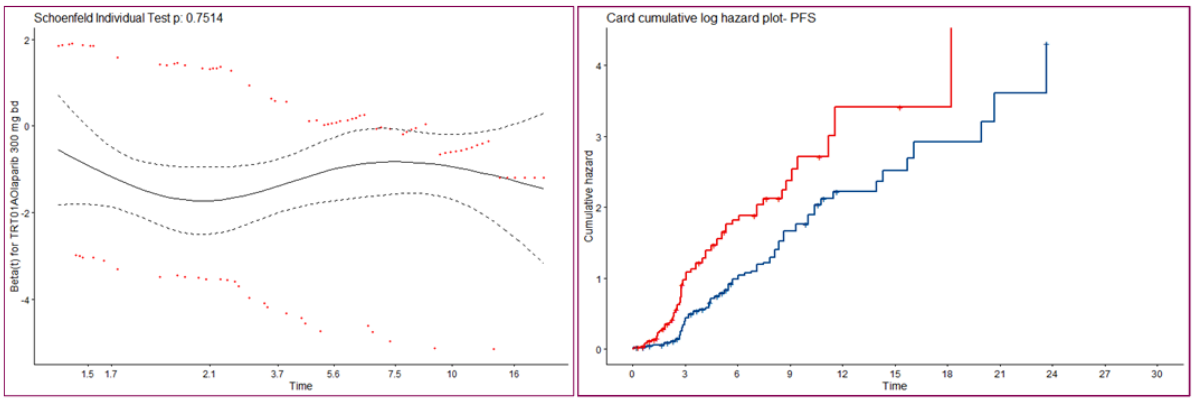
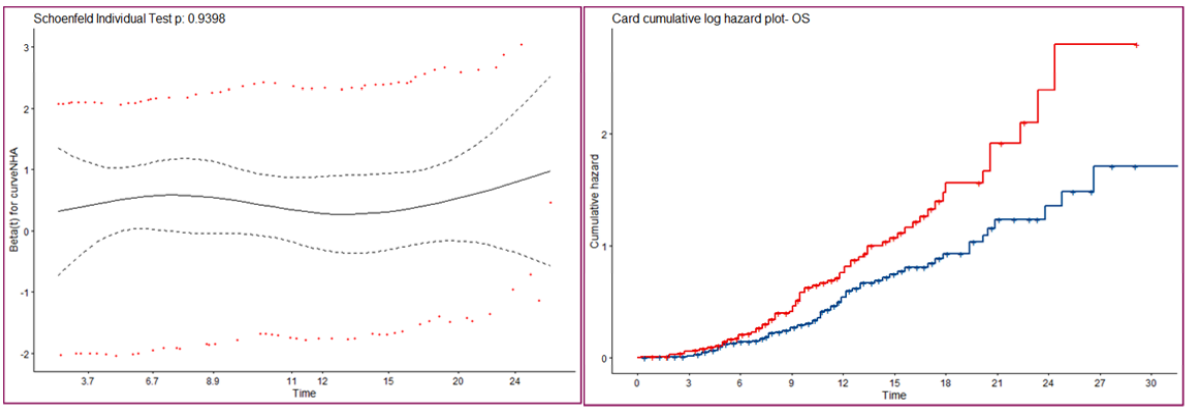



*Figure 33 CARD OS: Schoenfeld (left) and log-cumulative hazards (right) plots*




Visual inspection of the log-cumulative hazards plots for rPFS and OS indicates that proportional hazards assumption holds for both endpoints. This is further confirmed by the Schoenfeld individual tests, which resulted in p-values of 0.75 and 0.94 for PFS and OS, respectively, indicating that there was no evidence against the null hypothesis of proportional hazards at the 95% significance level. Hence, the evidence of proportional hazards across both rPFS and OS endpoints supports the use of constant hazard ratios to generate comparative evidence for olaparib and cabazitaxel. Given similar efficacy profiles between docetaxel and cabazitaxel, same approach was taken for modelling PFS and OS for both taxanes.

### 11.3.1 BRCAm no prior taxane subgroup

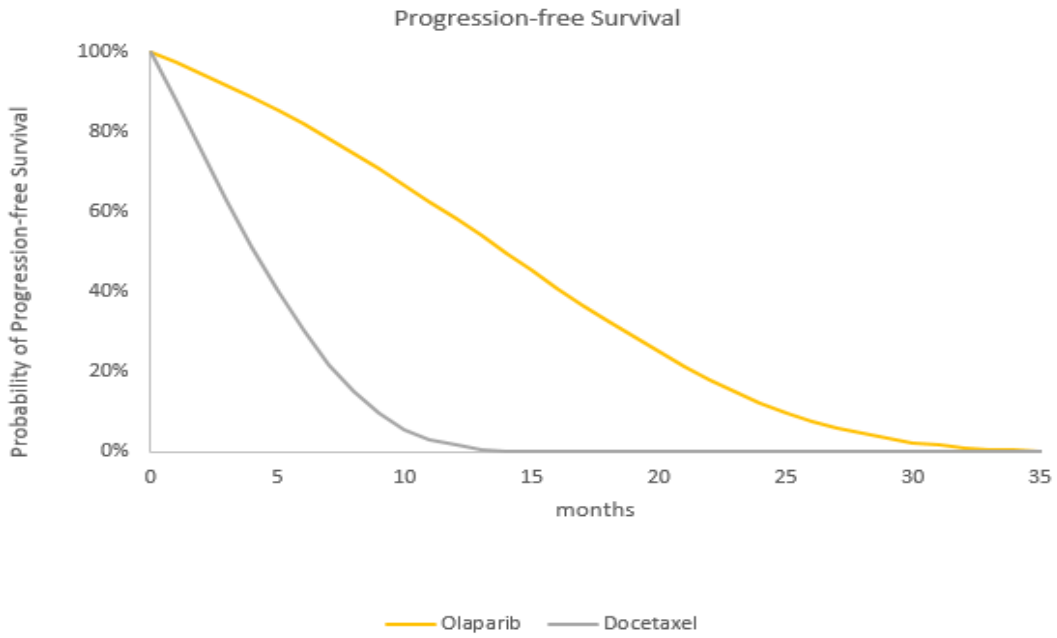
#### Docetaxel (vs. NHA)

For docetaxel, no comparative efficacy data vs. NHA in the target population was found in the clinical systematic literature review. However, as discussed earlier, a real-world evidence study based on Flatiron data[1], published at ASCO 2020, assessed docetaxel compared with NHA in patients with metastatic prostate cancer previously treated with an NHA at centers in the United States (Swami 2020). Given that no clinical trials in the post-NHA mCRPC setting were identified, these data are considered the best available observational data to inform the comparative effectiveness of docetaxel compared with NHA in the taxane-naïve and post-NHA setting.

The OS HR for docetaxel versus NHA, sourced from the Swami publication (Swami 2020), was 1.29 (95% CIs: 1.04; 1.60); in absence of rPFS data reported in the publication, rPFS was assumed to be equivalent to NHA (HR=1.00), since the mean rPFS duration for NHA was 0.55 years or 28.7 weeks, which equates to the maximum number of recommended docetaxel treatment cycles in Denmark (10 x three-weekly cycles).

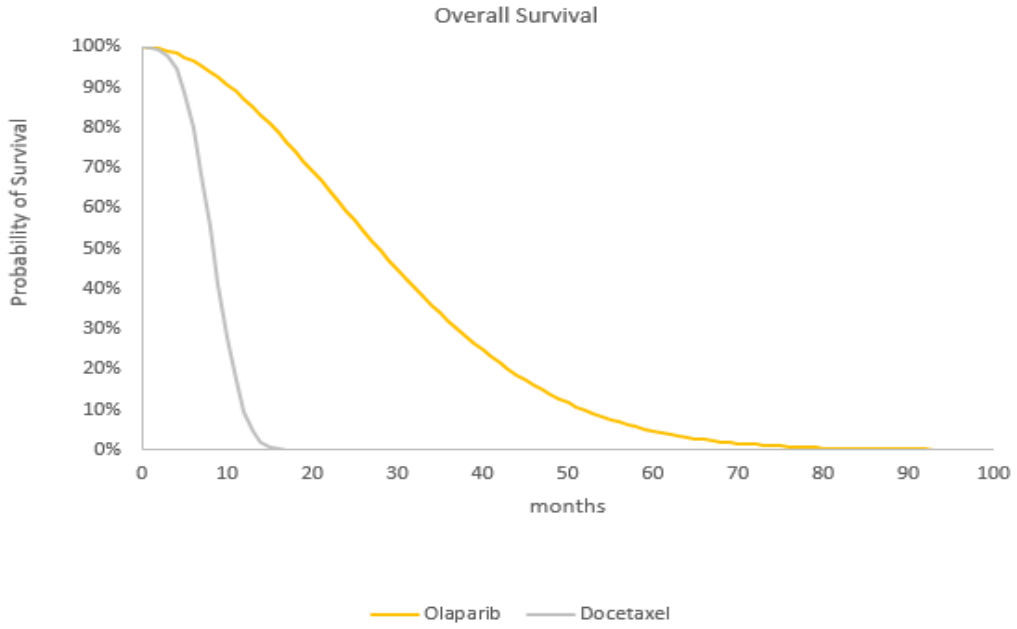
**In absence of comparative rPFS data for docetaxel, it was assumed that HR for docetaxel versus NHA was 1; for modelling docetaxel OS, HRs versus NHA were sourced from an observational study (HR=1.29).**

*Figure 34 PFS projections for olaparib and docetaxel in the BRCAm no prior taxane subgroup*




[1] The Flatiron Health database is a longitudinal demographically and geographically diverse database derived from quality-controlled, real-world electronic health record data. It includes data from over 280 community oncology clinics and academic centers throughout the US. Flatiron Health works closely with FDA which collects real-world outcomes from patients with cancer with the aim of further understanding newly approved therapies and has published RWD studies across different cancer types, including prostate cancer.

*Figure 35 OS projections for olaparib and docetaxel in the BRCAm no prior taxane subgroup*




## 11.3.2 BRCAm prior taxane subgroup

### Cabazitaxel (vs. NHA)

The base case HRs for cabazitaxel vs. NHA were based on data from the CARD study. rPFS HR for cabazitaxel vs. NHA is 0.54 (0.40-0.73, p<0.001) and OS HR for cabazitaxel vs. NHA is 0.64 (0.46-0.89, p=0.008) (de Wit 2019). As cabazitaxel is only indicated for a prior-taxane setting, the HRs are only applicable to this subgroup.

In the base case, rPFS and OS for cabazitaxel are modelled using constant HRs vs. NHA, derived from the CARD study, which compared cabazitaxel with NHA in a similar setting as PROfound.

*Figure 36 PFS projections for olaparib and cabazitaxel in the BRCAm prior taxane subgroup*

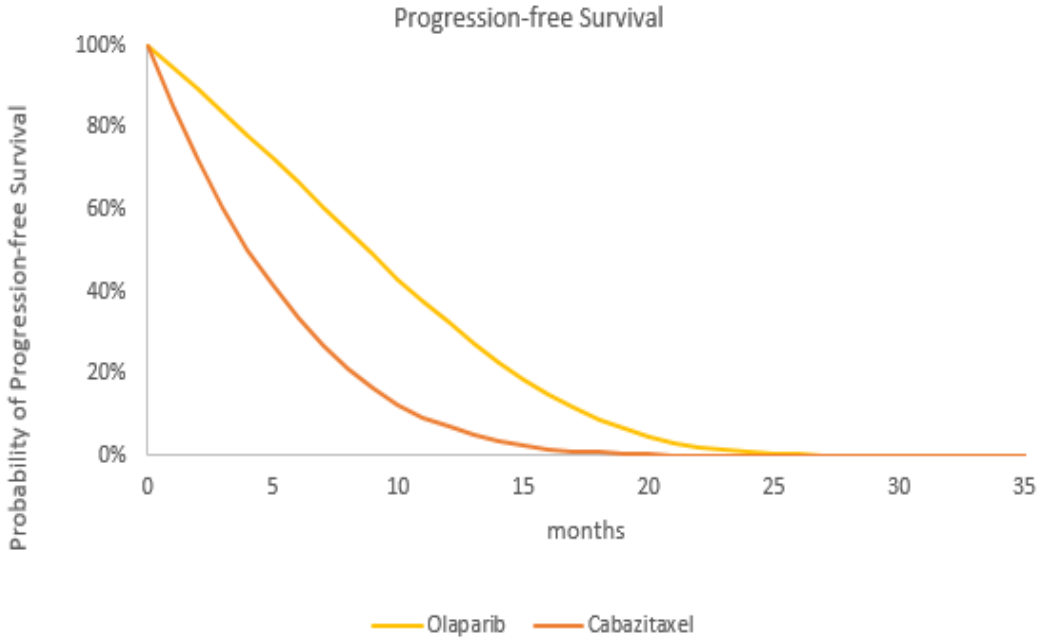
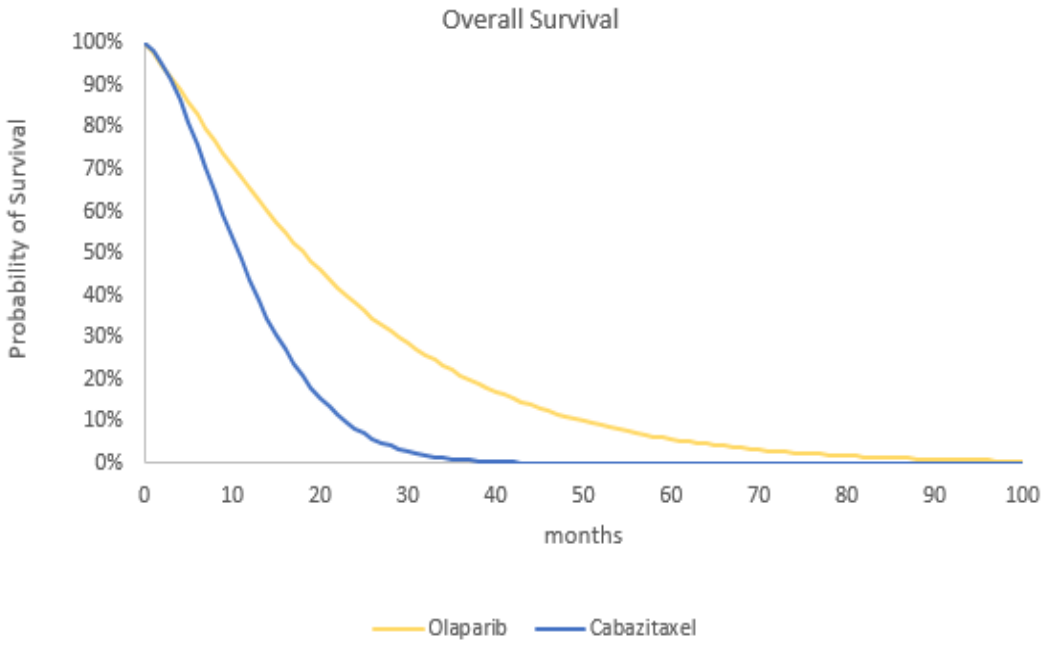


*Figure 37 OS projections for olaparib and cabazitaxel in the BRCAm prior taxane subgroup*




The estimated survival landmarks in the cabazitaxel arm were validated against the real-world evidence study of Rouyer et al. (2019). This study was designed to confirm the real-life overall and progression-free survival and safety of cabazitaxel in mCRPC. The study was performed in multiple centers in France and included 401 patients. Although we do not know the proportion of BRCAm positive patients in the French study, the patient population was similar in terms of age and had a high proportion of previous NHA use. Patient characteristics in the study are presented below:

- Median age – 70 years
- Main metastatic sites were bones (87%), lymph nodes (42%), and visceral (20%)
- 18% had cabazitaxel in 2L, 39% in 3L, and 43% in 4L+
- All patients had received prior docetaxel
- 82% of patients received prior NHA (abiraterone, enzalutamide or both).
- Median duration of cabazitaxel treatment was 3.4 months

Based on visual inspection of the modelled PFS curve for cabazitaxel overlaid with the PFS curve in the study of Rouyer et al. (2019) (Figure 38), it can be concluded that the modelled PFS matches the observed PFS in the real-life setting well. Similar conclusions can be drawn for the comparison between the modelled and observed OS curves (Figure 39). The inconsistency between the curves beyond 12 months way be explained by differences in patient characteristics (e.g. more patients receiving treatment in earlier lines in the real-life study) that may indicate better prognosis and longer OS. It should also be noted that BRCA mutations are associated with more aggressive course of disease and worse prognosis compared to non-BRCA mutation carriers (Taylor 2017, Castro 2013) which may explain the observed separation between the extrapolated and the RWE-based curves.

*Figure 38 PFS reported in the RWE study overlaid with modelled PFS for cabazitaxel (orange curve – extrapolated PFS for cabazitaxel)*

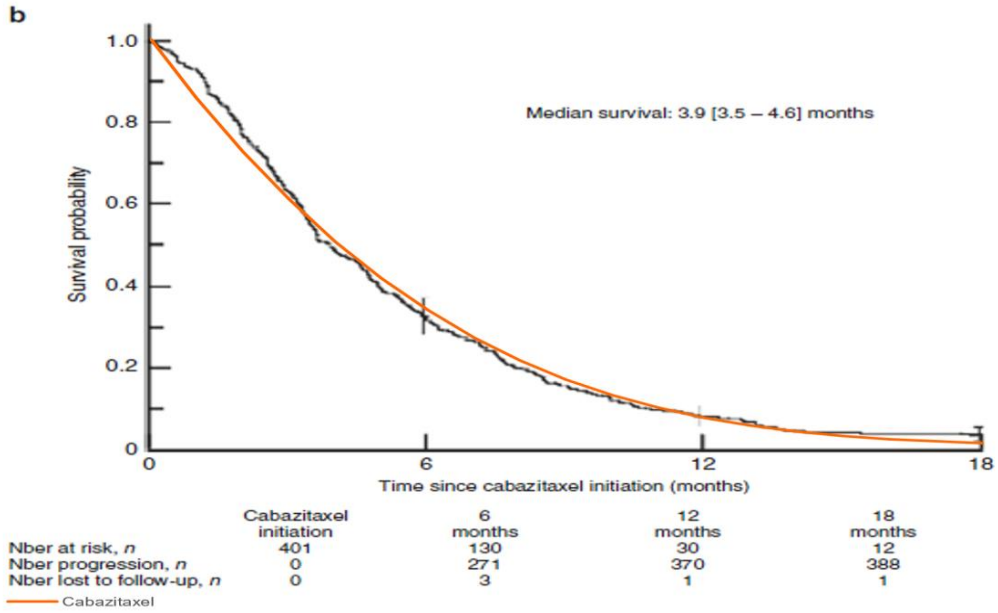
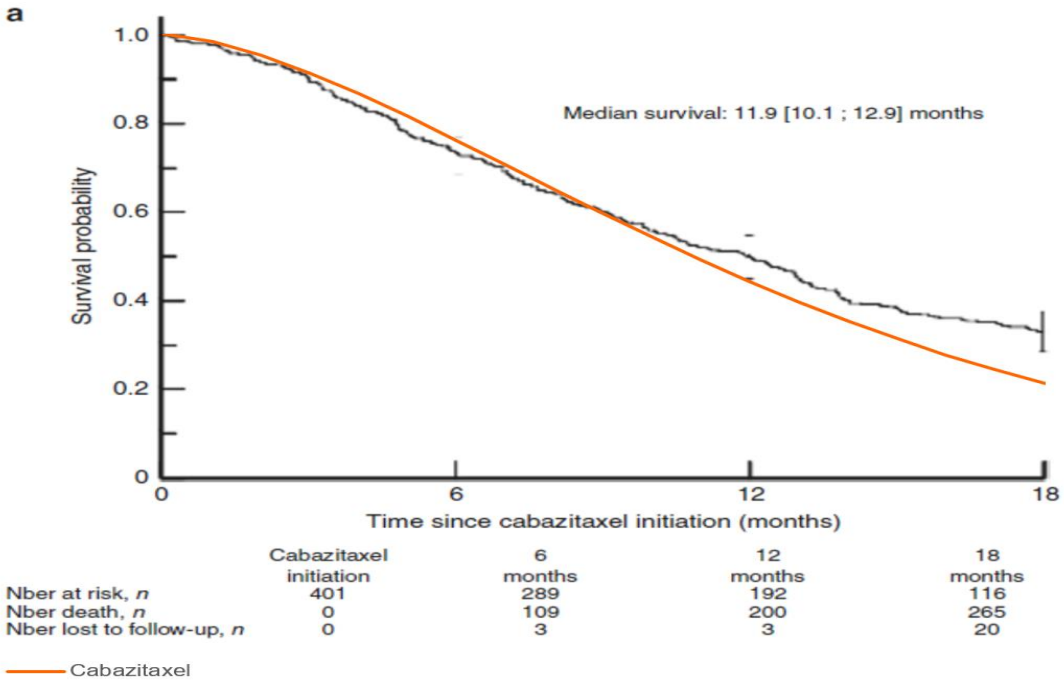



*Figure 39 OS reported in the RWE study overlaid with modelled OS for cabazitaxel (orange curve – extrapolated PFS for cabazitaxel)*




## 11.4 Time on Treatment

### 11.4.1 Olaparib and NHA

It was observed in PROfound that some patients received treatment beyond rPFS BICR in both arms. This is not in line with the real-world practice, where patients discontinue treatment upon progression. To reflect the real-world clinical practice, patients are assumed to be treated until progression for olaparib and NHA. No maximum treatment cap was applied for NHA or olaparib.

### 11.4.2 Taxanes

For cabazitaxel and docetaxel, no published TTD curves were available. Therefore, rPFS curves are used as a proxy for TTD. This is also in line with clinical practice, where these treatments are indicated to be received until progression or until a maximum number of cycles is reached.

**In line with real-world clinical practice, and in absence of TTD data for comparators outside PROfound, treat-to-progression is assumed for all treatments. Therefore, rPFS is always used as a proxy for TTD in the base case.**

A maximum of 8 treatment cycles are applied to cabazitaxel in line with data on the number of cycles in CARD (de Wit). A maximum of 10 treatment cycles is applied to docetaxel based on the maximum number of treatment cycles indicated in the Danish clinical guidelines. This value is used as the number of treatment cycles was not reported from the study by Swami et al. (2020).

## 11.5 Adverse events

The model includes grade 3 and above AEs occurring in at least 2% of patients in the olaparib arm of PROfound trial. This is a commonly accepted approach as grade ≥3 AEs reflect events that are likely to require hospitalization; therefore, having the greatest burden on resources and quality of life. In addition, AEs that required more resources than other AEs (e.g. pulmonary embolism and neutropenia) were included.

The AE incidence data for olaparib and NHA were informed by the PROfound trial, and the AE incidence data for cabazitaxel was derived from the CARD trial (treatment-related grade ≥3 AEs that were reported in at least 3% of the patients in either treatment group-safety population) (de Wit 2019). Docetaxel was informed by the TAX 327 study (Tannock 2004) (which reported grade 3/ 4 AEs for docetaxel plus prednisone that occurred or worsened during treatment) and drug label. The AE probabilities are listed in Table 12.

*Table 12 Probability of patients experiencing AEs by treatment*

| AE Lists | Probability of Experiencing Grade 3+ Adverse Events per Model Cycle | | | |
|---|---|---|---|---|
| | Olaparib | NHA | Cabazitaxel | Docetaxel |
| Anaemia | 22.66% | 5.38% | 8.00% | 5.00% |
| Neutropenia | 3.91% | 0.00% | 44.72% | 32.00% |
| Thrombocytopenia | 3.52% | 0.00% | 3.20% | 1.00% |
| Pneumonia | 3.13% | 2.31% | 0.00% | 0.00% |
| UTI | 1.95% | 3.85% | 0.00% | 0.00% |
| Sepsis | 1.17% | 2.31% | 0.00% | 3.30% |
| Pulmonary embolism | 2.73% | 0.77% | 0.00% | 0.00% |
| Dyspnea | 2.34% | 0.00% | 0.00% | 0.60% |
| Vomiting | 2.34% | 0.77% | 0.00% | 1.20% |
| Asthenia | 1.56% | 3.08% | 3.97% | 0.00% |
| Fatigue | 1.56% | 2.31% | 3.97% | 5.00% |
| Hypertension | 1.17% | 2.31% | 2.38% | 0.00% |

| AE Lists | Probability of Experiencing Grade 3+ Adverse Events per Model Cycle | | |
|---|---|---|---|
| Source (details) | PROfound (Cohort A+B) DCO2 [AE grade 3+ among >2% patients in either arm] | CARD trial [AEs of grade 3+ (safety population) | TAX 327 Study (Tannock 2004) [Grade 3/ 4 AEs for docetaxel + prednisone that occurred or worsened during treatment]; (Docetaxel SmPC) for infection, vomiting and dyspnea (and sepsis assumed as infection) |
| Abbreviations: AE = adverse event; NHA = new hormonal agent; SmPC = summary of product characteristics; UTI = urinary tract infection | | | |

## 11.6 Skeletal-related events (SREs)

The SREs are common complications of bone metastases and have serious negative consequences for patients with mCRPC. SREs pose a significant health and economic burden (Krupski 2007, Weinfurt 2005). The SREs included in the model are spinal cord compression, pathological bone fracture, radiation to the bone and surgery to the bone. The distribution of SREs is based on the AFFIRM trial (derived from cabazitaxel NICE submission, TA316).

Although patients may have more than one SRE during disease progression, the model uses the proportion of patients who have had at least one SRE occurred as a proxy for the proportion experiencing SRE (the number of patients with at least one SRE divided by the number of patients progressed). This is due to the lack of patient-level trial data to inform the comparators. Table 13 presents the distribution of SREs, and the probability of occurrence of at least one SRE for each treatment.

*Table 13 SRE probability*

| SRE | Distribution (%) | Probability of at least one SRE | | | |
|---|---|---|---|---|---|
| | | Olaparib | NHA | Cabazitaxel | Docetaxel |
| Spinal Cord Compression | 19.20% | 23.58%[b] | 27.94% [b] | 27.94% [b] | 27.94% [b] |
| Pathological Bone Fracture | 10.93% | | | | |
| Radiation to the Bone | 63.47% | | | | |
| Surgery to the Bone | 6.40% | | | | |
| Source | AFFIRM (TA316) | Profound trial (Cohort A)[a] | Profound trial (Cohort A) [a] | Assumption: same as NHA | Assumption: same as cabazitaxel |
| Note: NHA = new hormonal agent; SRE= skeletal-related event: a= assumed the same frequency between BRCAm and Cohort A in the PROfound trial; b = # patients with at least one SRE/# of patients progressed | | | | | |

## 11.7 Resource use and costs

The model uses 2021 prices in Danish krona (kr). The model includes the following costs:

- Treatment-related costs (acquisition and administration);
- Subsequent treatment costs (acquisition and administration);
- Concomitant medication costs (acquisition and administration);
- Routine care and follow-up costs (disease management costs);
- Adverse events (AEs) and Skeletal-related events (SREs)
- Terminal care costs;
- BRCA mutation testing costs.

### 11.7.1 Treatment-related costs

#### 11.7.1.1 Treatment acquisition costs

Medication acquisition costs per monthly model cycle (Table 16) were calculated for each treatment based on the dosing schedules (Table 16) and unit costs for each pack or vial (AIP, accessed May 2021,(Table 15) sourced from medicinpriser.dk. Dose reductions and interruptions for olaparib were captured by using the relative dose intensity reported in PROfound (Table 14).

*Table 14 Mean relative dose intensity (%) for olaparib, abiraterone, and enzalutamide as reported in PROfound*

| Regimen | Intended daily dose | Mean relative dose intensity | Source |
|---|---|---|---|
| Olaparib | 300 mg × 2 = 600 mg | 91.5% (549 mg) | CSR, Table 14.3.1.5 |

Cabazitaxel and docetaxel are dosed according to patients' body surface area (BSA, $m^2$). The mean BSA was not available from the PROfound or CARD studies, therefore, a mean BSA value of 1.91 $m^2$ was sourced from Sacco et al. (2010) which provided the average BSA of adult cancer patients in the UK. A mean weight of 80 kg, based on Cohort A in the PROfound trial was used.

Although cabazitaxel is indicated for use at a dose of 25 mg/$m^2$, a 20 mg/$m^2$ dose is specified in the protocol by Medicinrådet. Hence, a dose of 20 mg/$m^2$ is applied in the model assuming equal efficacy between 25 mg/$m^2$ and 20 mg/$m^2$ doses.

*Table 15 Unit price (AIP) of treatments included*

| Treatment | Product Name | Route | Strength | Pack/Vial Size | Price |
|---|---|---|---|---|---|
| Olaparib | LYNPARZA | Oral | 100 mg | 56 | 18 219.87 kr |
| | | Oral | 150 mg | 56 | 18 219.87 kr |
| Abiraterone acetate | ZYTIGA | Oral | 500 mg | 56 | 0.00 kr |
| Enzalutamide | XTANDI | Oral | 40 mg | 112 | 0.00 kr |
| Docetaxel | Docetaxel | IV Infusion | 20 mg/ml | 1 | 71.90 kr |
| | | IV Infusion | 80 mg/ ml | 1 | 151.02 kr |
| | | IV Infusion | 160 mg ml | 1 | 444.00 kr |
| Cabazitaxel | JEVTANA | IV Infusion | 60 mg/1.5 ml | 1.5 ml | 28 309.52 kr |
| Prednisolone | Prednisolone | Oral | 5 mg | 105 | 123.95 kr |

*Table 16 Per cycle costs for each treatment*

| Treatment | Dependency | Dose | Cost per dose [a] | # of admin per treatment cycle | Cost per treatment cycle | # of weeks per treatment cycle | Medication costs/model cycle | Administration costs /model cycle |
|---|---|---|---|---|---|---|---|---|
| **Olaparib** | | | | | | | | |
| Olaparib | Fixed dose | 274.5 mg | 595-40 kr | 56 | 33 342.36 kr | 4 | 36 244.93 kr | 0.00 kr |
| **Cabazitaxel** | | | | | | | | |
| Cabazitaxel | BSA | 20.0 mg/$m^2$ | 28 309.52 kr | 1 | 28 309.52 kr | 3 | 41 031.95 kr | 2436.00 kr |
| Prednisolone | Fixed dose | 10.0 mg | 0.83 kr | 21 | 17.35 kr | 3 | 25.15 kr | 0.00 kr |
| **Docetaxel** | | | | | | | | |
| Docetaxel | BSA | 75.0 mg/$m^2$ | 302.04 kr | 1 | 302.04 kr | 3 | 437.78 kr | 2436.001 kr |
| Prednisolone | Fixed dose | 5.0 mg | 0.41 kr | 42 | 17.35 kr | 3 | 25.15 kr | 0.00 kr |
| Note: a – based on the lowest cost per mg | | | | | | | | |

#### 11.7.1.2 Treatment administration costs

The drug administration costs for IV treatments is 1681 kr based on DRG 12MA98 (MDC12 1-dagsgruppe, pat. mindst 7 år, DRG takster 2021). These unit costs are converted to per model cycle costs based on dosing schedule of each IV drug and then applied to each model cycle.

#### 11.7.1.3 Medication wastage

Medication wastage was estimated using a "method of moments" approach, which uses a standard normal distribution fitted around the mean and standard deviation of body surface area (used to estimate dose) to estimate the proportion of patients requiring a certain number of vials. A weighted mean total number of vials is then derived from the distribution described above, to estimate actual usage with wasted medication.

A vial-sharing approach which estimates IV medication costs from the lowest mean cost per mg for each drug, multiplied by its mean mg dosing is tested in a sensitivity analysis. This method assumes minimum waste, and maximum efficiency in terms of medication costs.

#### 11.7.1.4 Mutation testing costs

The model includes the one-off testing cost of BRCA1 and BRCA2 mutations. The costs of BRCAm testing are calculated as unit cost of test multiplied by the inverse of the prevalence of BRCAm in patients with mCRPC. The unit cost of BRCA mutation testing was 4113.00 kr based on a testing cost from Rigshospitalet in Copenhagen: DNABRCA1, DNA(spec.)-BRCA1-gen;sekv.var. Rigshospitalets Labportal (https://labportal.rh.dk/Metodeliste.asp).

The BRCAm prevalence of 9.7% was derived from the PROfound trial (de Bono 2019, 2020).

#### 11.7.1.5 Concomitant medication

Six concomitant medications are included in the model: zoledronic acid, antihistamine, PPI, anti-emetic, corticosteroid, and G-CSF (Table 17). Concomitant medications are in line with recommendations by the Danish treatment guidelines for mCRPC.

The percentages of patients receiving each concomitant medication were derived from the PROfound trial for olaparib and NHA, and from the TROPIC trial (Oudard 2011) for cabazitaxel. The recommended dosing regimen for each concomitant medication is taken from the SmPC, the unit costs (AIP) are sourced from medicinprise.dk (Table 17) Concomitant medication costs are applied to patients on treatment. The cost and frequency of use per model cycle are presented in Table 18.

The treatment administration cost of the concomitant medications is not considered in the base case analysis. Although it is suggested that some concomitant medications are intravenous, oral medicinal formulations were available and assumed for the model. Furthermore, the administration costs associated with the initial treatment are already included to cover a complete treatment cycle.

#### Neutropenia prophylaxis

Clinical guidelines currently recommend the administration of antiemetic prophylaxis (oral or IV) to reduce the risk of neutropenia complications (febrile neutropenia, prolonged neutropenia or neutropenic infection) before the occurrence of any clinical event when there is a high risk of febrile

neutropenia with treatment with chemotherapy (e.g. cabazitaxel or docetaxel) (Aapro 2011, Heidenreich 2014, Klastersky 2016, Smith 2006).

In the CARD study, which was used to derive comparative efficacy for cabazitaxel in the model, 100% of patients were mandated by protocol to receive prophylactic G-CSF at each treatment cycle to help prevent neutropenia-related complications. In the Danish clinical practice, the G-CSF is used only for few patients initiated on taxanes (communication with Danish clinical experts). Hence, the model base case analysis assumes that 10% of patients in the cabazitaxel arm receive prophylactic The dosing schedule for granulocyte-colony stimulating factor (G-CSF) is up-to 5 administrations per 3-week cycle as per clinical guidance.  Same proportion of patients receiving G-CSF is assumed for docetaxel.

*Table 17 Concomitant medication dosing and unit costs*

| Concomitant medication | Form: Route | Dosing | Strength per Unit | # Units per Pack | Cost of Pack |
|---|---|---|---|---|---|
| Bisphosphonates (Zoledronic Acid) | SOL: Infusion | 4 mg every 3 to 4 weeks - for prevention of skeletal-related events in patients with advanced malignancies involving bone | 4.0 mg | 1 | 70.06 kr |
| Antihistamine (promethazin) | TAB: Oral | 1 tablet (25 mg) once a day for allergy relief | 25.0 mg | 100 | 63.70 kr |
| PPI (esomeprazole) | Effervescent TAB: Oral | 20 mg once daily | 20.0 mg | 100 | 42.55 kr |
| Anti-emetic (ondansetron) | Orodispersible film: Oral | 8 mg 1 to 2 hours before chemotherapy or radiotherapy, followed by 8 mg 12 hours (chosen) later. Ondansetron may be continued twice a day for up to 5 days after treatment | 4.0 mg | 100 | 159.40 kr |
| Corticosteroid (Dexamethasone) | Soluble TAB: Oral | Supportive treatment in malignant tumour: initially 8 (chosen)–16 mg/day, during longer lasting treatment 4–12 m [Common practice is one administration before chemotherapy administration; twice daily thereafter for around 3 days as per guidance from AZ medical advisors] | 4.0 mg | 100 | 595.95 kr |
| G-CSF (filgrastim) | SOL: Infusion | Recommended dose of filgrastim is 0.5 million units (mu)/kg/day (5 micrograms/kg/day) [Up-to 5 administrations per 3-week cycle as per clinical guidance from AZ medical advisors] | 48 miu | 1 | 1900 kr |
| Abbreviations: G-CSF = granulocyte-colony stimulating factor; SOL = solution; TAB = tablet | | | | | |

*Table 18 Concomitant medication cost and frequency of use*

| Concomitant medication | Cost- Per Model Cycle | Frequency of Use per Model Cycle | | | |
|---|---|---|---|---|---|
| | | Olaparib | BSC/NHA | Cabazitaxel | Docetaxel |
| Bisphosphonates (zoledronic acid) | 87.04 kr | 1.23% | 4.82% | 0.00% | 0.00% |
| Antihistamine (promethazin) | 5.17 kr | 6.17% | 6.02% | 100.00% | 100.00% |
| PPI (esomeprazole) | 194.27 kr | 11.11% | 6.02% | 100.00% | 100.00% |
| Corticosteroid (dexamethasone) | 120.93 kr | 50.00% | 48.19% | 100.00% | 100.00% |
| G-CSF (filgrastim) | 2294.89 kr | 2.47% | 1.20% | 10.00%[a] | 10.00%[a] |
| Source | | Profound (Cohort A) | Profound (Cohort A) | TA391 (NICE 2016) | Assumption: same as cabazitaxel |
| Notes: G-CSF = granulocyte-colony stimulating factor; a - assumption based on input from the Danish clinical experts. | | | | | |

### 11.7.1.6 Subsequent treatments

The subsequent treatments included in the model for olaparib and BSC/NHA are sourced from the PROfound trial. The proportion of patients who experience disease progression and receive subsequent treatment (Table 19), and the distribution of subsequent treatments (Table 20), were derived from PROfound for olaparib and NHA, and the CARD study (de Wit 2019) for cabazitaxel. For docetaxel, same proportion as for cabazitaxel was assumed.

*Table 19 Proportion of patients receiving subsequent treatments*

| | Prior line of treatment | | | |
|---|---|---|---|---|
| | Olaparib | NHA | Cabazitaxel | Docetaxel |
| % of patients receiving subsequent treatments | 52.02% | 25.39% | 57.50% | 57.50% |
| Source | PROfound (Cohort A) DCO2 | Profound (Cohort A) DCO2 | CARD (11) | Assumption: same as cabazitaxel |

Since the switching-adjusted (RPSFTM) OS data are used in the base case analysis, the distribution of subsequent treatments for BSC/NHA has been adjusted to remove subsequent olaparib and re-calibrated proportionally across all the other subsequent treatment options. In the PROfound study, mitoxantrone and Sipuleucel-T were used but these treatments are not recommended in Denmark and are not included in the subsequent treatments. As retreatment with NHAs are in general not recommended in Danish guidelines, these costs are also set to zero in the model. This is conservative, as retreatment with NHAs could still occur for some patients in clinical practice.

*Table 20 Subsequent treatment composition basket as per previous treatment (at base case- RPSFTM adjusted OS)*

| Subsequent treatment | Initial treatment | | | |
|---|---|---|---|---|
| | Olaparib | NHA | Cabazitaxel | Docetaxel |
| Cabazitaxel | 16.42% | 20.48% | 4.30% | 4.30% |
| Docetaxel | 22.35% | 21.69% | 2.99% | 2.99% |
| Mitoxantrone | 0.00% | 0.00% | 0.00% | 0.00% |
| Abiraterone | 6.25% | 10.84% | 21.68% | 21.68% |
| Enzalutamide | 13.88% | 9.64% | 21.68% | 21.68% |
| Radium-223 | 2.86% | 9.64% | 8.78% | 8.78% |

| | | | | |
|---|---|---|---|---|
| Sipuleucel-T | 0.00% | 0.00% | 0.00% | 0.00% |
| BSC | 35.91% | 10.84% | 40.57% | 40.57% |
| Source | PROfound (Cohort A) DCO2 | PROfound (Cohort A) DCO2 | CARD (de Wit 2019) [Frequencies or percentages re-weighted to sum to 100%] | Assumption: same as cabazitaxel |
| Abbreviations: BSC = best supportive care | | | | |

For patients who do not receive any treatments listed above (e.g. due to intolerance or frailty), other active palliative treatments are used. All other active subsequent treatments are categorized under "Best supportive care" (BSC) and is assumed to comprise analgesics, steroids, antiemetics and bone remodelling treatment with a one-off BSC cost per cycle of 2 784.06 kr (Table 21). According to the Danish clinical experts, many treatments are used in the BSC setting and this is just a selection of the most common ones. Many other treatments are used depending on the needs. As most of the treatments used for BSC are tablets, no costs have been assumed regarding administration.

*Table 21 BSC calculations and assumptions**

| Type of treatment | Component | Pack size | Cost/ pack | Cost/ model cycle |
|---|---|---|---|---|
| Analgesics | Contalgin 10 mg | 100 | 168.00 kr | 51.07 |
| RANKL inhibitor | Denosumab 120 mg | 1 vial | 2 049.33 kr | 2 224.99 kr |
| Antiemetic | Domperidon 10 mg | 30 | 30.55 kr | 92.87 kr |
| Antiemetic | Ondansetron 16 mg | 5 | 352 | 352 |
| Corticosteroids | Prednisone 25mg | 100 | 207.67 kr | 63.13 |
| Total | | | | 2 784.06 kr |
| *Based on Danish medical expert input | | | | |

The total costs of subsequent treatments following each prior line of treatment are calculated based on the average treatment duration (Table 22), distribution (Table 20) and unit cost of subsequent treatments (Table 23). The total costs of subsequent treatments are thereafter applied as a one-off cost to the proportion of patients who progress from the prior line of treatment (Table 19).

*Table 22 Average duration of subsequent treatments (months)*

| Subsequent Treatment | Duration (months) | Source |
|---|---|---|
| Cabazitaxel | 5.1 | 7 treatment cycles (22 weeks); Median duration of exposure reported in CARD (de Wit 2019) |
| Docetaxel | 6.9 | 10 treatment cycles (30 weeks); (Tannock 2004) Maximum recommended duration in mCRPC setting |
| Mitoxantrone | 0 | Assumption as not an active mCRPC treatment in ESMO guidelines and is not used in the Danish clinical practice. |
| Radium-223 | 5.5 | 6 injections (24 weeks); Median number of injections in ALSYMPCA (Parker 2013) (>50% in interim analysis and >80% in safety update) |
| Sipuleucel-T | 0 | Assumption as not approved in Europe |
| BSC | 6.6 | Assumption: average of the durations of other active anti-cancer subsequent treatments' (cabazitaxel, docetaxel, abiraterone, enzalutamide, and radium-223) duration due to lack of data. |
| Abbreviations: BSC = best supportive care; ESMO = European Society for Medical Oncology; mCRPC = metastatic castrate-resistant prostate cancer | | |

*Table 23 Medication acquisition and administration costs for subsequent treatments*

| Subsequent Treatments | Dosing Regimen | Route | Strength | Pack/ vial Size | Package Price | Treatment cost per mode cycle [a] |
|---|---|---|---|---|---|---|
| Prednisolone | 10 mg daily | Oral | 5 mg | 105 | 123.95 kr | |
| Cabazitaxel | 20 mg/m$^2$ every 3 weeks (+10 mg prednisolone daily) | IV | 60 mg | 1 | 28 309.52 kr | 43 493.55 kr |
| Docetaxel | 75 mg/m$^2$ every 3 weeks (+5 mg prednisolone twice daily) | IV | 20 mg/ml | 1 | 71.90 kr | 5441.87 kr |
| | | IV | 80 mg/ml | 1 | 151.02 kr | |
| | | IV | 160 mg/ml | 1 | 440.00 kr | |
| Radium-223 | 55 kBq/kg every 4-weeks for 6 injections (Xofigo SmPC) | IV | 6.6 MBq | 1 | 29 800.85 kr | 29 800.85 kr |
| BSC | Assumed a mix of prednisolone and Dexamethasone | Oral | 1 | 1 | 1 | 1 177.36 kr |

Notes: Price for radium-223 is sourced from TLV appraisal for Xofigo (May 2014), as no list price seems to be publically available in Denmark; a – includes medication acquisition and administration costs, for cabazitaxel abiraterone, docetaxel includes costs for prednisolone.

*Table 24 Total subsequent treatments costs (RPSFTM adjusted OS)*

| Subsequent treatment | Initial treatment | | | |
|---|---|---|---|---|
| | Olaparib | NHA | Cabazitaxel | Docetaxel |
| Cabazitaxel | 18 796.52 kr | 11 443.51 kr | 5 439.19 kr | 5 439.19 kr |
| Docetaxel | 2 325.99 kr | 1 101.44 kr | 343.96 kr | 343.96 kr |
| Radium-223 | 2 447.38 kr | 4 025.25 kr | 8 308.01 kr | 8 308.01 kr |
| BSC | 3 451.24 kr | 508.61 kr | 4 309.28 kr | 4 309.28 kr |
| **Total** | **27 021.14 kr** | **17 078.81 kr** | **18 400.44 kr** | **18 400.44 kr** |
| Notes: Abbreviations: BSC = best supportive care; NHA= new hormonal agent | | | | |

### 11.7.2 Routine care and follow-up costs

The cost of patient follow-up in the model was calculated by multiplying resource use (e.g. number of occasions a component of care was accessed in a cycle) by the unit cost for each resource item. The resource use data assigned to the PF and PD states were estimated based on input provided by a Danish clinical expert. A summary of unit costs used in this analysis is presented in Table 25. The unit costs were sourced from DRG price lists and represent the most recent costs (year 2021 price level).

*Table 25 Unit costs based on 2021 price lists in Denmark.*

| Cost component | Unit cost | Source |
|---|---|---|
| Oncologist consultation (outpatient visit) | 1681.00 kr | DRG 12MA98 (MDC12 1-dagsgruppe, pat. mindst 7 år, DRG takster 2021) |
| Nurse visit | 1681.00 kr | |
| Blood status | 37.00 kr | HB, B-Hæmoglobin, Hæmatologi (JNIE0647), Rigshospitalets Labportal: https://labportal.rh.dk/Metodeliste.asp?Pris=Show |
| Prostate specific antigen (PSA) | 95.00 kr | PSAT, P-Prostataspecifikt antigen, Immunkemi (Cobas) (LiA), Rigshospitalets Labportal: https://labportal.rh.dk/Metodeliste.asp?Pris=Show |
| Computer tomography | 2007.00 kr | DRG 30PR06 (CT-scanning, kompliceret, DRG takster 2021) |
| BRCAm test | 4113.00 kr | DNABRCA1, DNA(spec.)-BRCA1-gen;sekv.var. Rigshospitalets Labportal: https://labportal.rh.dk/Metodeliste.asp |
| Patient time cost | 179.00 kr | Medicinrådet guidelines |
| Patient transport | 100.00 kr | Medicinrådet guidelines |
| | | |

In the model, resource use is captured by patients being "on" or "off" the initial treatment, regardless of health states (i.e. PF or PD). Given that patients are assumed to be treated until progression (i.e. time on treatment equals rPFS) in the base case analysis, this approach will be equivalent to capturing resource use related to each health state (PF or PD). Monthly costs related to disease monitoring are accrued for patients on the first three months of treatment and from four months onwards for each treatment. This allows the model to capture the upfront monitoring of treatments or any difference in frequency of monitoring before and after the initial three months. Disease monitoring costs after discontinuation of initial treatment ("off treatment") are captured but are not differentiated by time spent off treatment (i.e. first three months versus from four months onwards). The model also provides the option to include an additional one-off cost associated with disease progression to each treatment, which is applied to the patients having a progression event (i.e. entering the PD health state). Yet, no one-off costs associated with progression are assumed in the base case analysis.

The summary of product characteristics for olaparib recommends that patients on olaparib should have a blood test every week for a first month and monthly afterwards. Additional resource use associated with treatment monitoring is included for patients on olaparib. Resource use and associated costs while on olaparib, NHA, and chemotherapy (cabazitaxel and docetaxel) treatment are presented in Table 26.

*Table 26 Resource use and associated costs while "on-treatment" per month*

| Resource item | Olaparib | | BSC/NHA | | Chemotherapy | |
|---|---|---|---|---|---|---|
| | First 3 months | Month 4+ | First 3 months | Month 4+ | First 3 months | Month 4+ |
| Outpatient oncologist consultation | 1.33[a] | 1.00 | 1.00 | 0.75 | 0.83[c] | 0.48 |
| Nurse visits | 0.50 | 0.75 | 0.50 | 0.75 | 0.37 | 0.42 |
| CT scan | 0.33[b] | 0.33 | 0.33 | 0.50 | 0.67 | 0.67 |
| Blood status | 1.33[d] | 1.00 | 1.00 | 0.75 | 2.67 | 2.67 |
| PSA level | 1.00 | 1.00 | 1.00 | 0.75 | 1.33 | 1.33 |
| Patient time | 0.78 | 0.75 | 0.67 | 0.75 | 0.73 | 0.63 |
| Patient transport | 4.32 | 4.16 | 3.66 | 4.00 | 3.72 | 3.13 |
| **Monthly costs** | 4453 kr | 4286 kr | 3801 kr | 4158 kr | 4074 kr | 3503 kr |

Note: PSA – Prostate specific antigen; a - 2 times over 3 months; b – 1 time over 3 months; c – every 3rd treatment;
d- based on frequency of additional blood status test every-week during the first month and monthly afterwards (4+2)/3 for olaparib; e – every 3 weeks

Once patients discontinue treatment (being 'off-treatment' means that patient's disease has progressed) resource use and costs are assumed to be equal across both arms, irrespective of subsequent treatment received. Estimates for resource use while being 'off-treatment' were validated by a clinical expert and presented in Table 27.

*Table 27 Resource use and associated costs while 'off-treatment'*

| Resource item | Olaparib/NHA/chemotherapy |
|---|---|
| Outpatient consultation | 0.33 |
| CT scan | 0.33 |
| Specialized nurse visit | 0.33 |

| | |
|---|---|
| Blood status | 0.33 |
| PSA level | 0.33 |
| Patient time | 0.39 |
| Patient transport | 1.98 |
| **Monthly costs** | 2082 kr |

### 11.7.3 Costs of end-of-life care

End stage care costs were applied as a one off-cost. According to the clinical experts, the absolute majority of patients (75%) received end-of-life care at home or at a hospice (15%) rather than at a hospital, but with variable intensity of care, which makes end of life care difficult to define. As an approximation, the end of life costs were estimated based on DRG 11MA08 (Sygdomme i prostata, ondartet sygdom, pat. mindst 18 år). This probably underestimates the costs of end-of-life care, as it represents the cost of just one hospital admission. The costs of end of life care are presented in Table 28.

*Table 28 Cost of end stage care*

| Resource | Total cost | Source |
|---|---|---|
| End stage care cost | 32 869 kr | DRG 11MA08 (Sygdomme i prostata, ondartet sygdom, pat. mindst 18 år) |

### 11.7.4 Adverse events

The total AE cost for each treatment was calculated based on the per event unit costs (Table 29), and the probability of experiencing AEs. AE costs are applied as a one-off cost to the proportion of patients on treatment at the beginning of the model. The unit costs of adverse events in the model were sourced from DRG price lists while resource use associated with managing AEs was based on input provided by Danish clinical expert. For example, dyspnea, vomiting, asthenia and fatigue are all associated with nurse consultation/doctors consult, blood test for anemia, test of $O_2$ saturation etc. For neutropenia, it is usually sufficient with a nurse consultation and patients are only treated if they have clinical signs of infection (Table 29).

*Table 29 Unit costs for AEs*

| Adverse event list | Unit cost | Specification | Source |
|---|---|---|---|
| Anaemia | 6042 kr | Transfusion af plasma og/eller behandlet blod | DRG 16PR01 |
| Neutropenia | 1681 kr | MDC12 1-dagsgruppe, pat. | DRG 12MA98 |
| Thrombocytopenia | 6042 kr | Transfusion af plasma og/eller behandlet blod | DRG 16PR01 |
| Pneumonia | 36 514 kr | Lungebetændelse og pleurit, pat. mindst 60 år | DRG 04MA13 |
| Urinary tract infection | 3581 kr | Infektioner i nyrer og urinvej, pat. mindst 16 år | DRG 11MA07 |
| Sepsis | 26 369 kr | Sepsis | DRG 18MA01 |
| Pulmonary embolism | 35 159 kr | Lungeemboli | DRG 04MA04 |

| | | | |
|---|---|---|---|
| Dyspnea | 1681 kr | MDC12 1-dagsgruppe, pat. | DRG 12MA98 |
| Vomiting | 1681 kr | MDC12 1-dagsgruppe, pat. | DRG 12MA98 |
| Asthenia | 1681 kr | MDC12 1-dagsgruppe, pat. | DRG 12MA98 |
| Fatigue | 1681 kr | MDC12 1-dagsgruppe, pat. | DRG 12MA98 |
| Hypertension | 7078 kr | Hypertension | DRG 05MA11 |

### 11.7.5 Skeletal-related events (SREs)

Skeletal-related event costs are calculated as a weighted average using the unit cost of each SRE sourced from the DRG costs and the distribution of SREs (Table 13). The proportion of patients who experience at least one SRE is calculated as the number of patients who experience at least one SREs divided by the number of patients who experience disease progression. The calculated total SRE cost is applied as one-off cost to the patients who progress. The assumption was applied as SRE is one of the key markers of bone progression and it is only expected to occur once patients progress (Parry 2019). Table 30 presents the unit cost per SRE.

*Table 30 Unit costs for SREs*

| SRE | Unit cost | Specification |
|---|---|---|
| Spinal Cord Compression | 66 938 kr | DRG 01MA02 Sygdomme og skader på rygmarven |
| Pathological Bone Fracture | 90 959 kr | DRG 08MP22 Frakturkirurgi, ryg/hals |
| Radiation to the Bone | 93 155 kr | DRG 27MP05 Strålebehandling, konventionel, mindst 5 fraktioner |
| Surgery to the Bone | 25 533 kr | DRGs 08MP63, 65 Øvrige kirurgiske procedurer, overekstremitet, store led; Øvrige kirurgiske procedurer, underekstremitet, store led |

## 11.8 Summary of base-case analysis inputs and assumptions

*Table 31. Base case settings and assumptions*

| Setting | Base case | Justification |
|---|---|---|
| Time horizon | 10 years | Consistent with survival data from PROfound |
| Discount rate for costs | 3.5% | Ministry of Finance (https://fm.dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021.pdf). |
| Model population | Patients with BRCA1 and BRCA2 mutated mCRPC | As per indication |
| Baseline age | 68.10 years | As in the PROfound trial |
| Weight | 80.00 kg | As in the PROfound trial |
| Body surface area | 1.91 $m^2$ | The study of Sacco et al. (2010) |
| OS treatment switching adjustment method | RPSFTM method adjusted OS | Selected to reflect the real-world practice and capture the true benefit of olaparib compared to NHA.<br>RPSFTM algorithm represents randomization-based methods for estimating counterfactual survival times (i.e. survival times that would have been observed in the absence of switching) (NICE DSU-TSD 16, 2014) |
| OS efficacy approach: Olaparib | Parametric fitting models derived from PROfound (Weibull) | Based on visual inspection, assessment of statistical fits and clinical expectations regarding long term progression risk for patients.<br>Since proportional hazard assumption was violated, individual parametric models were fitted to olaparib arm. As per DSU recommendations, same type parametric functions for treatment and comparator were selected (NICE DSU-TSD 14). |
| OS efficacy projection: NHA | Parametric fitting models derived from PROfound (Weibull) | Switching adjusted OS for NHA is modelled using a Weibull distribution in the base case, as it provides reasonable long-term projections for rPFS of NHA. |
| OS efficacy projection: cabazitaxel (prior taxane subgroup) | Constant HR using NHA as reference arm | CARD study reports the HR compared with NHA [HR= 0.64 (0.46-0.89)] |
| OS efficacy projection: docetaxel (no prior taxane subgroup) | Constant HR using NHA as reference arm | In absence of comparative data for docetaxel, HR for docetaxel versus NHA was sourced from an observational study (HR=1.29) (Swami 2020). |
| rPFS efficacy source | rPFS BICR | In line with the primary endpoints of the PROfound trial, rPFS BICR is selected as the base case measure of progression for all patients. |
| rPFS efficacy projection: olaparib | Parametric fitting models derived from PROfound trial (Gompertz) | Based on visual inspection, assessment of statistical fits and clinical expectations regarding long term projections. |
| rPFS efficacy projection: NHA | Parametric fitting models derived from PROfound trial (Gompertz) | Based on visual inspection, assessment of statistical fits and clinical expectations regarding long term projections. |
| rPFS efficacy projection: cabazitaxel | Constant HR using NHA as reference arm | CARD study HR= 0.54 (0.40-0.73) (de Wit 2019) |

| | | |
|---|---|---|
| rPFS efficacy projection: docetaxel | Constant HR using NHA as reference arm | In absence of comparative data, it is assumed that HR for docetaxel versus NHA is 1 indicating equal efficacy between docetaxel and NHA. |
| Treatment duration: olaparib | Treat until progression | In line with real-world clinical practice, and in absence of TTD data for comparators outside PROfound, treat-to-progression is assumed for all treatments. Therefore, rPFS is always used as a proxy for TTD in the base case. |
| Treatment duration: NHA | Treat until progression | |
| Treatment duration: cabazitaxel | Treat until progression | |
| Treatment duration: docetaxel | Treat until progression | |
| Gene mutation testing cost for olaparib | Include | Considered to be a conservative approach, as genetic testing is not only driven by the introduction of new treatment options. |
| Maximum treatment cycle | Olaparib: none<br>BSC: none<br>Cabazitaxel: 8 treatment cycles<br>Docetaxel: 10 treatment cycles | Maximum 8 treatment cycles in for cabazitaxel.<br>Maximum of 10 treatment cycles as recommended by the Danish guidelines. |
| Medication wastage | Cabazitaxel: include<br>Docetaxel: include | Including wastage is a conservative approach, as vial sharing could occur at some clinics. |
| % of patients receiving subsequent treatments (active anti-cancer treatments) | Olaparib: 52.02% (PROfound CSR DCO2)<br>Cabazitaxel: 57.50% (CARD)<br>Docetaxel: assumed the same as cabazitaxel | Subsequent treatment cost is applied as one-off to patients who progressed, therefore the % was adjusted by using the number of progressed patients as denominator. Olaparib and NHA arm adjusted to remove subsequent PARP inhibitor use in alignment with switching adjusted OS (base case) setting |
| Distribution of subsequent treatments | Olaparib: PROfound CSR<br>BSC/NHA: PROfound CSR<br>cabazitaxel: TROPIC study; de Wit 2019<br>docetaxel: assumed the same as cabazitaxel | Consistent with the % of patients receiving subsequent treatment inputs. |
| Frequency and % of patients receiving MRUs while on treatment | Different MRUs associated with first 3 months versus months 4+. | Clinical expert opinion |
| Frequency and % of patients receiving MRUs while off treatment | MRUs associated with off treatment, regardless of time length. | Clinical expert opinion |
| Probability of experiencing AE (grade 3+) | olaparib: PROfound CSR<br>NHA: PROfound CSR<br>cabazitaxel: CARD study; de Wit 2019<br>docetaxel: TAX 327 study; SmPC | Based on best available data. |
| Distribution of SREs | AFFIRM (TA316) (NICE 2014) | Based on best available data and assumptions |
| Probability of experiencing at least one SRE | olaparib: 23.58% (PROfound Cohort A)<br>NHA: 27.94% (PROfound Cohort A)<br>cabazitaxel and docetaxel: assumed the same as NHA | SRE cost is applied as one-off to patients who progressed, therefore the % was adjusted by using the number of progressed patients as denominator (assumed due to lack of data) |

Abbreviations: AE = adverse event; BICR = blinded independent central review; BRCA = BReast CAncer gene; HR = hazard ratio; NHA = new hormonal agent; KM = Kaplan-Meier; MRU = medical resource use; OS = overall survival; PARP = poly adenosine diphosphate-ribose

polymerase; rPFS = radiographic progression-free survival; RPSFTM = rank preserving structural failure time model; SmPC = summary of product characteristics; SRE = skeletal-related event;

*Table 32. PFS, TTD and OS in the base case analysis (BRCAm population).*

| Intervention | PFS | TTD | OS |
|---|---|---|---|
| Olaparib | 9.1 | 10.3 | 22.5 |
| BSC | 4.6 | 5.5 | 10.2 |
| Docetaxel | 8.2 | 9.5 | 13.0 |
| Cabazitaxel | 8.2 | 9.5 | 13.0 |

## 11.9 Patient population in the budget impact analysis

The model uses the total male population in Denmark as a starting point and the specific target population is estimated based on the overall incidence of prostate cancer and disease characteristics of patients in the indication, such as proportion of patients with metastatic disease, proportion receiving first line treatment with NHA, proportion of patients receiving second line treatment and BRCA mutation status.

Given the epidemiology and an assumption of the proportion of patients who receiving NHA treatment in the first line, it is estimated that around 52 patients per year would be eligible for treatment with olaparib in the BRCA positive mCRPC setting (Table 33, Figure 40).

In the protocol from Medicinrådet (page 5), it is estimated that approximately 5% of the total 1500 newly diagnosed patients with mCRPC patients per year in Denmark are BRCA mutated. This corresponds to at most 75 new patients per year with BRCAm mCRPC. Our own patient funnel estimates that around 52 patients would be eligible for treatment with olaparib in the setting, in spite a higher estimated occurrence of BRCA mutations (9.7%). This is because not all patients will receive treatment with NHA in the first line setting, not all patients will go on to second-line treatment and not all will be suitable for treatment with olaparib.

*Table 33 Model inputs used to estimate the number of patients eligible for treatment with olaparib.*

| | | |
|---|---|---|
| Total male population | 2 907 791 | Statistics Denmark: https://www.statbank.dk/10022 |
| Incidence of prostate cancer (per 100,000) | 0.16% | NordCan / Statistics Denmark |
| % patients with mCRPC | 30% | Protocol on olaparib in mCRPC, Medicinrådet (1500/4674 = 32%) |
| % of patients receiving 1L NHA treatment in mCRPC | 77% | Medicinrådet - Behandlingsvejledning, mCRPC |
| % patients who receive 2L treatment | 90% | Assumption, not all go with 2nd line treatment |
| % of patients with BRCAm | 9.7% | De Bono (2019) |
| Eligible for olaparib | 52% | De Bono (2019) & De Bono (2020) |
| Eligible population | 52 | |

Within the overall eligible population, the number of patients will vary depending on treatment path (Figure 40). For BRCAm positive patients, olaparib could be an alternative to docetaxel for patients

treated with docetaxel after NHA in the first line. Secondly, olaparib could also be an alternative for patients treated with docetaxel in the first line and NHA in the second. Thirdly, olaparib could be an alternative to best supportive care (BSC) for patients who have already been treated with NHA, docetaxel and cabazitaxel and who are running out of options.

For these pathways, the following potential patient numbers have been estimated based on epidemiology and patient characteristics:

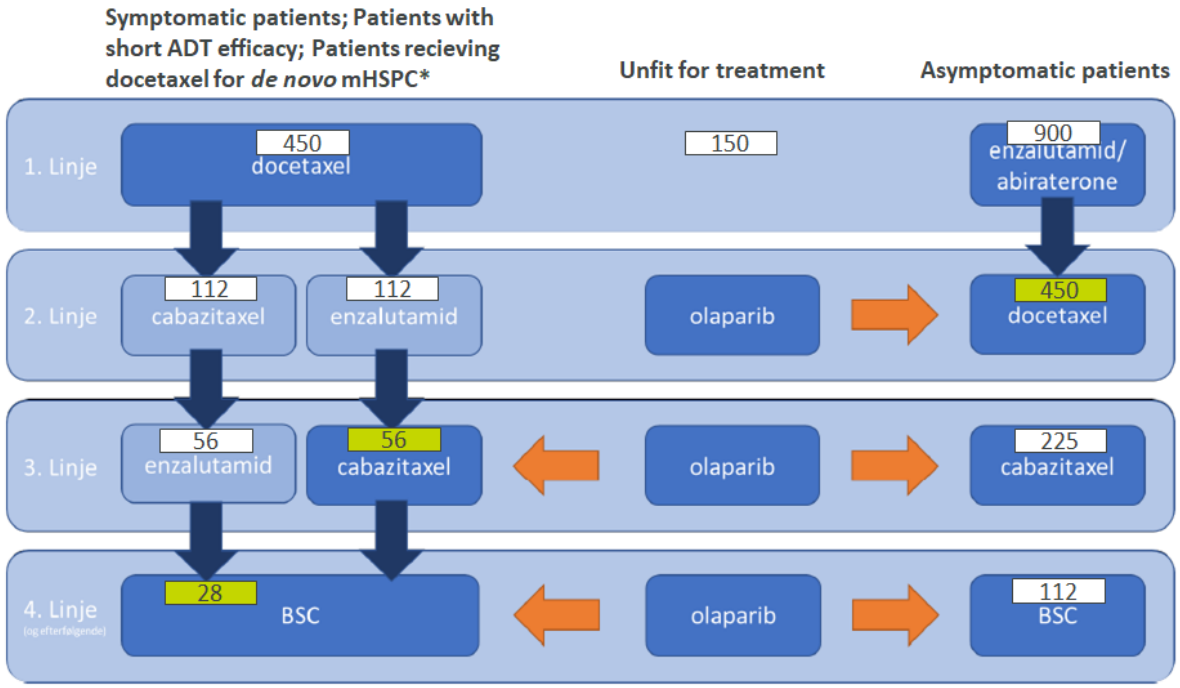
1) Full recommendation according to the EMA label: (450 + 56 + 28) x 9.7% = 52 patients.

2) Recommendation after docetaxel (and NHA): (225+56+28) x 9.7% = 30 patients

3) Recommendation after docetaxel and cabazitaxel (olaparib as alternative to BSC): (112 + 28) x 9.7% = 14 patients

These estimates assume 100% BRCA testing rate and identification of BRCA1/2-mut patients in time to get olaparib at the earliest possible point in the treatment pathway. Hence, the number of patients is likely to be smaller in clinical reality.

*Figure 40 Patient funnel for mCRPC in Denmark.*



## 11.10 Market shares in the budget impact analysis

Market shares for the overall BRCAm patient population are shown in Table 34 for scenario without olaparib and in Table 35 for scenario with olaparib. It is assumed that some prescriptions could occur even without a recommendation, but absolute patient numbers on olaparib in mCRPC would the be small, only 2-3 patients per year as last resort treatment. Market shares have also been estimated separately for each clinical question/subpopulation identified by Medicinrådet for scenario analyses (Tables 36-41). In the subpopulations, a simplifying assumption is made that olaparib has the same market share as in the overall population. This is probably not entirely true, as the market share might be higher in the prior taxane (post docetaxel) setting) and in particular in the comparison against BSC.

### 11.10.1 Overall population

Comparators: Docetaxel, Cabazitaxel and BSC.

*Table 34. Scenario without olaparib – overall population*

| | Year | | | | |
|---|---|---|---|---|---|
| **Treatment** | **2021** | **2022** | **2023** | **2024** | **2025** |
| Olaparib | 0% | 3% | 4% | 5% | 6% |
| Cabazitaxel (IV) | 10% | 12% | 15% | 14% | 14% |
| Docetaxel (IV) | 84% | 80% | 75% | 74% | 72% |
| BSC | 6% | 5% | 6% | 7% | 8% |

*Table 35. Scenario with olaparib – overall population*

| | Year | | | | |
|---|---|---|---|---|---|
| **Treatment** | **2021** | **2022** | **2023** | **2024** | **2025** |
| Olaparib | 15% | 45% | 60% | 66% | 67% |
| Cabazitaxel (IV) | 9% | 8% | 7% | 6% | 5% |
| Docetaxel (IV) | 71% | 41% | 27% | 23% | 23% |
| BSC | 5% | 6% | 6% | 5% | 5% |

### 11.10.2 Taxane-chemotherapy naive subgroup

Comparator: Docetaxel

*Table 36. Scenario without olaparib – Taxane-chemotherapy naive population*

| | Year | | | | |
|---|---|---|---|---|---|
| **Treatment** | **2021** | **2022** | **2023** | **2024** | **2025** |
| Olaparib | 0% | 3% | 4% | 5% | 6% |
| Cabazitaxel (IV) | 0% | 0% | 0% | 0% | 0% |
| Docetaxel (IV) | 100% | 97% | 96% | 95% | 94% |
| BSC | 0% | 0% | 0% | 0% | 0% |

*Table 37. Scenario with olaparib – Taxane-chemotherapy naive population*

| | Year | | | | |
|---|---|---|---|---|---|
| **Treatment** | **2021** | **2022** | **2023** | **2024** | **2025** |
| Olaparib | 15% | 45% | 60% | 66% | 67% |
| Cabazitaxel (IV) | 0% | 0% | 0% | 0% | 0% |
| Docetaxel (IV) | 85% | 55% | 40% | 34% | 33% |
| BSC | 0% | 0% | 0% | 0% | 0% |

### 11.10.3 Prior taxane subgroup

Comparator: Cabazitaxel (post-docetaxel setting)

*Table 38. Scenario without olaparib – Prior taxane population*

| | Year | | | | |
|---|---|---|---|---|---|
| **Treatment** | **2021** | **2022** | **2023** | **2024** | **2025** |
| Olaparib | 0% | 3% | 4% | 5% | 6% |
| Cabazitaxel (IV) | 100% | 97% | 96% | 95% | 94% |
| Docetaxel (IV) | 0% | 0% | 0% | 0% | 0% |
| BSC | 0% | 0% | 0% | 0% | 0% |

*Table 39. Scenario with olaparib – Prior taxane population*

| | Year | | | | |
|---|---|---|---|---|---|
| **Treatment** | **2021** | **2022** | **2023** | **2024** | **2025** |
| Olaparib | 15% | 45% | 60% | 66% | 67% |
| Cabazitaxel (IV) | 85% | 55% | 40% | 34% | 33% |
| Docetaxel (IV) | 0% | 0% | 0% | 0% | 0% |
| BSC | 0% | 0% | 0% | 0% | 0% |

### 11.10.4 Best supportive care population

Patients who have progressed after treatment with NHA, docetaxel and cabazitaxel and who do not have other treatment opportunities than best supportive care.

Comparator: Best supportive care (BSC)

*Table 40. Scenario without olaparib – BSC population*

| | Year | | | | |
|---|---|---|---|---|---|
| **Treatment** | **2021** | **2022** | **2023** | **2024** | **2025** |
| Olaparib | 0% | 3% | 4% | 5% | 6% |
| Cabazitaxel (IV) | 0% | 0% | 0% | 0% | 0% |
| Docetaxel (IV) | 0% | 0% | 0% | 0% | 0% |
| BSC | 100% | 97% | 96% | 95% | 94% |

*Table 41. Scenario with olaparib – BSC population*

| | Year | | | | |
|---|---|---|---|---|---|
| **Treatment** | **2021** | **2022** | **2023** | **2024** | **2025** |
| Olaparib | 15% | 45% | 60% | 66% | 67% |
| Cabazitaxel (IV) | 0% | 0% | 0% | 0% | 0% |
| Docetaxel (IV) | 0% | 0% | 0% | 0% | 0% |
| BSC | 85% | 55% | 40% | 34% | 33% |

# 12 Results

The results of the base case analysis along with scenario and sensitivity analyses for comparisons in BRCAm overall, no prior taxane (vs docetaxel), prior taxane (vs cabazitaxel) and best supportive care populations are presented below.

## 12.1 Base case results

### 12.1.1 Cost per patient – overall patient population

The key results from the base-case in the BRCAm overall population are summarized in Table 42. Over a 10-year time horizon, treatment with olaparib was associated with a higher total cost. The discounted costs over 10 years were DKK 574 840, compared with DKK 102 382 for docetaxel, DKK 268 933 for cabazitaxel and DKK 102 984 for best supportive care. The resulting incremental cost for olaparib versus docetaxel 472 458 kr, versus cabazitaxel 305 907 kr and versus BSC was 471 946 kr.

*Table 42 Base-case results (discounted) vs. comparators in the BRCAm overall population (10-year time horizon)*

| **Cost Outcomes** | **Olaparib** | **BSC** | **Cabazitaxel** | **Docetaxel** |
|---|---|---|---|---|
| **TOTAL Costs Discounted** | **574 840 kr** | **102 894 kr** | **268 933 kr** | **102 382 kr** |
| ***Direct Medical Costs*** | ***564 119 kr*** | ***98 294 kr*** | ***263 427 kr*** | ***96 875 kr*** |
| Drug costs: Treatment | 445 922 kr | 22 885 kr | 171 470 kr | 2 214 kr |
| Admin costs: Treatment | 0 kr | 0 kr | 10 176 kr | 11 650 kr |
| Concomitant medication costs | 1 561 kr | 383 kr | 3 650 kr | 4 185 kr |
| AE management costs | 4 829 kr | 3 600 kr | 1 730 kr | 2 426 kr |
| SSRE management costs | 13 125 kr | 18 442 kr | 16 723 kr | 16 723 kr |
| Disease management costs: On treatment | 40 164 kr | 12 414 kr | 18 940 kr | 18 940 kr |
| Disease management costs: Off treatment | 26 707 kr | 11 760 kr | 12 976 kr | 12 976 kr |
| Disease management costs: Progression | 6 079 kr | 7 210 kr | 6 538 kr | 6 538 kr |
| Disease management costs: Terminal care | 7 734 kr | 8 109 kr | 8 043 kr | 8 043 kr |
| Subsequent treatment costs | 17 998 kr | 13 491 kr | 13 180 kr | 13 180 kr |
| ***Direct Non-medical Costs*** | ***10 721 kr*** | ***4 600 kr*** | ***5 507 kr*** | ***5 507 kr*** |
| Patient time and transportation costs | 10 721 kr | 4 600 kr | 5 507 kr | 5 507 kr |
| **Cost difference olaparib vs. comparator** | | **471 946 kr** | **305 907 kr** | **472 458 kr** |

### 12.1.2 Budget impact

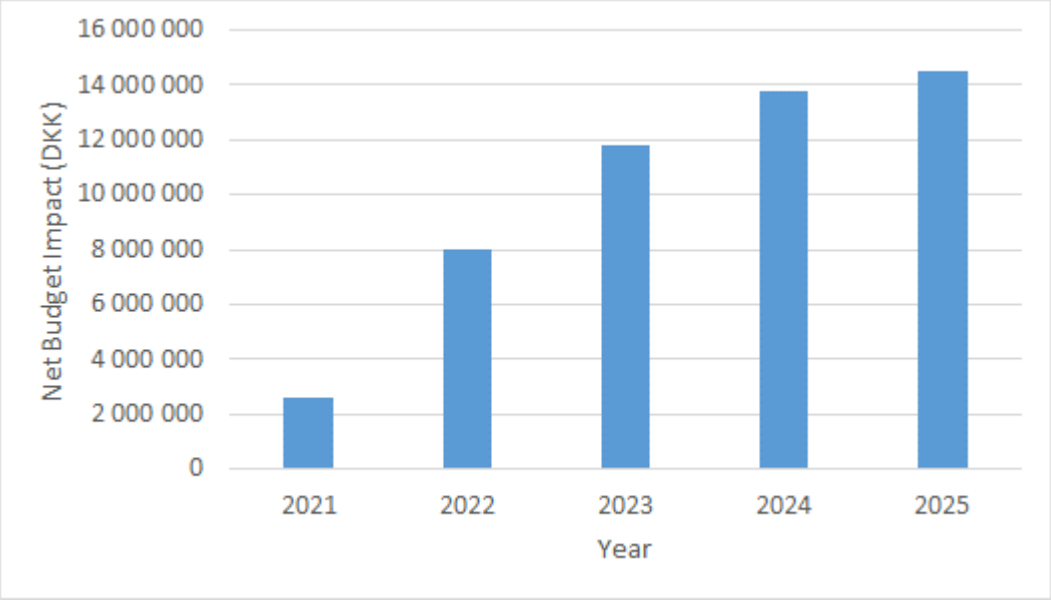
#### 12.1.2.1 Budget impact for the whole population

The key results from the base-case budget impact are summarized in Table 43. Over a 5-year time horizon, treatment with olaparib was associated with a higher total cost. The resulting net budget impact for olaparib versus a situation without olaparib recommended increased from 2.6 million DKK in 2021 to 14.5 million DKK in 2025.

*Table 43 Budget impact with 5-year time perspective (DKK)*

| **Budget impact by year** | **2021** | **2022** | **2023** | **2024** | **2025** |
|---|---|---|---|---|---|
| Gross budget impact with olaparib | 7 787 502 | 14 532 904 | 19 014 854 | 21 186 983 | 22 170 102 |
| Gross budget impact without olaparib | 5 205 083 | 6 514 698 | 7 178 735 | 7 385 615 | 7 667 040 |
| Net budget impact per year with olaparib | 2 582 420 | 8 018 206 | 11 836 119 | 13 801 368 | 14 503 061 |

*Figure 41 Net budget impact over time in the overall population.*



## 12.2 Scenario analyses

### 12.2.1 BRCAm no-prior taxane population

#### 12.2.1.1 Cost per patient - Comparison vs docetaxel

The key results from the base-case in a BRCAm no-prior taxane population are summarized in Table 44. Over a 10-year time horizon, treatment with olaparib was associated with a higher total cost (714 993 kr vs 88 388 kr). The resulting incremental cost for olaparib versus docetaxel was 626 605 kr.

*Table 44 Base-case results (discounted) vs. comparators in the BRCAm prior taxane population (10-year time horizon)*

| Cost Outcomes | Olaparib | Docetaxel |
|---|---|---|
| **TOTAL Costs Discounted** | **714 993 kr** | **88 388 kr** |
| ***Direct Medical Costs*** | ***702 341 kr*** | ***84 330 kr*** |
| Drug costs: Treatment | 567 619 kr | 2 058 kr |
| Admin costs: Treatment | 0 kr | 10 833 kr |
| Concomitant medication costs | 2 054 kr | 3 813 kr |
| AE management costs | 4 829 kr | 2 426 kr |
| SSRE management costs | 14 380 kr | 16 010 kr |
| Disease management costs: On treatment | 52 737 kr | 15 210 kr |
| Disease management costs: Off treatment | 26 672 kr | 6 922 kr |
| Disease management costs: Progression | 6 660 kr | 6 259 kr |
| Disease management costs: Terminal care | 7 672 kr | 8 180 kr |
| Subsequent treatment costs | 19 718 kr | 12 618 kr |
| ***Direct Non-medical Costs*** | ***12 651 kr*** | ***4 058 kr*** |
| Patient time and transportation costs | 12 651 kr | 4 058 kr |
| **Cost difference olaparib vs. comparator** | | **626 605 kr** |

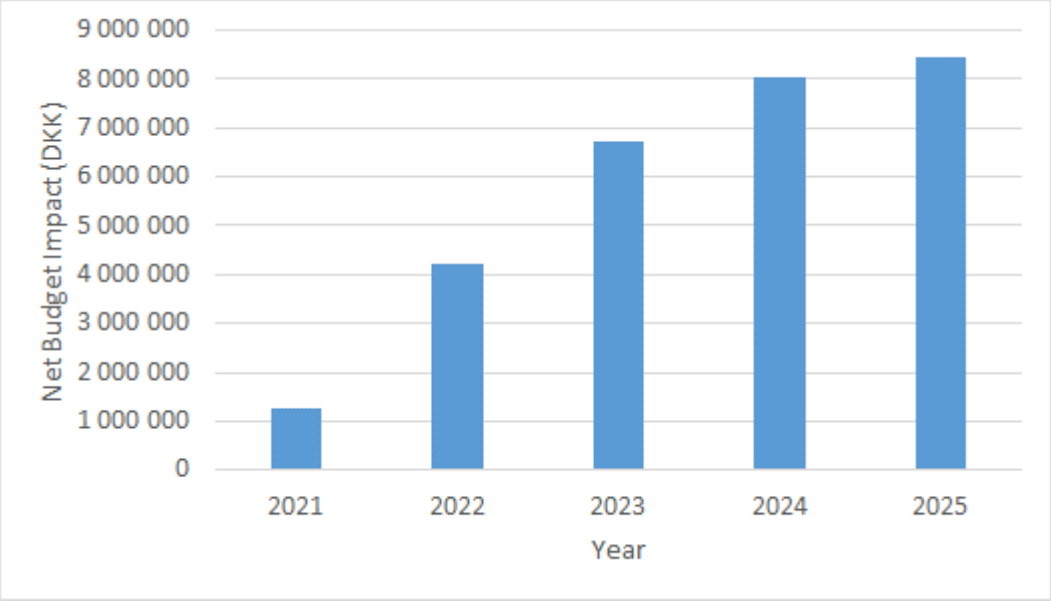
### 12.2.1.2 Budget impact - Comparison vs docetaxel

The key results from the budget impact comparing to docetaxel in the no-prior taxane population are summarized in Table 45. Over a 5-year time horizon, treatment with olaparib was associated with a higher total cost. The resulting net budget impact for olaparib versus a situation without olaparib recommended increased from DKK 1.3 million in 2021 to DKK 8.4 million in 2025.

*Table 45 Budget impact with 5-year time perspective (DKK)*

| **Budget impact by year** | **2021** | **2022** | **2023** | **2024** | **2025** |
|---|---|---|---|---|---|
| Gross budget impact with olaparib | 3 092 016 | 6 327 322 | 9 060 948 | 10 530 724 | 11 102 978 |
| Gross budget impact without olaparib | 1 827 400 | 2 118 307 | 2 342 165 | 2 504 030 | 2 654 998 |
| Net budget impact per year with olaparib | 1 264 617 | 4 209 016 | 6 718 783 | 8 026 694 | 8 447 980 |

*Figure 42. Net budget impact over time in the no-prior taxane population*



### 12.2.2 BRCAm prior taxane population

#### 12.2.2.1 Comparison vs cabazitaxel

The key results from the base-case in a BRCAm prior taxane population (post-docetaxel) are summarized in Table 46. Over a 10-year time horizon, treatment with olaparib was associated with a higher total cost (517 402 kr vs 253 283 kr). The resulting incremental cost for olaparib versus cabazitaxel was 264 119 kr.

*Table 46 Base-case results (discounted) vs. comparators in the BRCAm prior taxane population (10-year time horizon)*

| Cost Outcomes | Olaparib | Cabazitaxel |
|---|---|---|
| **TOTAL Costs Discounted** | **517 402 kr** | **253 283 kr** |
| ***Direct Medical Costs*** | ***507 853 kr*** | ***248 154 kr*** |
| Drug costs: Treatment | 398 694 kr | 160 167 kr |
| Admin costs: Treatment | 0 kr | 9 505 kr |
| Concomitant medication costs | 1 369 kr | 3 355 kr |
| AE management costs | 4 829 kr | 1 730 kr |
| SSRE management costs | 12 725 kr | 16 538 kr |
| Disease management costs: On treatment | 35 284 kr | 16 615 kr |
| Disease management costs: Off treatment | 23 805 kr | 12 683 kr |
| Disease management costs: Progression | 5 894 kr | 6 465 kr |
| Disease management costs: Terminal care | 7 804 kr | 8 062 kr |
| Subsequent treatment costs | 17 449 kr | 13 034 kr |
| ***Direct Non-medical Costs*** | ***9 549 kr*** | ***5 129 kr*** |
| Patient time and transportation costs | 9 549 kr | 5 129 kr |
| **Cost difference olaparib vs. comparator** | | **264 119 kr** |

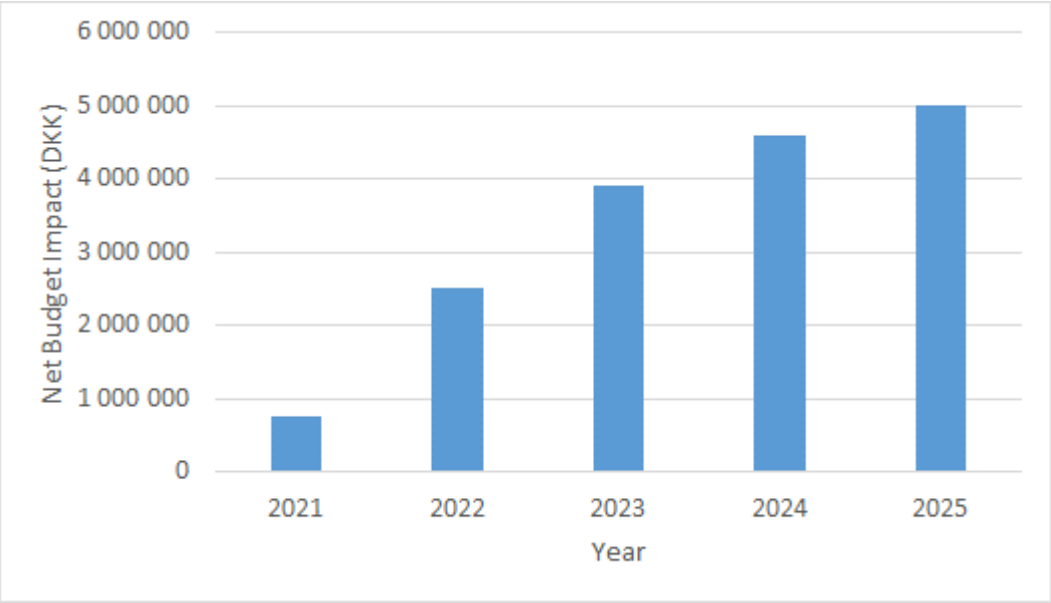
### 12.2.2.2 Budget impact - Comparison vs cabazitaxel

The key results from the budget impact in the prior taxane population are summarized in Table 47. Over a 5-year time horizon, treatment with olaparib was associated with a higher total cost. The resulting net budget impact for olaparib versus a situation without olaparib recommended increased from DKK 0.8 million in 2021 to DKK 5.0 million in 2025.

*Table 47 Budget impact with 5-year time perspective (DKK)*

| **Budget impact by year** | **2021** | **2022** | **2023** | **2024** | **2025** |
|---|---|---|---|---|---|
| Gross budget impact with olaparib | 7 869 608 | 10 114 768 | 11 677 981 | 12 474 911 | 12 987 429 |
| Gross budget impact without olaparib | 7 097 656 | 7 601 514 | 7 771 392 | 7 885 238 | 7 994 770 |
| Net budget impact per year with olaparib | 771 952 | 2 513 253 | 3 906 590 | 4 589 672 | 4 992 659 |

*Figure 43. Net budget impact over time in the prior taxane population*



### 12.2.3 Best supportive care population

#### 12.2.3.1 Comparison vs BSC

The key results from the base-case in a best supportive population are summarized in Table 48. Over a 10-year time horizon, treatment with olaparib was associated with a higher total cost (574 840 kr vs 102 894 kr). The resulting incremental cost for olaparib versus BSC was 471 946 kr.

*Table 48 Base-case results (discounted) vs. comparators in the BRCAm prior taxane population (10-year time horizon)*

| Cost Outcomes | Olaparib | BSC |
|---|---|---|
| **TOTAL Costs Discounted** | **574 840 kr** | **102 894 kr** |
| ***Direct Medical Costs*** | ***564 119 kr*** | ***98 294 kr*** |
| Drug costs: Treatment | 445 922 kr | 22 885 kr |
| Admin costs: Treatment | 0 kr | 0 kr |
| Concomitant medication costs | 1 561 kr | 383 kr |
| AE management costs | 4 829 kr | 3 600 kr |
| SSRE management costs | 13 125 kr | 18 442 kr |
| Disease management costs: On treatment | 40 164 kr | 12 414 kr |
| Disease management costs: Off treatment | 26 707 kr | 11 760 kr |
| Disease management costs: Progression | 6 079 kr | 7 210 kr |
| Disease management costs: Terminal care | 7 734 kr | 8 109 kr |
| Subsequent treatment costs | 17 998 kr | 13 491 kr |
| ***Direct Non-medical Costs*** | ***10 721 kr*** | ***4 600 kr*** |
| Patient time and transportation costs | 10 721 kr | 4 600 kr |
| **Cost difference olaparib vs. comparator** | | **471 946 kr** |

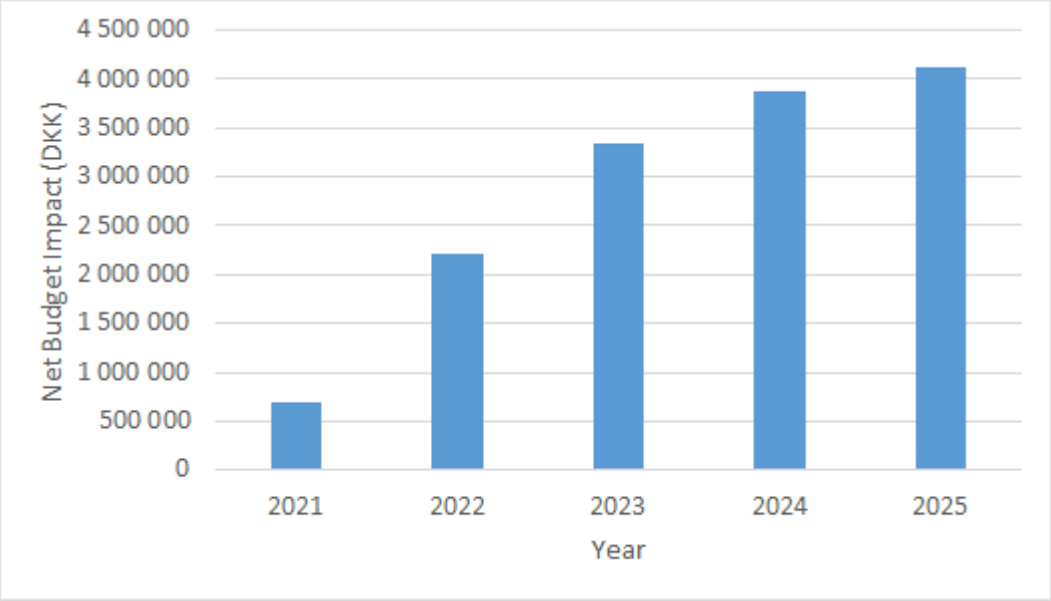
### 12.2.3.2 Budget impact - Comparison vs BSC

The key results from the budget impact in the BSC population are summarized in Table 49. Over a 5-year time horizon, treatment with olaparib was associated with a higher total cost. The resulting net budget impact for olaparib versus a situation without olaparib recommended increased from 0.7 million DKK in 2021 to 4.1 million DKK in 2025.

*Table 49 Budget impact with 5-year time perspective (DKK)*

| **Budget impact by year** | **2021** | **2022** | **2023** | **2024** | **2025** |
|---|---|---|---|---|---|
| Gross budget impact with olaparib | 1 987 773 | 3 729 444 | 4 961 296 | 5 572 445 | 5 900 350 |
| Gross budget impact without olaparib | 1 286 881 | 1 521 573 | 1 626 749 | 1 701 625 | 1 775 261 |
| Net budget impact per year with olaparib | 700 892 | 2 207 871 | 3 334 547 | 3 870 820 | 4 125 088 |

*Figure 44. Net budget impact over time in the BSC population.*



## 12.3 Further sensitivity and scenario analyses

A series of scenario analyses were conducted to assess the impact of using alternative parameter estimates. Table 49 and 50 present a list of scenarios that were explored along with the cost per patient and budget impact estimates.

The scenario analyses indicated that:

- Longer time horizons did not impact the cost or budget impact estimates, which demonstrates the 10-year time horizon in base case is enough to capture long-term survival projections and represents a lifetime time horizon.
- A shorter time horizon is associated with a slightly smaller cost per patient, but the difference is less than 1%.
- Scenarios with negligible differences from base case (reduced costs in most cases) were generated by the scenarios around discount rates and excluding costs for AEs and SREs, disease management, subsequent therapies and patient time and transportation costs.
- Excluding costs for gene mutation test cost had a larger impact on the costs (decreased by 9 – 14% depending on comparator).
- Using alternative parametric models for OS (Generalized gamma and Gompertz) had very little impact on the cost estimates
- Using alternative parametric models for PFS (Generalized gamma and Gompertz) had more impact on the cost estimates, but still relatively limited (between -2.2% and +5.8% depending on parametric model and comparator). Yet, the results are limited by the substantial uncertainties in the long-term OS projection with the tail lacking clinical plausibility (i.e. Gompertz underestimates the OS curve and Generalized gamma predicts an unrealistically flat tail in the NHA arm which overestimates the long-term rPFS) and, therefore should be interpreted with caution.
- Using time to treatment discontinuation instead (TTD) of PFS as a basis for the cost estimates had a similar impact, increasing the cost per patient with between 2.6% and 5.6% depending on parametric model and comparator.
- Not surprisingly, varying the cost of olaparib by +/- 20% had a large impact on the cost estimates (between -19.3% and +19.3%)
- On the other hand, varying the cost of disease management by +/- 20% had a relatively small impact on the cost per patient and budget estimates (between -2.0% and +2.0%).

*Table 50 Sensitivity and scenario analysis results for BRCAm overall population – Cost per patient*

| BRCAm overall population – Cost per patient analysis | | | | | |
|---|---|---|---|---|---|
| **Scenario description** | **Base Case** | **Alternative Scenario** | **Cost difference vs BSC** | **Cost difference vs cabazitaxel** | **Cost difference vs docetaxel** |
| **Base case** | | | **471 946 kr** | **305 907 kr** | **472 458 kr** |
| **General Setting** | | | | | |
| Time horizon | 10 years | 15 years | 472 007 kr | 305 968 kr | 472 519 kr |
| | | 5 years | 469 133 kr | 303 094 kr | 469 645 kr |
| Discount rate (health and cost outcomes) | 3.5% | 0% | 478 502 kr | 312 126 kr | 478 677 kr |
| | | 5% | 469 333 kr | 303 431 kr | 469 982 kr |
| **Efficacy Inputs** | | | | | |
| OS efficacy projection: olaparib and NHA | Parametric fitting based on PROfound trial patient-level data (Weibull) | Generalized gamma | 465 878 kr | 297 971 kr | 464 522 kr |
| | | Gompertz | 468 025 kr | 303 837 kr | 470 389 kr |
| rPFS efficacy projection: olaparib and NHA | Parametric fitting based on PROfound trial patient-level data (Gompertz) | Weibull | 502 277 kr | 330 806 kr | 501 774 kr |
| | | Generalized gamma | 471 760 kr | 311 688 kr | 477 057 kr |
| OS and rPFS efficacy projections for olaparib and NHA | Same as above | Generalized gamma | 465 244 kr | 302 918 kr | 468 287 kr |
| **Treatment Duration** | | | | | |
| Treatment duration | Treat until progression | Parametric fitting based on PROfound trial patient-level data TTD: Gompertz | 473 679 kr | 333 494 kr | 491 157 kr |
| | | Parametric fitting based on PROfound trial patient-level data TTD: Generalized Gamma | 467 936 kr | 322 992 kr | 485 211 kr |

| | | | | | |
|---|---|---|---|---|---|
| | | Parametric fitting based on PROfound trial patient-level data TTD:<br>Olaparib: Gompertz (best fit)<br>NHA: Lognormal (best fit) | 473 150 kr | 326 652 kr | 489 723 kr |
| Cost Inputs | | | | | |
| Gene mutation testing cost | Include | Exclude | 429 544 kr | 263 505 kr | 430 056 kr |
| Subsequent treatment cost | Include | Exclude | 467 439 kr | 301 089 kr | 467 640 kr |
| AE costs | Include | Exclude | 470 717 kr | 302 808 kr | 470 056 kr |
| SRE costs | Include | Exclude | 477 262 kr | 309 504 kr | 476 055 kr |
| Disease management costs | Include | Exclude | 424 634 kr | 266 506 kr | 433 057 kr |
| Patient time and transportation costs | Include | Exclude | 465 824 kr | 300 692 kr | 467 243 kr |
| Cost of olaparib | List price (AIP) | -20% on AIP | 391 242 kr | 225 203 kr | 391 754 kr |
| | | +20% on AIP | 552 650 kr | 386 611 kr | 553 162 kr |
| Disease management costs | List prices | -20% | 462 483 kr | 298 027 kr | 462 538 kr |
| | | +20% | 481 408 kr | 313 787 kr | 482 378 kr |

*Table 51 Sensitivity and scenario analysis results for BRCAm overall population – Budget impact*

| BRCAm overall population – Budget impact analysis | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Scenario description | Base case | Alternative scenario | Budget impact (DKK) | | | | | Percent change vs base case | | | | |
| | | | 2021 | 2022 | 2023 | 2024 | 2025 | 2021 | 2022 | 2023 | 2024 | 2025 |
| Base case | | | 2 582 420 | 8 018 206 | 11 836 119 | 13 801 368 | 14 503 061 | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% |
| Efficacy Inputs | | | | | | | | | | | | |
| OS efficacy projection: olaparib and NHA | Parametric fitting based on PROfound trial patient-level data (Weibull) | Generalized gamma | 2 585 148 | 8 021 711 | 11 827 901 | 13 765 390 | 14 438 286 | 0.1% | 0.0% | -0.1% | -0.3% | -0.4% |
| | | Gompertz | 2 590 911 | 8 055 018 | 11 907 768 | 13 877 227 | 14 511 120 | 0.3% | 0.5% | 0.6% | 0.5% | 0.1% |
| rPFS efficacy projection: olaparib and NHA | Parametric fitting based on PROfound trial patient-level data (Gompertz) | Weibull | 2 526 177 | 7 949 247 | 12 041 375 | 14 406 236 | 15 341 127 | -2.2% | -0.9% | 1.7% | 4.4% | 5.8% |
| | | Generalized gamma | 471 760 kr | 311 688 kr | 477 057 kr | 471 760 kr | 311 688 kr | 0.8% | 0.9% | 0.9% | 0.9% | 0.9% |
| OS and rPFS efficacy projections for olaparib and NHA | Same as above | Generalized gamma | 2 605 952 | 8 095 043 | 11 942 672 | 13 891 326 | 14 546 807 | 0.9% | 1.0% | 0.9% | 0.7% | 0.3% |
| Treatment Duration | | | | | | | | | | | | |
| Treatment duration | Treat until progression | Parametric fitting based on PROfound trial patient-level data TTD: Gompertz | 2 727 891 | 8 465 712 | 12 430 201 | 14 414 415 | 15 098 016 | 5.6% | 5.6% | 5.0% | 4.4% | 4.1% |
| | | Parametric fitting based | 2 679 282 | 8 338 664 | 12 263 097 | 14 216 104 | 14 886 216 | 3.8% | 4.0% | 3.6% | 3.0% | 2.6% |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | on PROfound trial patient-level data TTD: Generalized Gamma | | | | | | | | | | |
| | | Parametric fitting based on PROfound trial patient-level data TTD: Olaparib: Gompertz (best fit) NHA: Lognormal (best fit) | 2 715 286 | 8 423 207 | 12 366 975 | 14 347 104 | 15 027 235 | 5.1% | 5.1% | 4.5% | 4.0% | 3.6% |
| **Cost Inputs** | | | | | | | | | | | | |
| Gene mutation testing cost | Include | Exclude | 2 251 235 | 7 087 578 | 10 590 950 | 12 440 333 | 13 137 249 | -12.8% | -11.6% | -10.5% | -9.9% | -9.4% |
| Subsequent treatment cost | Include | Exclude | 2 603 005 | 8 019 794 | 11 755 856 | 13 666 288 | 14 312 977 | 0.8% | 0.0% | -0.7% | -1.0% | -1.3% |
| Disease management costs | Include | Exclude | 2 536 673 | 7 800 791 | 11 345 023 | 13 034 684 | 13 307 678 | -1.8% | -2.7% | -4.1% | -5.6% | -8.2% |
| AE costs | Include | Exclude | 2 563 903 | 7 963 408 | 11 762 648 | 13 722 557 | 14 424 227 | -0.7% | -0.7% | -0.6% | -0.6% | -0.5% |
| SRE costs | Include | Exclude | 2 648 656 | 8 153 180 | 11 948 078 | 13 890 049 | 14 573 639 | 2.6% | 1.7% | 0.9% | 0.6% | 0.5% |
| Cost of olaparib | List price (AIP) | -20% on AIP | 2 083 473 | 6 485 159 | 9 586 914 | 11 243 836 | 11 887 592 | -19.3% | -19.1% | -19.0% | -18.5% | -18.0% |
| | | +20% on AIP | **3 081 366** | **9 551 253** | **14 085 324** | **16 358 900** | **17 118 531** | 19.3% | 19.1% | 19.0% | 18.5% | 18.0% |
| | List prices | -20% | 2 561 168 | 7 938 286 | 11 692 898 | 13 600 052 | 14 217 725 | -0.8% | -1.0% | -1.2% | -1.5% | -2.0% |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Disease management costs | | +20% | 2 603 671 | 8 098 125 | 11 979 339 | 14 002 684 | 14 788 398 | 0.8% | 1.0% | 1.2% | 1.5% | 2.0% |

# 13 Discussion and conclusions

## 13.1 Summary of results

Metastatic castrate-resistant prostate cancer (mCRPC) is currently considered an incurable disease with high incidence and mortality rates worldwide. Following progression to castration-resistant disease, therapeutic options are limited, with a decrease in the duration of response with each line of treatment. New hormonal agents (NHA) circumvent ADT resistance but cancer progression is almost inevitable, limiting later-line treatment availability (Berruti 2018, Saeterdal 2016). Taxane-based chemotherapy is also associated with treatment resistance and cross-resistance to abiraterone and enzalutamide (van Soest 2013). Furthermore, limited guidance is currently available on the optimal sequencing of NHAs and taxanes to both prolong survival and minimize the economic burden (Akaza 2018). HRR gene mutations, including those found in *BRCA1*, *BRCA2* and *ATM,* have recently been identified in patients with mCRPC, and it has been suggested that these individuals experience more aggressive disease than those without such mutations (Nombela 2019, Castro 2019, Pritchard 2016). The recent approval of the PARP inhibitor olaparib for patients with a *BRCA1* or *BRCA2* mutated mCRPC who have progressed following a prior new hormonal agent (NHA, e.g. abiraterone and enzalutamide) widens treatment options in a population where there were previously no approved BRCAm-targeted therapies (Robinson 2015).

PROfound is an open-label, head-to-head international multicenter phase III randomized trial. It is the first positive biomarker-selected phase III trial evaluating a molecularly targeted therapy in men with mCRPC. PROfound investigates the efficacy of olaparib compared with investigator's choice of new hormonal agent (icNHA) (i.e., either enzalutamide or abiraterone acetate plus prednisone) for patients with mCRPC who have failed prior treatment with a new hormonal agent (e.g., enzalutamide and/or abiraterone acetate) and have a qualifying tumour mutation. The PROfound study met its primary endpoint, demonstrating a statistically significant and clinically meaningful 66% reduction in the risk of BICR-assessed rPFS in the olaparib arm of Cohort A compared with the physicians' choice of NHA arm. Olaparib was also associated with a statistically significant and clinically meaningful increase in OS despite approximately two-thirds of patients in the physicians' choice of NHA arm switching to the olaparib post-BICR-assessed progression at DCO1 or investigator-assessed progression at DCO2. The olaparib-related treatment benefit is further supported by the outcomes of the treatment switching analysis (RPSFTM), which estimated an HR for OS for olaparib vs. physicians' choice of NHA, used as a proxy for BSC in the cost analysis. In addition, the indirect treatment comparison estimated an HR for OS for olaparib vs. cabazitaxel. Patients who received olaparib generally experienced a longer time to deterioration across a range of patient-reported symptoms, functioning and HRQoL measures than those who received physicians' choice of NHA. As pain and SREs significantly contribute to reduced HRQoL in patients with mCRPC. Olaparib was well tolerated, with a safety profile consistent with that for existing indications in breast, ovarian and pancreatic tumors.

To assess whether the clinical benefits associated with olaparib can be achieved at a reasonable cost, a cost analysis using a lifetime survival partition modelling approach was performed to estimate the cost per patient of olaparib vs. relevant comparators in the treatment of mCRPC. In the base case, , the results on average cost per patient showed that for patients treated with olaparib, the discounted costs over 10 years were DKK 574 840, compared with DKK 102 382 for docetaxel, DKK 305 907 for cabazitaxel and DKK 102 894 for best supportive care. The drug acquisition constitutes the major part of the costs for olaparib (78% of the total cost), and therefore results were most sensitive to changes in drug acquisition costs for olaparib, and relatively insensitive to most other variables.

The yearly budget impact of treatment with olaparib compared with docetaxel, cabazitaxel and BSC increased from DKK 2.6 million in 2021 to DKK 14.5 million in 2025.

## 13.2 Strengths and limitations of the economic model

The economic model was designed after careful consideration of the clinical and treatment pathways for patients with mCRPC to ensure that key aspects of the disease and treatment practices were captured in the model. The model was developed based on a thorough review of published economic modelling approaches and available HTA submissions.

A few limitations and considerations should be highlighted and discussed to properly interpret the results of this analysis. Firstly, due to lack of head-to-head comparisons between olaparib and taxanes, a relative efficacy of olaparib vs. taxanes was established by an indirect treatment comparison informing PFS and OS.

For comparison against docetaxel, in absence of relevant clinical trials, the OS HR for docetaxel versus NHA was sourced from observational data in mPC. These data are currently the best available evidence to inform the comparative evidence for docetaxel in a post-NHA mCRPC setting. In absence of rPFS data, docetaxel was assumed equivalent to NHA, since the mean rPFS time approximated for the maximum reimbursed treatment duration for docetaxel. At a minimum, these observational data suggest that docetaxel is equivalent to NHA with regards to efficacy in the no prior taxane setting.

It was observed in PROfound that some patients received treatment beyond rPFS (BICR) in both the arms. A possible explanation for this observation is that in PROfound, when the investigator determined progression, the radiological scans were sent for BICR, but in some cases the blinded independent reviewers decided that the patient actually had a progression event at an earlier timepoint. Therefore, the BICR-progression point in PROfound may have occurred earlier than the discontinuation point. However, in real-world practice, patients would continue treatment only up to the investigator-assessed progression point or until directed to cease treatment by a physician. In line with real-world setting, this additional time on treatment beyond BICR-progression was not considered in the base case analysis, and all treatments were considered to be administered up to progression. This was in line with reimbursement guidance for comparators outside PROfound, where no TTD data was available.

## 13.3 Conclusions

The cost per patient and budget impact for olaparib in mCRPC varied in a predictable way depending on scenario and comparator. The scenario analysis indicated that the cost results were stable for most variables. The total budget impact of olaparib in mCRPC is relatively low in absolute terms, with an estimated budget impact of around DKK 14.5 million at peak year sales.

# Appendix A. PROfound Patient Characteristics

*Table Appendix 1. Demographic characteristics for Cohort A (full analysis set) and BRCAm overall population*

| Demographic Characteristic | | Cohort A | | | BRCAm patients | | |
|---|---|---|---|---|---|---|---|
| | Statistic | Olaparib 300 mg bd (N=162) | NHA (N=83) | Total (N=245) | Olaparib 300 mg bd (N=102) | NHA (N=58) | Total (N=160) |
| Age (years) | Mean | 68.0 | 68.1 | 68.1 | 67.0 | 67.1 | 67.1 |
| | Standard deviation | 8.23 | 7.36 | 7.93 | 8.19 | 7.61 | 7.96 |
| | Median | 68.0 | 67.0 | 68.0 | 68.0 | 67.0 | 67.0 |
| | Minimum | 47 | 49 | 47 | 47 | 49 | 47 |
| | Maximum | 86 | 86 | 86 | 86 | 86 | 86 |
| Age group (years), n (%) | <65 | 54 (33.3) | 23 (27.7) | 77 (31.4) | 33 (32.4) | 21 (36.2) | 54 (33.8) |
| | >=65 | 108 (66.7) | 60 (72.3) | 168 (68.6) | 69 (67.6) | 37 (63.8) | 106 (66.3) |
| Race, n (%) | White | 109 (67.3) | 55 (66.3) | 164 (66.9) | 67 ( 65.7) | 41 (70.7) | 108 (67.5) |
| | Black or African American | 2 (1.2) | 1 (1.2) | 3 (1.2) | 2 ( 2.0) | 0 | 2 (1.3) |
| | Asian | 43 (26.5) | 19 (22.9) | 62 (25.3) | 27 (26.5) | 10 (17.2) | 37 (23.1) |
| | Other | 1 (0.6) | 1 (1.2) | 2 (0.8) | 0 | 1 (1.7) | 1 ( 0.6) |
| | Missing | 7 (4.3) | 7 (8.4) | 14 (5.1) | 6 ( 5.9) | 6 (10.3) | 12 (7.5) |
| Ethnic group, n (%) | Hispanic or Latino | 12 (7.4) | 9 (10.8) | 21 (8.6) | 7 ( 6.9) | 4 ( 6.9) | 11 ( 6.9) |
| | Not Hispanic or Latino | 145 (89.5) | 69 (83.1) | 214 (87.3) | 91 ( 89.2) | 49 ( 84.5) | 140 ( 87.5) |
| | Missing | 5 (3.1) | 5 (6.0) | 10 (4.1) | 4 ( 3.9) | 5 (8.6) | 9 (5.6) |

# Appendix B. Systematic literature review for relative efficacy

## Methods

An SLR was conducted in January 2020 in order to identify published clinical evidence on the use but not limited to PARP inhibitors, taxane-based chemotherapy and radium-223 in patients with mCRPC who have experienced progression following treatment with an NHA including abiraterone and/or enzalutamide. Publications that reported outcomes with docetaxel and radium-223 without specifying previous NHA use were also tagged as of interest, but data were not extracted. The patient population of this SR was not limited by HRR mutation status to ensure it was sufficiently broad to support upcoming health technology assessment (HTA) activities; however, publications that report outcomes in patients with a mutation in the HRR pathway, particularly those with a mutation in BRCA1, BRCA2 or ATM are of interest.

MEDLINE® and MEDLINE In-Process®, Embase® and the Cochrane Library were searched on 29 January 2020 via Ovid 1974–2020 for clinical evidence using a mixture of free text and Medical Subject Headings (MeSH) terms. Supplementary searches included interrogation of relevant appraisal data (manufacturer submissions and evidence review/assessment group reports) from relevant National Institute for Health and Care Excellence HTA submissions, and of relevant congresses from up to three years before the search date.

The titles and abstracts of publications identified by electronic searching were screened by two independent reviewers against predefined population, intervention, comparator, outcomes and study design (PICOS) eligibility criteria. The full texts of all relevant full-text publications were subsequently rescreened against the same criteria. The following data were extracted from each included publication: overall survival; progression-free survival; time to pain progression; time to first symptomatic skeletal-related event; time to opiate use for cancer-related pain; time to radiographic progression; time to prostate-specific antigen progression; second progression or death; circulating tumour cell conversion; mutation status and health-related quality of life.

## Search results

Databases were interrogated for clinical evidence on 29 January 2020.

Initial searching identified 6006 publications (Embase, 3325; MEDLINE, 1590; Cochrane Library, 1091), of which 13 were removed as duplicates before title/abstract screening and 4205 were subsequently excluded at title/abstract screening. A total of 123 publications from the electronic searches were considered eligible for inclusion at full text review. A further 364 publications that reported outcomes with docetaxel or radium-223 with no previous NHA use were tagged as of interest according to the protocol. Twenty-five unique abstracts were identified through supplementary searching. ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (WHO ICRP) were also interrogated for relevant clinical trials and retrieved 54 entries meeting the eligibility criteria of which six had data published through ClinicalTrials.gov. In total, 203 publications (124 from electronic screening, 25 from hand searching of congresses, 34 from ClinicalTrials.gov and 20 from WHO ITRP) met the inclusion criteria.

## Summary of evidence identified

Of the 77 studies identified by this SR, 21 (10 full-text publications, 21 abstracts) reported outcomes for key interventions of interest in patients with mCRPC whose disease progressed following treatment with an NHA. Key interventions are defined as PARP inhibitors, cabazitaxel, docetaxel, radium-223, mitoxantrone, platinum-based chemotherapies and sipuleucel-T and discussions in this report are restricted to studies relating to them. Eight studies reported on the PARP inhibitors niraparib, olaparib and rucaparib (2 full-text publications, 13 abstracts), six studies reported on cabazitaxel (5 full-text publications, 3 abstracts), six on docetaxel (3 full-text publications, 3 abstracts), one on radium-223 (two abstracts) and one on carboplatin (1 abstract; also reported on cabazitaxel). Four trials assessing the efficacy and safety of PARP inhibitors reported outcomes in patients with DDR or HRR mutations; no other evidence in patients with a DDR or HRR mutation was identified. A full description of keywords, methodology, eligibility criteria, search results are given in a separately provided report *Systematic literature review of the clinical evaluation in prostate cancer*.

The SLR identified six studies (5 full-text publications; 3 abstracts) that reported on cabazitaxel in patients with mCRPC whose disease had progressed following an NHA (Louhanepessy 2018; de Wit 2019; de Wit, de Bono 2019; Massard 2017; Saad 2016; Saad 2014; Shiota 2020; van Soest 2015). The studies identified included two RCTs (the phase 4 CARD trial [NCT0248591] (de Wit 2019; de Wit de Bono 2019; Saad 2014) and an open-label phase 2 trial [NCT number not reported]) (van Soest 2015) and four single arm trials (one phase 3b/4 single-arm study [NCT01254279] (Saad 2016; Saad 2014), one phase 1/2 single-arm study [NCT01511536] (Massard 2017) and a further two where trial ID and phase were not reported) (Louhanepessy 2018; Shiota 2020). Of these, only one study - CARD (NCT02485691) (de Wit 2019) – included a cabazitaxel arm as well as an NHA arm (as in PROfound), allowing for a comparative analysis between olaparib and cabazitaxel via an anchored indirect treatment comparison.

As described previously, CARD is an ongoing Phase IV RCT that assessed the efficacy and safety of cabazitaxel compared with an NHA (enzalutamide or abiraterone plus prednisolone) in patients with mCRPC, who had received previous treatment with docetaxel and an NHA. As all patients enrolled in the CARD trial were required to have received previous docetaxel, the patient population is closely aligned with the prior-taxane subpopulation of the PROfound study.

The CARD study was also not restricted to those patients who have mutations in HRR genes, which are associated with more aggressive disease and worse outcomes in mCRPC patients. The primary endpoint in CARD was rPFS (same as PROfound, although not assessed by BICR); OS was a secondary endpoint in both studies. Collectively, this makes a comparison on outcomes relevant for an economic evaluation possible.

The remaining publications identified in the SLR that reported outcomes in patients who received cabazitaxel were small single-arm studies (often conducted in a single country or center; for example, Saad *et al.* 2014, Saad *et al.* 2016, Massard *et al.* 2017, Louhanepessey *et al.* 2018, and Shiota *et al.* 2020 (12) or cabazitaxel combination studies (with and without budesinone; van Soest *et al.* 2015 . In the absence of a common comparator with PROfound, only unanchored comparisons are feasible between these studies and the prior-taxane group of the PROfound trial. As indicated by the NICE DSU, unanchored comparisons should only be considered in the absence of anchored comparisons. Since

data from CARD provided the necessary evidence base for an anchored comparison; these studies were not considered relevant for evidence synthesis.

Furthermore:

- Louhanepessey *et al.* 2018 and Massard *et al.* 2017 were abstract-only publications that only reported aggregate data with no associated Kaplan–Meier plots; no associated full text publications were identified. Aggregate data are unsuitable for an ITC, particularly if no published Kaplan–Meier data are available.

- Saad *et al.* 2016 and Saad *et al.* 2014 assessed outcomes from the Canadian cabazitaxel early access programme (NCT01254279), but did not report OS or rPFS, therefore, precluding an comparative analysis of these key endpoints.

In light of these factors, the CARD study was considered the most relevant source of evidence for cabazitaxel in the post-NHA setting and was used to inform the PFS and OS versus olaparib.

# Appendix C. Real-world evidence study to inform comparative effectiveness for the comparison against docetaxel in the no-prior taxane subgroup

## Journal of Clinical Oncology

### Overall survival (OS) with docetaxel (D) vs novel hormonal therapy (NHT) with abiraterone (A) or enzalutamide (E) after a prior NHT in patients (Pts) with metastatic prostate cancer (mPC): Results from a real-world dataset.

Umang Swami, Jennifer Anne Sinnott, Ben Haaland, Benjamin Louis Maughan, Nityam Rathi, Taylor Ryan McFarland, Manish Kohli, Roberto Nussenzveig, Sumanta K. Pal, Neeraj Agarwal

**Background:** NHT (A and E) are approved first-line (1L) treatment (Rx) for mPC. After progression on NHT, Rx include either alternate NHT or D. However, OS from a randomized trial comparing NHT vs D after progression on 1L NHT has not been reported.

**Methods:** Pts data were extracted from the Flatiron Health EHR-derived de-identified database. Inclusion: diagnosis of mPC; 1L Rx with single agent A or E only, single-agent Rx with alternate NHT (E or A) or D in second line (2L). Exclusion: > 180 days between date of diagnosis of mPC and date of next visit to ensure Pts were actively engaged in care at data-providing site; Rx with NHT in non-metastatic setting, any prior exposure to D. OS was compared using Cox proportional hazards model stratified by Rx propensity score. Each Pts' probability of receiving D (rather than NHT) was modeled via a random forest based on Pts and disease characteristics which may drive treatment selection. These included pre-2L Rx ECOG scores, PSA, LDH, ALPH, Hb, age, ICD codes for liver metastasis, diabetes, neuropathy, and heart failure; insurance payer, year of start of 2L Rx, time on 1 L NHT, Gleason score, PSA at the original diagnosis of mPC. Subgroup analyses included 1L Rx duration < 12 mos.

**Results:** 1165 Pts between 2/5/2013 to 9/27/2019 were eligible. Median follow up 8 months (range 0.1-64.5). Median OS after 1L A was higher with E as compared to D (15.7 vs. 9.4 months). Median OS after 1L E was higher with A as compared to D (13.3 vs. 9.7 months) (table). Propensity distributions were overlapping among Rx arms and showed only modest imbalance. In 2L, D had a worse adjusted hazard ratio of 1.29 and 1.35 as compared to E and A respectively ($p < 0.05$). Similar results were seen with 1L Rx duration of < 12 months ($p < 0.05$).

**Conclusions:** These hypothesis-generating data provide real-world OS estimates with 2L D & NHT in mPC. In propensity-stratified analyses, mPC Pts who progressed on NHT had a worse OS with 2L D as compared to alternate NHT. Results were consistent in unadjusted analysis & subgroup analyses of 1L Rx < 12 mos. Results are subject to residual confounding and missingness. After prospective validation these data may aid in Rx sequencing, Pts counselling, and design of future clinical trials in this setting.

*Propensity score adjusted OS analyses.*

| | A-->D vs E | E-->D vs A |
|---|---|---|
| Overall no. of patients | 206 vs 514 | 137 vs 308 |
| HR; 95% CI, p-value | **1.29**; 1.04-1.60, 0.02 | 1.35; 1.03, 1.77, 0.03 |
| No. of patients with 1L <12 mos | 172 vs. 344 | 108 vs. 192 |
| HR; 95% CI, p-value | 1.33; 1.07-1.65, 0.01 | 1.36; 1.01-1.82, 0.04 |
| A: Abiraterone, D: Docetaxel, E : Enzalutamide. | | |

Reference: DOI: 10.1200/JCO.2020.38.15_suppl.5537 *Journal of Clinical Oncology* 38, no. 15_suppl (May 20, 2020) 5537-5537. (Also available as poster presented at 2020 ASCO Annual Meeting, May 29th – June 2nd, Chicago, IL)

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Medicinrådet

# Medicinrådets protokol for vurdering vedrørende olaparib til behandling af BRCA1/2-muteret metastaserende kastrationsresistent prostatacancer

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 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 sin endelige ansøgning. Til hvert spørgsmål knytter sig en definition af patientgruppen, det lægemiddel, Medicinrådet undersøger, den behandling, Medicinrådet 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 vedr. nye lægemidler og indikationsudvidelser*, 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 den ansøgende virksomhed få besked.*

| **Dokumentoplysninger** | |
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# Indholdsfortegnelse






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# 1. Begreber og forkortelser

**ADT:** Androgen deprivationsterapi

**BSC:** *Best supportive care*

**BRCA:** *Breast cancer gene*

**DNA:** *Deoxyribo-Nucleic Acid*

**EMA:** Det Europæiske Lægemiddelagentur (*European Medicines Agency*)

**EPAR:** *European Public Assessment Report*

**EUnetHTA:** *European Network for Health Technology Assessment*

**FACT-P:** *Functional Assessment of Cancer Therapy – Prostate*

**FDA:** *The Food and Drug Administration*

**FINOSE:** Finland, Norge og Sveriges samarbejde om medicinske teknologivurderinger

**GRADE:** System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)

**HRD:** *Homologous recombination deficiency*

**HTA:** Medicinsk teknologivurdering (*Health Technology Assessment)*

**IQWIG:** *The Institute for Quality and Efficiency in Healthcare*

**ITT:** *Intention to treat*

**LHRH:** *Luteinising Hormone Releasing Hormone*

**mCRPC:** Metastaserende kastrationsresistent prostatakræft (*metastatic castration-resistant prostate cancer)*

**MKRF:** Mindste klinisk relevante forskel

**NHA:** *New Hormonal Agent* (enzalutamid og abirateron)

**NICE:** *The National Institute for Health and Care Excellence*

**OS:** Samlet overlevelse (*overall survival*)

**PARP:** *Poly-ADP ribose polymerase*

**PFS:** Progressionsfri overlevelse

**PICO:** Population, intervention, komparator og effektmål (*Population, Intervention, Comparison and Outcome)*

**PP:** *Per Protocol*

**RECIST:** *Response Evaluation Criteria in Solid Tumors*

**RR:** Relativ risiko

**SMD:** *Standardized Mean Difference*

# 2. Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra AstraZeneca, som ønsker, at Medicinrådet vurderer olaparib til BRCA1/2-muteret metastatisk kastrationsresistent prostatakræft (mCRPC). Medicinrådet modtog den foreløbige ansøgning den 6. november 2020.

## 2.1 Metastaserende kastrationsresistent prostatakræft

Prostatakræft er den hyppigste kræftform hos mænd i Danmark. Prostatakræft viser sig især efter 60-årsalderen [1]. I 2018 blev der registreret 4.674 nye sygdomstilfælde [1]. Ved udgangen af 2018 var antallet af mænd med prostatakræft i Danmark 42.318 [1].

Patienter med prostatakræft, der endnu ikke har modtaget kastrationsbehandling med androgen deprivationsterapi (ADT) eller responderer på behandling med ADT, kaldes hormonsensitive. De fleste hormonsensitive prostatakræfttilfælde vil over tid udvikle sig til kastrationsresistente. Kastrationsresistent prostatakræft (CRPC) defineres ved serum testosteron i kastrationsniveau[1] og progression enten biokemisk eller radiologisk [2]. Patienter med CRPC opdeles i to grupper i forhold til tilstedeværelse af metastaser. Metastaserende CRPC (mCRPC) defineres som prostatakræft med påviste metastaser involverende enten knogler, lymfeknuder uden for det lille bækken eller parenkymatøse organer.

Fagudvalget vurderer, at maksimalt 5 % af patienter med mCRPC har mutationer i *breast cancer* (BRCA) 1- eller 2-genet. Disse mutationer kan både være arvelige og somatiske. Tilstedeværelsen af BRCA 1/2-mutationer hos patienter med mCRPC er forbundet med en dårlig prognose relativt til patienter uden BRCA-mutationer [3][4]. I modsætning til andre kræftsygdomme (fx kræft i æggestokkene) er betydningen af BRCA-mutationer for sygdomsprognosen og -forekomsten ikke velbeskrevet i litteraturen [3][5].

Fagudvalget vurderer, at ca. 1.500 patienter årligt diagnosticeres med mCRPC. Dermed forventer fagudvalget, at maksimalt ca. 75 patienter årligt vil have mCRPC med BRCA 1/2-mutationer.

## 2.2 Olaparib

Olaparib (Lynparza) er indiceret som monoterapi til behandling af voksne patienter med metastatisk kastrationsresistent prostatakræft som har BRCA 1/2-mutationer (*germline* eller somatiske), som har progredieret under tidligere behandling, der omfattede et nyt hormonmiddel (NHA; enzalutamid og abirateron, se afsnit 2.3).

Den anbefalede dosis af olaparib er 300 mg (2 x 150 mg tabletter) indtaget to gange dagligt, svarende til en samlet daglig dosis på 600 mg.

[1] 0,5 ng/mL eller 1,7 nmol/L

Olaparib inhiberer humane poly (ADP-ribose) polymeraseenzymer (PARP-1, PARP-2 og PARP-3) og hæmmer dermed tumorvækst. PARP'er er nødvendige for effektiv reparation af enkeltstrengsbrud på Deoxyribo-Nucleic Acid (DNA). Når olaparib bindes til det aktive site på PARP-enzymet, blokeres for DNA-reparation, og der akkumuleres DNA-skader, hvilket slutteligt forårsager kræftcellens død. Til forskel fra raske celler har kræftceller ofte defekter i deres DNA-reparationsmekanismer, hvilket gør dem mere sårbare overfor inhibering af PARP-enzymerne. Effekten af PARP-inhibition synes at være særlig udtalt hos patienter med BRCA 1/2-mutation [6].

Olaparib er også godkendt af EMA til kræft i bughinden, brystkræft, æggestokkræft og bugspytkirtelkræft. Medicinrådet har anbefalet olaparib som mulig standardbehandling til patienter med nydiagnosticeret avanceret high-grade BRCA-muteret kræft i æggestokkene, æggelederne eller primær kræft i bughinden.

## 2.3 Nuværende behandling

Mænd med mCRPC er uhelbredeligt syge, hvorfor sigtet med behandlingen er palliation og levetidsforlængelse. Patienterne behandles livslangt med ADT, enten ved bilateral orkiektomi (kirurgisk fjernelse af testikler) eller medicinsk kastration med *Luteinising Hormone Releasing Hormone* (LHRH)-analoger [7]. Herudover behandles patienter med mCRPC i dansk klinisk praksis med docetaxel, cabazitaxel, abirateron (+ prednisolon), enzalutamid og radium-223 diklorid [7].

Der findes ikke god evidens for den optimale sekvens af de anbefalede behandlinger for mCPRC. Sekvensen af behandlinger afhænger af den enkelte patients tidligere behandling, sygdomsprogression og sygdomsbyrde samt performance status (metode til at graduere patienters helbredsstatus med henblik på at vurdere, hvorvidt en patient forventes at tåle f.eks. kemoterapi og strålebehandling).

Asymptomatiske patienter og patienter med få symptomer i god performance status 0-1 behandles i 1. linje med enzalutamid eller altenativt abirateron [7,8]. I 2. linje anvendes docetaxel, og i 3. linje kan anvendes cabazitaxel.

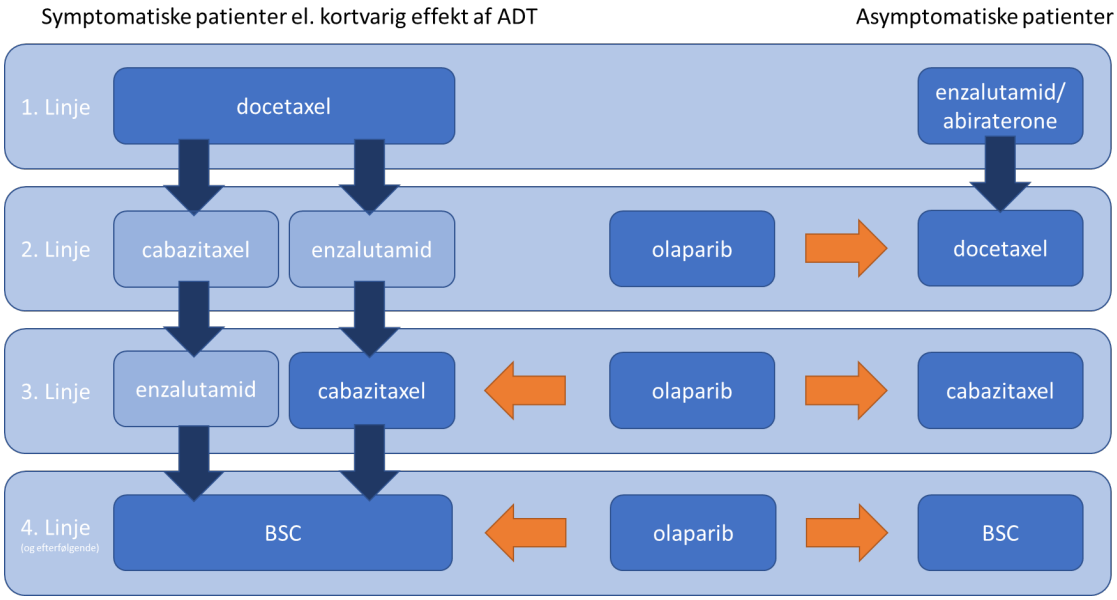
Symptomatiske patienter i performance status 0-2 og patienter med hurtig progression på ADT i den hormonsensitive fase af prostatakræft behandles med docetaxel i 1. linje, såfremt der ikke er givet docetaxel i den hormonsensitive fase [7,8]. Patienter med mCRPC, som progredierer efter 1. linje docetaxel, behandles med enten enzalutamid eller cabazitaxel i 2. linje. Patienter genbehandles som udgangspunkt ikke med samme stof [8].

Radium-223 anvendes til patienter med symptomatiske knoglemetastaser (og uden viscerale metastaser), som tidligere har modtaget mindst 2 linjer behandling for mCRPC.

I Danmark screenes der ikke rutinemæssigt for BRCA-mutationer ved prostatacancer. Patienter med BRCA-mutationer behandles derfor efter nuværende guidelines på lige fod med andre patienter med mCRPC. De nuværende behandlingsregimer er dog ikke godt belyst for patienter med BRCA-mutationer. Studier tyder på, at behandling med docetaxel har en dårligere effekt for BRCA-muterede patienter med mCRPC [9].

Hvis olaparib anbefales af Medicinrådet som mulig standardbehandling, vil screening af patienter med mCRPC for BRCA1/2-mutationer være en forudsætning for ibrugtagning. Dette gøres allerede rutinemæssigt for patienter med kræft i æggestokkene og for en del patienter med brystkræft. Fagudvalget bemærker, at kendskab til BRCA1/2-mutationer hos patienter med mCRPC vil give klinikerne mulighed for at give en målrettet behandling til en lille gruppe patienter med mCRPC, som har en særligt dårlige prognose.

Da størstedelen af patienter med mCRPC modtager kemoterapi, ønsker fagudvalget en sammenligning af olaparib overfor henholdsvis docetaxel og cabazitaxel (figur 1). Ligeledes ønsker fagudvalget en analyse, hvor der sammenlignes med 'best supportive care' (BSC), for at belyse effekten hos patienter, hvor øvrige behandlingsmuligheder er udtjente eller vurderet uegnede, dvs. patienter, som er progredieret på [enzalutamid eller abirateron] samt docetaxel og cabazitaxel eller ikke vurderes egnede til kemoterapi (figur 1). Fagudvalget finder det ikke relevant at sammenligne med Radium-223, da denne behandling kun gives i sjældne tilfælde.




**Figur 1. Simpel oversigt over olaparibs mulige placering i behandlingsalgoritmen for mCRPC. Orange pile indikerer, hvad fagudvalget vil vurdere olaparib som alternativ til. BSC = best supportive care.**

# 3. Kliniske spørgsmål

Medicinrådet bruger kliniske spørgsmål til vurderinger af lægemidlers værdi for patienterne. Til hvert spørgsmål knytter sig en definition af patientgruppen (population), af det lægemiddel, Medicinrådet undersøger (interventionen), af den behandling, Medicinrådet sammenligner med (komparator(er)), og af effektmålene.

## 3.1 Klinisk spørgsmål 1

Hvilken værdi har olaparib sammenlignet med docetaxel for patienter med BRCA1/2-muteret metastaserende kastrationsresistent prostatakræft, der er progredieret på enten enzalutamid eller abirateron?

*Population*
Patienter med metastatisk kastrationsresistent prostatakræft med BRCA1/2-mutationer (germline og/eller somatiske), der er progredieret efter behandling med enten enzalutamid eller abirateron.

*Intervention*
300 mg olaparib tabletter to gange dagligt til progression eller uacceptabel toksicitet.

*Komparator*
75 mg/m$^2$ docetaxel hver tredje uge op til 10 serier.

*Effektmål*
De valgte effektmål fremgår af tabel 1.

## 3.2 Klinisk spørgsmål 2

Hvilken værdi har olaparib sammenlignet med cabazitaxel for patienter med BRCA1/2-muteret metastaserende kastrationsresistent prostatakræft, der er progredieret efter behandling med [enzalutamid eller abirateron] samt docetaxel?

*Population*
Patienter med metastatisk kastrationsresistent prostatakræft med BRCA1/2-mutationer (germline og/eller somatiske), der er progredieret efter behandling med [enzalutamid eller abirateron] samt docetaxel.

*Intervention*
300 mg olaparib tabletter to gange dagligt til progression eller uacceptabel toksicitet.

*Komparator*
20 mg/m$^2$ cabazitaxel hver 3. uge.

*Effektmål*
De valgte effektmål fremgår af tabel 1.

## 3.3 Klinisk spørgsmål 3

Hvilken værdi har olaparib sammenlignet med *'best supportive care'* (BSC) for patienter med BRCA-muteret metastaserende kastrationsresistent prostatakræft, der ikke har andre behandlingsalternativer?

*Population*
Patienter med metastatisk kastrationsresistent prostatakræft med BRCA1/2-mutationer (germline og/eller somatiske), der er progredieret efter behandling med [enzalutamid eller abirateron], docetaxel og cabazitaxel, og som ikke har andre behandlingsmuligheder.

*Intervention*
300 mg olaparib tabletter to gange dagligt til progression eller uacceptabel toksicitet.

*Komparatorer*
BSC.

*Effektmål*
De valgte effektmål fremgår af tabel 1.

**Effektmål**
Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, der er nævnt i tabel 1. For hvert effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel (MKRF). I det følgende afsnit argumenterer Medicinrådet for valget af effektmål og MKRF.

**Tabel 1. Oversigt over valgte effektmål**

| Effektmål* | Vigtighed | Effektmålsgruppe** | Måleenhed | Mindste klinisk relevante forskel |
|---|---|---|---|---|
| Samlet overlevelse | Kritisk | Dødelighed | Median OS i antal mdr. | 3 mdr. |
| | | | OS-rate ved 1 år | 5 %-point |
| Uønskede hændelser / bivirkninger | Kritisk | Livskvalitet samt alvorlige symptomer og bivirkninger | Andel af patienter med grad 5 bivirkninger | 5 %-point |
| | Vigtig | | Andel af patienter med grad 3-4 uønskede hændelser | 10 %-point |
| | | | Kvalitativ gennemgang | - |
| Progressionsfri overlevelse | Vigtig | Livskvalitet samt alvorlige symptomer og bivirkninger | Median PFS i antal mdr. | 3 mdr. |
| | | | PFS-rate ved 1 år | 10 %-point |
| Livskvalitet | Vigtig | Livskvalitet samt alvorlige symptomer og bivirkninger | Andelen af patienter, som oplever ≥ 10 points reduktion fra baseline ved kort (2-6 mdr.) og lang (> 6 mdr.) opfølgning | 10 %-point |

*For alle effektmål ønsker Medicinrådet data med længst mulig opfølgningstid, medmindre andet er angivet.
** Effektmålsgruppe refererer til de væsentlighedskriterier, som Medicinrådet lægger til grund for kategoriseringen af de relative forskelle i effekt, bivirkninger eller livskvalitet.

### 3.3.1 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 median OS og OS-rate til at vurdere den absolutte effekt. Fagudvalget betragter OS som et kritisk effektmål, da metastaserende kastrationsresistent prostatakræft er en dødelig sygdom. Fagudvalget estimerer, at medianoverlevelsen for BRCA1/2-muterede patienter med mCRPC, som er progredieret på enten enzalutamid eller abirateron, er ca. 12 måneder [10]. For patientgruppen, som har modtaget [enzalutamid eller abirateron] samt docetaxel og cabazitaxel, vurderer fagudvalget, at overlevelsen er væsentlig kortere. Fagudvalget vurderer, at en forskel på 3 måneder i median OS og en forskel på 5 procentpoint i andelen af patienter, der er i live efter 1 år, er klinisk relevant.

**Bivirkninger grad 5**
Fagudvalget vurderer, at grad 5 bivirkninger er særligt kritiske, idet de omhandler mortalitet som følge af behandlingen. Fagudvalget ønsker en opgørelse over andelen af patienter, der får grad 5 bivirkninger samt en kort beskrivelse af disse og en angivelse af, hvornår i behandlingsforløbet bivirkningen er opstået. Den mindste klinisk relevante forskel er sat til 5 procentpoint.

### 3.3.2 Vigtige effektmål

**Uønskede hændelser grad 3-4**
Uønskede hændelser har betydning for den enkelte patients livskvalitet og efterlevelse af behandling. Fagudvalget anser derfor uønskede hændelser grad 3-4 som et vigtigt effektmål. Fagudvalget ønsker en sammenligning af andelen af patienter, der får uønskede hændelser grad 3-4. Fagudvalget vurderer, at den mindste klinisk relevante forskel er 10 procentpoint.

Kvalitativ bivirkningsgennemgang
Fagudvalget ønsker derudover en kvalitativ gennemgang af hændelsestyperne for olaparib med henblik på at vurdere alvorlighed, hyppighed og håndterbarhed af hændelserne. Ansøger bedes derfor bidrage med en narrativ beskrivelse af bivirkningsprofilen for lægemidlet baseret på EMAs produktresumé. Ved kardiovaskulære hændelser ønsker fagudvalget desuden en opgørelse af type (hjerteinfarkt, cerebralt infarkt, cerebral hæmoragi, atrieflimren, hypertension eller venøs emboli).

**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 [11], progression i knogler iht. kriterier fra *Prostate Cancer Clinical Trials Working Group 3* eller til død. PFS anvendes som mål for sygdomsbyrde og sygdomskontrol i vurderingen af olaparib til BRCA-muteret mCRPC. Fagudvalget vurderer, at det er et mål i sig selv at forsinke progressionen, fordi det betyder, at patienterne har længere levetid med færre symptomer.

Fagudvalget vurderer derfor, at PFS er et vigtigt effektmål. Fagudvalget vurderer, at patienter med metastaserende kastrationsresistent prostatakræft, der har modtaget behandling med NHA, har en median PFS på maksimalt 6 måneder og en PFS-rate på omkring 10 % ved 1 år. Fagudvalget vurderer, at en absolut forskel i PFS-rate på 10 %-point ved 1 år og en forskel i median PFS på 3 måneder mellem intervention og komparator er klinisk relevant.

**Livskvalitet**
Fagudvalget betragter livskvalitet som et vigtigt effektmål, idet behandling med olaparib er livsforlængende og ikke kurativ. Mange patienter har mange symptomer og dårlig livskvalitet. Fagudvalget mener derfor, at det er vigtigt at sikre, at patienternes livskvalitet ikke påvirkes i betydelig negativ retning ved behandling med olaparib. Fagudvalget forventer, at dette effektmål kan give en indikation af, om eventuelle bivirkninger ved produktet påvirker patienternes livskvalitet. Fagudvalget ønsker livskvalitet målt ved FACT-P (*Functional Assessment of Cancer Therapy – Prostate*), som er et valideret spørgeskema, der bruges i vurdering af den helbredsrelaterede livskvalitet hos mænd med prostatakræft [12]. En høj samlet score på en skala fra 0-156 point indikerer høj livskvalitet. En ændring i score på mindst 6-10 point indikerer en klinisk relevant forbedring eller forværring i livskvalitet. Fagudvalget ønsker effektmålet opgjort som forskellen i andelen af patienter, som oplever ≥ 10 points reduktion fra baseline ved

kort (mellem 2 og 6 måneder) og lang (> 6 måneder) opfølgningstid baseret på Basch et al. 2013, som benytter en mere konservativ grænse [13]. Fagudvalget vurderer, at den mindste klinisk relevante forskel er 10 procentpoint.

# 4. Litteratursøgning

Medicinrådets vurdering af lægemidlets værdi vil i udgangspunktet være baseret på data fra fuldtekstartikler publiceret i videnskabelige, fagfællebedømte (peer-reviewed) tidsskrifter og data fra Det Europæiske Lægemiddelagenturs (EMAs) European Public Assessment Reports (EPAR). Anvendelse af upublicerede data sker ift. Medicinrådets princippapir[2] . Data skal derudover stemme overens med protokollens beskrivelser. Hvis ansøger har kendskab til upublicerede data, der kan belyse eventuelle angivne mangler, kan de indgå/indsendes, jf. Medicinrådets princippapir.

Medicinrådet er i den foreløbige ansøgning blevet orienteret om, at der ikke findes studier, hvor olaparib er sammenlignet direkte med docetaxel eller docetaxel efterfulgt af cabazitaxel. Derfor skal ansøger søge efter studier til en indirekte sammenligning. Søgestrengene fremgår af bilag 1. Derudover skal ansøger konsultere EMAs EPAR for både det aktuelle lægemiddel og dets komparatorer.

Medicinrådet er i den foreløbige ansøgning blevet orienteret om, at der findes et studie, hvor olaparib er sammenlignet direkte med enzalutamid eller abirateron (sekventiel brug). Studiet er rapporteret i følgende publikation:

- de Bono J, et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. New England Journal of Medicine. 2020;382(22):2091-102. **NCT02987543**

Fagudvalget ønsker at se data fra dette studie i besvarelsen af klinisk spørgsmål 3. Fagudvalget ønsker kun at se data for BRCA1/2-populationen. Det er ikke normal dansk klinisk praksis at anvende enzalutamid og abirateron sekventielt, som det er gjort i komparatorarmen i det kliniske studie. Det skal nævnes, at det ofte tidligere har været udenlandsk praksis at behandle sekventielt, og mange forskningsprotokoller er bygget op på denne måde. Fagudvalget ønsker alligevel at se data for det pågældende studie, fordi effekten af sekventiel behandling forventes at være lille og tilnærmelsesvis repræsentativ for *best supportive care*.

Det er tilstrækkeligt datagrundlag til at besvare klinisk spørgsmål 3. Ansøger skal derfor ikke søge efter yderligere data vedrørende dette spørgsmål, men skal konsultere EMAs EPAR for både det aktuelle lægemiddel og dets komparator.

[2] For yderligere detaljer se Medicinrådets principper for anvendelse af upublicerede data

**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, fx 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 det/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 først ekskludere 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.

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. Den endelige ansøgning

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 (population, intervention, komparator og effektmål) 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 (fx 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 (jf. 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 (jf. 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'-modeller 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.

**Sundhedsøkonomiske analyser**
En sundhedsøkonomisk ansøgning består af en sammenhængende, dynamisk sundhedsøkonomisk model og et teknisk dokument, hvor modellen og de antagelser, der er bygget ind i modellen, beskrives, og hvor ansøgers sundhedsøkonomiske analyse fremgår. Ved dynamisk forstås, at en variabel kun skal ændres ét sted for at være gennemgående for hele modellen. Anvend eventuelt Medicinrådets metodevejledning og tjekliste til sundhedsøkonomiske modeller til at teste modellens dynamik, og at modellen overholder formelle krav.

En sundhedsøkonomisk analyse er ikke et resultat, men er en bred analyse af modellens dynamik, hvilke parametre der har indflydelse på resultaterne, samt hvorfor og hvordan disse parametre indgår. Derfor skal det tekniske dokument som minimum indeholde følgende:

- Beskriv den valgte modelstruktur grundigt.
- Beskriv, hvis der er anvendt en indirekte analyse, hvordan den vil blive håndteret i den sundhedsøkonomiske analyse.
- Begrund og beskriv samtlige antagelser i modellen, og lad specifikke analysevalg fremgå tydeligt.
- Beskriv alle de inkluderede studier, argumentér for deres relevans, og beskriv, hvor og hvordan data anvendes i modellen.
- Begrund både de inkluderede og ekskluderede omkostninger.
- Beskriv, hvad der driver modellen, fx behandlingslængde eller lægemiddelomkostninger.
- Ekstrapoleret data skal beskrives.

- Udfør følsomhedsanalyser, som belyser, hvilke parametre i modellen der har størst indflydelse på resultatet.
- Argumentér for eventuelle afvigelser fra protokollen og den kliniske ansøgning.
- Budgetkonsekvensanalysen skal være dynamisk med omkostningsanalysen, uden diskontering og patientomkostninger.

# 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 man kan have tiltro til den evidens, Medicinrådet baserer vurderingen af lægemidlets værdi på.

# 7. Andre overvejelser

Medicinrådet ønsker informationer, der kan belyse, 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.

**Diagnostik**
Der testes ikke rutinemæssigt for BRCA-mutationer hos patienter med mCRPC, men fagudvalget påpeger, at dette vil være en forudsætning for ibrugtagning af olaparib. Fagudvalget vurderer, at dette er håndterbart i Danmark, hvor der allerede screenes for BRCA-mutationer hos patienter med æggestokkræft. Fagudvalget ønsker ansøgers overvejelser omkring, hvilken type test der vil være nødvendig for at identificere patienter, der kan have gavn af olaparib, samt hvor stor en andel af mCRPC-patienterne, der i Danmark har BRCA1/2-mutationer og reelt ville være kandidater til behandling med olaparib.

# 8. Relation til behandlingsvejledning

Medicinrådet vil i forbindelse med vurderingen af olaparib tage stilling til, hvor lægemidlet foreløbigt kan placeres i RADS' behandlingsvejledning for metastatisk kastrationsresistent prostatakræft.

# 9. Referencer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3. Messina C, Cattrini C, Soldato D, Vallome G, Caffo O, Castro E, et al. BRCA Mutations in Prostate Cancer: Prognostic and Predictive Implications. Bd. 2020, Journal of Oncology. 2020.
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10. de Bono J, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med. 2020;382(22):2091–102.
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# 10. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

**Medicinrådets fagudvalg vedrørende kræft i blærehalskirtlen**

| **Sammensætning af fagudvalg** | |
|---|---|
| **Formand** | **Indstillet af** |
| Joen Svejstrup<br>*Afdelingslæge* | Region Hovedstaden |
| **Medlemmer** | **Udpeget af** |
| Edo Koco<br>*Afdelingslæge* | Region Nordjylland |
| Jimmi Søndergaard<br>*Overlæge* | Region Nordjylland |
| Michael Borre<br>*Lærestolsprofessor og overlæge* | Region Midtjylland |
| Simon Buus<br>*Afdelingslæge* | Region Midtjylland |
| Steinbjørn Hansen<br>*Overlæge* | Region Syddanmark |
| Mads Hvid Aaberg Poulsen<br>Afdelingslæge | Region Syddanmark |
| Redas Trepiakas<br>*Overlæge* | Region Sjælland |
| Lisa Lindeborg<br>*Afdelingslæge* | Region Sjælland |
| Rasmus Bisbjerg<br>*Overlæge* | Region Hovedstaden |
| Leif Otterstrøm<br>*Patient/patientrepræsentant* | Danske Patienter |
| Ole Jensen<br>*Patient/patientrepræsentant* | Danske Patienter |

| Sammensætning af fagudvalg | |
|---|---|
| Stine Trolle Poulsen<br>*Farmaceut* | Dansk Selskab for Sygehusapoteksledelse |
| Jesper Hallas<br>*Professor, overlæge* | Dansk Selskab for Klinisk Farmakologi |
| Marie Thue Pank<br>*Afdelingslæge* | Dansk Urologisk Selskab |


**Medicinrådets sekretariat**

Medicinrådet

Dampfærgevej 27-29, 3.th.

2100 København Ø

+45 70 10 36 00

medicinraadet@medicinraadet.dk

# 11. Versionslog

| Versionslog | | |
|---|---|---|
| **Version** | **Dato** | **Ændring** |
| 1.0 | 14. april 2021 | Godkendt af Medicinrådet |

# 12. Bilag

## Bilag 1: Søgestrenge

Søgestreng til PubMed: https://pubmed.ncbi.nlm.nih.gov/advanced/

| # | Søgestreng | Kommentar |
|---|---|---|
| 1 | prostate[ti] AND (cancer[ti] OR carcinoma[ti] OR adenocarcinoma[ti]) | Population |
| 2 | castration resistant[ti] OR castrationresistant[ti] OR hormone-refractory[ti] OR hormone-resistant[ti] OR androgen-independent[ti] | |
| 3 | #1 AND #2 | |
| 4 | Prostatic Neoplasms, Castration-Resistant[mh] AND drug therapy[sh] | |
| 5 | CRPC[ti] | |
| *6* | #3 OR #4 OR #5 | |
| *7* | Neoplasm Metastasis[mh] | |
| *8* | metasta*[ti] | |
| *9* | #6 AND (#7 OR #8) | |
| 10 | mCRPC[ti] | |
| 11 | #9 OR #10 | |
| 12 | olaparib[nm] OR olaparib[tiab] OR Lynparza*[tiab] | Intervention og komparator |
| 13 | Docetaxel[mh] OR docetaxel[tiab] OR Taxotere*[tiab] | |
| 14 | #11 AND (#12 OR #13) | |
| 15 | abiraterone[tiab] OR enzalutamide[tiab] OR new hormonal agent*[tiab] OR novel hormonal agent*[tiab] OR second generation hormone therap*[tiab] OR second HT[tiab] | Krav til tidl. behandling |
| 16 | androgen receptor target*[tiab] OR androgen receptor-axis-target*[tiab] OR androgen-signaling-target*[tiab] OR ASTI*[tiab] OR ARAT*[tiab] | |
| 17 | #14 AND (#15 OR #16) | |
| 18 | docetaxel-naive[ti] OR chemotherapy-naive[ti] OR castrate-naive[ti] | Eksklusionskriterier |

| | | |
|---|---|---|
| 19 | Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR Review[pt] OR Systematic Review[pt] OR case report[ti] | |
| 20 | #17 NOT (#18 OR #19) | |
| 21 | english[la] AND hasabstract | Afgræsning til referencer på engelsk, der har abstract |
| 22 | #20 AND #21 | Endelig søgning |

Søgestreng til CENTRAL: https://www.cochranelibrary.com/advanced-search/search-manager

| # | Søgestreng | Kommentar |
|---|---|---|
| #1 | (prostate near/2 (cancer or carcinoma or adenocarcinoma)):ti | |
| #2 | (castration next resistant or castrationresistant or (hormone next (refractory or resistant)) or androgen next independent):ti | |
| #3 | #1 and #2 | |
| #4 | castration resistant prostate cancer:kw | |
| #5 | CRPC:ti | Population |
| #6 | #3 or #4 or #5 | |
| #7 | metasta*:ti,kw | |
| #8 | #6 and #7 | |
| #9 | mCRPC:ti | |
| #10 | #8 or #9 | |
| #11 | (olaparib or Lynparza*):ti,ab,kw | Intervention og komparator |
| #12 | (docetaxel or Taxotere*):ti,ab,kw | |
| #13 | #10 and (#11 OR #12) | |
| #14 | (abiraterone or enzalutamide or ((new or novel) next hormonal next agent*) or "second generation hormone" next therap* or second next HT):ti,ab | Krav til tidl. behandling |
| #15 | (androgen near/3 target* or ASTI* or ARAT*):ti,ab | |
| #16 | #13 and (#14 OR #15) | |
| #17 | ((docetaxel or chemotherapy or castrate) next naive):ti | |
| #18 | ("conference abstract" or review):ti,pt | |
| #19 | (clinicaltrials.gov or trialsearch):so | |
| #20 | (meeting or conference or proceedings):so | Eksklusionskriterier |
| #21 | nct*:au | |
| #22 | #17 or #18 or #19 or #20 or #21 | |

| | | |
|---|---|---|
| #23 | #16 not #22 | |
| #24 | #23 not pubmed:an in Trials | Endelig søgning afgrænset til Trials med eksklusion af referencer, der kommer fra Pubmed |