Medicinrådet

Baggrund for Medicinrådets anbefaling vedrørende apalutamid til behandling af højrisiko ikke-metastaserende kastrationsresistent prostatakræft

Anb

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 baggrunden for Medicinrådets anbefaling

Baggrund for Medicinrådets anbefaling er en sammenfatning af lægemidlets værdi for patienterne, omkostninger for samfundet og en gengivelse af de vurderinger, der er grundlag for Medicinrådets anbefaling.

Anbefalingen er Medicinrådets vurdering af, om omkostningerne vedrørende brug af lægemidlet er rimelige, når man sammenligner dem med lægemidlets værdi for patienterne. I nogle tilfælde spiller sygdommens alvorlighed en særlig rolle i vurderingen.

Anbefalingen er et klinisk og økonomisk baseret råd til regionerne til brug for deres beslutning om at anvende et givet lægemiddel.

Læs eventuelt mere i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser – version 2, som du kan finde på Medicinrådets hjemmeside under siden Metoder.

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Indholdsfortegnelse

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1. Anbefaling vedrørende apalutamid til højrisiko ikke-metastaserende kastrationsresistent prostatakræft

Medicinrådet anbefaler apalutamid til patienter med højrisiko ikke-metastaserende kastrationsresistent prostatakræft, fordi behandlingen betyder, at patienterne lever længere, mens bivirkningerne er acceptable. Samtidig vurderer Medicinrådet, at sundhedsvæsenets omkostninger til lægemidlet vil være rimelige i forhold til lægemidlets effekt.

2. Medicinrådets konklusion vedrørende lægemidlets værdi

Medicinrådet vurderer, at apalutamid i kombination med androgen deprivationsterapi (ADT) til patienter med højrisiko ikke-metastaserende kastrationsresistent prostatakræft giver en moderat merværdi sammenlignet med ADT alene. Evidensens kvalitet vurderes at være lav. Høringen har ikke givet anledning til ændringer. Læs mere i Medicinrådets vurdering af lægemidlets værdi og den bagvedliggende protokol (se bilag).

3. Resultater af sundhedsøkonomiske analyser

Medicinrådet har vurderet, at det vil koste ca. 580.000 kr. mere at behandle én patient med apalutamid end med den behandling, man bruger i dag. Medicinrådet har også vurderet, at regionerne vil skulle bruge 52,0 mio. kr. mere i det femte år efter en anbefaling.

Beløbene er baseret på de officielle listepriser for lægemidlerne. Rådets beslutning er truffet på baggrund af priser på lægemidlerne, som Amgros har forhandlet med lægemiddelfirmaerne. De forhandlede priser er fortrolige efter firmaernes ønske, og derfor må Medicinrådet ikke offentliggøre hverken de reelle priser eller omkostninger.

Læs mere i den sundhedsøkonomiske afrapportering (se bilag 1).

4. Alvorlighed

Sygdommens alvorlighed er altid medtaget i Medicinrådets vurdering af et lægemiddels værdi. Det sker i forbindelse med valget af effektmål og den vægt, Medicinrådet tillægger effektestimaterne, hvilket er forskelligt alt efter typen af effektmål. Derudover har Medicinrådet formuleret et alvorlighedsprincip, som Medicinrådet kan inddrage i helt særlige situationer. Dette har ikke været nødvendigt i denne sag.

5. Anbefalingen betyder

Anbefalingen betyder, at Medicinrådet råder regionerne til at bruge apalutamid til patienter med højrisiko ikke-metastaserende kastrationsresistent prostatakræft, men ikke nødvendigvis som førstevalg til alle patienter.

Anbefalingen af apalutamid har betydning for valg af behandling i senere behandlingslinjer, da Medicinrådet forudsætter, at lægemidler med samme virkningsmekanisme ikke anvendes sekventielt.

6. Sagsbehandlingstid

Medicinrådet har brugt 16 uger og 2 dage på arbejdet med apalutamid til med højrisiko ikke-metastaserende kastrationsresistent prostatakræft.

7. Kontaktinformation til Medicinrådet

Medicinrådets sekretariat
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8. Versionslog

Versionslog		
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9. Bilag

1. Medicinrådets sundhedsøkonomiske afrapportering vedr. apalutamid, version 1.0
2. Forhandlingsnotat fra Amgros vedr. apalutamid til behandling af højrisiko ikke-metastaserende kastrationsresistent prostatakræft
3. Høringssvar fra ansøger
4. Medicinrådets vurdering vedr. apalutamid til behandling af højrisiko ikke-metastaserende kastrationsresistent prostatakræft, version 1.0
5. Ansøgers endelige ansøgning
6. Ansøgers tekniske dokument til den sundhedsøkonomiske ansøgning
7. Medicinrådets protokol for vurdering vedr. apalutamid til behandling af højrisiko ikke-metastaserende kastrationsresistent prostatakræft, version 1.0

Medicinrådet

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Medicinrådet

Sundhedsøkonomisk afrapportering

Apalutamid

Højrisiko ikke-metastaserende kastrationsresistent prostatakræft

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

Dette dokument indeholder en beskrivelse af den sundhedsøkonomiske analyse, som ligger til grund for ansøgningen for apalutamid i kombination med androgen deprivationsterapi (ADT) til patienter med højrisiko ikke-metastaserende kastrationsresistent prostatakræft samt en gennemgang af ansøgers modelantagelser til den sundhedsøkonomiske model. Sekretariatet vil kommentere på ansøgers modelantagelser under afsnittene "Sekretariatets vurdering". Her vil sekretariatets vurdering fremgå sammen med eventuelle ændrede modelantagelser og begrundelser herfor.

Afsnit 4.4 indeholder en tabel, der opsummerer både ansøgers og sekretariatets modelantagelser med det formål tydeligt at vise, hvordan sekretariatets sundhedsøkonomiske analyse afviger fra ansøgers sundhedsøkonomiske analyse. Resultatafsnittet baserer sig på sekretariatets modelantagelser og sundhedsøkonomiske analyse.

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1. Liste over forkortelser

ADT	Androgen deprivationsterapi
AIP	Apotekernes indkøbspris
BSA	Legemsoverflade
CRCP	Kastrationsresistent prostatakræft
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
ITT	*Intention-to-treat*
mCRPC	Metastaserende kastrationsresistent prostatakræft (*metastatic castration resistant prostate cancer*)
MDC	*Major Diagnostic Categories*
MFS	Metastasefri overlevelse
nmCRPC	Ikke-metastaserende kastrationsresistent prostatakræft (*non-metastatic castration resistant prostate cancer*)
OS	Samlet overlevelse
PFS	Metastatisk progressionsfri overlevelse
SAIP	Sygehusapotekernes indkøbspriser
SPC	Produktresumé
TTTD	*Time-to-treatment-discontinuation*

2. Opsummering

Baggrund

Apalutamid er i kombination med androgen deprivationsterapi (ADT) indiceret til behandling af patienter med højrisiko ikke-metastaserende kastrationsresistent prostatakræft (nmCRPC). Omkring 100 patienter kandiderer årligt til behandling af den ansøgte indikation i Danmark. Sekretariatets vurdering tager udgangspunkt i dokumentation indsendt af Janssen-Cilag A/S.

Analyse

Den sundhedsøkonomiske analyse estimerer de inkrementelle omkostninger pr. patient ved behandling med apalutamid i kombination med ADT over en tidshorisont på 20 år. Apalutamid i kombination med ADT sammenlignes med ADT alene.

Inkrementelle omkostninger og budgetkonsekvenser

I det scenarie, sekretariatet mener er mest sandsynligt, er de inkrementelle omkostninger for apalutamid i kombination med ADT ca. [redacted] DKK pr. patient sammenlignet med ADT alene over en tidshorisont på 20 år. Hvis analysen udføres med AIP, bliver de inkrementelle omkostninger til sammenligning ca. 580.000 DKK pr. patient.

Sekretariatet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af apalutamid i kombination med ADT som standardbehandling vil være ca. [redacted] DKK i år 5. Hvis analysen udføres med AIP, er budgetkonsekvenser ca. 52,0 mio. DKK i år 5.

Konklusion

Behandling med apalutamid er forbundet med inkrementelle omkostninger sammenlignet med behandling med ADT. De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne for apalutamid.

3. Baggrund for den sundhedsøkonomiske analyse

Janssen-Cilag A/S (herefter omtalt som ansøger) er markedsføringstilladelsesindehaver af apalutamid og har den 5. oktober 2020 indsendt en ansøgning til Medicinrådet om anbefaling af apalutamid i kombination med ADT som standardbehandling på danske hospitaler af den nævnte indikation. Som et led i denne ansøgning vurderer Medicinrådets sekretariat, på vegne af Medicinrådet, den sundhedsøkonomiske analyse, ansøger har indsendt. Denne rapport er sekretariatets vurdering af den fremsendte sundhedsøkonomiske analyse (herefter omtalt som analysen).

3.1 Patientpopulation

Prostatakræft er den hyppigste kræftform hos mænd i Danmark. Prostatakræft manifesterer sig især efter 60-års alderen [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. Fagudvalget vurderer, at 100 patienter årligt vil være kandidater til behandling med apalutamid.

3.1.1 Komparator

Medicinrådet har defineret ADT alene som komparator for populationen specificeret i afsnit 3.1, se Tabel 1.

Tabel 1: Defineret population og komparator.

Population	Komparator
Patienter med højrisiko ikke-metastaserende kastrationsresistent prostatakræft (nmCRPC). Højrisiko defineres som PSA-fordoblingstid på eller under 10 måneder.	ADT

3.2 Problemstilling

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af apalutamid i kombination med ADT som standardbehandling på danske hospitaler af den nævnte indikation.

Medicinrådet har vurderet den kliniske merværdi af apalutamid i kombination med ADT og specificeret følgende kliniske spørgsmål:

Klinisk spørgsmål 1:
Hvad er værdien af apalutamid i kombination med androgen deprivationsterapi (ADT) sammenlignet med ADT alene til patienter med højrisiko ikke-metastaserende kastrationsresistent prostatakræft?

4. Vurdering af den sundhedsøkonomiske analyse

Ansøger har indsendt en sundhedsøkonomisk analyse, der estimerer de inkrementelle omkostninger pr. patient for apalutamid i kombination med ADT, herefter omtalt som apalutamid, sammenlignet med ADT. I det nedenstående vil den sundhedsøkonomiske model, som ligger til grund for estimeringen af de inkrementelle omkostninger pr. patient, blive præsenteret.

4.1 Antagelser og forudsætninger for model

Den sundhedsøkonomiske model har til formål at estimere de inkrementelle omkostninger ved behandling af mænd med højrisiko nmCRPC.

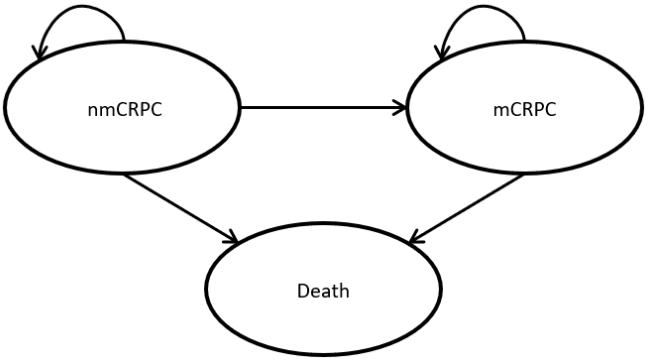
Sammenligningen mellem apalutamid og ADT er lavet på baggrund af data fra ét randomiseret klinisk fase-III-studie, SPARTAN, der direkte sammenligner apalutamid + ADT mod placebo + ADT hos patienter med højrisiko nmCRPC [2]. Det primære og sekundære endepunkt i SPARTAN-studiet var henholdsvis metastasefri overlevelse (MFS) og samlet overlevelse (OS).

Efter første data cut-off i SPARTAN-studiet blev patienter, der modtog placebo + ADT og ikke viste tegn på sygdomsprogression, tilbudt at krydse over til behandling med apalutamid + ADT, hvorefter blindingen blev brudt. Ansøger har derfor både indleveret data for *intention-to-treat* (ITT)-populationen og data justerede for *cross-over*, hvoraf ansøgers analyse bygger på data for ITT-populationen. Ved at justere data laves der en række antagelser, som kan have betydning for sammenligningen, derfor er ITT-analysen med ujusteret data det konservative valg.

4.1.1 Modelbeskrivelse

Ansøger har indleveret en *partitioned survival model*, der estimerer omkostninger baseret på den tid, patienten er i tre helbredsstadier: nmCRPC, metastaserende kastrationsresistent prostatakræft (mCRPC) og død. Patienterne er i nmCRPC-stadiet, indtil de progredierer, hvorefter de er i mCRPC-stadiet, indtil de dør. I løbet af nmCRPC-stadiet bliver patienterne behandlet med apalutamid, og behandlingsvarigheden estimeres ud fra data for *time-to-treatment discontinuation* (TTTD).

En cyklus i modellen er én uge. Ansøger har ikke anvendt *half-cycle correction* grundet den korte cykluslængde. Figur 1 viser modellens struktur.



Figur 1: Beskrivelse af modelstrukturen i omkostningsanalysen.

Ansøger modellerer tiden i de forskellige stadier ved at anvende ekstrapolerede Kaplan Meier (KM)-data for MFS og OS. Ansøger har anvendt en Weibull-funktion til at ekstrapolere MFS for både apalutamid og ADT, da Weibull-funktionen vurderes at have bedst statistisk fit på data, se henholdsvis Figur 2 og Figur 3.

Figur 2: Ekstrapolerede funktioner for MFS for apalutamid.

Figur 3: Ekstrapolerede funktioner for MFS for ADT.

For OS har ansøger udarbejdet en kombineret ekstrapolering for både apalutamid og ADT, hvor ansøger har anvendt ADT som referencekurve for apalutamid, se Figur 4. Ansøger har anvendt en Weibull-funktion til at ekstrapolere OS for den kombinerede model, da Weibull-funktionen vurderes at have bedst statistisk fit på data. Ansøger har derudover justeret ekstrapoleringerne i forhold til den generelle befolkningsdødelighed i Danmark [3].

Figur 4: Ekstrapolerede funktioner for OS for både apalutamid og ADT.

Ansøger har baseret behandlingslængden for apalutamid på TTTD-data fra SPARTAN-studiet, og ansøger har også her anvendt en Weibull-funktion til at ekstrapolere TTTD-kurven, da Weibull-funktionen vurderes at have bedst statistisk fit på data, se Figur 5. Ansøger antager, at behandlingen med ADT er livslang.

Figur 5: Ekstrapolerede funktioner for TTTD for apalutamid

Tabel 2 viser henholdsvis den gennemsnitlige tid til metastatisk progression i nmCRPC-stadiet, den gennemsnitlige overlevelse i mCRPC-stadiet samt den gennemsnitlige behandlingsvarighed af apalutamid og ADT i nmCRPC. Estimaterne er baseret på ekstrapolerede data fra SPARTAN-studiet.

Tabel 2: Tid i behandling samt tid til metastatisk progression og gennemsnitlige overlevelse.

	Apalutamid	ADT
Gennemsnitlig tid til metastatisk progression (år)		
Gennemsnitlig overlevelse (år)		
Gennemsnitlig behandlingsvarighed (år)		

Sekretariatets vurdering

Sekretariatet accepterer ansøgers tilgang vedr. modelantagelser.

4.1.2 Analyseperspektiv

Ansøgers omkostningsanalyse har et begrænset samfundsperspektiv. Analysen har en tidshorisont på 30 år. Ansøger argumenterer for, at denne tidshorisont er tilsvarende en livstidshorisont, hvis den gennemsnitlige alder for patienterne i SPARTAN-studiet (73,9 år) tages i betragtning. Omkostninger, der ligger efter det første år, er diskonteret med en rate på 4 %.

Sekretariatets vurdering
Sekretariatet bemærker, at der ikke er flere patienter i live i modellen efter 20 år. Sekretariatet ændrer derfor tidshorisonten til 20 år i sekretariatets hovedanalyse, da de efterfølgende 10 år i ansøgers analyse ikke har indflydelse på analysens resultat.

Sekretariatet accepterer ansøgers valg vedr. analyseperspektiv, men ændrer tidshorisonten til 20 år i egen hovedanalyse.

4.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af apalutamid i kombination med ADT sammenlignet med ADT. De inkluderede omkostninger i ansøgers analyse er lægemiddelomkostninger, hospitalsomkostninger, bivirkningsomkostninger, patient- og transportomkostninger og terminale omkostninger. Ansøger har derudover inkluderet omkostninger til efterfølgende behandling. Ansøgers estimering af lægemiddelomkostninger bygger på AIP, hvilket sekretariatet udskifter med SAIP.

4.2.1 Lægemiddelomkostninger

De anvendte doser er hentet i de respektive produktresuméer (SPC'er). Doseringen af apalutamid er daglig, oral dosering à 240 mg. Ansøger har på baggrund af SPARTAN-studiet antaget en relativ dosisintensitet på 93,35 % for apalutamid.

Ansøger antager, at ADT udgøres af fire ADT-regimer bestående af goserelin, leuprorelin, triptorelin og biculatamid, der hver udgør 25 %. Denne fordeling mellem ADT-regimerne anvendes, både når ADT gives alene og i kombination med apalutamid:

- Goserelin: 10,80 mg subkutan hver 3. måned
- Leuprorelin: 22,50 mg subkutan hver 3. måned
- Triptorelin: 11,25 mg subkutan hver 3. måned
- Biculatamid: 150 mg oralt dagligt.

Den relative dosisintensitet for ADT er 96,67 % og antages ligeledes på baggrund af SPARTAN-studiet.

Alle anvendte lægemiddelpriser er i SAIP, se Tabel 3.

Tabel 3: Anvendte lægemiddelpriser, SAIP (oktober 2020)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Apalutamid	60 mg	112 stk.	[redacted]	Amgros
Goserelin	10,8 mg	1 stk.	[redacted]	Amgros
Leuprorelin	22,5 mg	1 stk.	[redacted]	Amgros
Triptorelin	11,25 mg	1 stk.	[redacted]	Amgros

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Biculatamid	50 mg	30 stk.	[redacted]	Amgros

Sekretariatets vurdering
Fagudvalget vurderer, at kun leuprorelin og triptorelin anvendes i dansk klinisk praksis, og hvert lægemiddel udgør 50 % af ADT-behandling. Sekretariatet ekskluderer derfor goserelin og biculatamid samt øger andelen af leuprorelin og triptorelin til 50 % hver i sekretariatets hovedanalyse. Derudover forklarer fagudvalget, at patienter i dansk klinisk praksis vil få en depotinjektioner med ADT hver 6. måned i stedet for hver 3. måned, som ansøger antager.

Sekretariatet accepterer ansøgers antagelser vedr. lægemiddelomkostninger men ændrer antagelserne vedr. ADT-behandlingen, således at ADT-behandling udgøres af 50 % leuprorelin og 50 % triptorelin.

4.2.2 Hospitalsomkostninger

Til beregning af hospitalsomkostninger har ansøger inkluderet omkostninger forbundet med administration af de lægemidler, der gives subkutant, hvilket er gældende for goserelin, leuprorelin og triptorelin. Da både apalutamid og biculatamid administreres oralt, har ansøger ikke inkluderet administrationsomkostninger for disse lægemidler. Ansøger antager, at hver administration af subkutane lægemidler kræver et ambulant besøg med medicingivning ved subkutan injektion på hospitalet. Ansøger har valgt en enhedsomkostning for et ambulant besøg baseret på 2020 DRG-taksten 17MA98 (MDC17 1-dagsgruppe, pat. mindst 7 år) svarende til 3.235 DKK.

Udover administrationsomkostninger har ansøger også inkluderet terminale omkostninger i form af en engangsomkostning på 82.895 DKK, der tilskrives patienter, som dør. Ansøger baserer sit estimat for terminale omkostninger på et britisk studie fra 2014 [4], som opgør gennemsnitlige omkostning for terminal pleje i England for forskellige kræftsygdomme. Ansøger har omregnet estimatet fra britiske pund til danske kroner ved anvendelse af den gennemsnitlige valutakurs for 2019. Efterfølgende har ansøger justeret engangsomkostningen for inflation ved brug af en konstant inflationsrate på 0,7 % (2014-2019) pr. år.

Ansøger har ikke inkluderet omkostninger i forbindelse med monitorering, idet ansøger antager, at behandlingsforløbet er ens, uanset om patienterne behandles med apalutamid eller ADT.

Sekretariatets vurdering
Ansøger anvender en DRG-takst for et ambulant besøg, der dækker over *Major Diagnostic Categories* (MDC) kategorien Svulster i lymfatisk og bloddannende væv. Sekretariatet udskifter taksten, så enhedsomkostningen for et ambulant besøg er baseret på 2020 DRG-taksten 11MA98 (MDC11 1-dagsgruppe, pat. mindst 7 år) svarende til 1.932 DKK. Denne DRG-takst dækker over MDC-kategorien Nyre- og urinvejssygdomme, som inkluderer CRPC.

Sekretariatet vurderer, at estimatet for terminale omkostninger er meget usikkert, da det baseres på et britisk studie, og at ressourceforbruget er anderledes i England end i dansk klinisk praksis. I mangel på bedre estimater accepterer sekretariatet dog denne kilde. Sekretariatet vurderer dog, at ansøger ikke har omregnet det engelske estimatet til en dansk kontekst korrekt. Sekretariatet vælger først at korrigere for købekraftpariteten[1] mellem Danmark og England i 2014, hvorefter estimatet konverteres til danske kroner ved brug af den gennemsnitlige valutakurs for 2014. Derefter fremskrives estimatet til 2020 ved at anvende nettoprisindekset ekskl. energi. Dermed bliver de terminale omkostninger 104.518 DKK, hvilket sekretariatet anvender i egen hovedanalyse. Den ændring har minimal betydning for analysens resultat, da alle patienter dør i modellen og forskelle i terminale omkostninger mellem de to lægemidler derfor udelukkende er drevet af forskelle i diskontering afhængig af tidspunktet for død.

Fagudvalget er enig med ansøger i, at behandlingsforløbet mellem apalutamid og ADT vil være nogenlunde ens, da patienterne monitoreres ofte for at måle progression. Dog er der stor forskel i tid i nmCRPC og mCRPC for patienter, der behandles med apalutamid, og patienter, der behandles med ADT. Sekretariatet vurderer derfor, at der vil være forskel i monitoreringsomkostninger mellem de to behandlinger. Sekretariatet vurderer dog også, at disse omkostninger har en lille betydning for det samlede resultat, hvorfor sekretariatet accepterer ansøgers antagelse.

Sekretariatet udskifter DRG-taksten for et ambulant besøg og anvender et estimat for terminale omkostning på 104.518 DKK i egen hovedanalyse.

4.2.3 Bivirkningsomkostninger

Ansøger har inkluderet bivirkningsomkostninger for apalutamid og ADT. Ansøger inkluderer frekvenser for bivirkninger af grad 3-4, som forekom i minimum 5 % af patienterne. Bivirkningsfrekvenserne er taget fra SPARTAN-studiet, se Tabel 4.

Til estimering af ressourcebrug i forbindelse med bivirkninger har ansøger baseret sig på 2020 DRG-taksten 11MA98 (MDC11 1-dagsgruppe, pat. mindst 7 år) svarende til 1.932 DKK.

Tabel 4: Rapporterede bivirkningsfrekvenser ved behandling med apalutamid eller ADT.

	Apalutamid	ADT
Hypertension	16,31 %	12,31 %
Udslæt	5,23 %	0,25 %

Sekretariatets vurdering

Sekretariatet accepterer ansøgers tilgang vedr. bivirkningsomkostninger.

[1] Købekraftpariteten udtrykker de relative priser. I dens simpleste form defineres en købekraftparitet som prisforholdet mellem nationale valutaer for den samme vare eller tjeneste i forskellige lande [6].

4.2.4 Efterfølgende behandling

Ansøger inkluderer omkostninger til efterfølgende behandling, da modellen inkluderer mCRPC-stadiet, hvor efterfølgende behandlinger gives. Ansøger antager, at patienter, som progredierer fra nmCRPC til mCRPC, vil modtage samme ADT-behandling som i nmCRPC-stadiet i kombination med én af nedenstående:

- Abirateron: 1.000 mg oralt i kombination med 10 mg prednisolon dagligt
- Enzalutamid: 160 mg oralt dagligt
- Docetaxel: 75 mg/m^2 kropsoverflade intravenøst i kombination med 10 mg prednisolon og 24 mg dexamethason oralt hver 3. uge i 10 cyklusser
- Cabazitaxel: 25 mg/m^2 kropsoverflade intravenøst i kombination med 10 mg prednisolon og 0,05 mg/kg filgrastim subkutant hver 3. uge i 10 cyklusser
- Radium-223: 55 kBq/kg intravenøst hver 4. uge i 6. cyklusser

For lægemidler doseret efter legemsoverfladearealet (BSA) antager ansøger en gennemsnitlig BSA på 1,80 m^2, mens en gennemsnitlig vægt på 87 kg fra SPARTAN-studiet anvendes for lægemidler, som doseres efter vægt.

Alle anvendte lægemiddelpriser til efterfølgende behandling er i SAIP, se Tabel 5.

Tabel 5: Anvendte lægemiddelpriser til efterfølgende behandling, SAIP (oktober 2020).

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Abirateron	500 mg	56 stk.	[redacted]	Amgros
Prednisolon	5 mg	100 stk.	[redacted]	Amgros
Enzalutamid	40 mg	112 stk.	[redacted]	Amgros
Docetaxel	160 mg/8 ml	8 ml	[redacted]	Amgros
Dexamethason	4 mg	100 stk.	[redacted]	Amgros
Cabazitaxel	60 mg/1,5 ml	1,5 ml	[redacted]	Amgros
Filgrastim	30 ME/0,5 ml	2,5 ml	[redacted]	Amgros
Radium-223	1000 mg	6 ml	[redacted]	Bayer

Ansøger antager, at alle patienter, der progredierer til mCRPC, får både 1. linje-, 2. linje- og 3. linjebehandling i mCRPC. Ansøger antager, at fordelingen af efterfølgende behandling består af tre behandlingslinjer, og at fordelingen er afhængig af, hvilken behandling patienterne modtog i nmCRPC. Fordelingen kan ses i Tabel 6.

Tabel 6: Ansøgers estimat af fordelingen af efterfølgende behandling.

Behandling i nmCRPC	Apalutamid			ADT		
Behandlingslinje i mCRPC	1. linje	2. linje	3. linje	1. linje	2. linje	3. linje
Abirateron	10 %	16 %	40 %	20 %	50 %	20 %
Enzalutamid	30 %	12 %	13 %	60 %	30 %	20 %
Docetaxel	52 %	40 %	18 %	12 %	10 %	30 %
Cabazitaxel	7 %	25 %	19 %	7 %	5 %	20 %
Radium-223	1 %	7 %	10 %	1 %	5 %	10 %

Ansøger tager udgangspunkt i mediane behandlingslængder på 10 måneder, 8,3 måneder og 6,6 måneder for hhv. 1. linje-, 2. linje-, og 3. linjebehandling for patienter, der har mCRPC, baseret på et prospektivt studie, der undersøger patienter med mCRPC, der modtog abirateron i 1. linjebehandling i mCRPC [5]. Efterfølgende justerer ansøger de mediane behandlingslængder proportionalt i forhold til tiden i mCRPC-stadiet i modellen, idet de mediane behandlingslængder fra det prospektive studie er kortere end tiden i mCRPC-stadiet i modellen, se Tabel 7.

Tabel 7: Proportionelt justerede behandlingslængder for efterfølgende behandlingslinjer.

Behandlingslinje	Median behandlingslængde for behandlingslinjerne	Justerede behandlingslængder for apalutamid	Justerede behandlingslængder for ADT
1. linjebehandling	10 måneder	14,3 måneder	18,3 måneder
2. linjebehandling	8,3 måneder	11,8 måneder	15,2 måneder
3. linjebehandling	6,6 måneder	9,4 måneder	12,1 måneder

Ansøger antager, at den relative dosisintensitet for den efterfølgende behandling er 100 %, men for docetaxel, cabazitaxel og radium-223 er den mediane behandlingsvarighed hhv. 9,5 cyklusser, 6 cyklusser og 58 % injektioner. For docetaxel og cabazitaxel er disse estimater baseret på medianer, mens estimatet for radium-223 er et gennemsnit.

Ansøger inkluderer omkostninger forbundet med administration af de lægemidler, der gives intravenøst, hvilket er gældende for docetaxel, cabazitaxel og radium-223. Ansøger antager, at hver administration af intravenøse lægemidler kræver et ambulant besøg med medicingivning ved intravenøs infusion på hospitalet. Ansøger har valgt en enhedsomkostning for et ambulant besøg baseret på 2020 DRG-taksten 17MA98 (MDC17 1-dagsgruppe, pat. mindst 7 år) svarende til 3.235 DKK.

Sekretariatets vurdering

Fagudvalget mener, at det er urealistisk at antage, at alle patienter, der progredierer til mCRPC, vil modtage både 1. linje-, 2. linje- og 3. linjebehandling, idet en stor del af patienterne vil stoppe i behandling undervejs. Fagudvalget estimerer, at 80 % vil modtage 1. linjebehandling, 50 % vil modtage 2. linjebehandling og 33 % vil modtage 3. linjebehandling. Fagudvalget er heller ikke enige i ansøgers fordeling af behandlinger i de tre efterfølgende behandlingslinjer. Fagudvalgets estimering af fordelingen af efterfølgende behandling kan ses i Tabel 8.

Tabel 8: Fagudvalgets estimat af fordeling af efterfølgende behandling.

Behandling i nmCRPC	Apalutamid			ADT		
Behandlingslinje i mCRPC	1. linje	2. linje	3. linje	1. linje	2. linje	3. linje
Abirateron	0 %	0 %	50 %	0 %	0 %	5 %
Enzalutamid	0 %	0 %	0 %	80 %	0 %	0 %
Docetaxel	100 %	0 %	0 %	20 %	100 %	0 %
Cabazitaxel	0 %	95 %	0 %	0 %	0 %	90 %
Radium-223	0 %	5 %	50 %	0 %	0 %	5 %

Derudover anser fagudvalget ansøgers estimerede behandlingslængder af efterfølgende behandlingslinjer som usikre, idet behandlingslængderne vurderes at være for lange. Fagudvalget er dog enig med ansøger i, at patienter i ADT-behandling vil have længere behandling i efterfølgende behandlingslinjer. Ligesom ansøgers estimater bygger fagudvalgets estimater for behandlingslængder for efterfølgende behandlingslinjer på medianer, se Tabel 9.

Tabel 9: Fagudvalgets estimat af behandlingslængder for efterfølgende behandlingslinjer.

Behandlingslinje	Behandlingslængder for apalutamid	Behandlingslængder for ADT
1. linjebehandling	10 måneder	15 måneder
2. linjebehandling	8 måneder	10 måneder
3. linjebehandling	4 måneder	8 måneder

Sekretariatet bemærker, at SPC'et ikke beskriver en maksimal behandlingsvarighed på cabazitaxel på 10 cyklusser, som ansøger har antaget. Ansøger argumenterer for, at denne antagelse er anvendt i en vurdering af cabazitaxel af det engelske prioriteringssystem, NICE. I dansk klinisk praksis kan cabazitaxel gives i mere end 10 cyklusser, dog vurderer fagudvalget, at medianen er 7 cyklusser. Fagudvalget har ikke et bud på et gennemsnitlig antal cyklusser men vurderer, at nogle patienter får mere end 10 cyklusser. Fagudvalget vurderer derudover, at filgrastim kun gives som profylaktisk

behandling til 50 % af de patienter, som behandles med cabazitaxel, for at minimere risikoen for hæmatologisk toksicitet. For docetaxel anslår fagudvalget, at den mediane behandlingsvarighed for patienter, der behandles med docetaxel, er 8 cyklusser.

Disse overnævnte ændringer inkluderer sekretariatet i egen hovedanalyse. Samlet har disse ændringer en vis betydning for analysens resultat.

Ligesom administrationsomkostninger for ADT udskifter sekretariatet DRG-taksten anvendt for et ambulant besøg, idet ansøger også her har anvendt en DRG-takst, der dækker over MDC-kategorien Svulster i lymfatisk og bloddannende væv. DRG-taksten udskiftes til en enhedsomkostning for et ambulant besøg baseret på 2020 DRG-taksten 11MA98 (MDC11 1-dagsgruppe, pat. mindst 7 år) svarende til 1.932 DKK.

Sekretariatet vurderer, at der er stor usikkerhed forbundet med efterfølgende behandling, idet anvendte behandlingslængder bygger på medianer i stedet for gennemsnit. Sekretariatet vælger derfor at udarbejde en følsomhedsanalyse, hvor efterfølgende behandling ekskluderes.

Sekretariatet ændrer andelen af patienter, der fortsætter i efterfølgende behandling, fordelingen af efterfølgende behandling, og behandlingslængderne af efterfølgende behandlingslinjer, således at disse bygger på fagudvalgets estimater. Derudover udskifter sekretariatet DRG-taksten for et ambulant besøg.
Sekretariatet vælger at udarbejde en følsomhedsanalyse, hvor efterfølgende behandling ekskluderes.

4.2.5 Patientomkostninger

Ansøger har inkluderet patientomkostninger relateret til transport og patienttid i forbindelse med administration af subkutane og intravenøse lægemidler på hospitalet. For ADT gælder dette goserelin, leuprorelin og triptorelin, mens det gælder docetaxel, cabazitaxel og radium-223 for efterfølgende behandling.

Ansøger anvender en enhedsomkostning for patienttid på 179 DKK pr. time og en transportomkostning på 100 DKK, jf. Medicinrådets Værdisætning af enhedsomkostninger. Ansøger antager, at administration af både subkutane injektioner og intravenøs infusion varer 60 minutter.

Ansøgers estimerede patienttid og transport kan ses i Tabel 10.

Tabel 10: Ansøgers estimat af effektiv patienttid og transport pr. år.

Lægemiddel	Patienttid (timer)	Transport (antal gange)
ADT	4,0	4,0
Docetaxel	9,5	9,5
Cabazitaxel	6,5	6,5
Radium-223	3,48	3,48

Sekretariatets vurdering

Fagudvalget vurderer, at subkutan injektion med ADT kun varer 30 min., hvorimod intravenøs infusion varer 1,5 time. Fagudvalgets estimerede patienttid og transport kan ses i Tabel 11. Fagudvalgets estimater vedr. transport for ADT, docetaxel og cabazitaxel varierer også fra ansøgers, idet fagudvalget antager en anden behandlingsvarighed for docetaxel og cabazitaxel samt injektion hver 6. måned med ADT.

Tabel 11: Fagudvalgets estimat af effektiv patienttid og transport pr. år.

Lægemiddel	Patienttid (timer)	Transport (antal gange)
ADT	1	2
Docetaxel	12	8
Cabazitaxel	10,5	7
Radium-223	5,22	3,48

Sekretariatets ændrer varigheden af subkutan injektion til 30 min. og intravenøs infusion til 1,5 time i egen hovedanalyse.

4.3 Følsomhedsanalyser

Formålet med følsomhedsanalyserne er at undersøge usikkerhederne i analysen. Ansøger har udarbejdet en række følsomhedsanalyser, hvor effekten af variation i forskellige parametre undersøges. Følgende følsomhedsanalyser er udført:

- Diskonteringsrate - 0 % og 5 %
- Tidshorisont - 10 år og 15 år
- OS og TTTD justeres for cross-over
- Den parametriske funktion Gompertz for TTTD, MFS og OS
- Metastatisk progressionsfri overlevelse (PFS) i stedet for MFS til at definere progression til mCRPC
- Individuel modellering af kurverne for OS for apalutamid og ADT

- Behandlingsvarigheden defineres af TTTD median (SPARTAN)
- Ekskludering af spild
- Terminale omkostninger halveres – 41.447,50 DKK

Sekretariatets vurdering
Sekretariatet vurderer, at ansøgers følsomhedsanalyser er relevante, dog vælger sekretariatet kun at præsentere resultatet af ansøgers følsomhedsanalyser, som undersøger progression og overlevelse, da disse har betydning for analysens resultat. Dette drejer sig om følsomhedsanalyserne, hvor data for OS og TTTD er justeret for cross-over, hvor kurverne for OS for apalutamid og ADT modelleres individuelt og hvor PFS anvendes i stedet for MFS til at definere progression til mCRPC. Fagudvalget vurderer, at ekstrapolering med den parametriske funktion Weibull for TTTD, MFS og OS var den ekstrapolering, som gav det mest klinisk plausible udfald på progression og overlevelse, hvorfor sekretariatet ikke vælger at vise resultatet af følsomhedsanalysen, hvor den parametriske funktion Gompertz anvendes. I tillæg til ansøgers følsomhedsanalyser udarbejder sekretariatet en følsomhedsanalyse, hvor efterfølgende behandling ekskluderes.

Sekretariatet vælger at præsentere et udvalg af ansøgers følsomhedsanalyse og yderligere en følsomhedsanalyse udarbejdet af sekretariatet.

4.4 Opsummering af basisantagelser

I Tabel 12 opsummeres basisantagelserne for ansøgers hovedanalyse sammenlignet med de ændringer, som sekretariatet har lavet i egen hovedanalyse.

Tabel 12: Basisantagelser for ansøgers og sekretariatets hovedanalyse.

Basisantagelser	Ansøger	Sekretariatet
Tidshorisont	30 år	20 år
Diskonteringsrate	4 %	4 %
Inkluderede omkostninger	Lægemiddelomkostninger Hospitalsomkostninger Bivirkningsomkostninger Efterfølgende behandling Patientomkostninger	Lægemiddelomkostninger Hospitalsomkostninger Bivirkningsomkostninger Efterfølgende behandling Patientomkostninger
Behandlingslinje	1. linjebehandling	1. linjebehandling
Behandlingsvarighed		
Apalutamid:	[redacted] år	[redacted] år
ADT:	[redacted] år	[redacted] år

Basisantagelser	Ansøger	Sekretariatet
Behandlingslængder af efterfølgende behandling		
Apalutamid:	1. linje = 14,3 måneder 2. linje = 11,8 måneder 3. linje = 9,4 måneder	1. linje = 10 måneder 2. linje = 8 måneder 3. linje = 4 måneder
ADT:	1. linje = 18,3 måneder 2. linje = 15,2 måneder 3. linje = 12,1 måneder	1. linje = 15 måneder 2. linje = 10 måneder 3. linje = 8 måneder
Parametriske funktioner for TTTD for apalutamid	Weibull	Weibull
Parametriske funktioner for MFS		
Apalutamid:	Weibull	Weibull
ADT:	Weibull	Weibull
Parametriske funktioner for OS		
Apalutamid:	Weibull	Weibull
ADT:	Weibull	Weibull
Inkludering af spild	Ja	Ja

5. Resultater

5.1 Resultatet af sekretariatets hovedanalyse

Sekretariatets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse, men med følgende justeringer:

- Ændring af tidshorisont til 20 år
- Ændring af fordelingen af ADT-behandling samt behandlingsinterval
- Ændring af enhedsomkostning for ambulant besøg
- Ændring af enhedsomkostning for terminale omkostninger
- Ændring af andel af patienter, der modtager efterfølgende behandling
- Ændring af fordelingen af efterfølgende behandling
- Ændringer af behandlingslængder for efterfølgende behandlingslinjer

- Ændring af behandlingsvarighed for cabazitaxel og docetaxel i efterfølgende behandling
- Ændring af varighed for subkutan injektion og intravenøs infusion

Den inkrementelle omkostning pr. patient bliver ca. [redacted] DKK over en tidshorisont på 20 år i sekretariatets hovedanalyse. Udføres analysen med AIP bliver den inkrementelle omkostning pr. patient ca. 580.000 DKK.

Resultaterne fra sekretariatets hovedanalyse præsenteres i Tabel 13.

Tabel 13: Resultatet af sekretariatets hovedanalyse ved sammenligning med ADT, DKK, diskonterede tal.

	Apalutamid	ADT	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	94.174	91.179	2.995
Bivirkningsomkostninger	416	243	174
Efterfølgende behandling	[redacted]	[redacted]	[redacted]
Patientomkostninger	1.073	547	526
Totale omkostninger	[redacted]	[redacted]	[redacted]

5.1.1 Resultatet af sekretariatets følsomhedsanalyser

Ved samme antagelser som i sekretariatets hovedanalyse, udfører sekretariatet følsomhedsanalyser som beskrevet i afsnit 4.3 Følsomhedsanalyser, se Tabel 14.

Tabel 14: Resultatet af sekretariatets følsomhedsanalyse sammenlignet med hovedanalysen, DKK

Scenarie	Inkrementelle omkostninger
Resultatet af hovedanalysen	[redacted]
Data for OS og TTTD, der er justeret for cross-over	[redacted]
Kurverne for OS for apalutamid og ADT modelleres individuelt	[redacted]
PFS anvendes i stedet for MFS til at definere progression til mCRPC	[redacted]
Ekskludering af efterfølgende behandling	[redacted]

6. Budgetkonsekvenser

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

- Apalutamid bliver anbefalet som standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler
- Apalutamid bliver ikke anbefalet som standardbehandling

Budgetkonsekvenserne bliver differencen mellem budgetkonsekvenserne i de to scenarier.

6.1 Ansøgers estimat af patientantal og markedsandel

Ansøger estimerer, at 100 patienter årligt forventes at kandidere til behandling med apalutamid jf. Medicinrådets protokol.

Ansøger antager, at ved en anbefaling af apalutamid vil apalutamid overtage 40 % af markedsandelen i år 1, 60 % i år 2 og 70 % i de resterende år. Ansøgers estimat af antal patienter årligt i budgetkonsekvenserne kan ses i Tabel 15. Ansøger antager desuden, at patienterne starter i behandling jævnt fordelt ud over hvert år, således at 7,7 patienter starter i behandling hver uge.

Tabel 15: Ansøgers estimat af antal nye patienter pr. år.

	År 1	År 2	År 3	År 4	År 5
Anbefales					
Apalutamid	40	60	70	70	70
ADT	60	40	30	30	30
Anbefales ikke					
Apalutamid	0	0	0	0	0
ADT	100	100	100	100	100

Sekretariatets vurdering
Fagudvalget vurderer, at apalutamid vil have et noget højere markedsoptag, hvis apalutamid anbefales, idet apalutamid, udover ADT, et det eneste andet behandlingsalternativ for patienter med nmCRPC. Fagudvalget anslår, at apalutamid vil have 90 % markedsoptag i år 1 og 100 % i de resterende år, se Tabel 16.

Tabel 16: Fagudvalgets estimat af antal nye patienter pr. år.

	År 1	År 2	År 3	År 4	År 5
Anbefales					
Apalutamid	90	100	100	100	100
ADT	10	0	0	0	0
Anbefales ikke					
Apalutamid	0	0	0	0	0
ADT	100	100	100	100	100

Sekretariatet accepterer ikke, at ansøger antager, at patienter opstartes i behandling jævnt fordelt over hvert år i budgetkonsekvenserne, da dette vil medføre en underestimering af budgetkonsekvenserne. Formålet med budgetkonsekvensanalysen er at beregne de totale budgetkonsekvenser for regionerne for behandling af patienterne i 5 år. Sekretariatet ændrer derfor disse antagelser til, at alle patienter opstartes i behandling ved start af hvert år i sekretariatets budgetkonsekvensanalyse.

Sekretariatet udfører egen budgetkonsekvensanalyse, hvor markedsoptaget for apalutamid ændres til 90 % i år 1 og 100 % i de resterende år, samtidig med at alle patienter opstartes i behandling ved start af hvert år i sekretariatets budgetkonsekvensanalyse.

6.2 Sekretariatets budgetkonsekvensanalyse

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

- Markedsoptaget for apalutamid ændres til 90 % i år 1 og 100 % i de resterende år
- Alle patienter opstartes i behandling ved start af hvert år

Sekretariatet estimerer, at anvendelse af apalutamid vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Udføres analysen med AIP, bliver budgetkonsekvenserne ca. 52,0 mio. DKK i år 5.

Resultatet af budgetkonsekvensanalysen er præsenteret i Tabel 17.

Tabel 17: Sekretariatets analyse af totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal.

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

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

7. Diskussion

Behandling med apalutamid er forbundet med inkrementelle omkostninger sammenlignet med behandling med ADT. De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne for apalutamid.

7.1 Usikkerheder

Efterfølgende behandling har en vis betydning for analysens resultat. Dette hænger sammen med, at de efterfølgende behandlingslinjer, som patienter tilbydes, når de progredierer på ADT, i gennemsnit er dyrere behandlinger end apalutamid. Samtidig har tiden i mCRPC også en betydning, idet patienter, der behandles med ADT, har ca. 10 måneder ekstra i mCRPC, hvor patienterne modtager behandling. Hvis efterfølgende behandling ekskluderes, stiger de inkrementelle omkostninger med ca. [redacted] DKK pr. patient.

I SPARTAN-studiet blev progression defineret ud fra MFS, hvilket analysen bygger på. Hvis progression derimod defineres ud fra PFS, stiger de inkrementelle omkostninger med ca. [redacted] DKK pr. patient. Dette skyldes, at patienterne progredierer senere, hvormed tiden i nmCRPC øges, hvilket øger lægemiddelomkostningerne for begge lægemidler og dermed øger de inkrementelle omkostninger.

8. Referencer

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9. Bilag

9.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK over en tidshorisont på 30 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 18.

Tabel 18: Resultatet af ansøgers hovedanalyse, DKK, diskonterede tal.

	Apalutamid	ADT	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	92.904	81.907	10.997
Bivirkningsomkostninger	416	243	174
Efterfølgende behandling	[redacted]	[redacted]	[redacted]
Patientomkostninger	2.370	1.209	1.161
Totale omkostninger	[redacted]	[redacted]	[redacted]

9.2 Ansøgers budgetkonsekvensanalyse

Med de ovenstående antagelser om patientantal og markedsandel, estimerer ansøger, at anvendelse af apalutamid i kombination med ADT vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5.

Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 19.

Tabel 19: Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal.

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

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Forhandlingsnotat

Dato for behandling i Medicinrådet	27-01-2021
Leverandør	Janssen-Cilag
Lægemiddel	Apalutamid (Erleada)
Ansøgt indikation	Apalutamid er indiceret til behandling af voksne mænd med ikke-metastatisk kastrationsresistent prostatacancer (nmCRPC), som har høj risiko for at udvikle metastatisk sygdom.

Forhandlingsresultat

Amgros har opnået følgende pris på apalutamid:

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP (kr.)	Forhandlet SAIP (kr.)	Rabatprocent ift. AIP
Apalutamid	240 mg	112 stk.	22.369,85	[redacted]	[redacted]

Der er indgået en aftale mellem Amgros og leverandøren, med kontraktstart d. 25.01.2021, som løber indtil d. 30.09.2021, med mulighed for 3x6 måneders forlængelse.

[redacted]

[redacted]

Vurdering af forhandlingsresultatet

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

- Leverandøren lægger vægt på at lægemidlet har fået en **moderat** klinisk merværdi

[redacted]

Konklusion

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

[redacted]

Relation til markedet

I nedenstående tabel ses den årlige lægemiddelpris for de tre lægemidler, der er godkendt i EMA til samme patientpopulation. Darolutamid er medtaget i sammenligningen, men er endnu ikke godkendt til standardibrugtagning i Danmark.

Lægemiddel	Godkendt i Medicinrådet	Styrke/dosis	Pakningsstørrelse	Pakninger 1 år	SAIP (kr)	1 års behandling (kr)
Apalutamid	Beslutning 27/1	240 mg	112 stk.	13,04	[redacted]	[redacted]
Enzalutamid	Forventer genansøgning primo 2021	160 mg	112 stk.	13,04	[redacted]	[redacted]
Darolutamid	Dag 0 d. 9/12	1200 mg	112 stk.	13,04	[redacted]	[redacted]

*Prisen for darolutamid er angivet i AIP, da Amgros endnu ikke har forhandlet prisen på dette lægemiddel.

Status fra andre lande

Lægemidlet er godkendt til standardbehandling i Norge pr. 1/10 2020.

Fra:	Petersen, Jacob [JACDK]
Til:	Mette Hesselager
Emne:	RE: Høring over godkendt vurdering af lægemidlets værdi for apalutamid til højrisiko ikke-metastaserende kastrationsresistent prostatakræft
Dato:	14. december 2020 15:27:35
Vedhæftede filer:	image002.jpg image004.jpg image003.jpg

Kære Mette,

Mange tak for tilsendte.

Janssen-Cilag har ikke kommentarer til evalueringen, men vil gerne benytte lejligheden til at takke Sekretariatet for en god proces og et godt samarbejde.

Med venlig hilsen,
Jacob

Jacob Petersen
Country HEMAR Manager | External Affairs

Janssen-Cilag A/S
Bregnerødvej 133
Birkerød, 3460 DK
Phone +45 29998254
jpeter68@its.jnj.com

From: Mette Hesselager <mhe@medicinraadet.dk>
Sent: 9. december 2020 18:40
To: Petersen, Jacob [JACDK] <jpeter68@ITS.JNJ.com>
Subject: [EXTERNAL] Høring over godkendt vurdering af lægemidlets værdi for apalutamid til højrisiko ikke-metastaserende kastrationsresistent prostatakræft

Kære Jacob!

Sekretariatet fremsender hermed den endelige vurdering af lægemidlets værdi for apalutamid til højrisiko ikke-metastaserende kastrationsresistent prostatakræft, som Medicinrådet godkendte på rådsmødet i dag d. 9. december 2020. Jeg vedhæfter både den blændede og den ublændede version.

Medicinrådet var enigt med fagudvalgets konklusion om lægemidlets værdi, som derfor svarer til det resultat, I tidligere har haft i høring.

Der var ingen ændringer til de sundhedsøkonomiske modelantagelser, og de er dermed som tidligere fremsendt.

Vi ser frem til at modtage jeres eventuelle høringssvar senest den 16. december 2020.

Mvh

Mette Hesselager

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Medicinrådet

Medicinrådets vurdering vedrørende apalutamid til behandling af højrisiko ikke-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	9. december 2020
Dokumentnummer	100851
Versionsnummer	1.0

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1. Medicinrådets konklusion

Medicinrådet vurderer, at apalutamid i kombination med ADT til patienter med højrisiko ikke-metastaserende kastrationsresistent prostatakræft giver en moderat merværdi sammenlignet med ADT alene.

Evidensens kvalitet vurderes at være lav.

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
CI:	Konfidensinterval *(confidence interval)*
CRPC	Kastrations-resistent prostatakræft *(castration resistant prostate cancer)*
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EPAR:	*European Public Assessment Report*
FACT-P	*Functional Assessment of Cancer Therapy – Prostate*
GRADE:	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HR:	*Hazard ratio*
ITT:	*Intention-to-treat*
LHRH:	*Luteinising Hormone Releasing Hormone*
nmCRPC:	Ikke-metastaserende kastrations-resistent prostatakræft *(non-metastatic castration resistant prostate cancer)*
PSA:	Prostataspecifikt antigen
PICO:	Population, intervention, komparator og effektmål (*Population, Intervention, Comparator and Outcome)*
RCT:	Randomiseret kontrolleret studie *(Randomised Controlled Trial)*
RR:	Relativ risiko

3. Introduktion

Formålet med Medicinrådets vurdering af apalutamid til af højrisiko ikke-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 Janssen-Cilag A/S. Medicinrådet modtog ansøgningen den 5. oktober 2020.

Det kliniske spørgsmål er: Hvad er værdien af apalutamid i kombination med androgen deprivationsterapi (ADT) sammenlignet med ADT alene til patienter med højrisiko ikke-metastaserende kastrationsresistent prostatakræft?

3.1 Højrisiko ikke-metastaserende kastrationsresistent prostatakræft

Prostatakræft er den hyppigste kræftform hos mænd i Danmark. Prostatakræft manifesterer 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]. I perioden 2016-2018 var overlevelsen 99 % efter 1 år og 89 % efter 5 år [2].

Patienter med prostatakræft, der endnu ikke har modtaget kastrationsbehandling (ADT) eller responderer på behandling med ADT, kaldes kastrationssensitive. De fleste kastrationssensitive prostatakræfttilfælde vil over tid udvikle sig til kastrationsresistente. Kastrationsresistent prostatakræft (CRPC) defineres ved serum testosteron i kastrationsniveau (< 0,5 ng/mL eller 1,7 nmol/L) og progression enten biokemisk eller radiologisk [4]. Fagudvalget estimerer, at ca. 1.500 udvikler CRPC årligt [3].

Patienter med CRPC opdeles i to grupper i forhold til tilstedeværelse af metastaser. Ikke-metastaserende CRPC defineres som CRPC uden påviste fjernmetastaser og betegnes nmCRPC (non-metastatic castration resistant prostate cancer). De fleste patienter med nmCRPC er asymptomatiske og har forholdsvis god livskvalitet. Sygdommen betegnes som højrisiko nmCRPC i de tilfælde, hvor fordoblingstiden af prostataspecifikt antigen (PSA) er på 10 måneder eller mindre. PSA er en af de mest betydende faktorer for prognose før igangsættelse af behandling samt monitorering af behandlingseffekt. PSA-fordoblingstid på 10 måneder eller mindre er forbundet med en øget risiko for udvikling af metastaser [4]. Fagudvalget vurderer, at 100 patienter årligt vil være kandidater til behandling med apalutamid.

Median metastasefri overlevelse blandt mænd med højrisiko nmCRPC er mellem 16-18 måneder [4]. Fagudvalget estimerer, at medianoverlevelsen for patienter med højrisiko nmCRPC er ca. 3 år. Det anslås, at 5-års-overlevelsen er ca. 20 % [4].

3.2 Apalutamid

Apalutamid er et antiandrogen, som virker ved at hæmme signalering fra androgenreceptorer, hvorved aktiviteten af androgener blokeres. Apalutamid gives i kombination med ADT [5]. ADT virker ved at reducere androgenproduktionen i testiklerne, men påvirker ikke androgenproduktionen i binyrerne eller i tumoren i prostata, hvorfor testosteron stadig kan detekteres i serum. Behandling med apalutamid i kombination med ADT vil resultere i, at effekten af tilstedeværende androgener reduceres.
Apalutamid er godkendt af EMA som førstelinjebehandling i kombination med ADT til voksne patienter med højrisiko nmCRPC [5].

Apalutamid gives som 60 mg tabletter i en daglig dosis á 240 mg (fire tabletter). Behandlingen fortsættes indtil første tegn på fjernmetastaser.

3.3 Nuværende behandling

I udgangspunktet tilbydes patienter med højrisiko nmCRPC behandling med livsforlængende sigte. Patienterne behandles i dag med ADT, enten ved bilateral orkiektomi (kirurgisk fjernelse af testikler) eller medicinsk kastration med Luteinising Hormone Releasing Hormone (LHRH)-analoger [6].

Der findes på nuværende tidspunkt ikke nogen anden standardbehandling til patienter med højrisiko nmCRPC, hvor eneste tegn på sygdomsprogression er stigende PSA-niveau uden radiologisk bevis for fjernmetastaser.

4. Metode

Medicinrådets protokol for vurdering af apalutamid til behandling af højrisiko ikke-metastaserende kastrationsresistent prostatakræft, version 1.0 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

5.1.1 Litteratur

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

Ansøgningen baserer sig på de tre artikler fra det kliniske studie SPARTAN, der er angivet i protokollen [7–10] og en nyligt publiceret artikel, som indeholder data med længere opfølgning fra samme studie [11]. Desuden er anvendt data fra EMAs European public assessment reports (EPAR) for apalutamid [12].

Studiekarakteristika

SPARTAN (NCT01946204) er et randomiseret, dobbeltblindet, placebo-kontrolleret fase 3-studie. Det inkluderer 1207 patienter med højrisiko ikke-metastaserende kastrationsresistent prostatakræft. Patienterne blev randomiseret 2:1 til behandling med apalutamid (240 mg) (806 patienter) eller placebo (401 patienter) en gang dagligt. Alle patienter modtog fortsat behandling med ADT. Patienterne er stratificeret efter PSA-fordoblingstid (< 6 måneder mod ≥ 6 måneder), brug af lægemidler rettet mod knoglerne (ja mod nej) og klassifikation af lokal eller regional nodal sygdom (N0 vs. N1) ved studiestart.

Studiets primære endepunkt er metastasefri overlevelse (MFS). Studiets sekundære endepunkter er tid til metastase, progressionsfri overlevelse (PFS), tid til symptomatisk progression, samlet overlevelse (OS) og tid til igangsættelse af cytotoksisk kemoterapi. Patientrapporterede endepunkter er livskvalitet målt med spørgeskemaerne Functional Assessment of Cancer Therapy–Prostate (FACT-P) og European Quality of Life–5 Dimensions (EQ-5D-3L).

Baselinekarateristika

Nedenfor rapporteres de relevante baselinekarakteristika for patienter i apalutamid- og placebogruppen i SPARTAN (tabel 1). Fagudvalget vurderer overordnet set, at studiepopulationen er sammenlignelig med en tilsvarende dansk patientpopulation.

Tabel 1. Baselinekarakteristika for patienter i SPARTAN

	Apalutamid (n = 806)	Placebo (n = 401)
Alder, år		
Median	74	74
Range	48-94	52–97
PSA fordoblingstid		
Median, mdr.	4,40	4,50
≤ 6 mdr., n (%)	576 (71,5)	284 (70,8)
> 6 mdr., n (%)	230 (28,5)	117 (29,2)
Brug af knogle-targeteret lægemiddel, n (%)		

Ja	82 (10,2)	39 (9,7)
Nej	724 (89,8)	362 (90,3)
Klassifikation af lokal og regional nodal sygdom, n (%)		
N0	673 (83,5)	336 (83,8)
N1	133 (16,5)	65 (16,2)
Tidligere behandling for prostatakræft, n (%)		
Prostatektomi eller strålebehandling	617 (76,6)	307 (76,6)
Gonadotropin releasing hormon (GnRH) analog agonist	780 (96,8)	387 (96,5)
Første generation antiandrogen*	592 (73,4)	290 (72,3)
*Flutamid, bicalutamid og nilutamid		

5.1.2 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag, databehandling og analyse for hvert effektmål beskrevet. Medicinrådet har ikke fundet anledning til at foretage ændringer af beregninger foretaget af ansøger eller supplere med yderligere beregninger.

Data fra SPARTAN studiet er tilgængelige fra tre data cut-offs:

- Første interimanalyse (IA1) havde data cut-off den 19. maj 2017. IA1 var den initielle analyse af SPARTAN i henhold til studieprotokollen. På tidspunktet for IA1 var den mediane opfølgningstid 20,3 måneder. Ved IA1 blev der påvist statistisk signifikans for MFS, tid til metastase, PFS og tid til symptomatisk progression, og disse endepunkter blev derfor betragtet som endelige. Analyse af det primære effektmål MFS blev dermed udført, da 378 hændelser havde fundet sted. Studieblindingen blev brudt efter IA1, hvorefter de tilbageværende 76 patienter (20 %) i placeboarmen krydsede over til den aktive behandlingsarm.
- Anden interimanalyse (IA2) blev udført på baggrund af forespørgsler fra regulatoriske myndigheder og havde data cut-off den 1. februar 2019. Den mediane opfølgningstid for IA2 var 41,0 måneder.
- Den endelige analyse havde data cut-off den 1. februar 2020 og den mediane opfølgningstid var 52,0 måneder. Resultatet for OS er baseret på den endelige analyse (428 dødsfald).

Effektanalyser er udført i intention-to-treat (ITT)-populationen. På grund af den indbyggede overkrydsning fra placebo til apalutamid ved IA1, er de statistiske analyser for effektmålene suppleret med to eksplorative sensitivitetsanalyser (*naive censoring* og *inverse probability of censoring weighted analysis*).

Sikkerhedsanalyser er baseret på sikkerhedspopulationen bestående af alle patienter, der har modtaget mindst én behandlingsdosis (803 patienter behandlet med apalutamid og 398 behandlet med placebo) og er i denne ansøgning foretaget på IA1 og det endelige datasæt. Den mediane behandlingslængde var 32,9 og 11,5 måneder i henholdsvis apalutamid- og placebogruppen.

Resultater for livskvalitet er baseret på patienter i ITT-populationen, som havde færdiggjort baseline assessment og mindst en post-baseline assessment af FACT-P eller EQ-5D-3L.

5.1.3 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 1).

Fagudvalget bemærker, at der for ét ud af seks af de efterspurgte effektmål ikke er data, og der kan derfor ikke laves en GRADE-vurdering for dette effektmål.

Der er ikke nedgraderet for risiko for bias. Der er nedgraderet ét niveau for inkonsistens for alle effektmål, fordi der kun er ét studie. Der er ikke nedgraderet for indirekthed, da der er overensstemmelse mellem studiepopulationen og den danske population, og ingen betydelige forskellige, hvad angår behandlingspraksis. Der er nedgraderet ét niveau for unøjagtighed for effektmålet grad 5 bivirkninger, grad 3-4 uønskede hændelser og livskvalitet målt ved FACT-P, da konfidensintervallet indeholder én beslutningsgrænse. Der er nedgraderet ét niveau for effektmålet skeletrelaterede hændelser, da *'optimal information size'* (OIS) ikke er opfyldt.

Evidensens kvalitet er lav, hvilket betyder, at nye studier med moderat 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 (tabel 2) fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 1.

Tabel 2 Resultater for klinisk spørgsmål 1

Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Samlet overlevelse (OS)	Median OS i antal måneder (MKRF: 6 mdr.)	Kritisk	14 mdr. (ikke bestemt)	Kan ikke kategoriseres	HR: 0,78 (0,64; 0,96)	Merværdi af ukendt størrelse	Merværdi af ukendt størrelse
	OS-rate ved 3 år (MKRF: 5 %-point)	Kritisk	4,90 % (ikke bestemt)	Kan ikke kategoriseres			
Bivirkninger / uønskede hændelser	Andel patienter med grad 5 bivirkninger (MKRF: 2 %-point)	Kritisk	[redacted]	Ingen dokumenteret merværdi	[redacted]	Kan ikke kategoriseres	Ingen dokumenteret merværdi
	Andel patienter med grad 3-4 uønskede hændelser (MKRF: 5 %-point)	Vigtig	19,5 % (13,6; 25,3)	Negativ værdi	RR: 1,54 (1,33; 1,77)	Negativ værdi	Negativ
	Kvalitativ gennemgang af hændelsestyperne	Vigtig	Narrativ vurdering				
Metastasefri overlevelser (MFS)	Median MFS i antal måneder (MKRF: 12 mdr.)	Vigtig	24,3 mdr. (ikke bestemt)	Kan ikke kategoriseres	HR: 0,28 (0,23; 0,35)	Stor merværdi	Stor merværdi
	MFS-rate ved 3 år (MKRF: 20 %-point)	Vigtig	44 % (ikke bestemt)	Kan ikke kategoriseres			

Skeletrelaterede hændelser (SRE'er)	Andel patienter, der er frie for skeletrelaterede hændelser efter 3 år (MKRF: 5 %-point)	Vigtig	2,7 % (ikke bestemt)	Kan ikke kategoriseres	HR: 0,62 (0,41; 0,96)	Merværdi af ukendt størrelse	Ingen dokumenteret merværdi
Tid til kræftrelaterede procedurer	Median tid for udsættelse til kræftrelaterede procedurer (MKRF: 6 mdr.)	Vigtig	Data ikke indsamlet, kan ikke beregnes				
Livskvalitet målt ved FACT-P	Andel patienter, som oplever en ≥ 10 points reduktion fra baseline ved 2, 6, 12 og 24 mdr (MKRF: 10 %-point)	Vigtig	3,4 % (-1,4;8,2) 0,5 % (-5,1;6.0) 3,9 % (-2,4;10,2) -1,3 % (-11,9; 9,3)	Kan ikke kategoriseres	HR: 1,05 (0,89; 1,22)	Kan ikke kategoriseres	Kan ikke kategoriseres
Konklusion							
Samlet kategori for lægemidlets værdi	Moderat						
Kvalitet af den samlede evidens	Lav						

CI = konfidensinterval, HR = Hazard Ratio, RR = relativ risik

Samlet overlevelse (OS)
Som beskrevet i protokollen er effektmålet samlet overlevelse (OS) kritisk for vurderingen af lægemidlets værdi for patienterne, fordi forbedret OS med mindst mulig toksicitet er det optimale mål for kræftbehandling.

Med en median opfølgningstid på 52 måneder (endelig analyse), er median OS 73,9 (61,2; øvre grænse ikke nået) måneder i apalutamidgruppen og 59,9 (52,8; øvre grænse ikke nået) måneder i placebogruppen [11]. Den absolutte forskel i median overlevelse mellem apalutamid- og placebogruppen er dermed 14,0 måneder, hvilket overstiger den mindste klinisk relevante forskel på 6 måneder. Punktestimatet for den absolutte effektforskel afspejler dermed en klinisk relevant effektforskel. Dog findes der ikke en standardmetode til at beregne konfidensintervallet for medianen, og derfor kan den foreløbige værdi af apalutamid ikke kategoriseres efter Medicinrådets metoder.

OS-raten ved 3 år er 81,8 % (78,8; 84,4) for apalutamidgruppen mod 76,9 % (72,2; 80,9) for placebogruppen. Det svarer til en absolut forskel på 4,90 %, hvilket ikke overstiger den mindste klinisk relevante forskel på 5 %-point. Punktestimatet for den absolutte effektforskel afspejler dermed ikke en klinisk relevant effektforskel. Dog findes der ikke en standardmetode til at beregne konfidensintervallet for raten, og derfor kan den foreløbige værdi af apalutamid ikke kategoriseres efter Medicinrådets metoder.

Baseret på den relative effektforskel (hazard ratio (HR): 0,78 (0,64; 0,96)) [11] , som fremgår af tabel 2, har apalutamid foreløbigt en merværdi af ukendt størrelse vedr. samlet overlevelse.

De supplerende sensitivitetsanalyser, som tager højde for overkrydsning, viser en absolut forskel i henholdsvis median OS mellem apalutamid og placebo på 21,1 måneder og forskel i OS-rate ved 3 år mellem apalutamid og placebo på 7,4 %-point. Den relative effektforskel baseret på sensitivitetsanalyserne (HR) er 0,69 (0,56; 0,84) [11].

Fagudvalget vurderer, at apalutamid aggregeret har en merværdi af ukendt størrelse vedr. samlet overlevelse. Der er opnået merværdi af ukendt størrelse for den relative effektforskel. Fagudvalget vurderer, at de absolutte forskelle underbygger denne værdi. Forskellen i median OS overstiger den mindste klinisk relevante forskel væsentligt, mens forskellen for OS-raten ved 3 år ligger lige under den mindste klinisk relevante forskel.

Fagudvalget bemærker desuden, at de supplerende sensitivitetsanalyser for OS, som tager højde for studiets design med overkrydsning, kategoriserer effekten på OS som stor. Dog er sensitivitetsanalyserne forbundet med usikkerhed, idet de bygger på antagelser om hændelsesforløbet, hvorfor de skal tolkes med forbehold.

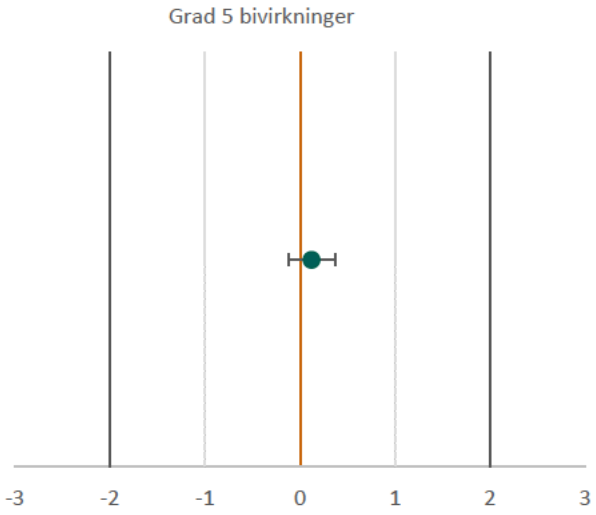
Bivirkninger / Uønskede hændelser

Grad 5 bivirkninger

Som beskrevet i protokollen er effektmålet grad 5 bivirkninger kritisk for vurderingen af lægemidlets værdi for patienterne, fordi det omhandler mortalitet som følge af behandling.

Ved den endelige analyse var i alt 24 patienter (3,0 %) døde som følge af uønskede hændelser i gruppen behandlet med apalutamid og 2 patienter (0,5 %) døde i gruppen behandlet med placebo [11]. For tidspunktet for analysen var behandlingslængden med apalutamid næsten 3 gange så lang som behandlingslængden med placebo (32,9 måneder vs. 11,5 måneder). Når der justeres for forskelle i behandlingslængden, er den justerede incidens af grad 5 uønskede hændelser 1,1 hændelse per 100 patient-år for apalutamidgruppen og 0,4 hændelser per 100 patient-år for placebogruppen. De hyppigste grad 5 uønskede hændelser optræder inden for kategorierne infektioner og hjertesygdomme.

Der er rapporteret 1 (0,12 %) grad 5 bivirkning i apalutamidgruppen (myokardieinfarkt) og ingen i placebogruppen [11].



Figur 1. Punktestimat og 95 % konfidensinterval for den absolutte forskel for grad 5 bivirkninger. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Den absolutte forskel er vist i figur 1 ovenfor.

Punktestimatet for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel. Den øvre grænse for konfidensintervallet er tættere på 0 (ingen effekt) end på en negativ klinisk relevant forskel. Derfor har apalutamid foreløbigt ingen dokumenteret merværdi vedr. grad 5 bivirkninger.

Baseret på den relative effektforskel, som fremgår af tabel 2 [redacted] kan apalutamid ikke kategoriseres efter Medicinrådets metoder. Dette skyldes få hændelser og derfor stor usikkerhed omkring effektestimatet, hvilket afspejles i et bredt konfidensinterval.

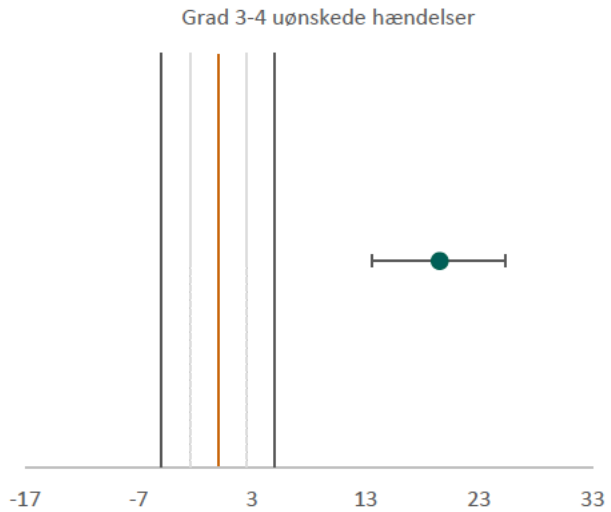
Fagudvalget vurderer, at apalutamid aggregeret har ingen dokumenteret merværdi vedr. grad 5 bivirkninger. Der er opnået ingen dokumenteret merværdi for den absolutte effektforskel. Det understøttes af de få observerede hændelser i begge grupper, som indikerer, at der ikke er forskel på de to behandlinger, hvad angår grad 5 bivirkninger.

Fagudvalget bemærker, at der ses en større andel af grad 5 uønskede hændelser i gruppen behandlet med apalutamid end i gruppen behandlet med placebo, men finder ikke dette bekymrende taget forskellen i behandlingslængde og hændelsestyperne i betragtning.

Grad 3-4 uønskede hændelser

Som beskrevet i protokollen er effektmålet grad 3-4 uønskede hændelser vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi det har betydning for den enkelte patients livskvalitet og efterlevelse af behandling.

449 patienter ud af 803 patienter (55,9 %) behandlet med apalutamid og 145 ud af 398 patienter (36,4 %) behandlet med placebo oplevede mindst en uønsket hændelse af grad 3-4 [11].



Figur 2. Punktestimat og 95 % konfidensinterval for den absolutte forskel for grad 3-4 uønskede hændelser. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Den absolutte forskel er vist i figur 2 ovenfor.

Punktestimatet for den absolutte effektforskel afspejler en negativ klinisk relevant effektforskel. Den nedre grænse for konfidensintervallet er tættere på en negativ klinisk relevant forskel end på 0 (ingen effektforskel). Derfor har apalutamid foreløbigt en negativ værdi vedr. grad 3-4 uønskede hændelser.

Baseret på den relative effektforskel, som fremgår af tabel 2 (1,54 (1,33; 1,77)), har apalutamid foreløbigt en negativ værdi vedr. grad 3-4 uønskede hændelser.

Fagudvalget bemærker, at der ved IA2 blev observeret grad 3–4 uønskede hændelser hos 53,1 % af patienterne i apalutamidgruppen og 36,7 % af patienterne i placebogruppen (ved IA2). Når der justeres for forskelle i behandlingslængden er raten af grad 3–4 uønskede hændelser ved IA2 henholdsvis 54 % i apalutamidgruppen og 68 % i placebogruppen [10].

Grad 3-4 uønskede hændelser (apalutamid vs. placebo) af særlig interesse inkluderer udslæt (5.2 % vs. 0.3 %), frakturer (4.9 % vs. 1.0 %), fald (2.7 % vs. 0.8 %), iskæmisk hjertesygdom (2.6 % vs. 1.8 %) og iskæmisk cerebrovaskulær sygdom (1.6 % vs. 0.8 %).

Fagudvalget bemærker desuden, at andelen af patienter, der stoppede behandlingen på grund af uønskede hændelser var 15 % i apalutamidgruppen og 7,3 % i placebogruppen [11].

Kvalitativ gennemgang af bivirkninger
Som beskrevet i protokollen ønskes en narrativ beskrivelse af bivirkningsprofilen for lægemidlet baseret på EMA's produktresumé. Ansøger har leveret en narrativ beskrivelse af udvalgte grad 3-4 uønskede hændelser baseret på SPARTAN [10]. I stedet for denne beskrivelse vil der i overensstemmelse med protokollen blive lagt vægt på en kvalitativ gennemgang af bivirkningsprofilen for apalutamid baseret på EMAs produktresumé [5], som følger nedenfor.

De hyppigst observerede bivirkninger er træthed, udslæt, forhøjet blodtryk, hedeture, ledsmerter, diarré, fald, frakturer, og nedsat vægt. Andre væsentlige bivirkninger omfatter iskæmisk hjertesygdom, krampeanfald og hypothyroidisme.

Produktinformationen for apalutamid nævner, at effekt og sikkerhed for patienter med klinisk signifikant hjertesygdom inden for de sidste 6 måneder ikke er etableret. Patienter med klinisk signifikant hjertesygdom bør monitoreres for risikofaktorer såsom hyperkolesterolæmi, hypertriglyceridæmi eller andre kardio-metaboliske sygdomme og behandles for disse i henhold til etablerede behandlingsvejledninger. I tilfælde af krampeanfald bør behandling med apalutamid afbrydes permanent.

Samlet vurdering vedr. grad 3-4 uønskede hændelser og kvalitativ gennemgang af bivirkninger
Fagudvalget vurderer, at apalutamid har en negativ værdi vedr. grad 3-4 uønskede hændelser og den kvalitative gennemgang af bivirkninger. Fagudvalget bemærker dog, at der i opgørelsen ikke er taget højde for forskellen i behandlingslængden ved opgørelse af grad 3-4 uønskede hændelser

Fagudvalget vurderer dog, at bivirkningsprofilen er håndterbar i klinisk praksis.

Metastasefri overlevelse (MFS)
Som beskrevet i protokollen er effektmålet metastasefri overlevelse (MFS) vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi det belyser perioden under sygdomsforløbet, hvor sygdommen er i ro og således ikke har metastaseret. Udvikling af metastaserende sygdom er forbundet med kræftrelaterede komplikationer og øget risiko for død.

Median metastasefri overlevelse for patienter behandlet med apalutamid og placebo er henholdsvis 40,5 og 16,2 måneder (IA1) [8]. Det svarer til en absolut forskel på 24,3 måneder til fordel for apalutamid, hvilket overstiger den mindste klinisk relevante forskel på 12 måneder. Punktestimatet for den absolutte effektforskel afspejler en klinisk relevant effektforskel. Dog findes der ikke en standardmetode til at beregne konfidensintervallet for medianen, og derfor kan den foreløbige værdi af apalutamid ikke kategoriseres efter Medicinrådets metoder.

Ved 3 år er 57,4 % (50,6; 63,7) metastasefri i apalutamidgruppen, mens 13,4 % (1,7; 37,1) er metastasefri i placebogruppen [8]. Det svarer til en absolut forskel på 44 %-point, hvilket overstiger den mindste klinisk relevante forskel på 20 %-point. Punktestimatet for den absolutte effektforskel afspejler en klinisk relevant effektforskel. Dog kan konfidensintervallet ikke beregnes og derfor kan den foreløbige værdi ikke kategoriseres efter Medicinrådets metoder.

Baseret på den relative effektforskel, som fremgår af tabel 2 (HR: 0,28 (0,23; 0,35)), har apalutamid foreløbigt en stor merværdi vedr. metastasefri overlevelse.

Fagudvalget vurderer, at apalutamid aggregeret har en stor merværdi vedr. metastasefri overlevelse. Der er opnået stor merværdi for den relative effektforskel. De absolutte forskelle underbygger denne værdi, da forskellen for median MFS og MFS-raten ved 3 år overstiger den mindste klinisk relevante forskel væsentligt.

Skeletrelaterede hændelser (SRE'er)
Som beskrevet i protokollen er effektmålet skeletrelaterede hændelser (SRE'er) vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi det er en alvorlig begivenhed, som kan være relateret til knoglemetastaser.

Ved 3 år er 94,4 % (92,4; 95,9) frie for skeletrelaterede hændelser i apalutamidgruppen, mens 91,7 % (88,1; 94,3) er frie for skeletrelaterede hændelser i placebogruppen. Det svarer til en absolut forskel på 2,7 %-point, hvilket ikke overstiger den mindste klinisk relevante forskel på 5 %-point. Punktestimatet for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel. Dog kan konfidensintervallet ikke beregnes, og derfor kan den foreløbige værdi af apalutamid ikke kategoriseres efter Medicinrådets metoder.

Baseret på den relative effektforskel, som fremgår af tabel 2 (HR: 0,62 (0,41; 0,96)), har apalutamid foreløbigt en merværdi af ukendt størrelse vedr. skeletalrelaterede hændelser.

Fagudvalget vurderer, at apalutamid aggregeret har ingen dokumenteret merværdi vedr. skeletrelaterede hændelser. Der er opnået merværdi af ukendt størrelse for den relative effektforskel, men fagudvalget finder ikke, at den absolutte forskel underbygger denne værdi, da forskellen for SRE-raten ved 3 år ligger væsentligt under den mindste klinisk relevante forskel.

Tid til kræftrelaterede procedurer
Som beskrevet i protokollen er effektmålet tid til kræftrelaterede procedurer vigtigt for vurderingen af lægemidlets værdi for patienterne, da det beskriver lokalvækst af prostata og er et udtryk for klinisk betydende sygdomsprogression, som har direkte indflydelse på patientens livskvalitet

Ansøger har ikke leveret data for dette effektmål, da det ikke er opgjort i det inkluderede studie. Den kliniske værdi sammenlignet med placebo kan derfor ikke vurderes.

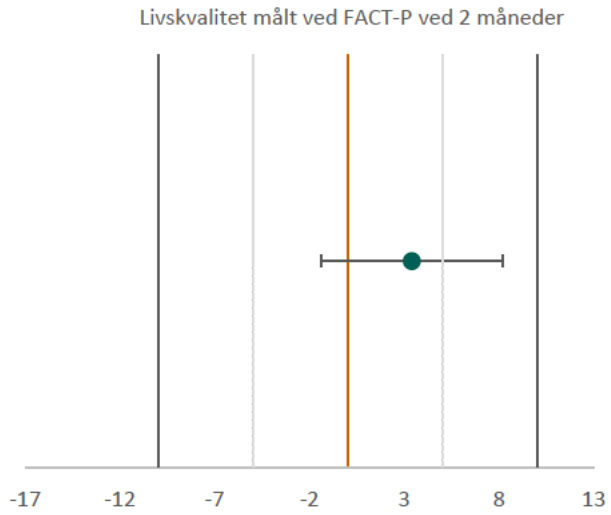
Livskvalitet målt ved FACT-P
Som beskrevet i protokollen er effektmålet livskvalitet målt ved FACT-P vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi behandling med apalutamid er livsforlængende og ikke-kurativ. De fleste nmCRPC-patienter er asymptomatiske og har forholdsvis god livskvalitet. Forventningen er, at dette effektmål kan give en indikation af, om eventuelle bivirkninger ved lægemidlet påvirker patienternes livskvalitet.

Andelen af patienter der oplever ≥ 10 points reduktion fra baseline ved 2, 6, 12 og 24 måneder, ses i tabel 3. Den mindste klinisk relevante forskel på 10 % point er ikke opnået ved nogen tidspunkter.

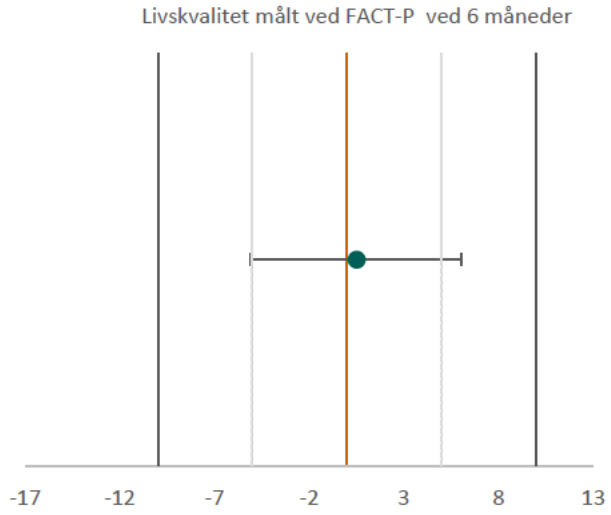
Tabel 3. Resultater for livskvalitet målt ved FACT-P ved 2, 6, 12 og 24 måneder

Tidspunkt	Andel patienter der oplever ≥ 10 points reduktion fra baseline				Forskel (95% CI)
	Apalutamid		Placebo		
	N	%	N	%	
2 måneder (cyklus 3)	162	21	67	18	3,4 %-point (-1,4; 8,2)
6 måneder (cyklus 7)	137	20	56	20	0,5 %-point (-5,1; 6;0)
12 måneder (cyklus 13)	135	22	38	19	3,9 %-point (-2,4; 10,2)
24 måneder (cyklus 25)	120	25	20	26	-1,3 %-point (-11,9; 9,3)

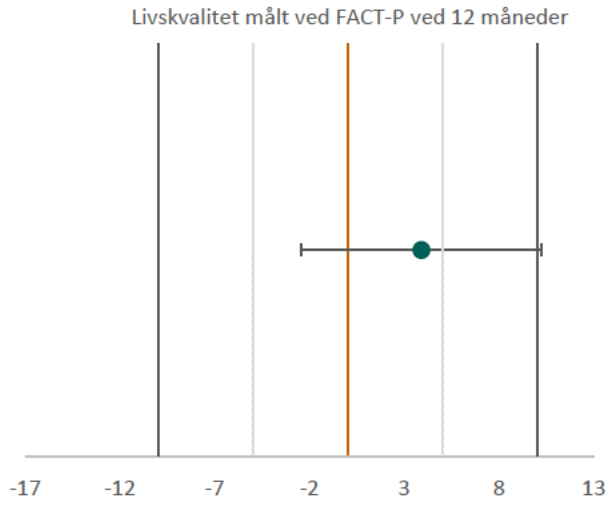
De absolutte forskelle er vist i figurerne 3-6 nedenfor ved henholdsvis 2, 6, 12 og 24 måneder.



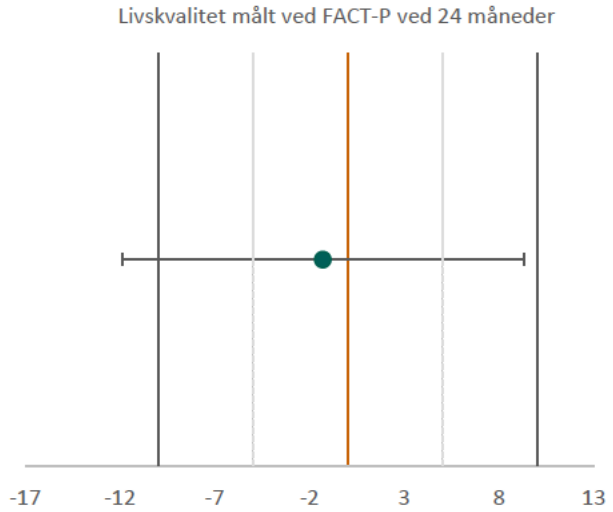
Figur 3. Punktestimat og 95 % konfidensinterval for den absolutte forskel for livskvalitet (målt ved FACT-P) ved 2 måneder. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.



Figur 4. Punktestimat og 95 % konfidensinterval for den absolutte forskel for livskvalitet (målt ved FACT-P) ved 6 måneder. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.



Figur 5. Punktestimat og 95 % konfidensinterval for den absolutte forskel for livskvalitet (målt ved FACT-P) ved 12 måneder. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.



Figur 6. Punktestimat og 95 % konfidensinterval for den absolutte forskel for livskvalitet (målt ved FACT-P) ved 24 måneder. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Punktestimatet for de absolutte effektforskelle (2, 6, 12 og 24 måneder) afspejler ikke en klinisk relevant effektforskel. De øvre grænser for konfidensintervallerne ligger tættere på en negativ klinisk relevant forskel end på 0 (ingen effektforskel). Derfor kan den foreløbige værdi af apalutamid vedr. livskvalitet målt ved FACT-P ved 2, 6, 12 og 24 måneder ikke kategoriseres efter Medicinrådets metoder.

Baseret på den relative effektforskel, som fremgår af tabel 2 (HR: 1,05 (0,89; 1,22)), kan apalutamid ikke kategoriseres efter Medicinrådets metoder.

Fagudvalget vurderer, at apalutamid aggregeret ikke kan kategoriseres vedr. livskvalitet målt ved FACT-P. Fagudvalget bemærker, at data indikerer, at patienternes livskvalitet ikke påvirkes betydeligt i hverken negativ eller positiv retning ved behandling med apalutamid, hvilket de finder positivt.

5.1.5 Fagudvalgets konklusion

Fagudvalget vurderer, at apalutamid i kombination med ADT til patienter med højrisiko ikke-metastaserende kastrationsresistent prostatakræft giver en moderat merværdi sammenlignet med ADT alene.

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

- har merværdi af ukendt størrelse vedr. det kritiske effektmål samlet overlevelse, hvor der foreligger modne overlevelsesdata. De supplerende sensitivitetsanalyser for samlet overlevelse, som tager højde for overkrydsning i studiet, kategoriserer effekten som stor og indikerer dermed, at effekten kan være større end den der ses i hovedanalysen.

- har stor merværdi vedr. det vigtige effektmål metastasefri overlevelse. Fagudvalget vurderer, at forlænget metastasefri overlevelse har stor værdi for patienten, da det belyser perioden under sygdomsforløbet, hvor sygdommen er i ro, og patienten oftest er symptomfri.

- har ingen dokumenteret merværdi vedr. det kritiske effektmål grad 5 bivirkninger. Kun en enkelt hændelse (myokardieinfarkt) i gruppen behandlet med apalutamid er vurderet at være relateret til lægemidlet.

Fagudvalget fremhæver desuden, at apalutamid er forbundet med bivirkninger, men lægger vægt på, at bivirkningsprofilen er håndterbar i klinisk praksis. Fagudvalget påpeger desuden, at data for livskvalitet indikerer, at behandlingen ikke medfører en forringelse af patienternes livskvalitet.

Samlet set understreger fagudvalget, at gevinsten på samlet overlevelse og metastasefri overlevelse samt de håndterbare bivirkninger betyder, at apalutamid er en vigtig ny behandling til patienter med høj-risiko ikke-metastaserende kastrationsresistent prostatakræft.

6. Andre overvejelser

Fagudvalget er opmærksomme på, at en eventuel indplacering af apalutamid eller andre lægemidler inden for samme lægemiddelklasse tidligt i behandlingsforløbet vil få betydning for valg af behandling i senere behandlingslinjer, da Medicinrådet forudsætter, at lægemidler med samme virkningsmekanisme ikke anvendes sekventielt.

7. Relation til behandlingsvejledning

Der foreligger en RADS-behandlingsvejledning, men denne inkluderer ikke patienter med højrisiko ikkemetastaserende kastrationsresistent prostatakræft (nmCRPC).

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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 Afdelingslæge, ph.d.	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
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Rikke Tandrup Nielsen *Overlæge*	Region Hovedstaden
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Ole Jensen *Patientrepræsentant*	Danske Patienter
Leif Otterstrøm *Patientrepræsentant*	Danske Patienter

Sammensætning af fagudvalg	
Tidligere medlemmer, som har bidraget til arbejdet	**Udpeget af**
Annette Nørkær Pedersen *Afdelingsleder, farmaceut*	Dansk Selskab for Sygehusapoteksledelse

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10. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	9. december 2020	Godkendt af Medicinrådet

11. Bilag 1: Evidensens kvalitet

11.1 Cochrane – risiko for bias

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

Tabel B1 Vurdering af risiko for bias - SPARTAN, NCT01946204 [8–11]

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Randomisering er generet ved hjælp af *Interactive Voice Randomization System* (IVRS). Patienterne er stratificeret efter PSA-fordoblingstid (< 6 måneder mod ≥ 6 måneder), brug af lægemidler rettet mod knoglerne (ja mod nej) og klassifikation af lokal eller regional nodal sygdom (N0 vs N1) ved studiestart. Ingen betydelige forskelle i baselinekarakteristika
Effekt af tildeling til intervention	**Lav**	Allokering til behandling er dobbelt-blindet. Studieblindingen blev brudt efter IA1, hvorefter de tilbageværende 76 patienter (20 %) i placeboarmen krydsede over til den aktive behandlingsarm.
Manglende data for effektmål	**Lav**	Transparent og begrænset frafald. 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**	Effektmålene forventes ikke påvirket grundet blinding. Afblinding ved IA1 kan influere alle effektmål på nær OS og MFS.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Protokol er offentlig tilgængelig. Der rapporteres på alle effektmål
Overordnet risiko for bias	**Lav**	

11.2 GRADE

Klinisk spørgsmål 1 – Apalutamid i kombination med ADT sammenlignet med ADT alene til behandling af højrisiko ikke-metastaserende kastrationsresistent prostatakræft

Tabel B2 GRADE evidensprofil for klinisk spørgsmål 1

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Apalutamid+ADT	Placebo+ADT	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
OS – Median OS i antal måneder (opfølgning: median 52 mdr.)												
1	RCT	Ikke alvorlig	Alvorlig [a]	Ikke alvorlig	Alvorlig [b]	Ingen	73,9 mdr.	59,9 mdr.	-	14 mdr. (0; 0)	⨁⨁◯◯ LAV	KRITISK
OS – OS-rate ved 3 år (opfølgning: median 52 mdr.)												
1	RCT	Ikke alvorlig	Alvorlig [a]	Ikke alvorlig	Alvorlig [b]	Ingen	-/806 (81,8 %)	-/401 (76,9 %)	HR 0,69 (0,56; 0,84)	4,9 %	⨁⨁◯◯ LAV	KRITISK
Andel patienter med grad 5 bivirkninger												
1	RCT	Ikke alvorlig	Alvorlig [a]	Ikke alvorlig	Alvorlig [c]	Ingen	1/803 (0,12 %)	0/401 (0 %)	RR 1,50 (0,06; 36,8)	0,12 % (-0,12; 0,37)	⨁⨁◯◯ LAV	KRITISK
Andel patienter med grad 3-4 uønskede hændelser												

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Apalutamid+ADT	Placebo+ADT	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
1	RCT	Ikke alvorlig	Alvorlig [a]	Ikke alvorlig	Alvorlig [c]	Ingen	449/803 (55,9 %)	145/398 (36,4 %)	RR 1,54 (1,33; 1,77)	19,5 % (1,6; 25,3)	⨁⨁◯◯ LAV	VIGTIG
MFS - Median MFS i antal måneder												
1	RCT	Ikke alvorlig	Alvorlig [a]	Ikke alvorlig	Ikke alvorlig	Ingen	40,3 mdr.	16,2 mdr.	-	24,3 mdr. (0; 0)	⨁⨁⨁◯ MODERAT	VIGTIG
MFS - MFS-rate ved 3 år												
1	RCT	Ikke alvorlig	Alvorlig [a]	Ikke alvorlig	Ikke alvorlig	Ingen	-/806 (57,4 %)	-/401 (13,4 %)	HR 0,28 (0,23; 0,35)	44,0%	⨁⨁⨁◯ MODERAT	VIGTIG
Skeletrelaterede hændelser (SRE'er)												
1	RCT	Ikke alvorlig	Alvorlig [a]	Ikke alvorlig	Alvorlig [c]	Ingen	-/806 (94,4 %)	-/401 (91,7 %)	HR 0,62 (0,41; 0,96)	2,7 %	⨁⨁◯◯ LAV	VIGTIG
Tid til kræftrelaterede procedurer												
Data ikke indsamlet, kan ikke beregnes												VIGTIG
Livskvalitet målt ved FACT-P ved 2. mdr.												

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Apalutamid+ADT	Placebo+ADT	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
1	RCT	Ikke alvorlig	Alvorlig [a]	Ikke alvorlig	Alvorlig [c]	Ingen	162/767 (21,1 %)	67/379 (17,7 %)	HR 1,05 (0,89; 1,22)	3,4 % (-1,4; 8,2)	⨁⨁◯◯ LAV	VIGTIG
Livskvalitet målt ved FACT-P ved 6. mdr.												
1	RCT	Ikke alvorlig	Alvorlig [a]	Ikke alvorlig	Alvorlig [c]	Ingen	137/679 (20,2 %)	56/284 (19,7 %)	HR 1,05 (0,89; 1,22)	0,5 % (-5,1; 6,0)	⨁⨁◯◯ LAV	VIGTIG
Livskvalitet målt ved FACT-P ved 12. mdr.												
1	RCT	Ikke alvorlig	Alvorlig [a]	Ikke alvorlig	Alvorlig [c]	Ingen	135/602 (22,4 %)	38/205 (18,5 %)	HR 1,05 (0,89; 1,22)	3,9 % (-2,4; 10,2)	⨁⨁◯◯ LAV	VIGTIG
Livskvalitet målt ved FACT-P ved 24. mdr.												
1	RCT	Ikke alvorlig	Alvorlig [a]	Ikke alvorlig	Alvorlig [c]	Ingen	120/480 (25,0%)	20/76 (26,3 %)	HR 1,05 (0,89; 1,22)	-1,3 % (-11,9; 9,3)	⨁⨁◯◯ LAV	VIGTIG
Kvalitet af den samlede evidens			LAV[d]									

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

[b] Der er nedgraderet ét niveau, da kriteriet for OIS ikke er opfyldt.

[c] Der er nedgraderet ét niveau, da konfidensintervallet indeholder én beslutningsgrænse.

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

Medicinrådet

Erleada™ (apalutamide) 60 mg tablets

Application for the assessment of ERLEADA® (apalutamide) for high-risk non-metastatic castration-resistant prostate cancer (nmCRPC)

janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Information marked with yellow represents confidential information

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1 Basic information

Table 1: Contact information

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Table 2: Overview of the pharmaceutical

Proprietary name	ERLEADA®
Generic name	Apalutamide
Marketing authorization holder in Denmark	Janssen-Cilag A/S Bregnerødvej 133 DK-3460 Birkerød
ATC code	L02BB05
Pharmacotherapeutic group	Endocrine therapy, anti-androgens
Active substance(s)	Apalutamide
Pharmaceutical form(s)	Film-coated tablet
Mechanism of action	Selective Androgen Receptor inhibitor
Dosage regimen	The recommended dose is 240 mg (four 60 mg tablets) as an oral single daily dose.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	For the treatment of adult men with non-metastatic castration-resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease.
Other approved therapeutic indications	ERLEADA is also approved for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT) in adult men (1)
Will dispensing be restricted to hospitals?	Yes

Combination therapy and/or co-medication	Medical castration with gonadotropin releasing hormone analogue (GnRHa) should be continued during treatment in patients not surgically castrated.
Packaging – types, sizes/number of units, and concentrations	PVC-PCTFE foil blister with an aluminum push-through foil sealed inside a wallet pack: Each 28-day carton contains 112 film coated tablets in 4 cardboard wallet packs of 28 film-coated tablets each. Each film-coated tablet contains 60 mg of apalutamide.
Orphan drug designation	No

2 Abbreviations

Table 3: Abbreviations used in the application

Abbreviation	Definition
ADT	Androgen-deprivation therapy
AE	Adverse event
BICR	Blinded independent central review
CI	Confidence interval
CRPC	Castration resistant prostate cancer
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
FACT-G/P	Functional Assessment of Cancer Therapy - General/Prostate
HR	Hazard ratio
HRQoL	Health-Related Quality of Life
ITT	Intent-to-treat
IA	Interim-analysis
IPCW	Inverse probability of censoring weighted (IPCW)
mCRPC	Metastatic castration resistant prostate cancer
MFS	Metastasis-free survival
mHSPC	Metastatic hormone-sensitive prostate cancer
nmCRPC	Non-metastatic castration resistant prostate cancer
NR	Not reached
OS	Overall survival
PCWG	Prostate Cancer Working Group
PFS	Progression-free survival
PFS2	Progression-free survival from randomization until failure on the first subsequent therapy
PRO	Patient-reported outcome
PSA	Prostate-specific antigen
PSADT	Prostate-specific antigen doubling time
P-Y	Patient-years
RR	Relative Risk
SmPC	Summaries of product characteristics
SRE	Skeletal-related event
TEAE	Treatment-emergent adverse events
TOI	Trial outcome index
TSH	Thyroid-stimulating hormone

Table 4: Terms used throughout application

Primary term used in this application	Term considered interchangeable (for this application)
Absolute difference	Risk difference
Outcome measure	Endpoint

3 Summary

The objective of this application is to answer the clinical question specified in the protocol for apalutamide by the Expert Committee: *What is the clinical added value of apalutamide in combination with androgen deprivation therapy (ADT) compared to ADT alone for men with high-risk non-metastatic castration-resistant prostate cancer (nmCRPC)?* (2). This will be addressed by analyzing specified outcome measures stated in the protocol (2) and following the methodology applied by the Medicines Council (3).

Metastatic disease is a turning point in castration-resistant prostate cancer (CRPC); progression to metastases is associated with poor survival, severe symptoms and significant reductions in health-related quality of life. The prevention of metastases is to delay progression and prolong the non-metastatic disease stage represents an important and urgent treatment goal in patients with nmCRPC, especially for those at high risk.

In the international, double-blinded, placebo-controlled, randomized (2:1 active treatment vs placebo) phase III study (SPARTAN trial) involving men with castration-resistant prostate cancer and a prostate-specific antigen doubling time of 10 months or less (high risk) with a median follow-up of 52 months, patients treated with apalutamide had a median overall survival (OS) of more than 6 years (73.9 months) compared with 59.9 months in the placebo + ADT arm, representing a 14-month extension in survival with apalutamide. The 4-year OS rate was 69.9% (95% CI: 66.4%, 73.1%) for apalutamide + ADT and 62.0% (95% CI: 56.5%, 66.9%) for placebo + ADT representing a 7.4% (95% CI: 1.7%, 14.2%) absolute difference in favor of apalutamide. A 22% reduction in the risk of death when receiving apalutamide + ADT vs. placebo + ADT was observed (HR: 0.78; 95% CI: 0.64, 0.96). After adjusting for cross-over to evaluate the true treatment effect of apalutamide, the median OS was 73.9 months in the apalutamide + ADT arm and 52.8 months in the placebo + ADT arm demonstrating prolongation of OS by 21.1 months. The 4-year OS rate (adjusted for cross-over) was 69.9% (95% CI: 66.4%, 73.1%) for apalutamide + ADT and 57.1% (95% CI: 50.9%, 62.8%) for placebo + ADT representing a 12.8% (95% CI: 5.8%, 19.8%) absolute difference in favor of apalutamide. A 31% reduction in the risk of death when receiving apalutamide + ADT vs. placebo + ADT was observed (HR adjusted for cross-over: 0.69; 95% CI: 0.56, 0.84).

The median MFS for patients treated with apalutamide + ADT was 40.5 months and 16.2 months for patients treated with placebo + ADT representing 24.3 months additional metastasis-free years for apalutamide + ADT. The 3-year MFS rate was 57.4% (95% CI: 50.6%, 63.7%) for apalutamide + ADT and 13.4% (95% CI: 1.7%, 37.1%) for placebo + ADT representing a 44% absolute difference in favor of apalutamide. There was a significant reduction in the risk of developing metastases or the risk of death by 72% (HR: 0.28; 95% CI: 0.23, 0.35).

The share of patients that experienced grade 5 adverse reactions (assessed by investigator as drug related) was 0.12% for apalutamide + ADT and 0% for placebo + ADT resulting in a [redacted] absolute difference. The relative risk (RR) was [redacted] The share of patients that experienced grade 3-4 adverse events (not necessarily drug related) was 55.9% for apalutamide + ADT and 36.4% for placebo + ADT representing a 19.5% (95% CI: 13.6%, 25.3%) absolute difference. The RR was 1.54 (95% CI: 1.33, 1.77).

The analysis of skeletal-related events showed results in favor of apalutamide. The events at 3-years was 94.4% (95% CI: 92.4%, 95.9%) for apalutamide + ADT and 91.7% (95% CI: 88.1%, 94.3%) for placebo + ADT representing an absolute difference of 2.7% (95% CI: 0%, 6.1%). At 4-years, it was 91.9% (95% CI: 89.4%, 93.9%) for apalutamide + ADT and 87.9% (95% CI: 83.2%, 91.3%) for placebo + ADT representing an absolute difference of 4.1% (95% CI: 0%, 8.5%). The stratified HR was 0.62 (95% CI: 0.41, 0.96) in favor of apalutamide.

Health related quality of life (measured by FACT-P) was maintained when treated with apalutamide + ADT. There was no statistically significant difference between apalutamide + ADT vs. placebo + ADT. The time to deterioration in FACT-P (total score) by 10 points was; HR: 1.045 (95% CI: 0.89, 1.22). No statistical difference in FACT P reduction was observed between apalutamide + ADT and placebo + ADT in the patient population with a FACT-P reduction >=10 at month 2, 6, 12 or 24.

Overall, apalutamide provides men with high risk nmCRPC with a treatment option with a superior efficacy profile, and a manageable tolerability and toxicity profile allowing patients an effective treatment before developing metastases.

4 Literature search

A head-to-head trial, SPARTAN (ARN-509-003) is available which includes the intervention (apalutamide + androgen deprivation therapy (ADT)) and comparator (placebo + ADT) of interest. Therefore, a systematic literature search has not been performed which is in line with the request specified in the protocol for apalutamide. The Secretariat (Medicines Council) found that the articles from the relevant clinical trial SPARTAN can be used for direct comparison of all defined outcome measures (2). An updated manuscript with longer follow-up has recently been published for the SPARTAN trial (4). The Secretariat was consulted and expressed that the new manuscript can be included in the application.

In addition to these publications, the European public assessment reports (EPAR) published by the European Medicines Agency (EMA) was consulted for both apalutamide and the comparator; ADT, according to the protocol. The main characteristics and the associated publications of the SPARTAN trial are presented in Table 5.

Table 5: Main characteristics of the SPARTAN trial

Trial name	A Study of Apalutamide (ARN-509-003) in Men with high risk Non-Metastatic Castration-Resistant Prostate Cancer (SPARTAN)
NCT number	NCT01946204
Objective	To evaluate the efficacy and safety of apalutamide in adult men with high risk non-metastatic castration-resistant prostate cancer.
Publications – title, author, journal, year	Apalutamide Treatment and Metastasis-Free Survival in Prostate Cancer. Smith, M. et al., The New England Journal of Medicine, 2018 (5). Effect of apalutamide on health-related quality of life in patients with non-metastatic castration-resistant prostate cancer: an analysis of the SPARTAN randomised, placebo-controlled, phase 3 trial. Saad, F. et al., Lancet Oncology, 2018 (6). Apalutamide and overall survival in non-metastatic castration-resistant prostate cancer. Small, E. et al., Annals of Oncology, 2019 (7). Apalutamide and Overall Survival in Prostate Cancer. Smith, M. et al., Eur Urol, 2020, https://doi.org/10.1016/j.eururo.2020.08.011 (4).
Study type and design	SPARTAN is a multinational, randomized (2:1 active treatment vs placebo), double-blind, phase III study evaluating the efficacy and safety of apalutamide compared with placebo when used in addition to ADT in patients with high risk non-metastatic castration-resistant prostate cancer (nmCRPC). The study consisted of a screening phase, a double-blind treatment phase, and a long-term follow-up phase. Patients remained on study treatment until blinded independent central review (BICR) confirmed detection of distant metastatic disease, development of unacceptable toxicity, or withdrawal of consent. Patients who continued study treatment to the BICR-confirmed metastasis-free survival (MFS) endpoint were also offered the option to be treated with ZYTIGA® in the long-term follow-up phase. Patients discontinuing study treatment entered the long-term follow-up phase and remained on study until death, loss of follow-up, or withdrawal of consent, whichever came first. After the initial interim analysis (IA), the SPARTAN study was unblinded and 76 patients (corresponding to 19% of the initial population randomized to placebo) in the placebo arm crossed over to receive active treatment. The study is ongoing, but not recruiting. Estimated study completion is November 29, 2022 (8).

Follow-up time	In the SPARTAN trial, data from three clinical cut-offs (CCO)s dates are available: • IA1 (CCO 19 May 2017, 20.3 months follow-up) (5, 6) • IA2 (CCO 01 February 2019, 41 months follow-up) (7) • Final analysis (CCO 01 February 2020, 52 months follow-up) (4). IA1 was the per protocol initial analysis of the SPARTAN trial after which the study was unblinded. At IA1, MFS, time to metastasis, progression-free survival (PFS), and time to symptomatic progression with statistical significance; therefore, primary analysis was considered the final analysis for these endpoints. Based on these data, the study was unblinded and placebo-treated patients who were eligible and without evidence of disease progression were able to crossover to receive open-label apalutamide. After unblinding, all patients were followed for survival, with crossover patients analyzed as part of the placebo group intent-to-treat (ITT) population. For IA1, the median survival follow-up time for all patients was 20.3 months (5). IA2 is an additional IA that was performed based on requests for updated data from governing agencies. For IA2, median follow-up time for all patients was 41.0 months (7) In the final analysis only selected and prespecified endpoints in the statistical analysis plan were analyzed. The median follow-up for all patients was 52.0 months (4).
Population (inclusion and exclusion criteria)	**Inclusion Criteria:** • Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features with high risk for development of metastases, defined as prostate-specific antigen doubling time (PSADT) less than or equal to (<=) 10 months. PSADT is calculated using at least 3 prostate-specific antigen (PSA) values obtained during continuous ADT • Castration-resistant prostate cancer demonstrated during continuous ADT, defined as 3 PSA rises, at least 1 week apart, with the last PSA greater than (>) 2 nanogram per milliliter (ng/mL) • Maintain castrate levels of testosterone (< 50 ng/dL [1.72 nmol/L]) within 4 weeks prior to randomization and throughout the study • Patients currently receiving bone loss prevention treatment with bone-sparing agents must be on stable doses for at least 4 weeks prior to randomization • Patients who received a first-generation anti-androgen (for example, bicalutamide, flutamide, nilutamide) must have at least a 4-week washout prior to randomization AND must show continuing disease (PSA) progression (an increase in PSA) after washout • At least 4 weeks must have elapsed from the use of 5-alpha reductase inhibitors, estrogens, and any other anti-cancer therapy prior to randomization • At least 4 weeks must have elapsed from major surgery or radiation therapy prior to randomization • Eastern Cooperative Oncology Group Performance Status 0 or 1 • Resolution of all acute toxic effects of prior therapy or surgical procedure to Grade <= 1 or baseline prior to randomization • Adequate organ function according to protocol-defined criteria • Administration of growth factors or blood transfusions will not be allowed within 4 weeks of the hematology labs required to confirm eligibility **Exclusion Criteria:** • Presence of confirmed distant metastases, including central nervous system and vertebral or meningeal involvement. Exception: pelvic lymph nodes < 2 cm in short axis (N1) located below the iliac bifurcation are allowed • Symptomatic local or regional disease requiring medical intervention

<table>
<tr><td></td><td>

Prior treatment with second generation anti-androgens
Prior treatment with CYP17 inhibitors
Prior treatment with radiopharmaceutical agents, or any other investigational agent for non-metastatic castration-resistant prostate cancer
Prior chemotherapy for prostate cancer except if administered in the adjuvant/neoadjuvant setting
History of seizure or condition that may pre-dispose to seizure
Concurrent therapy with protocol-defined excluded medications
History or evidence of any of the following conditions: any prior malignancy (other than adequately treated basal cell or squamous cell skin cancer, superficial bladder cancer, or any other cancer in situ currently in complete remission) within 5 years prior to randomization; severe/unstable angina, myocardial infarction, symptomatic congestive heart failure, arterial or venous thromboembolic events, or clinically significant ventricular arrhythmias within 6 months prior to randomization; uncontrolled hypertension; gastrointestinal disorder affecting absorption; active infection; and, any other condition that, in the opinion of the investigator, would impair the patient's ability to comply with study procedures

</td></tr>
<tr><td>Intervention</td><td>Apalutamide 240 mg tablets administered orally on a continuous once daily dosing regimen + ADT. 806 was randomized to apalutamide + ADT and 803 received the treatment.</td></tr>
<tr><td>Baseline characteristics</td><td>
Table 6: Patient baseline characteristics in the SPARTAN trial
<table>
<tr><td></td><td colspan="2">SPARTAN trial (4, 5, 7)</td></tr>
<tr><td></td><td>Apalutamide plus ADT (n=806)</td><td>ADT alone (n=401)</td></tr>
<tr><td colspan="3">Age, years</td></tr>
<tr><td>Mean (SD)</td><td>73.7 (8.07)</td><td>74.1 (7.92)</td></tr>
<tr><td>Median</td><td>74.0</td><td>74.0</td></tr>
<tr><td>Range</td><td>(48; 94)</td><td>(52; 97)</td></tr>
<tr><td colspan="3">Ethnicity</td></tr>
<tr><td>Hispanic or Latino</td><td>11 (1.4%)</td><td>5 (1.2%)</td></tr>
<tr><td>Not Hispanic or Latino</td><td>659 (81.8%)</td><td>338 (84.3%)</td></tr>
<tr><td>Not reported</td><td>136 (16.9%)</td><td>58 (14.5%)</td></tr>
<tr><td colspan="3">Race</td></tr>
<tr><td>White</td><td>524 (65.0%)</td><td>276 (68.8%)</td></tr>
<tr><td>Black or African American</td><td>48 (6.0%)</td><td>20 (5.0%)</td></tr>
<tr><td>Asian</td><td>93 (11.5%)</td><td>47 (11.7%)</td></tr>
<tr><td>American Indian or Alaska Native</td><td>4 (0.5%)</td><td>0</td></tr>
<tr><td>Native Hawaiian or other Pacific Islander</td><td>0</td><td>0</td></tr>
<tr><td>Other</td><td>1 (0.1%)</td><td>1 (0.2%)</td></tr>
<tr><td>Multiple</td><td>1 (0.1%)</td><td>0</td></tr>
<tr><td>Not reported</td><td>135 (16.7%)</td><td>57 (14.2%)</td></tr>
<tr><td colspan="3">Weight, kg</td></tr>
<tr><td>Mean (SD)</td><td>87.8 (19.45)</td><td>85.4 (17.41)</td></tr>
<tr><td>Median</td><td>85.0</td><td>83.2</td></tr>
<tr><td>Range</td><td>(45; 182)</td><td>(43; 161)</td></tr>
<tr><td colspan="3">Time from initial diagnosis to randomization, months</td></tr>
<tr><td>Mean (SD)</td><td>8.93 (5.227)</td><td>8.78 (5.099)</td></tr>
</table>
</td></tr>
</table>

	Median	7.95	7.85
	Range	(0.3; 30.4)	(0.8; 26.3)
	ECOG performance status at baseline		
	0	623 (77.3%)	311 (77.8%)
	1	183 (22.7%)	89 (22.3%)
	Gleason Score at baseline		
	<7	152 (19.4%)	72 (18.6%)
	7	291 (37.1%)	146 (37.7%)
	>7	341 (43.5%)	169 (43.7%)
	PSA doubling time, months		
	Mean (SD)	4.74 (2.305)	4.76 (2.247)
	Median	4.40	4.50
	Range	(0.8; 10.0)	(0.7; 10.0)
	Previous prostate cancer therapy		
	Surgery	159 (19.7%)	69 (17.2%)
	Radiotherapy	157 (19.5%)	85 (21.2%)
	Both	301 (37.3%)	153 (38.2%)
	Hormonal	801 (99.4%)	400 (99.8%)
	GnRH analogue	780 (96.8%)	387 (96.5%)
	Orchiectomy	47 (5.8%)	24 (6.0%)
	First generation anti-androgen	592 (73.4%)	290 (72.3%)
	Other	17 (2.1%)	9 (2.2%)
	Chemotherapy	17 (2.1%)	7 (1.7%)

Primary and secondary endpoints

Primary efficacy endpoint:

- Metastasis-free survival (MFS). MFS was defined as the time from randomization to the time of first evidence of BICR-confirmed bone or soft tissue distant metastasis or death due to any cause, whichever occurred first.

Secondary efficacy endpoints:

- Time to metastasis (TTM). TTM was defined as the time from randomization to the time of the scan that showed first evidence of BICR-confirmed radiographically detected bone or soft tissue distant metastasis.
- Progression-free survival (PFS). PFS defined as time from randomization to first documentation of BICR-confirmed radiographic progressive disease (PD) (development of distant/local/regional metastasis)/death due to any cause whichever occurred first.
- Time to symptomatic progression (SymProg). Time to symptomatic progression was defined as the time from randomization to documentation in the CRF of any of the following (whichever occurred earlier): a) development of a skeletal-related event ; b) pain progression or worsening of disease-related symptoms requiring initiation of a new systemic anti-cancer therapy; or c) development of clinically significant symptoms due to loco-regional tumor progression requiring surgical intervention or radiation therapy.
- Overall survival (OS). OS was defined as the time from randomization to the date of death due to any cause.
- Time to initiation of cytotoxic chemotherapy (CytoChemo). Time to initiation of cytotoxic chemotherapy was defined as the time from randomization to the date of initiation of cytotoxic chemotherapy for prostate cancer.

	Other efficacy endpoint of particular interest: • Second progression-free survival (PFS2). PFS2 begins from randomization, extends over progression on study treatment and the reach of mCRPC state, continues as any indicated treatment for mCRPC is initiated at the discretion of the treating physician and eventually, when patient progresses on this treatment or if death occurs before that, PFS2 is reached. • Prostate-specific Antigen (PSA) response. PSA response rate was defined as the percentage of patients who had a decline from baseline in the PSA level of at least 50%, according to Prostate Cancer Working Group 2 (PCWG2) criteria. • Time to PSA progression. Time to PSA progression was defined as the time from randomization to PSA progression, according to PCWG2 criteria. *Patient reported outcomes:* 1. Functional Assessment of Cancer Therapy – Prostate (FACT-P) • The FACT-P consists of 39 items that assess physical, functional, emotional, and social or family well-being, including concerns specific to prostate cancer; scores range from 0 to 156, with higher scores indicating more favorable health-related quality of life. 2. EQ-5D-3L • The EQ-5D-3L consists of the EQ-5D descriptive system and the EQ visual-analogue scale; scores on the EQ visual-analogue scale range from 0 to 100, with 0 indicating the worst health imaginable and 100 the best health imaginable.
Method of analysis	Analysis sets: • Intent-to-Treat (ITT) Population (patients randomized). • Safety Population (all patients who received a dose of study drug). The Kaplan–Meier method was used to estimate medians for each trial group. The primary statistical method of comparison for time-to-event end points was a log-rank test with stratification according to the prespecified factors. Cox proportional-hazards models were used to estimate the hazard ratios and 95% confidence intervals.
Subgroup analyses	Subgroup analysis were pre-specified and non-stratified. The pre-specified subgroups were: • Age (<65 yrs; 65≤75 yrs; ≥75 yrs) • Race (White; Black; Asians; Others) • Region (North America; Europe; Rest of the World) • Prior hormonal therapy number (1; ≥2) • Baseline ECOG value (0; 1) • Baseline PSA value (At or below median; Above median) • PSA doubling-time (≤6 months; >6 months) • Bone-sparing agent (Yes; No) • Loco-regional disease (N0; N1)

5 Clinical questions

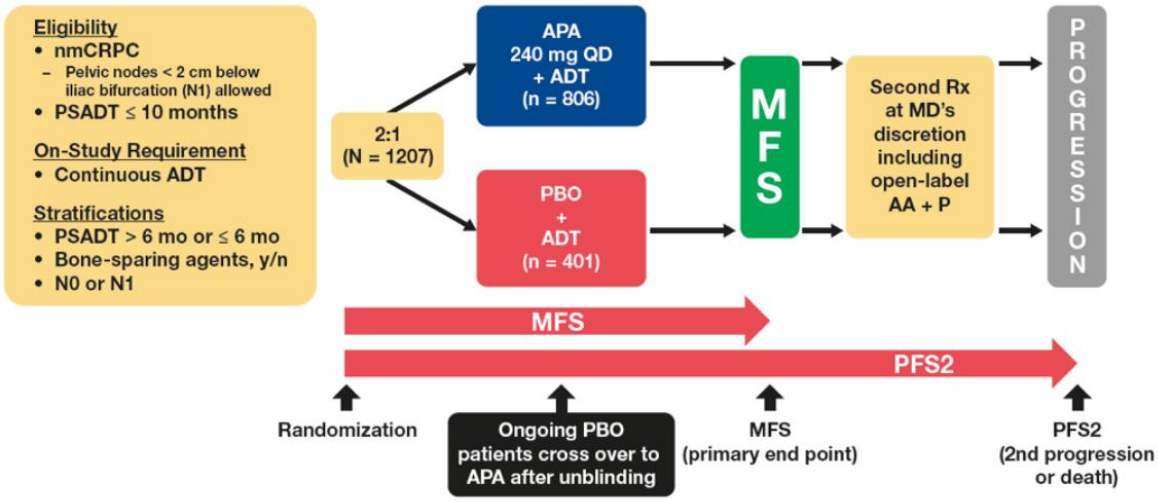
5.1 What is the clinical added value of apalutamide in combination with androgen deprivation therapy (ADT) compared to ADT alone for men with high-risk non-metastatic castration-resistant prostate cancer?

5.1.1 Presentation of the SPARTAN study

This section describes the SPARTAN study which will be used to answer the clinical question specified by the Expert Committee as well as evaluating the related outcome measures.

SPARTAN is a multinational, randomized, double-blind, phase III study evaluating the efficacy and safety of apalutamide compared with placebo when used in addition to ADT in patients with high risk nmCRPC (Figure 1). The study population in SPARTAN included adult men with high risk nmCRPC. High risk was defined as a PSA doubling time (PSADT) ≤10 months (5). Inclusion and exclusion criteria for the SPARTAN trial are provided in Table 5 above.

Figure 1: SPARTAN study design (9)



AA = abiraterone acetate; APA = apalutamide; ADT = androgen-deprivation therapy; MD = medical doctor; MFS = metastasis-free survival; nmCRPC = non-metastatic castration resistant prostate cancer; PBO = Placebo; PFS = progression-free survival; PFS2 = progression-free survival with the first subsequent therapy; PRED = prednisone; PSADT = prostate-specific antigen doubling time; QD = once-daily

A total of 1207 patients were randomized and comprised the ITT population (806 patients in the apalutamide + ADT arm and 401 patients in the placebo + ADT arm). Six patients (three from each treatment arm) were randomized but not treated; therefore, the safety population consisted of 1,201 patients (803 patients treated with apalutamide + ADT and 398 patients treated with placebo + ADT) (5).

The primary efficacy endpoint was MFS. IA1 was executed when 24% (104 of 427 anticipated events) of the anticipated death events had occurred (5). At the time of IA1, 19% of placebo patients were still on treatment; these 76 patients crossed over to receive active treatment (apalutamide + ADT). IA2 was executed after 65% of anticipated death events had occurred (277 of 427 events). The final analysis of the SPARTAN trial was executed after 428 death events had occurred (4). At the time of the final analysis, 30% of patients in the apalutamide + ADT treatment arm were continuing study treatment; no patients continued placebo treatment after the study was unblinded following IA1, and patients were allowed to cross over to active treatment (4). Of 76 patients who crossed over from placebo to active treatment, 46 patients (61%) were still receiving treatment with apalutamide (4).

The demographic and clinical characteristics were balanced between the two study arms (10). Patient demographics and baseline characteristics for the ITT population are presented in Table 6 above.

5.2 Results per study

It is stated in the protocol that for all outcome measures, data with the longest follow-up is requested unless another limit is indicated. For outcome measures where a specific time point is indicated, additional data is presented where available, such as the OS-rate at 4 years. This data is expected to support in decision-making other than solely looking at one time point (e.g. at 3 years). The results per study can also be found in the requested template format in the Appendix.

5.2.1 Comparative analysis

The following outcome measures have been requested in the protocol for apalutamide (2) and will be addressed separately in the next section. The outcome measures have been translated from the protocol written in Danish to English.

Table 7: Outcome measures specified in the protocol for apalutamide (2)

Outcome measure	Importance	Unit of measurement (for absolute difference)	Minimal clinically relevant difference	Adjusted minimal clinically relevant difference
Overall survival	Critical	Median OS in months (ITT)	6 months	-
		OS-rate at 3 years (ITT)	5%-points	2.5% points
Side effects / Adverse events	Critical	Share of patients experiencing grade 5 adverse reactions	2%-points	1%-points
	Important	Share of patients experiencing grade 3-4 AEs	5%-points	2.5% points
		Qualitative assessment of the event types	Narrative assessment	-
MFS	Important	Median MFS in months (ITT)	12 months	-
		MFS-rate at 3 years (ITT)	20%-points	10%-points
Skeletal related events (SREs)	Important	Share of patients that are free from skeletal related events after 3 years	5%-point	2.5%-point
Time to cancer related procedures	Important	Median time for delay from cancer-related procedures	6 months	-
Quality of life measured by FACT-P	Important	Share of patients who experience a ≥ 10 points reduction from baseline at 2, 6, 12, and 24 months	10%-points	5%-points

*For all outcome measures, data with the longest possible follow-up is requested unless another threshold is indicated.

As per the methodology applied by the Medicines Council, the relative difference and the absolute difference are requested as well as the related confidence intervals (3). For OS (OS-rate, unadjusted for cross-over, and adjusted for cross-over), grade 5 adverse reactions (share of patients), and grade 3-4 AEs (share of patients), the confidence intervals for the absolute difference was approximated using Wald type method. It is important to note that the confidence interval for the absolute difference is dependent upon a single time point. It should be interpreted with caution as it compares only a single point, and the power may not be optimal, and CI can be wide at a distant time point. The confidence intervals for the medians was not estimable due to the small number of patients at risk.

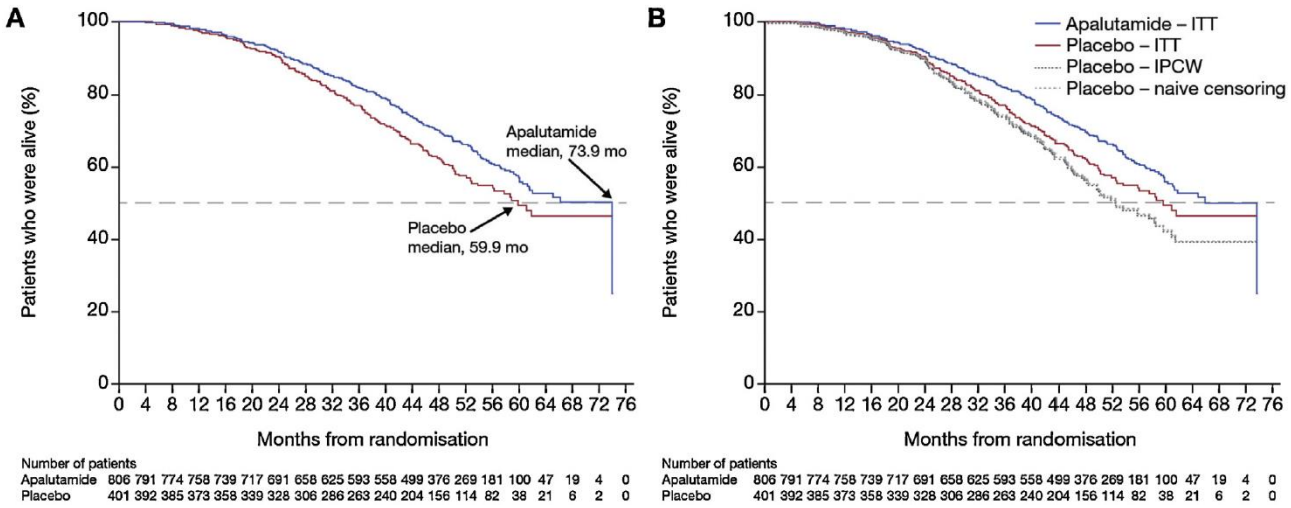
5.2.1.1 Overall survival

As requested in the protocol for apalutamide, the data with the longest follow-up is reported. With a median follow-up of 52 months, the median overall survival for the ITT population in SPARTAN was 73.9 months (95% CI: 61.2, not reached [NR]) in the apalutamide + ADT group and 59.9 months (95% CI: 52.8, NR) in the placebo + ADT group. Apalutamide + ADT is demonstrating more than 6 years of median OS and extending survival by 14 months compared with placebo + ADT (4). The results from the final analysis of the SPARTAN trial demonstrate a significant reduction in the risk of death with the addition of apalutamide to ADT, despite substantial cross-over and subsequent active therapy after unblinding reducing the risk of death by 22% (HR: 0.78 (95% CI: 0.64, 0.96; p=0.016; Figure 2)), The p value for OS confirmed a statistically significant improvement of OS, crossing the prespecified O'Brien-Fleming boundary of 0.046. 76 patients [19.0% of randomized placebo patients, or 64% of the ongoing placebo patients at unblinding] crossed-over from placebo to apalutamide (4). The patients that crossed-over from placebo + ADT to apalutamide + ADT may have gained survival time attributed to apalutamide during the open-label extension. Consequently, the clinical benefit associated with apalutamide when reported in an ITT analysis will be underestimated. It is therefore of interest to estimate the overall survival adjusted for bias introduced by cross-over.

Two exploratory sensitivity analyses of OS accounting for patients who crossed-over from placebo to apalutamide revealed similar results (Figure 2). With naive censoring, median OS was 73.9 months (95% CI: 61.2, NR) in the apalutamide group and 52.8 months (95% CI: 48.5, 61.1) in the placebo group; HR: 0.69 ((95% CI: 0.56, 0.84); nominal *p*-value, 0.0002)) (4). Similarly, with the inverse probability of censoring weighted (IPCW) analysis, median OS was 73.9 (95% CI: 61.2; NR) months with apalutamide and 52.8 (95% CI: 48.5, 59.9) months with placebo (HR: 0.69 (95% CI: 0.56, 0.84); nominal *p*-value, 0.0003)) (4, 11). IPCW is a model-based method that reweights patients using inverse probability weighting method. 1) Patients are artificially censored at the time of crossover. 2) To compensate for selection bias induced by this artificial censoring, the patients still on the original treatment were reweighted over time by the inverse of their time-dependent probability to stay on treatment, in order to represent similar patients who were censored before. These time-dependent stabilized weights are calculated using repeated logistic regression, modelling the probability to stay on treatment at any time interval. The denominator of the stabilized weights is obtained by including baseline and time-varying covariates in the model, while only baseline covariates are included for the numerator (12). 3) IPCW-adjusted hazard ratio (HR) for OS was calculated using a stratified Cox proportional hazards model, including the time-dependent weights and the same set of baseline characteristics.

After adjusting for cross-over to evaluate the true treatment effect of apalutamide, an OS advantage of 21.1 months was observed with apalutamide + ADT compared with placebo + ADT for both of the exploratory sensitivity analyses conducted (4). These results are in line with the strong positive trend for OS observed at the first and second interim analyses of the SPARTAN trial (IA1 and IA2) (5, 7).

Figure 2: Kaplan-Meier plot of overall survival; ITT population and crossover adjusted



(Left) Kaplan-Meier estimate of OS for the ITT population; (Right) Kaplan-Meier estimate of OS adjusted for patient crossover from placebo to Apalutamide. Analyses for the Kaplan-Meier estimate of OS (Left) were stratified. Note: (Right), inverse probability of censoring weighted (IPCW) and naive-censored Kaplan-Meier estimates of OS for the placebo group are presented along with the standard Kaplan-Meier estimates of OS for both the apalutamide and placebo groups. Patients at risk are presented for the naive-censored curve. Patients at risk for the IPCW curve are not included because of lack of clear clinical interpretation of the number of patients at risk associated with the weighted methodology.
CI = confidence interval; ITT: Intent-to-treat; IPCW: inverse probability of censoring weighted;
Figure reprinted from: Smith MR, et al. Apalutamide and Overall Survival in Prostate Cancer. Eur Urol (2020), https://doi.org/10.1016/j.eururo.2020.08.011 (4)

As requested in the protocol, the OS-rate is also presented.

The OS rate at 3-years for the ITT population was 81.8% (95% CI: 78.8%, 84.4%) for apalutamide + ADT vs. 76.9% (95% CI: 72.2%, 80.9%) for placebo + ADT which accounts for an absolute difference of 4.90% (95% CI: 0.2%, 10.0%). A more accurate measure is the cross-over adjusted OS-rate. The corresponding results were 81.8% (95% CI: 78.8%, 84.4%) vs. 74.4% (95% CI: 69.2%, 78.9%) which accounts for an absolute difference of 7.4% (95% CI: 1.8%, 12.9%) (4, 11).

The OS-rate at 4-years was also analyzed. The results for the ITT population was 69.9% (95% CI: 66.4%, 73.1%) for apalutamide + ADT vs. 62.0% (95% CI: 56.5%, 66.9%) for ADT which accounts for an absolute difference of 7.9% (95% CI: 1.7%, 14.2 %). Similarly, a more accurate measure is the cross-over adjusted OS-rate. The corresponding results were 69.9% (95% CI: 66.4%, 73.1%) for apalutamide + ADT vs. 57.1% (95% CI: 50.9%, 62.8%) for placebo + ADT applying the naïve censoring analysis which represents an absolute difference of 12.8% (95% CI: 5.8%, 19.8%) in favor of apalutamide (4, 11).

5.2.1.2 Metastasis-free survival (MFS)

Treatment with apalutamide + ADT significantly reduced the risk of distant metastasis or death by 72% compared with placebo + ADT in patients with high risk nmCRPC, HR: 0.28 (95% CI: 0.23, 0.35; p<0.001; Figure 3). Median MFS was 40.5 months in the apalutamide + ADT arm and 16.2 months in the placebo + ADT arm (5) resulting in 24.3 additional metastatis-free months for apalutamide + ADT compared to placebo + ADT.

Figure 3: Kaplan-Meier estimates of metastasis-free survival

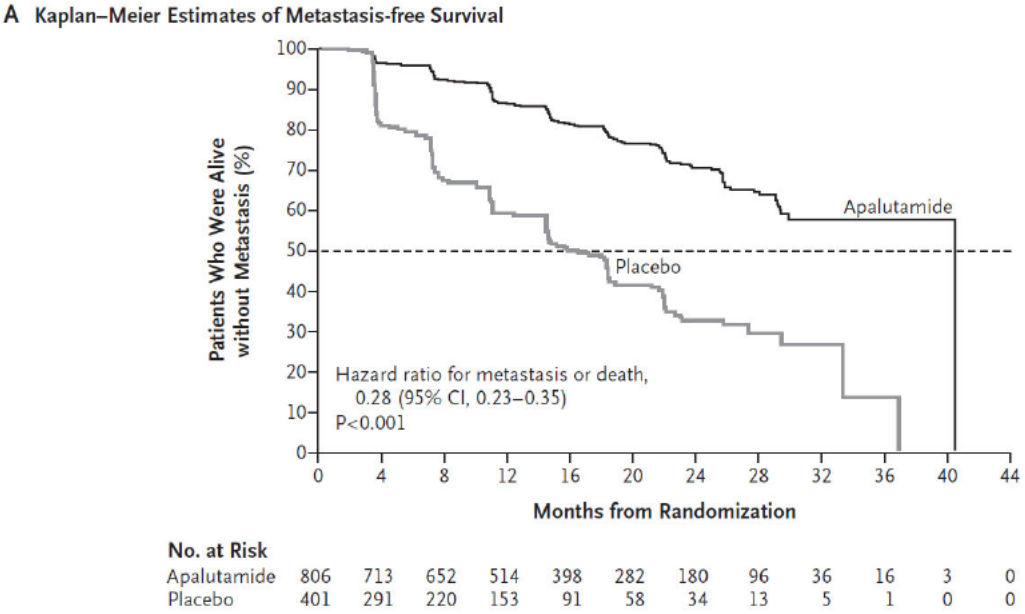


Figure reprinted from: Smith MR, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Graff JN, et al. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. N Engl J Med. 2018;378(15):1408-18 (5)

As requested in the protocol, the MFS-rate at 3-years is also presented. The MFS-rate at 3-years for the ITT population was 57.4% (95% CI: 50.6%, 63.7%) for apalutamide + ADT and 13.4% (95% CI: 1.7%, 37.1%) for placebo + ADT (10) which represents an absolute difference of 44.0%. Since the median was reached before 4 years in both arms, the MFS-rate at 4-years is not presented. The data originates from IA1 which is the final analysis for MFS.

5.2.1.3 Grade 5 adverse reactions

As stated in the protocol, the Expert Committee has requested an estimate of the proportion of patients who experience grade 5 adverse reactions (2).

At the first interim analysis (CCO 17 May 2017), adverse reactions (assessed to be drug-related) leading to death were evaluated by the investigator. For adverse reactions, one death was considered by the investigator as related to study drug (a myocardial infarction in a patient who had prior history of myocardial infarction) (10) accounting for 0.12% in the apalutamide + ADT arm and zero deaths (0%) was reported in the placebo + ADT arm. The absolute difference is [redacted] RR=[redacted] The death happened [redacted] after treatment initiation (13).

Treatment-emergent adverse events leading to death were reported for 3.0% of the patients in the apalutamide + ADT arm and 0.5% of the patients in the placebo + ADT arm with a median follow-up of 52 months (final analysis) (4). It should be noted that the study was randomized apalutamide:placebo (2:1). Additionally, exposure to apalutamide at the time of the final analysis was nearly 3 times longer than placebo (median exposure: apalutamide: 32.85 months versus placebo: 11.48 months). Hence, these numbers must be interpreted in the context of a 2:1 (apalutamide:placebo) randomization and nearly 3 times longer exposure on apalutamide (11).

The proportion of patients reported with TEAEs leading to death at the first interim analysis (CCO 17 May 2017) was 1.2% for the apalutamide arm and 0.3% for the placebo arm (5). Given the 32 months of additional study follow-up time for this analysis (CCO 01 February 2020), the exposure-adjusted incidence of TEAEs leading to death is 1.1 events per 100 patient-years (P-Y) for the apalutamide + ADT arm and 0.4 events per 100 P-Y for the placebo + ADT arm.

Further supporting the low number of study drug related deaths, it is stated in the EPAR (IA1) for apalutamide: "*In study ARN-509-003 AEs leading to death occurred in 10 (1.2%) patients in the apalutamide arm (11 subjects in the combined apalutamide group). The majority of deaths were related to the SOC of cardiac disorders and infections and infestations (3 [0.4%], each). Only one of the deaths was considered by the investigator as related to study drug (a myocardial infarction in a patient who had prior history of myocardial infarction)"* (10) p. 126. And it is concluded in the EPAR that: "*all in all, the safety profile of apalutamide is considered acceptable and sufficiently characterized"* (10) p. 128.

In the EPAR for metastatic hormone-sensitive prostate cancer (mHSPC) (14), the TEAEs leading to death are reported for both the TITAN trial and the SPARTAN trial. Combined, the two trials show 1.7% for apalutamide + ADT and 1.9% for placebo + ADT, suggesting there is no difference between the apalutamide + ADT vs. placebo + ADT in terms of TEAEs leading to death. The TEAEs are defined as any adverse events occurring or worsened in severity, on or after the first dose and within 28 days of last dose of study drug for SPARTAN, and within 30 days of last dose of study drug for TITAN. Patients are counted only once for any given events, regardless of the number of times they actually experienced the events (14).

5.2.1.4 Grade 3 and 4 adverse events

As stated in the protocol, the Expert Committee has requested a comparison of the proportion of patients who experience grade 3-4 AEs as well as a narrative description of these AEs based on the summary of product characteristics (SmPC) (2).

At IA1, grade 3 or 4 adverse events (AEs) were reported in 45.1% of patients in the apalutamide + ADT arm and 34.2% of patients in the placebo + ADT arm (5).

At IA2, grade 3–4 AEs, without regard to attribution, were observed in 53.1% of patients in the apalutamide group and 36.7% of patients in the placebo group (7). After adjusting for the difference in time of exposure, rates of grade 3– 4 events were 54% and 68% for the apalutamide and placebo groups, respectively (7). At IA2, exposure-adjusted grade 3–4 AEs (apalutamide versus placebo) included skin rash (2.7% versus 0.2%), falls (1.2% versus 0.7%), and fractures (2.0% versus 0.9%). After adjusting for the exposure difference, incidence of rash, falls, and fractures in the apalutamide group (event rates/100 patient-years) did not change substantially after IA1 [IA1 versus IA2: grade 3–4 rash (4.2 versus 2.7), falls (1.2 versus 1.2), fractures (2.1 versus 2.0)] (7). Cumulative incidence plots demonstrated no increasing trend in incidence of grades 3–4 falls, fractures, or skin rash with continued apalutamide treatment of 60 months. Incidences of grade 3–4 AEs plateaued by 32 months (7).

Based on data from the final analysis, 55.9% experienced grade 3-4 AEs in the apalutamide + ADT arm vs. 36.4% in the placebo + ADT arm accounting for an absolute difference of 19.5% (95% CI: 13.6%, 25.3%); RR=1.535 (95% CI: 1.330, 1.772).

The AEs, by preferred term, reported most frequently in patients who received apalutamide were fatigue, hypertension, diarrhoea, and fall; the most frequent AEs among patients receiving placebo were fatigue, hypertension, and nausea. Grade 3–4 AEs, irrespective of attribution, were observed in 56% of patients in the apalutamide group and 36% of patients in the placebo group. Adjusting for the difference in duration of exposure, rates of grade 3–4 events were 51% and 68% for the apalutamide and placebo groups, respectively. Grade 3–4 AEs (apalutamide vs placebo) included skin rash (5.2% vs 0.3%), fractures (4.9% vs 1.0%), falls (2.7% vs 0.8%), ischaemic heart disease (2.6% vs 1.8%), and ischaemic cerebrovascular disorders (1.6% vs 0.8%). The rates of rash, falls, and fractures by group term in the apalutamide group (event rate/100 patient-yr) did not change substantially after the first and second interim analyses (7).

The data from the SmPC reports AEs across trials and different grades. There is no specific section for the adverse events grade 3-4 as requested in the protocol for apalutamide in the SmPC. The data from the EPAR is reported instead of the data from the SmPC as it may addresses the outcome measure of interest more directly and focusing on grade 3-4 AEs (10).

Skin rash

Grade 3 events were reported for 5.2% of apalutamide-treated patients and 0.3% of placebo-treated patients. There were no reported events of toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome (SJS) in the safety population. No Grade 4 event of skin rash was reported in the EPAR.

Fall

Falls that require hospitalization (Grade 3) were reported for 14 patients (1.7%) in the apalutamide arm and 3 patients (0.8%) in the placebo arm. Events of fall led to drug interruption for 3 apalutamide-treated patients (0.4%) and for 0 placebo-treated patients. No event of fall led to dose reduction. One patient (0.1%) in the apalutamide arm had an event of fall which led to discontinuation of study drug.

Fracture

A Grade 3 event of fracture was reported for 22 apalutamide-treated patients (2.7%) and 3 placebo-treated patients (0.8%) in the SPARTAN Study. No Grade 4 event of fracture was reported in any of the 3 studies (SPARTAN study, ARN-509-001, 56021927PCR1019) addressed in the EPAR. Events of fracture led to drug interruption for 6 apalutamide-treated patients (0.7%) and for 3 placebo-treated patients (0.8%) in the SPARTAN Study, and for 8 patients (0.8%) in the combined apalutamide group (the 2 additional patients were from Study ARN-509-001). No event of fracture led to dose reduction. One patient (0.1%) in the SPARTAN apalutamide arm had an event of fracture (rib) which led to discontinuation of study drug. Fractures were often preceded by fall. Patients who had an event of fracture reported a fall within 0-7 days prior in the apalutamide (40%) and placebo (50%) arms.

Seizure

Two patients had an event of seizure, both in the apalutamide arm of the SPARTAN Study. One of the events (Grade 2) was considered by the investigator to be related to the study drug. The other event (Grade 1) was considered to be secondary to Grade 3 fall. Both events of seizure were reported as serious adverse events. Neither event of seizure had an outcome of death. As mandated by the study protocol, both events of seizure led to discontinuation of study drug.

Hypothyroidism

Elevation of thyroid-stimulating hormone (TSH) generally occurred early during treatment, with the median time to first increased TSH being 113 days. Exposure-standardized rates (events per 100 P-Y) were 7.6 in the apalutamide arm and 2.2 in the placebo arm. No Grade 3 or 4 events of hypothyroidism were reported in any of the 3 studies from the EPAR (10). No event of hypothyroidism led to drug interruption. Events of hypothyroidism led to dose reduction for 1 apalutamide-treated patient (0.1%) in the SPARTAN Study. One patient (0.1%) in the SPARTAN apalutamide arm had an event of hypothyroidism which led to discontinuation of study drug.

5.2.1.5 Skeletal-related events

According to the protocol for apalutamide, a comparison of skeletal-related events (SREs) is requested. The data for SREs has been derived based on data from the outcome measure; symptomatic progression.

Time to symptomatic progression (TTSP) includes the outcome measure of interest, namely development of an SRE. TTSP was defined as the time from randomization to documentation of any of the following (whichever occurs earlier) (15):

- Development of an SRE (pathologic fracture, spinal cord compression, or need for surgical intervention or radiation therapy to the bone)
- Pain progression or worsening of disease-related symptoms requiring initiation of a new systemic anti-cancer therapy
- Development of clinically significant symptoms due to loco-regional tumor progression requiring surgical intervention or radiation therapy

In total, 264 patients experienced symptomatic progression, 156 of 806 in the apalutamide group and 108 of 401 of the placebo group. The data from the final analysis confirmed the benefit observed with apalutamide in hazard reduction of symptomatic progression compared with placebo (HR: 0.57 (95% CI: 0.44, 0.73); nominal *p*<0.0001; Figure 4). Median was not reached in either group (4).

Figure 4: Kaplan-Meier plot of time to symptomatic progression; ITT population (4)

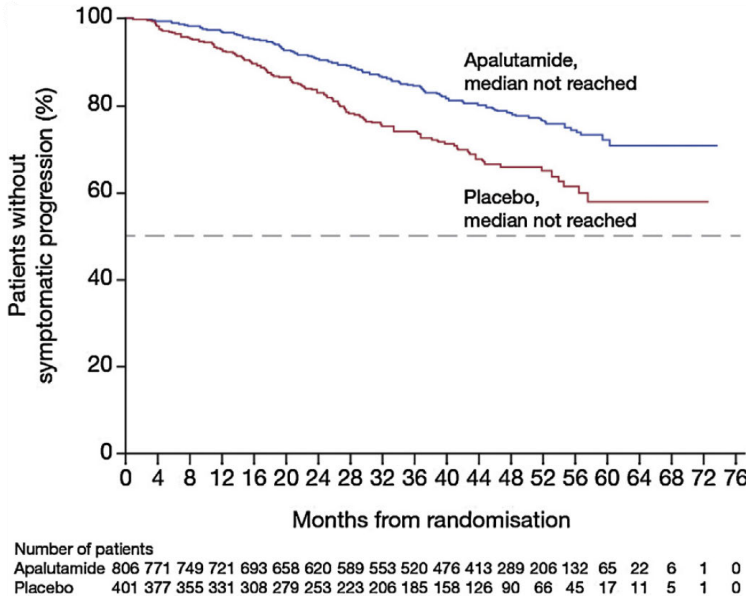


Figure reprinted from: Smith MR, et al. Apalutamide and Overall Survival in Prostate Cancer. Eur Urol (2020), https://doi.org/10.1016/j.eururo.2020.08.011 (4)

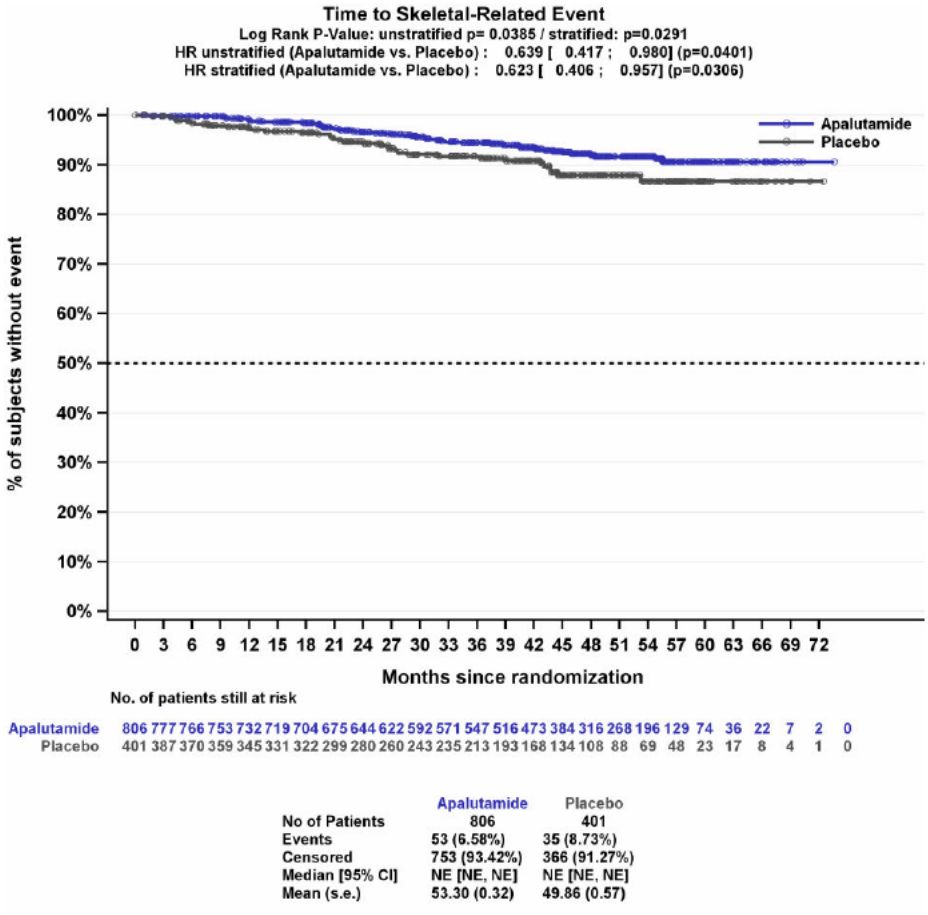
For SREs, the data is reported below in Table 8. It is important to consider the number of patients in each group (2:1 apalutamide + ADT vs placebo + ADT) when assessing these numbers.

Table 8: Skeletal-related event

Skeletal-related events (11)	Placebo + ADT (n=401)	Apalutamide + ADT (n=806)
Patients with skeletal-related event	35	53
Skeletal-related event only	20	34
Skeletal-related event, pain progression or worsening of disease-related symptoms	9	13
Skeletal-related event, loco-regional tumor progression	4	3
Skeletal-related event, pain progression or worsening of disease-related symptoms, loco-regional tumor progression	2	3

Source: Janssen Research & Development. Clinical Study Report, 2020 (11)

Figure 5: Time to Skeletal-Related Event



Source: Janssen Research & Development. Clinical Study Report, 2020 (11)

The analysis of the time to SRE showed a HR (stratified) of 0.623 (95% CI: 0.406, 0.957; p=0.0306) in favor of apalutamide which is equivalent to a reduction of 37.7% for the risk of skeletal-related events occurring.

The time to skeletal-related event at 3 years was 94.4% (95% CI: 92.4%, 95.9%) for apalutamide + ADT and 91.7% (95% CI: 88.1%, 94.3%) for placebo + ADT representing an absolute difference of 2.7% (95% CI: 0%, 6.1%).

The time to skeletal-related event at 4 years was 91.9% (95% CI: 89.4%, 93.9%) for apalutamide + ADT and 87.9% (95% CI: 83.2%, 91.3%) for placebo + ADT representing an absolute difference of 4.1% (95%: 0%, 8.5%)

5.2.1.6 Time to cancer-related procedure

Time to cancer-related procedure was not captured in the SPARTAN trial and is therefore not reported in this application.

5.2.1.7 Health Related Quality of Life by FACT-P

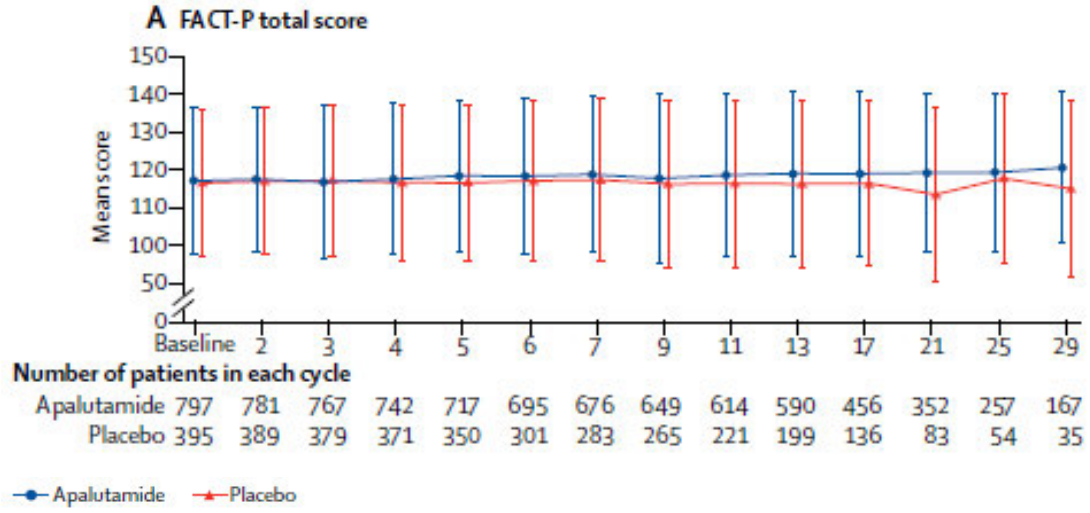
In the SPARTAN study, the Functional Assessment of Cancer Therapy-Prostate (FACT-P) patient-reported outcome questionnaire was used to assess prostate cancer symptoms, pain related symptoms, and overall health-related quality of life (HRQoL). FACT-P is a 39-item questionnaire that was developed and validated specifically in patients with prostate cancer (16). The scores for five FACT-P subscales (physical wellbeing, social and family wellbeing, emotional wellbeing, functional wellbeing, and prostate cancer subscale) can be added together to make a single overall score. The FACT-P overall score ranges from 0 to 156. Higher values of FACT-P total and all subscales indicate a higher HRQoL.

Patients were required to complete the self-administered patient-reported outcome questionnaire before any other interventions or examinations on the day of the clinic visit. FACT-P were given and collected during the treatment phase at baseline, on day 1 of cycle 1 (before dose), day 1 of cycles 2–6, day 1 of every two cycles starting at cycle 7 to cycle 13, then day 1 of every four cycles, unless otherwise specified. This frequency enabled assessment of treatment tolerability and patients' HRQoL over time (6). In patients who developed metastases and moved on to the post-progression follow-up phase, FACT-P were given at the end-of-treatment visit and at 4, 8, and 12 months from start of post progression follow-up. This data was collected to compare the experience in the post-metastatic period for patients originally assigned to receive apalutamide plus ADT versus patients given placebo plus ADT (6).

Overall, FACT-P were maintained with apalutamide from baseline until treatment cycle 29 (Figure 6) based on data from IA1. Maintenance of HRQoL was also observed with placebo (Figure 6). There was a greater decrease in HRQoL in the placebo group compared with the apalutamide group, as shown by the mean changes from baseline in FACT-P total Score (Figure 7).

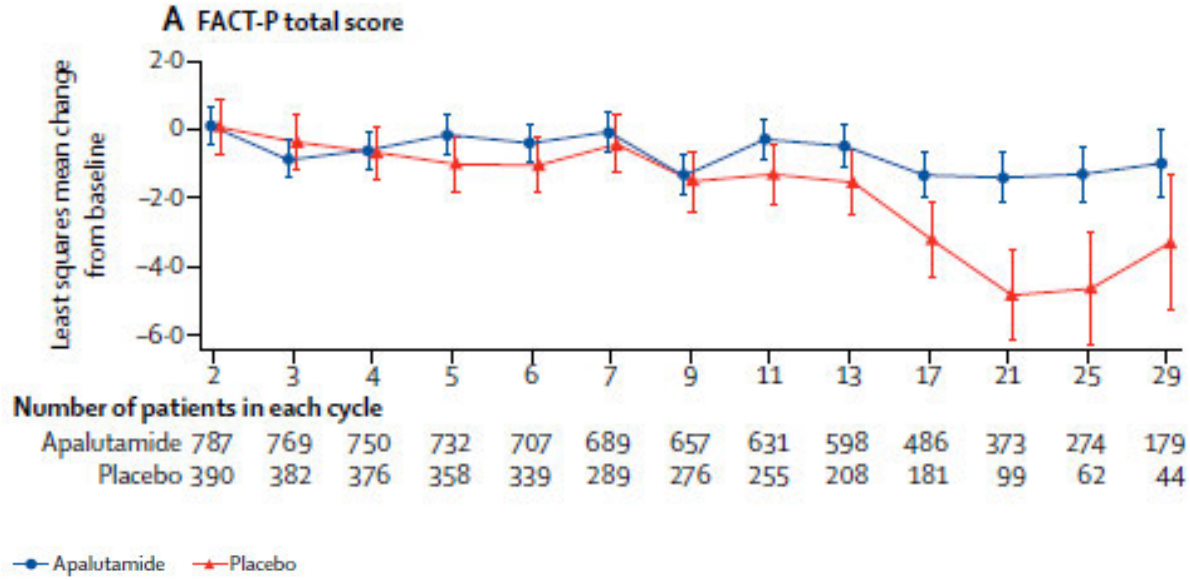
Across most of the patient-reported outcome scales, there were numerical separations, beginning at cycle 11 and continuing until cycle 29, in favor of apalutamide, suggestive of greater deterioration in FACT-P total scores in the placebo + ADT group (6). In the subgroup of patients who experienced symptomatic progression, mean FACT-P total scores were higher with apalutamide + ADT than with placebo + ADT both before and after symptomatic progression occurred (Figure 8).

Figure 6: Mean FACT-P total scores over time, ITT population (6)



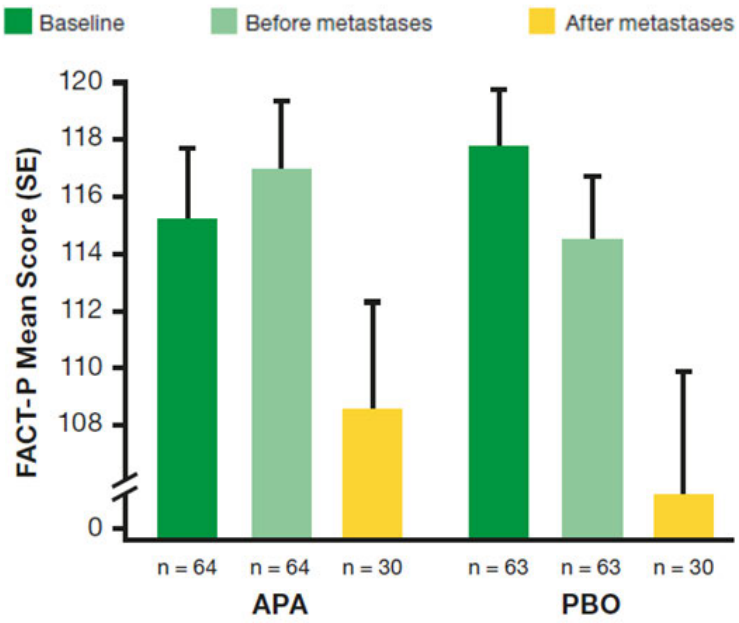
Above figure is based on data from IA1 (6).
FACT P = Functional Assessment of Cancer Therapy – Prostate.
Figure reprinted from: Saad, F., Cella, D., Basch, E., Hadaschik, B. A., Mainwaring, P. N., Oudard, S., ... & Lawson, J. (2018). Effect of apalutamide on health-related quality of life in patients with non-metastatic castration-resistant prostate cancer: an analysis of the SPARTAN randomised, placebo-controlled, phase 3 trial. The Lancet Oncology, 19(10), 1404-1416 (6).

Figure 7: Mean FACT-P total scores change from baseline, ITT population (6)



Above figure is based on data from IA1 (6).
FACT P = Functional Assessment of Cancer Therapy – Prostate.
Figure reprinted from: Saad, F., Cella, D., Basch, E., Hadaschik, B. A., Mainwaring, P. N., Oudard, S., ... & Lawson, J. (2018). Effect of apalutamide on health-related quality of life in patients with non-metastatic castration-resistant prostate cancer: an analysis of the SPARTAN randomised, placebo-controlled, phase 3 trial. The Lancet Oncology, 19(10), 1404-1416 (6).

Figure 8: Group mean FACT-P total scores in the subgroup of patients who experienced symptomatic progressive disease (6)



Above figure is based on data from IA1 (6).
FACT P = Functional Assessment of Cancer Therapy – Prostate; APA = Apalutamide; PBO = Placebo

Treatment with apalutamide had longer time to symptomatic progression compared with placebo HR 0.45 (95% CI: 0.32, 0.63; p<0·0001) (IA1). In this analysis, there were similar decreases in HRQoL from baseline for both treatment groups after post-symptomatic progression was reached. In the protocol for apalutamide, HRQoL has been requested and should be measured by FACT-P, % of pts experiencing >= 10 pts reduction from baseline at 2, 6, 12 and 24 months. The results are presented at cycles (length 28 days) due to the way HRQoL data was collected in SPARTAN. Cycle 1 is the baseline and cycle 3 corresponds to month 2 etc. The requested data is presented below in Table 9.

Table 9: QoL measured by FACT-P, % of pts experiencing >= 10 pts reduction from baseline at 2,6,12 and 24 months (presented by cycles)

			Apalutamide	Placebo	difference and 95%CI
Mean total FACT-P score at baseline			117.2 (19.2)	116.6 (19.3)	0.5736 [-1.7493 2.8965]

	cycle 3				
	Apalutamide		Placebo		difference and 95%CI
TOT-FACTP Reduction >=10	N	%	N	%	
No	605	79%	312	82%	
Yes	162	21%	67	18%	3.4% [-1.4% ; 8.2%]; p=0.1602
Total	767	100%	379	100%	

	cycle 7				
	Apalutamide		Placebo		difference and 95%CI
TOT-FACTP Reduction >=10	N	%	N	%	
No	542	80%	228	80%	
Yes	137	20%	56	20%	0.5% [-5.1% ; 6.0%]; p=0.8708
Total	679	100%	284	100%	

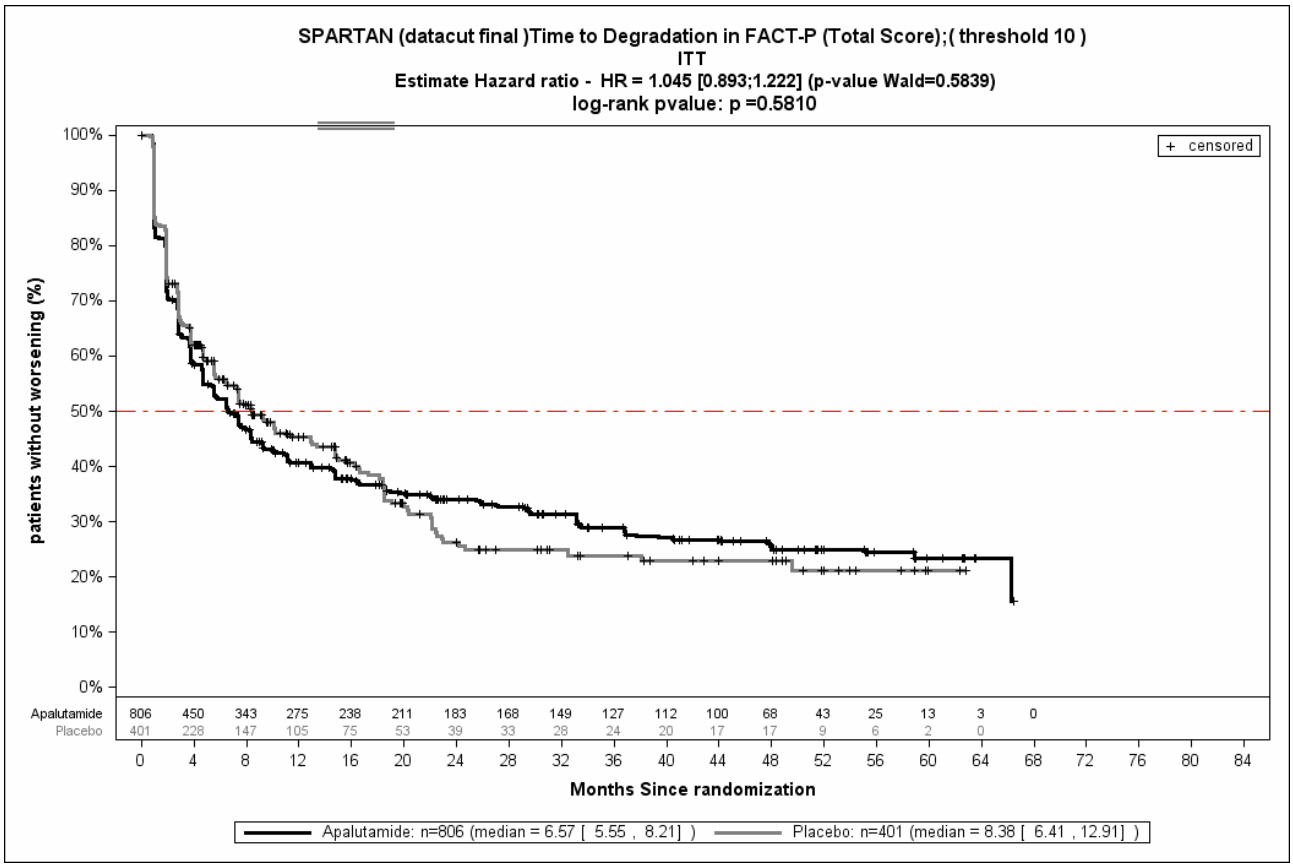
	cycle 13				
	Apalutamide		Placebo		difference and 95%CI
TOT-FACTP Reduction >=10	N	%	N	%	
No	467	78%	167	81%	
Yes	135	22%	38	19%	3.9% [-2.4% ; 10.2%]; p=0.2246
Total	602	100%	205	100%	

	cycle 25				
	Apalutamide		Placebo		difference and 95%CI
TOT-FACTP Reduction >=10	N	%	N	%	
No	360	75%	56	74%	
Yes	120	25%	20	26%	-1.3% [-11.9% ; 9.3%]; p=0.8083
Total	480	100%	76	100%	

Source: Janssen Research & Development. Clinical Study Report, 2020 (11)

There was no statistically significant difference between apalutamide + ADT vs. placebo + ADT. It was observed that the majority of patients were able to maintain their FACT-P score over time and not experiencing a FACT P reduction >= 10. The hazard ratio for the time to deterioration in FACT-P (Total Score) by 10 points was; HR=1.045 (CI 95%: 0.893, 1.222).

Figure 9: QoL measured by FACT-P, Time to degradation in FACT-P



Source: Janssen Research & Development. Clinical Study Report, 2020 (11)

5.2.2 Other supporting evidence

Guidelines and health technology assessments from other countries

National and international guidelines, including European guidelines on prostate cancer, as well as clinical experts, have already recognized the urgent need to treat patients with high risk nmCRPC and therefore recommend treatment with novel anti-androgens based on strong evidence from recent trials (17-22). The use of apalutamide for treatment of high-risk nmCRPC is already recommended in the European Association of Urology (EAU) guidelines, the European Society for Medical Oncology (ESMO) guidelines and the French AFU Guideline for urology, as well as the National Comprehensive Cancer Network (NCCN) and American Urological Association (AUA) guidelines in the United States, all with the highest level of evidence rating (EAU Strong rating, ESMO-MCBS v1.1 score 3 and grade IB, AFU rating A, NCCN category 1, AUA grade A) (17-20, 22). Furthermore, the French health technology assessment body has concluded that apalutamide in combination with ADT provides 'important' medical benefit in this indication and delivers a 'moderate improvement in actual benefit' vs ADT (ASMR III rating) based on data from the SPARTAN trial. Similarly, German assessment bodies IQWiG concluded that the addition of apalutamide to ADT provides a benefit to patients (considerable added benefit) (23, 24).

Important additional evidence of long-term efficacy outcome– PFS2

To gain an increased understanding of the long-term efficacy of treatment with apalutamide, the SPARTAN study assessed progression-free survival from randomization until failure on the first subsequent therapy (PFS2). PFS2 was defined as the time from randomization to investigator-assessed disease progression (by PSA, imaging, or symptom development) during or after the first subsequent treatment, or death from any cause, whichever occurred first, and time to PSA progression as time from randomization to PSA progression according to Prostate Cancer Working Group 2 criteria.

Based on the final analysis of the SPARTAN study, the median PFS2 was extended by 14.4 months with apalutamide + ADT (55.6 months) compared with placebo + ADT (41.2 months) and reduced the hazard of second progression or death by 45% versus placebo (HR: 0.55 (95% CI: 0.46, 0.66); nominal p<0.0001; Figure 10) (4). In addition, the difference between median MFS and PFS2 in SPARTAN is 15.1 months, which is close to the median radiographic PFS of 16.5 months reported in COU-AA-302 (abiraterone acetate in mCRPC patients without prior chemotherapy) (25). Thus, early treatment of nmCRPC with apalutamide delays metastasis and, as shown by both PFS2 and OS, lays the foundation for long-term clinical benefits. Overall, this supports that men treated early with apalutamide in the nmCRPC stage, followed by approved treatments for mCRPC, have significantly better long-term outcomes compared with men who receive ADT until they develop metastases and only start active treatment thereafter (4, 11). Patients gain a benefit of more than one year (14.4 months) when using apalutamide + ADT first in the nmCRPC setting (4, 11). These findings confirm the results observed in IA1 and IA2 of the SPARTAN study (5, 7, 26). Therefore, treating with apalutamide first delays the transition to the incurable metastatic stage of prostate cancer and the associated symptoms and decline in HRQoL.

Figure 10: Second progression-free survival (PFS2)

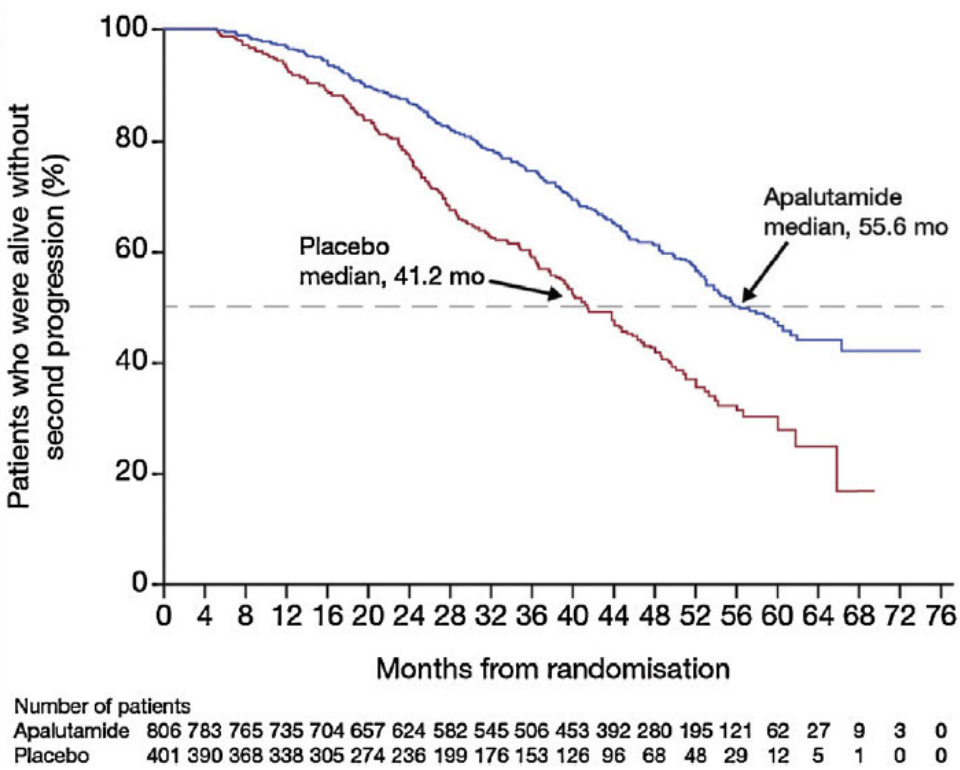


Figure reprinted from: Smith MR, et al. Apalutamide and Overall Survival in Prostate Cancer. Eur Urol (2020), https://doi.org/10.1016/j.eururo.2020.08.011 (4)

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7 Appendix

7.1.1 Results per study

Table 10: Comparative analysis of critical efficacy measures in the SPARTAN trial

The requested data is reported below. Since only results from the SPARTAN trial has been utilized, the comparative analysis of the outcome measures stated in the protocol can be found below.

Trial name:	SPARTAN											
NCT number:	NCT01946204											
				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**	**Hazard/Odds/ Risk ratio**	**95% CI**	***P* value**		
Overall survival *Median overall survival, months ITT*	Apa+ADT	806	73.9 (61.2, NR) months	14 months	NE		HR: 0.78	0.64, 0.96	0.016	*ITT*	Smith et al. 2020 (4) *Absolute difference calculated*
	Placebo+ADT	401	59.9 (52.8, NR) months								
Overall survival *Median overall survival Adjusted for Crossover*	Apa+ADT	806	73.9 (61.2, NR) months	21.1 months	NE		HR: 0.69	0.56, 0.84	0.0002	Naïve censoring analysis nominal P value	Smith et al. 2020 (4) *Absolute difference stated in publication*
	Placebo+ADT	401	52.8 (48.5, 61.1) months								
Overall survival *Median overall survival Adjusted for Crossover*	Apa+ADT	806	73.9 (61.2, NR) months	21.1 months	NE		HR: 0.69	0.56, 0.84	0.0003	inverse probability of censoring weighted analysis (IPCW) nominal P value	Smith et al. 2020 (4). 95% CIs from CSR (11) *Absolute difference stated in pub.*
	Placebo+ADT	401	52.8 (48.5, 59.9) months								
Overall survival *3 year overall survival rate, %*	Apa+ADT	806	81.8% (78.8%, 84.4%)	4.90%	0.2%, 10.0%		HR: 0.78	0.64, 0.96	0.0161	Estimated absolute difference approximated	Data from CSR, final analysis (11); OS
	Placebo+ADT	401	76.9%								

ITT			(72.2%, 80.9%)							CI using Wald method	curve can be found in Smith et al. 2020 (4) *Absolute difference calculated*
<u>Overall survival</u> 3 year overall survival rate, % Adjusted for cross over	Apa+ADT	806	81.8% (78.8%, 84.4%)	7.4%	1.8%, 12.9%		HR: 0.69	0.56, 0.84	0.0003	Naïve censoring analysis nominal P value. The results of Naive and IPCW are identical and the adjusted Kaplan-Meier curves are also identical, hence, naïve has been applied.	Data from CSR, final analysis (11); OS curve can be found in Smith et al. 2020 (4) *Absolute difference calculated*
	Placebo+ADT	401	74.4% (69.2%, 78.9%)								
<u>Overall survival</u> 4 year overall survival rate, % ITT	Apa+ADT	806	69.9% (66.4%, 73.1%)	7.9%	1.7%, 14.2%		HR: 0.78	0.64, 0.96	0.0161	Estimated absolute difference approximated CI using Wald method	Data from CSR, final analysis (11); OS curve can be found in Smith et al. 2020 (4) *Absolute difference calculated*
	Placebo+ADT	401	62.0% (56.5%, 66.9%)								
4 year overall survival rate, % Adjusted for cross over	Apa+ADT	806	69.9% (66.4%, 73.1%)	12.8%	5.8%, 19.8%		HR: 0.69	0.56, 0.84	0.0002	Naïve censoring analysis nominal P value	Data from CSR, final analysis (11); OS curve can be found in Smith et al. 2020 (4)
	Placebo+ADT	401	57.1% (50.9%, 62.8%)								

											Absolute difference calculated
Share of patients experiencing grade 5 adverse reactions	Apa+ADT	1/803	0.12%	[redacted]							
	Placebo+ADT	0/401	0%								
Share of patients experiencing grade 3-4 AEs	Apa+ADT	449/803	55.9%	19.5%	13.6%, 25.3%		RR: 1.535	1.330, 1.772	NA	Estimated absolute difference approximated CI using Wald method	Smith et al. 2020 (4) *Absolute difference calculated*
	Placebo+ADT	145/398	36.4%								
Median MFS, months	Apa+ADT	806	40.5 months	24.3 months	NE		HR: 0.28	0.23, 0.35	P<0.001		Smith et al. 2018 (5) *Absolute difference calculated*
	Placebo+ADT	401	16.2 months								
MFS-rate at 3 years	Apa+ADT	806	57.4% (50.6%, 63.7%)	44.0%	NE					95% CI: NE since only a small number of patients were at risk at year 3.	Data from CSR (IA1) (13). MFS curve can be found in Smith et al. 2018 (5).
	Placebo+ADT	401	13.4% (1.7%, 37.1%)								
Time to skeletal-related event, 3-year rate, %	Apa+ADT	806	94.4% (92.4%, 95.9%)	2.7%	0%, 6.1%		HR: 0.62	0.41, 0.96	0.0306	Time to Skeletal-Related Events. HR stratified.	Data from CSR, final analysis (11). Time to skeletal-related events. See 5.2.1.5 for detailed results
	Placebo+ADT	401	91.7% (88.1%, 94.3%)								
Time to skeletal-related event,	Apa+ADT	806	91.9% (89.4%, 93.9%)	4.1%	0%, 8.5%		HR: 0.62	0.41, 0.96	0.0306		

4-year rate, %	Placebo+ADT	401	87.9% (83.2%, 91.3%)								
QoL measured by FACT-P, share of pts experiencing >= 10 pts reduction from baseline at 2,6,12 and 24 mths	Apa+ADT	797/803	Mean total FACT-P score 117.2 (19.2)	0.5736	-1.749, 2.896					To match the given Mean total FACT-P score numbers – only measurements before initiation of subsequent therapy were considered. 1 month= 1 cycle = 28 days. Difference in means	Data from CSR, final analysis (11).
	Placebo+ADT	395/398	Mean total FACT-P score 116.6 (19.3)								
	Apa+ADT	162/767	Change from baseline. Month 2 21.1%	3.4%	-1.4%, 8.2%		HR: 1.045	0.893, 1.222	0.5839	Difference in proportions of patients experiencing >= 10 pts FACT-P reduction from baseline HR for FACT-P: Time to Deterioration in FACT-P (Total Score) by 10 points	
	Placebo+ADT	67/379	Change from baseline. Month 2 17.7%								
	Apa+ADT	137/679	Change from baseline. Month 6 20.2**%**	0.5%	-5.1%, 6.0%						
	Placebo+ADT	56/284	Change from baseline. Month 6 19.7%								
	Apa+ADT	135/602	Change from baseline. Month 12 22.4%	3.9%	-2.4%, 10.2%						
	Placebo+ADT	38/205	Change from baseline. Month 12 18.5%								
	Apa+ADT	120/480	Change from baseline. Month 24 25.0%	-1.3%	-11.9%, 9.3%						

	Placebo+ADT	20/76	Change from baseline. Month 24 26.3%								

Apa: Apalutamide; NR: Not reached; CSR: Clinical Study Report

Health economic analysis of apalutamide plus androgen deprivation therapy for the treatment of non-metastatic castration resistant prostate cancer

Technical report

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Abbreviations

Table 1: Overview of applied abbreviations and corresponding definitions

Abbreviation	Definition
ADT	Androgen deprivation therapy
AE	Adverse Event
AIC	Akaike Information Criterion
AR	Androgen Receptor
BIC	Bayesian Information Criterion
BICR	Blinded Independent Central Review
BSA	Body Surface Area
CCO	Clinical Cut-off
CHMP	Committee for Medicinal Products for Human Use
CRPC	Castration Resistant Prostate Cancer
CTCAE	Common Terminology Criteria for Adverse Events
DSU	Decision Support Unit
EAU	European Association of Urology
EMA	European Medicines Agency
FA	Final analysis
FDA	Food and Drug Administration
HR	Hazard ratio
IA	Interim Analysis
ITT	Intent-to-Treat
mCRPC	Metastatic Castration Resistant Prostate Cancer
MFS	Metastasis-free survival
mHSPC	Metastatic Hormone Sensitive Prostate Cancer
NICE	National Institute for Health and Care Excellence
nmCRPC	Non-metastatic Castration Resistant Prostate Cancer
OS	Overall Survival
PFS	Progression-free Survival
PH	Proportional Hazards
PSA	Prostate-specific antigen
PSM	Partitioned Survival Model
RPSFTM	Rank preserving structural failure time model
TEAE	Treatment emergent adverse events
TTTD	Time-to-Treatment Discontinuation

Executive summary

Background

Prostate cancer is the second most common cancer among men worldwide [1]. After the launch of prostate-specific antigen (PSA) screening tests, an increasing number of patients are diagnosed in early localized stages of prostate cancer. If rising PSA levels occur after a primary treatment (e.g. radiation or surgery) androgen-deprivation therapy (ADT) or observation is the standard of care for these patients [2–4]. A significant proportion of these patients becomes resistant to ADT and develops castration-resistant prostate cancer (CRPC) [5, 6]. If a patient with CRPC has no radiographic evidence of metastasis, the disease is defined as non-metastatic castration resistant prostate cancer (nmCRPC) [7–10]. Eventually, these patients will develop metastatic CRPC (mCRPC), which is associated with poor survival [11].

Apalutamide is a potent antagonist of the androgen receptor (AR). The efficacy and safety of apalutamide is assessed in the robust, large randomized, double-blind, placebo-controlled SPARTAN trial which included nmCRPC patients who are at high-risk of developing metastatic disease defined as a prostate-specific antigen doubling time (PSADT) ≤10 months. SPARTAN trial patient-level data based on the first (19 May 2017) [12] and Final Analysis (FA) (01 February 2020) [13, 14] clinical cut-off (CCO) date of the SPARTAN trial was used for this health economic analysis.

Objective

The objective of this economic evaluation is to evaluate the incremental cost per patient and budget impact of ERLEADA® (apalutamide) + Androgen Deprivation Therapy (ADT) as a treatment for men with high-risk nmCRPC. For this purpose, a health economic model has been developed. The analysis was conducted from the Danish societal perspective with some restrictions as per guidance by the Medicines Council [15].

Methods

Target population

In line with the marketing authorization for apalutamide, the population addressed within this health economic analysis evaluates apalutamide + ADT in adult men with nmCRPC who are at high-risk of developing metastatic disease. This also reflects the patient population of the SPARTAN trial [16].

Comparators

The comparator for apalutamide + ADT is ADT alone [17].

Model structure

The model consists of three health states: nmCRPC, mCRPC and death. The model was populated from the societal perspective in Denmark with some restrictions. A lifetime horizon (30 years) with a weekly cycle

length was used. An annual discounting rate of 4.0% was applied for the costs which is in line with the Danish Ministry of Finance [18] and the Medicines Council [15].

A partitioned survival modelling (PSM) approach was selected to capture nmCRPC disease progression to death. The PSM combines parametric survival curves fitted over the most recent survival data from the SPARTAN trial to define the time spent in each health state; metastasis-free survival (MFS) (interim analysis 1 (IA1), clinical cut-off (CCO) 19 May 2017) [12] and overall survival (OS) (FA, CCO 01 February 2020) [14]. Treatment duration of apalutamide + ADT in nmCRPC was determined by the time-to-treatment discontinuation (TTTD) curve (FA, CCO 01 February 2020) [14] from the SPARTAN trial. Multiple standard parametric survival distributions (Weibull, exponential, lognormal, loglogistic, Gompertz and gamma) were fitted to extrapolate TTTD, MFS and OS data. The model allows the user to select different parametric model settings.

Costs considered in nmCRPC health state included treatment acquisition, administration, adverse event (AE) and patient costs (consisting of transportation and patient time costs). Costs considered in mCRPC health state included treatment acquisition, administration, patient costs (consisting of transportation and patient time costs) and end-of-life costs.

The main outcome of the model was the incremental costs per patient. To characterize the model drivers and uncertainty around the predicted base case results, scenario analyses were conducted.

The budget impact has been assessed over a period of 5 years by multiplying the cost per patient each week, estimated in the health economic model by the number of patients treated each week and the assigned market share. The budget impact model assumed that a new cohort of patients are starting their nmCRPC treatment every 4th week. The number of patients starting treatment is assumed to be evenly distributed throughout the year based on an entered number of patients expected to start annually.

Results

The base-case analysis shows an incremental cost of 394,869 kr (DKK) per patient when comparing apalutamide + ADT to ADT alone. In most of the performed scenario analyses, the results are close to the base case.

The estimated budget impact over a period of 5-year shows higher incremental costs over time for apalutamide + ADT versus ADT alone, ranging from 2,820,255 kr in the first year to 15,923,583 kr in the fifth year.

Conclusions

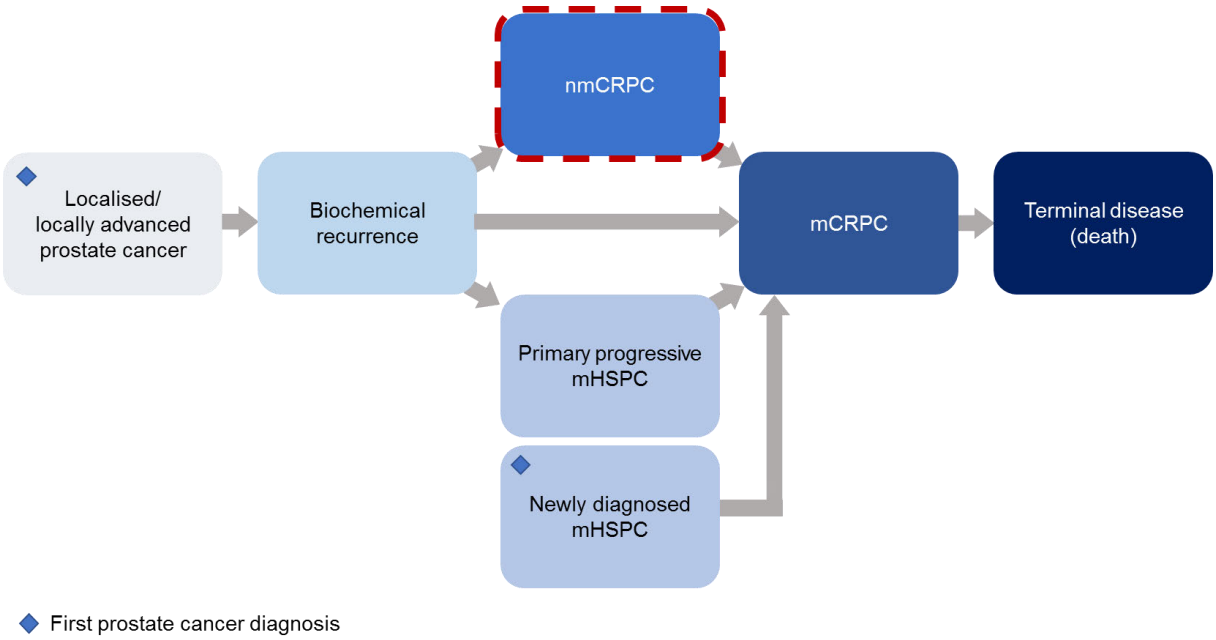
In Denmark, there is a clear need for an effective treatment option for patients with nmCRPC that is able to delay progression, extend survival, and maintain health-related quality of life of these patients. ERLEADA fills an unmet medical need as it has an immediate, meaningful and durable impact on PSA levels when used in combination with ADT in patients with nmCRPC. Apalutamide + ADT extends survival, delays progression to metastases, extends time to symptomatic progression and allows patients to maintain their health-related quality of life at a level similar to the general population. The model suggests that the incremental costs are 394,869 kr per patient treated with apalutamide + ADT instead of ADT alone. The budget impact estimated over 5 years resulted in higher incremental costs for apalutamide + ADT compared to ADT alone, with 2,820,255 kr, 7,845,662 kr, 11,521,748 kr, 13,824,852 kr, and 15,923,583 kr in year 1, year 2, year 3, year 4, and year 5, respectively.

1. Background

Prostate cancer is the second most common cancer among men worldwide [19]. Nowadays, an increasing number of patients are diagnosed with localized, asymptomatic prostate cancer and are treated with primary therapy such as radical prostatectomy or radiation therapy when possible [2–4] . Approximately one third of patients with localized disease experience rising prostate-specific antigen (PSA) levels following primary therapy, referred to as biochemical recurrence (Figure 1) [4].

Although most patients with biochemically recurrent prostate cancer initially respond to androgen deprivation therapy (ADT; achieved by surgical or medical castration), the vast majority of patients will go on to develop progressive disease (known as castration resistant prostate cancer [CRPC]) within approximately 5 years of diagnosis [5, 6]. CRPC is defined by biochemical progression (rising PSA levels) despite castrate levels of testosterone (<50ng/dL).

Figure 1: Prostate cancer disease progression

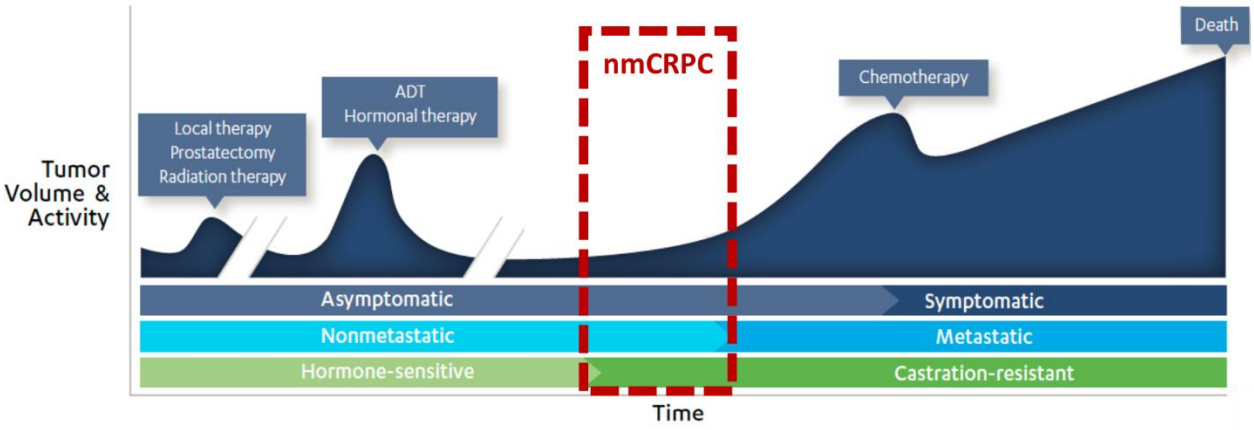


mHSPC= metastatic hormone sensitive prostate cancer; mCRPC= metastatic castration resistant prostate cancer; nmCRPC= non-metastatic castration resistant prostate cancer

Patients with CRPC and no radiographic evidence of metastasis are defined as having non-metastatic castration resistant prostate cancer (nmCRPC; Figure 2) [6, 20]. Patients with nmCRPC ultimately progress over time, with 33% to 48% of patients developing metastases within 2 years of CRPC diagnosis [7–10]. This later stage of the disease is referred to as metastatic castration resistant prostate cancer (mCRPC; Figure 2) and is associated with poor survival and severe symptoms including pain and skeletal-related

events (SREs). Delaying the disease progression to metastatic CRPC represents an important treatment goal [16]. For further details, please refer to clinical part of this application.

Figure 2: Prostate cancer patient journey



ADT= Androgen Deprivation Therapy; nmCRPC= Non-metastatic Castration Resistant Prostate Cancer

1.1 Apalutamide

Apalutamide is a next-generation oral androgen receptor (AR) inhibitor. Efficacy and safety of apalutamide + ADT was assessed and compared with ADT alone in the robust, large randomized, double-blind, placebo-controlled SPARTAN trial in patients with high risk nmCRPC [16]. In the SPARTAN trial, overall survival, metastasis-free survival (MFS) and time to symptomatic progression were found to be significantly longer with apalutamide + ADT arm than with ADT alone.

2. Methods

2.1 Economic evaluation objective

The objective of the current health economic evaluation was to evaluate the incremental cost per patient as well as the budget impact of apalutamide + ADT, for the treatment of men with high-risk (PSADT≤10 months) nmCRPC from the Danish societal perspective [15].

2.2 Type of Economic Evaluation

The main outcome of this health economic evaluation is the incremental cost per patient of apalutamide + ADT versus ADT alone in the management of nmCRPC for a time period that extends beyond the duration of the SPARTAN clinical trial.

2.3 Target patient population

The target population of this model is adult men who have confirmed adenocarcinoma of the prostate, but no radiographic evidence of detectable distant metastases prior to model entry. The study population is consistent with SPARTAN study population [16].

2.4 Model comparators

The model includes one comparator, ADT alone, based on the published protocol by the Medicines Council [17]. ADT alone was included as a comparator in the model based on the head-to-head comparison data of apalutamide + ADT versus ADT alone available from the SPARTAN trial [16].

2.5 Perspective

The model uses a societal perspective but excluding productivity losses as recommended by the Medicines Council [15]. The model includes treatment acquisition costs, administration costs, adverse event (AE) costs, and patient costs (consisting of transportation and patient time costs).

2.6 Time Horizon

The analysis was conducted over a time horizon of 30 years, which is equivalent to a lifetime time horizon, given the mean age of patients in the SPARTAN trial and at start of the model is 73.9 years (range: 48–97 years) [16]. The impact of using alternative time horizons (10 years and 15 years was tested in scenario analyses.

2.7 Annual discount rate

Costs were discounted at a rate of 4.0% per year as applied by the Ministry of Finance [18] and recommended by the Medicines Council [15]. Alternative annual rates (0% and 5%) were assessed in the scenario analyses.

2.8 Cycle length

A weekly cycle length was adopted. Half-cycle correction was not deemed necessary as the cycle length is very short and will therefore be able to capture the timing of events accurately.

2.9 Modelling

2.9.1 Model Description

The model was developed in Microsoft Excel® 2010. It was designed to provide maximum clarity and transparency, to allow all variables to be changed independently, and to facilitate broad re-analysis of the reference case, if and as required. Visual Basic for Applications (VBA) macros were employed to facilitate navigation and to automate the running of sensitivity analyses.

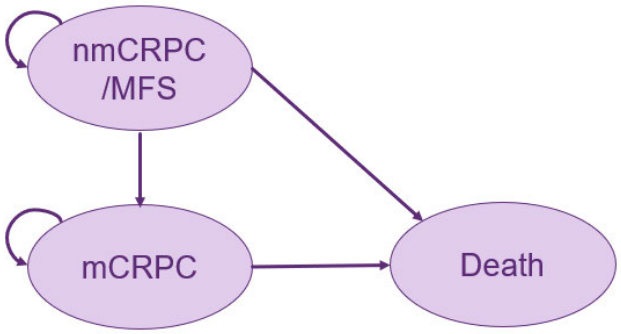
2.9.2 Model structure

A decision analytical model was developed to evaluate the incremental costs per patient of apalutamide + ADT versus ADT alone. The model has three mutually exclusive health states, which present the key sequence of events that patients experience over the course of their treatment for nmCRPC and subsequent progressed disease:

- **nmCRPC state**: Patients in this health state do not have radiographically detectable bone or soft tissue distant metastases and incur the costs associated with drug treatment for nmCRPC, management of AEs, and patient time and transportation costs. Patients are assumed to receive treatment for nmCRPC, but patients receiving apalutamide + ADT may discontinue treatment prior to progression.
- **mCRPC state**: Once metastases have been detected and radiographically confirmed, patients transition to the mCRPC health state. At this point, the drug treatment for nmCRPC has been discontinued and subsequent treatment can be initiated. Patients in this health state incur costs associated with drug treatment for mCRPC, and patient time and transportation costs.
- **Death**: This is an absorbing health state. All patients who die incur one-off end-of-life costs.

For each treatment regimen, a hypothetical nmCRPC patient population enters the model in the MFS health state, where they remain until they progress to mCRPC or die. The model structure does not allow for patients to improve their health state, i.e. patients cannot return to a previous health state, which reflects the progressive nature of nmCRPC.

Figure 3: Model structure



mCRPC= Metastatic Castration Resistant Prostate Cancer; MFS= Metastasis-Free Survival; nmCRPC= Non-metastatic Castration Resistant Prostate Cancer

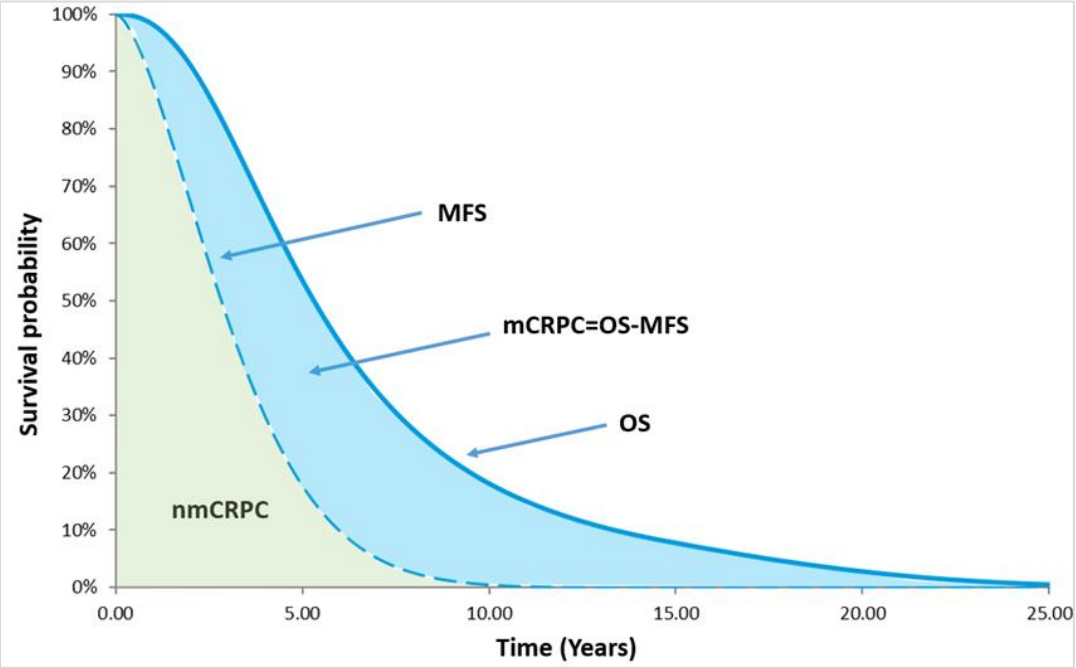
2.9.3 Modelling approach

The analysis was based on a partitioned survival model (PSM) approach, which is a commonly used modelling approach within cost-utility analyses of oncology products. The PSM does not require explicit transition probabilities, but instead relies on the most recent MFS (Interim analysis (IA) 1, clinical cutoff [CCO] 19 May 2017) [12] and OS (final analysis [FA], CCO 01 February 2020) [14] data from the SPARTAN trial at each time point.

The PSM estimates the proportion of the modeled cohort in each health state for each model cycle based on the difference in parametric survival distributions fitted on the MFS and OS data. The MFS data is used to define the time in nmCRPC health state. The time in mCRPC is the difference between the area under the curve of the MFS and OS curves. An illustration of the patient flow over the health states and the relation with MFS and OS is shown in the Figure 4.

Costs were applied at each model cycle according the number of patients in each health state. Total costs for each treatment arm were estimated over the time horizon of the model by aggregating the cycle-specific costs according to the number of patients or frequency of events in each model cycle.

Figure 4: Patient flow in the partitioned survival model (illustration)



mCRPC= Metastatic Castration Resistant Prostate Cancer; MFS= Metastasis-Free Survival; nmCRPC= Non-metastatic Castration Resistant Prostate Cancer; OS= Overall Survival

2.9.4 Justification of the modelling approach

Within the framework of the PSM, it was assumed that the health states (MFS, mCRPC and death) of the model represent the key sequence of events that patients may experience over the course of their treatment for prostate cancer, with the assumption that these events are progressive, mutually exclusive, and irreversible. When patients with nmCRPC develop metastases, they enter mCRPC health state and cannot revert to earlier health states. This assumption is consistent with the definitions of MFS and OS from the SPARTAN clinical trial [16]. Previous appraisals of prostate cancer treatments were reviewed, and the economic approach taken in this submission was designed to be broadly consistent with these previous appraisals [21, 22].

2.9.5 Summary of data included in the model

Table 2 presents an overview of the included data in the economic model and the corresponding data source.

Table 2: Included data in the economic model

Data	Data source

Clinical data for the economic model	The SPARTAN trial [12, 14]]
	• Clinical efficacy:
	  ○ MFS of apalutamide + ADT and placebo + ADT (IA1, CCO 19 May 2017) [12]
	  ○ OS of apalutamide + ADT and placebo + ADT (FA, CCO 01 February 2020) [14]
	• TTTD of apalutamide + ADT (FA, CCO 01 February 2020) [14]
	• Safety: Frequency of AEs (TEAEs of grade 3/4, reported in ≥5% frequency in apalutamide + ADT and placebo + ADT study cohorts) (FA, CCO 01 February 2020) [14]

Treatment cost data	Dosing and frequency of apalutamide were derived from the European Medicines Agency (EMA) SmPC for apalutamide [23]. The cost of apalutamide (Erleada) was derived from the Medicines price list of the Danish Medicines Agency [24]. Dosing, frequencies and costs of ADT were derived from the Medicines price list [24] and Product summaries [25] of the Danish Medicines Agency. Dosing and frequencies for subsequent therapies were taken from EMA [26–31]. The costs were derived from the Medicines price list of the Danish Medicines Agency [24]. In case no costs in Denmark were available, costs were derived from FASS [32]
Market shares of ADT regimens and subsequent treatments	The market shares of ADT regimes were based on assumptions (equal market shares) as no market share data for Denmark was readily available.
	The market shares of subsequent treatments were based on expected Danish market shares.
Administration costs	Administration costs were taken from the DRG tariffs list [33] based on Medicines Council guidelines [34].
Adverse event cost data	AE costs were derived from the DRG tariffs list [44].
End-of-life cost data	End-of-life cost are based on estimations from a UK study which included prostate-cancer patients [35]
Patient time costs	The patient time costs were derived from the Medicines Council [36]. 1 hour of patient time per intravenous administration was assumed to be needed. Transportation costs were derived from the Medicines Council [36].

ADT = Androgen deprivation therapy; AE= Adverse Event; CCO= Clinical cut-off; FA= final analysis; IA= Interim Analysis; mCRPC= Metastatic Castration Resistant Prostate Cancer; MFS= Metastasis-Free Survival; nmCRPC= Non-metastatic Castration Resistant Prostate Cancer; OS= Overall Survival; TEAE= Treatment Emergent Adverse Events; TTTD= Time-to-Treatment Discontinuation

2.10 Data sources

2.10.1 Overview of the SPARTAN trial

SPARTAN is a multinational, randomized, double-blind, placebo-controlled Phase 3 study of apalutamide + ADT compared with ADT alone in subjects with high risk nmCRPC [16].

The primary objective of the trial was to demonstrate superiority in MFS when apalutamide + ADT was compared to ADT + placebo. OS was compared as a secondary objective. Also, AEs of each treatment arm were recorded, and patient reported outcomes of health-related quality of life and prostate cancer-specific symptoms were compared.

Three CCOs (IA1, CCO 19 May 2017 [12], IA2, CCO 01 February 2019 [37] and FA, CCO 01 February 2020 [14]) of the SPARTAN trial are available.

IA1 was the per protocol initial analysis of the SPARTAN trial after which the study was unblinded. At IA1, MFS, time to metastasis, progression-free survival (PFS), and time to symptomatic progression with statistical significance; therefore, primary analysis was considered the final analysis for these end points. Based on these data, the study was unblinded and placebo-treated patients who were eligible and without evidence of disease progression were able to crossover to receive open-label apalutamide. After unblinding, all patients were followed for survival, with crossover patients analyzed as part of the placebo group intent-to-treat (ITT) population. For IA1, the median survival follow-up time for all subjects was 20.3 months.

IA2 is an additional interim analysis that was performed based on requests for updated data from governing agencies. In IA2 only selected endpoints were analyzed: OS, time to cytotoxic chemotherapy and second PFS (PFS2) [37]. For IA2, median follow-up time for all subjects was 41.0 months.

In the FA OS, time to cytotoxic chemotherapy, time to symptomatic progression, PFS2, time to prostate-specific antigen (PSA) progression and PSA response, and TTTD were analyzed [14]. For FA, median follow-up for all subjects was 52.0 months. The model inputs derived from the SPARTAN trial include:

- Efficacy outcomes:
    - MFS (IA1, CCO 19 May 2017): Defined as the time from randomization to the time of the scan that showed first evidence of Blinded Independent Central Review (BICR)-confirmed radiographically detectable bone or soft tissue distant metastasis (simply referred to as “metastasis” from this point forward) or death due to any cause (whichever occurs earlier) [12].
    - OS (FA, CCO 01 February 2020): Defined as the time from randomization to the date of death due to any cause [14]

- TTTD (FA, CCO 01 February 2020): Defined as the time from randomization to the date of treatment discontinuation of or death due to any cause, whichever occurs first [14].

- Incidence of AEs (FA, CCO 01 February 2020) [14]

2.10.1.1 Efficacy outcomes

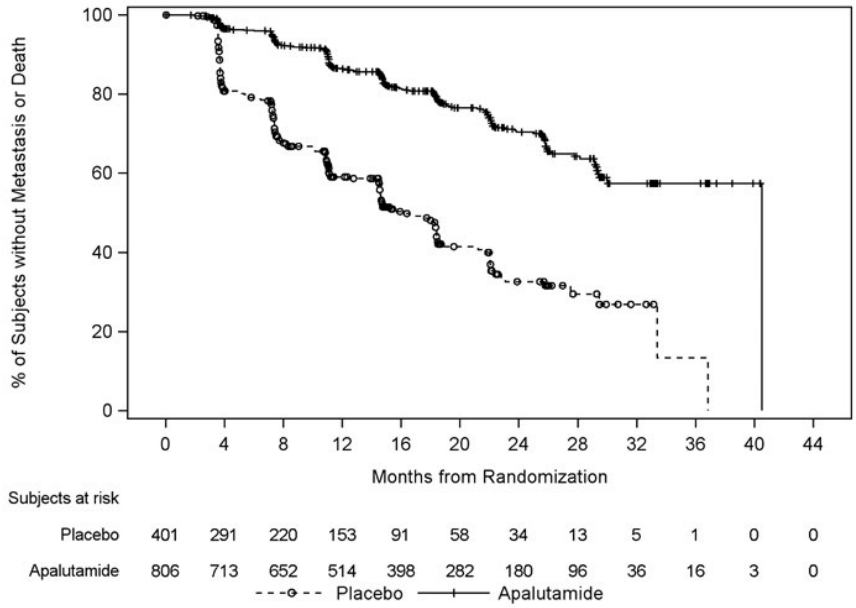
Efficacy analyses were performed using the ITT population with a total number of 1,207 randomized patients (806 patients in the apalutamide + ADT arm and 401 patients in the ADT alone arm) where 803 were treated with apalutamide + ADT and 398 with ADT alone.

2.10.1.1.1 Metastasis-free survival (MFS)

MFS was the primary endpoint in the SPARTAN trial and was considered to be the most appropriate endpoint to use in this health economic evaluation. Use of PFS instead of MFS was examined in scenario analyses.

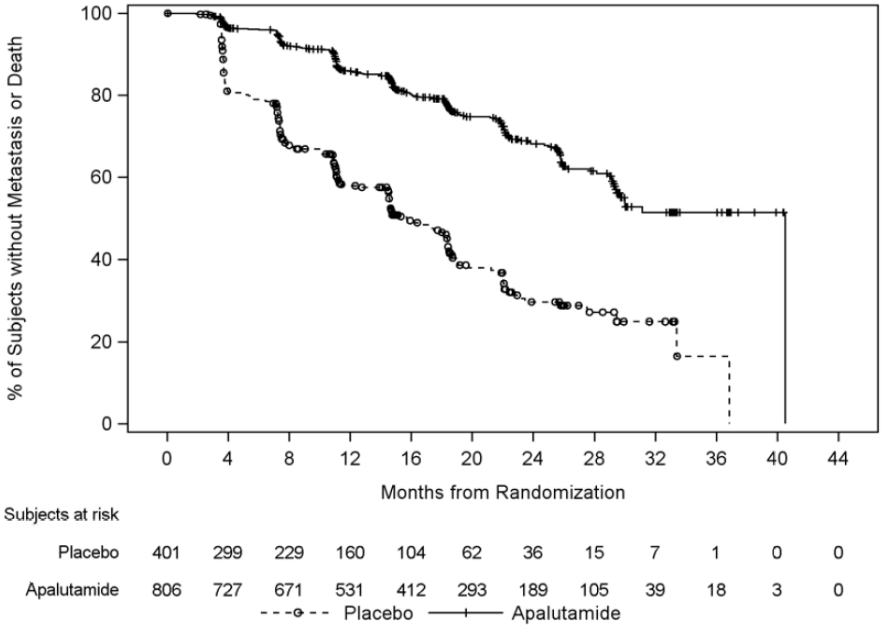
In the SPARTAN trial, MFS (IA1, CCO 19 May 2017) was assessed using both US censoring and ex-US/EMEA censoring rules [12]. In analysis of MFS with the US censoring rules, apalutamide + ADT significantly decreased the risk of distant metastasis or death by 72% compared with ADT alone (hazard ratio (HR): 0.280; 95% CI: 0.227, 0.346; p<0.0001) by BICR. The median MFS was 40.5 months for the apalutamide + ADT arm and 16.2 months for the ADT alone arm. Similar results were found when EMEA censoring rules were applied (median MFS of 40.5 months for apalutamide + ADT and 15.7 months for ADT alone; HR=0.297; 95% CI: 0.24, 0.36; p<0.001). Figure 5 and Figure 6 present the Kaplan-Meier plots of MFS of the SPARTAN study based on US- and ex-US censoring, respectively. The difference in definitions between US and ex-US censoring rules is explained in Table 3.

Figure 5: Kaplan-Meier plot of progression-free survival for US regulatory; ITT population – IA1, CCO 19 May 2017



CCO= Clinical cut-off; IA= Interim Analysis; ITT= Intent-to-Treat; US = United States of America
Figure reprinted from: CHMP assessment report, Procedure No. EMEA/H/C/004452/0000, 15 November 2018, figure 6 p. 77 [38].

Figure 6: Kaplan-Meier plot of progression-free survival for ex-US regulatory; ITT population – IA1, CCO 19 May 2017



CCO= Clinical cut-off; IA= Interim Analysis; ITT= Intent-to-Treat; US = United States of America
Figure reprinted from: Erleada SmPC, 18 February 2020, figure 3 p. 12 [23].

Table 3: Overview of different censoring rules for MFS

Scenario	US regulatory guidance	Ex-US regulatory guidance
Data from subjects who are lost to follow-up or whose disease progression (development of metastasis) or death occurs after 2 or more consecutively missing or unevaluable tumour assessments	Censored on the date of the last tumour assessment that the patient was known to be metastasis-free	Time of progression will be determined using the first date when there is documented evidence of progression or death (whichever occurs earlier) regardless of missed or unevaluable tumour assessments
Subjects that receive new systemic anti-cancer therapy prior to documented disease progression (development of metastasis) or death	Censored on the date of the last tumour assessment prior to the start of the new systemic anti-cancer therapy	Time of progression will be determined using the first date when there is documented evidence of progression or death (whichever occurs earlier) regardless of change of therapy

MFS= Metastatic-free survival; US = United States of America

In this health economic model, the Ex-US censoring rules were applied.

2.10.1.1.2 Overall Survival (OS)

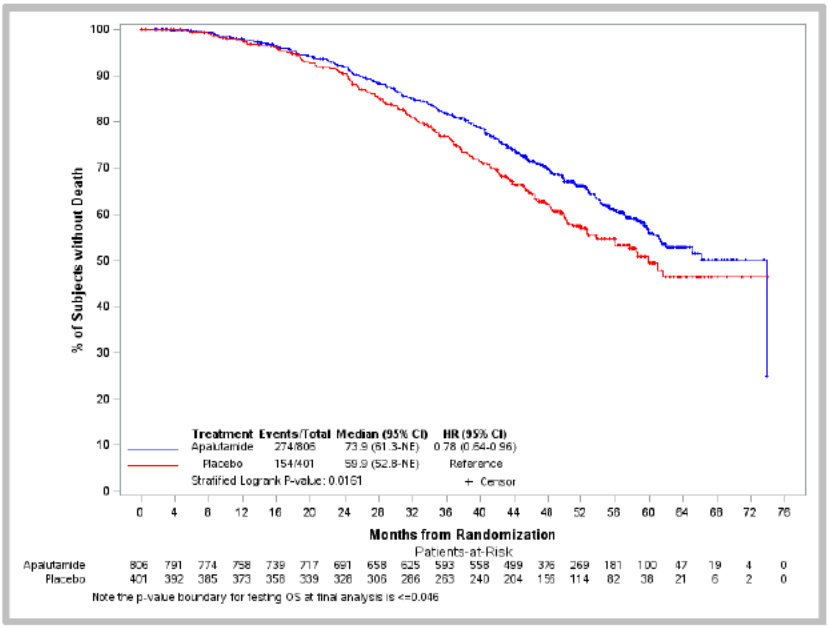
In the SPARTAN trial, three CCOs are available for OS; IA1 (CCO 19 May 2017) [12], IA2 (CCO 01 February 2019) [44], and FA (CC 01 February 2020) [13, 14]. The FA CCO (01 February 2020) was used for the purpose of this submission, as it is the most mature data available.

The FA (CCO 01 February 2020) [14] OS SPARTAN data is presented in Figure 7. In the FA, treatment with apalutamide + ADT significantly decreased the risk of death by 22% compared with ADT alone (HR (95% CI) = 0.784 (0.643, 0.956), 2-sided p=0.016). The median OS was 73.9 months for apalutamide + ADT group and 59.9 months for the ADT alone group. The pre-specified alpha boundary (p≤0.046) for this final analysis was crossed and statistical significance was achieved. 76 subjects [19.0% of randomized placebo subjects, or 64% of the ongoing placebo subjects at unblinding] were crossed over from placebo to apalutamide. These patients that switched from ADT + placebo to ADT + apalutamide may have gained survival time attributed to apalutamide during this open-label extension. As a consequence, the clinical benefit associated with apalutamide when reported in an ITT analysis (Figure 7) will be underestimated. It is therefore of interest to estimate the overall survival adjusted for bias introduced by crossover. The crossover adjustment was performed in line with the NICE DSU guidelines [39]. A Rank preserving structural failure time model (RPSFTM) was used in order to reconstruct the survival duration of ADT patients that crossed over to apalutamide, as if they had never received apalutamide. RPSFTM works by reconstructing the counterfactual survival time of patients who switched to experimental therapy (apalutamide), as if they had never received this therapy. It involves two steps: 1) Estimation of the OS benefits of the therapy to be adjusted for (APA) using an accelerated failure time survival model, generating an acceleration factor, which expresses the proportional prolongation of OS resulting from exposure to these treatments. 2) Estimation of the counterfactual survival times in the placebo arm (i.e. the survival time that would have been observed had crossover not occurred) by shrinking OS for time periods where placebo patients were exposed to apalutamide, which allows to estimate a hazard ratio, adjusted for the

treatment switching. The main assumption behind RPFSTM is the common treatment effect assumption, assuming that the benefit of the treatment is equal in patients exposed later in time to the active therapy (APA) compared to patients initiated on the active therapy earlier (in the active arm at baseline). The adjusted ADT alone Kaplan Meier data is presented in Figure 8. The resulting hazard ratio of the RPSFTM-adjusted curves is 0.6923 (95% CI: 0.550, 0.872, p=0.0018).

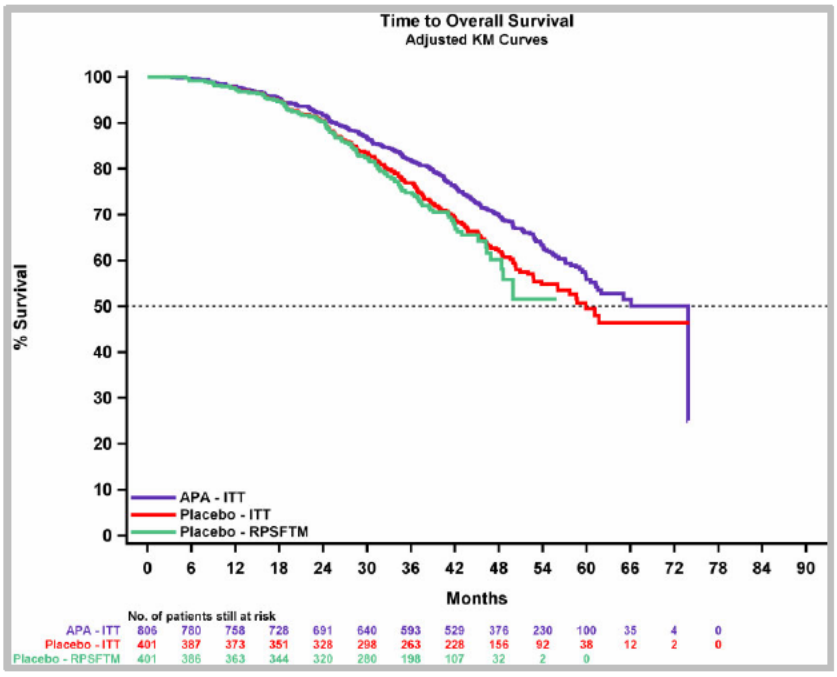
In the base case analysis, the unadjusted ITT curves (Figure 7) were applied to determine the survival of apalutamide + ADT and ADT alone. In a scenario analysis, the RPSFTM-adjusted curves (Figure 8) were used (see Appendix 1).

Figure 7: Kaplan-Meier Plot of Overall Survival; Intent-to-treat Population (Study ARN-509-003) – FA, CCO 01 February 2020 [14]



CCO= Clinical cut-off; CI= Confidence interval; HR= Hazard ratio; IA= Interim analysis; NE= Not estimable; OBF= O'Brien-Fleming

Figure 8: Kaplan-Meier Plot of Overall Survival; Intent-to-treat Population (Study ARN-509-003) – FA, CCO 01 February 2020 – Adjusted for crossover [14]



ADT= Androgen deprivation therapy; CCO= Clinical cut-off; IA= Interim analysis; ITT= Intent-to-Treat; RPSFTM= Rank preserving structural failure time model

2.10.1.1.3 TTTD

In the SPARTAN trial, two CCOs are available for TTTD; IA1 (CCO 19 May 2017) [40], and FA (CCO 01 February 2020) [14]. The FA CCO was used for the purpose of this submission, as it is the most mature data available.

TTTD was used to calculate treatment costs in the nmCRPC health state (paragraph 2.12.1.1). The FA (CCO 01 February 2020) TTTD SPARTAN data is presented in Figure 9 (red and purple curves) [14]. In the FA, 70.5% in the apalutamide + ADT arm, 100% in the ADT alone arm, and 39.5% in the ADT alone to apalutamide + ADT arm discontinued treatment. 100% of the patients in the ADT alone arm discontinued treatment since (after unblinding of the trial) those that did not progress and were in the ADT alone arm could receive apalutamide + ADT thereafter.

76 subjects [19.0% of randomized placebo subjects, or 64% of the ongoing placebo subjects at unblinding] crossed-over from placebo to apalutamide. These patients that switched from ADT + placebo to ADT + apalutamide may have different treatment discontinuation rates now attributed to apalutamide during this open-label extension. As a consequence, the treatment discontinuation rates associated with ADT when reported in an ITT analysis will be underestimated. It is therefore of interest to estimate the treatment discontinuation adjusted for crossover. The crossover adjustment was performed in line with the NICE DSU guidelines [39]. An RPSFTM was used in order to reconstruct the duration on treatment of ADT patients

that crossed over to apalutamide, as if they had never received apalutamide. The adjusted ADT alone Kaplan Meier data is presented in Figure 9 (green curve). The resulting HR of the RPSFTM-adjusted TTTD curves is 0.3767 (95% CI: 0.284, 0.499, p= <.0001).

In the base case analysis, for TTTD, the unadjusted ITT curves (red and purple curves in Figure 9) were applied to determine the treatment duration in nmCRPC. In a scenario analysis, for ADT, the RPSFTM-adjusted curve (green curve in Figure 9) was used. The adjustment does not have an impact on the incremental costs because ADT is taken over a lifetime, e.g. they do not discontinue treatment.

[redacted]

2.10.1.1 Adverse events in nmCRPC

Adverse events included in the model were derived for apalutamide + ADT and ADT alone from the SPARTAN trial. Treatment emergent adverse events (TEAE) were measured using the safety population. Subjects were assessed for AEs at each clinic visit during the study. TEAEs were graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 and coded to preferred term and system organ class using MedDRA version 19.1. Table 4 presents the number of grade 3 or 4 TEAEs with a frequency of at least of 5% in any nmCRPC treatment arm of the FA (CCO 01 February 2020) [14] of the SPARTAN trial.

Table 4: Number of subjects with treatment-emergent Grade 3-4 Adverse events with frequency of at least 5% in any Treatment Group by System Organ Class, Preferred term, and Toxicity grade (FA, CCO 01 February 2020) [14]

Preferred term	ADT alone		Apalutamide + ADT	
	N	%	N	%
Safety population	398		803	
Hypertension	49	12.31%	131	16.31%
Rash	1	0.25%	42	5.23%

Note: Percent is based on the Safety population.
Note: Treatment-emergent adverse events are those that occurred between the date of 1st dose of study drug and date of last dose of study drug +28 days.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with worst toxicity grade is used. If a subject has all adverse events with missing toxicity grades, the subject is only counted in the total column.
Note: Adverse events are coded using Medical Dictionary for Regulatory Activities Version 19.1.
Note: Toxicity Grade is based on NCI common toxicity criteria, version 4.0.

ADT= Androgen deprivation therapy; CCO= Clinical cut-off; FA: final analysis

2.11 Projection of survival beyond the SPARTAN trial

The proportion of patients in nmCRPC, mCRPC and death health states at each cycle in the model were defined by the MFS (Ex-US, IA1, CCO 19 May 2017) [12] and OS (FA, CCO 01 February 2020) [14] curves from the SPARTAN trial. As the follow-up of the SPARTAN trial was shorter (IA1: 3.5 years and FA: 6.2 years) than the model time horizon, extrapolation of the observed MFS and OS data was required. Two survival extrapolation approaches were considered; individually fitted models to each treatment arm and a combinedly fitting approach in which ADT alone is used as a reference curve and apalutamide + ADT as a covariate. In order to use combinedly fitted models, the assumption of proportional hazards (PH) needs to be met [41]. The PH assumption was assessed with log-cumulative hazard plots and confirmed with the Schoenfeld test.

Different parametric models (Weibull, exponential, lognormal, loglogistic, gamma and Gompertz) were fitted on the MFS and OS data. The selection of the best fitting model was based on the statistical Akaike information criterion/Bayesian information criterion (AIC/BIC) and visual fits. In determining the choice of parametric function adopted for the base case extrapolations for each treatment arm, consideration was given to the following in line with the Medicines Council guidelines [42] and NICE DSU guidelines on survival extrapolation [41]:

- AIC and BIC goodness-of-fit statistics (i.e. statistical fit)
- Visual inspection against the observed Kaplan-Meier curves
- Clinical plausibility for both short-term and long-term estimates of survival

All extrapolations were also adjusted for general population mortality of the Danish population [43]; if the predicted hazard based on the parametric survival curves fell below that of the general population, the general population mortality hazard was applied.

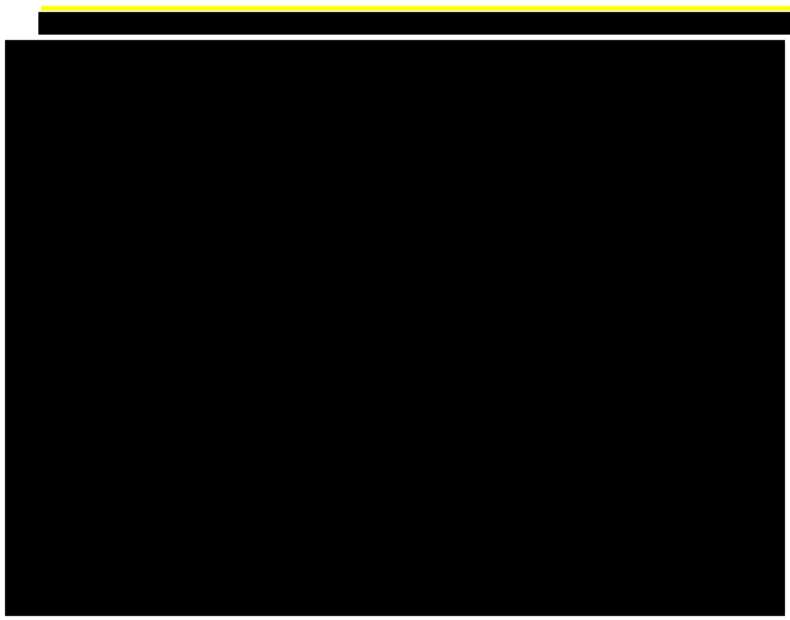
In the paragraphs below the assessment of proportional hazards and statistical fits and visual inspections of six different parametric curves will be described for each survival endpoint (e.g. MFS and OS). After this

description the base case curve selection is presented separately in paragraph 2.11.4 as this selection takes into account the relationship between MFS and OS.

2.11.1 Metastasis-free survival IA1 (Ex-US censoring rules)

2.11.1.1 Proportional hazard assumption

Figure 10 presents the log-cumulative hazard plot for MFS (IA1, CCO 19 May 2017) [12]. The plot showed that the curves only become parallel after the initial assessment of metastasis at week 16 of the trial follow-up, hence they are not parallel over the entire follow-up period. Once the proportionality of hazards was further assessed by the Schoenfeld test, the resulting p-value was significant (p=0.0118), further indicating that the PH assumption does not hold. Also, given that the MFS data of both arms is fairly mature, it was concluded that individually fitted parametric curves to the apalutamide + ADT and ADT alone arms could be used.



2.11.1.2 Independent parametric models

Six parametric distributions were fitted individually to each treatment arm over the MFS data (IA1, CCO 19 May 2017) [12]. Based on the statistical fits (AIC/BIC scores), the gamma distribution has the best fit on the ADT data. However, when looking at the long-term survival predictions, the generalized gamma fit on the ADT data may not be clinically plausible. The lognormal is the second-best fitting model on the ADT alone arm and the best fitting model on the apalutamide + ADT arm. For apalutamide + ADT, the Weibull, gamma and loglogistic distributions have a similar fit to the data (AIC/BIC scores are within 5 points of the lognormal scores) (Table 5). Figure 11 and Figure 12 present long-term projections of the fitted distributions. Based on these figures, all the distributions except the generalized gamma seem to fit the ADT Kaplan-Meier data of the SPARTAN data reasonably well. For apalutamide + ADT, all distributions, except the exponential seem to have a comparable fit on the data. However, there are differences between the long-term

extrapolations. It should be noted that extrapolations with any distributions except Weibull and Gompertz are characterized by long, potentially infeasible tails for the apalutamide + ADT arm.

As the selection of the parametric distribution for OS influences the selection of the parametric curve for MFS, the base case curve selection for each survival endpoint is described in paragraph 2.11.4.

[redacted]

[redacted]

[redacted]

2.11.2 Overall survival FA

2.11.2.1 Proportional hazard assumption

Figure 13 and Figure 14 present the log-cumulative hazard plots and Schoenfeld plots of OS (ITT population). The log-cumulative hazard plots show that the curves were relatively parallel over time but seemed to cross at multiple time points given the curves are very close to each other. Based on the Schoenfeld test, the PH assumption seemed to hold, as the resulting p-value was not significant (p= 0.4387). As the PH assumption holds, and to make efficient use of the data, it was considered more appropriate to apply combinedly fitted models within the base case, using the ADT alone arm as the reference curve and the apalutamide + ADT arm as a covariate. In a scenario analysis, the impact of the individually fitted models was assessed.

[redacted]

[redacted]

2.11.2.2 Combinedly fitted models

The goodness-of-fit statistics are presented in Table 6. The Weibull model has the best statistical fit; but the loglogistic model has very comparable fits (AIC/BIC scores lie within 5 points from the distribution with the lowest scores). The long-term projections are presented in Figure 15. The exponential, lognormal, and loglogistic curves are characterized by long, potentially infeasible tails for both the apalutamide + ADT arm and ADT arms.

[redacted]

[redacted]

[redacted]

2.11.3 Time to treatment discontinuation FA

Six parametric distributions were fitted on the FA apalutamide + ADT TTTD data from the SPARTAN trial [14] (Figure 16). Based on the statistical fit, if AIC and BIC are summed, the exponential distribution has the lowest AIC/BIC score and therefore is the best fitting model for apalutamide + ADT (Table 7). Note that as ADT is applied for a lifetime, the ADT TTTD extrapolations do not influence the model outcomes and are therefore not displayed here.

[redacted]

[redacted]

[redacted]

2.11.4 Base case curve selection

As there is a relationship between the different curves used within the model, the final decision on the base case curve selection was made based on the clinically plausibility of modelled outcomes which depend on the curves selected for MFS and OS. As explained, for MFS, extrapolations with any distributions except the Weibull and Gompertz are characterized by long, potentially infeasible tails. For OS, the lognormal, loglogistic and exponential models were not considered plausible as they predicted long survival tails. Therefore, in the base case analysis the Weibull distribution was used for TTTD, MFS and OS and a scenario analysis explored the outcomes when the Gompertz distribution was used for TTTD, MFS and OS.

2.12 Costs

In accordance with the Danish restricted societal perspective, the direct medical costs were taken into account in the model. The following cost items were included:

- Acquisition and administration costs of treatments
- Costs of handling AEs
- Patient costs (transportation and patient time costs)
- End-of-life costs

Medical resource utilization was not included in the analysis as it is assumed to be the same for apalutamide + ADT and the comparator arm ADT alone. ADT alone is administered in a hospital setting and is the same regimen as ADT in combination with apalutamide.

2.12.1 Acquisition and administration costs of treatments

Treatment costs for nmCRPC and mCRPC health states are calculated using the following sources:

- Treatment costs and treatment dosing schedules were based on several sources:
    - Apalutamide and ADT costs: Danish Medicines Agency [24].
    - mCRPC treatment costs: Danish Medicines Agency [24] and FASS [32] in case no Danish costs were available (radium-223).
- The dosing schedule of the subsequent treatments was derived from the summary of product characteristics of each treatment published on the European Medicines Agency (EMA) website [26–31]. For prednisone the daily dosage was based on the COU-AA-302 study [44].
- The average weight (87.0 kg) was derived from the SPARTAN trial [12]. The average body surface applied in the model is 2.00 m2 [45]. The body surface area (BSA) and weight were applied for determining the average dose applied of docetaxel, cabazitaxel and radium-223.

2.12.1.1 nmCPRC

Table 8 presents treatment costs of apalutamide and ADT. Dosing schedules of nmCRPC treatments were derived from EMA [23] / the Danish Medicines Agency [25]. The recommended dose of apalutamide is 240 mg (four 60 mg tablets) administered orally once daily [23]. No administration costs are assumed as this is an oral treatment. The compliance rate of apalutamide was derived from the SPARTAN trial (FA, CCO 01 February 2020) [14].

The treatment cost is based on the treatment costs of different ADT regimens taken from the Danish Medicines Agency [24, 25]. Administration cost of ADT is based on the DRG tariff; 17MA98 (3,235 kr) [33] based on the guidelines of the Medicines Council [34]. The market shares of the different ADT regimens in nmCRPC are based on assumptions. The total cost of each treatment was weighted with the corresponding

market share of each ADT regimen to derive the weighted annual treatment cost of ADT. The compliance rate of ADT was derived from the SPARTAN trial (FA, CCO 01 February 2020) [14].

Table 8: Treatment dosing and drug acquisition costs of apalutamide and ADT

	Brand name [23]	Dosage [23]	Frequency [23]	Package cost [24]	Package size [24]	Admin. costs per dose	Compliance [14]	Annual cost	
Apalutamide	ERLEADA®	4 tablets of 60 mg	Daily	22,943 kr	112 tablets	- kr (oral)	93.35%	Treatment costs: 288,847 kr (APA 279,386 kr + ADT 9,461 kr) Administration costs: 9,060 kr (related to ADT administration)	
ADT	**Brand name [25]**	**Dosage [25]**	**Frequency [25]**	**Package cost [24]**	**Package size [25]**	**Admin. costs per dose [34]**	**Market shares***	**Compliance [14]**	**Weighted annual cost**
Goserelin	Zoladex	1 vial of 10.80 mg	Every 3 months	3,174 kr	10.80 mg vial	3,235 kr	25.00%	96.67%	Treatment costs: 9,797 kr Aministration costs: 9,382 kr
Leuproreli n	Eligard	1 vial of 22.50 mg	Every 3 months	3,424 kr	22.50 mg vial	3,235 kr	25.00%		
Triptorelin	Pamorel in	1 vial of 11.25 mg	Every 3 months	3,194 kr	11.25 mg vial	3,235 kr	25.00%		
Bicalutamide	Sandoz	3 tablets of 50.00 mg	Daily	125 kr	100 tablet(s)	- kr (oral)	25.00%		

ADT= Androgen deprivation therapy

*The market shares for ADT were assumed to be equally divided over the four ADT regimens

The treatment duration of apalutamide was defined by the TTTD curve of apalutamide + ADT in the SPARTAN trial [14]. Weibull curves fitted on the SPARTAN TTTD curves were used in the base case to model TTTD to be in line with the MFS base case distribution. In case the TTTD curve crosses the extrapolated MFS curve, from that moment the MFS curve was used to determine the treatment duration; e.g. TTTD was assumed to be equal or smaller than MFS, as apalutamide is a treat-to-progression treatment. In a scenario analysis, treatment duration was estimated based on the median TTTD from the SPARTAN trial [14].

ADT was assumed to be administered over the lifetime of a patient [17].

2.12.1.1 Subsequent treatments

Table 9 presents treatment costs of each subsequent treatment:

- The recommended dose of abiraterone is 1000 mg (two 500 mg tablets) administered orally once daily [27]. As abiraterone is an oral treatment no administration costs are counted. Abiraterone is associated with a dose of 10 mg prednisone daily [46].
- The recommended dose of enzalutamide is 160 mg (four 40 mg tablets) administered orally once daily [28]. As enzalutamide is an oral treatment no administration costs are counted.
- The recommended dose of docetaxel is 75 mg/m^2 every 3 weeks for 10 cycles [29]. As docetaxel is administrated intravenously, administration costs in the hospital are considered [24]. Docetaxel is associated with a dose of 24 mg dexamethasone every 3 weeks for 10 cycles [29].
- The recommended dose of cabazitaxel is 25 mg/m^2 every 3 weeks for 10 cycles [30]. As cabazitaxel is administrated intravenously, administration costs in the hospital are considered [24]. Cabazitaxel is associated with a dose of 0.4 mg G-CSF [47].
- The recommended dose of radium-223 is 55 kBq/kg every 4 weeks for 6 cycles [31]. As radium-223 is administrated intravenously, administration costs in the hospital are considered [25].
- It was assumed that patients receive ADT beyond any of the subsequent treatments until death. To calculate the ADT cost for the mCRPC state, a similar approach as used to calculate ADT cost for nmCRPC state was used.
- For all intravenous treatments, wastage is considered; i.e. no vial-sharing is assumed.

Table 9: Subsequent treatment acquisition cost

mCRPC treatments	Brand name [25]	Dosage [26–31]	Frequency [25] (% patients complete full course)	Package cost [24, 32]	Package size [25, 32]	Admin. cost per dose [33, 34]	Compliance (assumption)	Weekly cost
Prednisone	DLF	2 tablets of 5 mg	Daily	31 kr	100 tablets	- kr	100%	Treatment: 2 kr Administration: 0 kr
Dexamethasone	Krka	6 tablets of 4 mg	Equal to docetaxel	688 kr	100 tablets	- kr	100%	Treatment: 14 kr Administration: 0 kr
G-CSF	Neupogen	0.3 vials of 1.5 mg	Equal to cabazitaxel	2,763 kr	1 vial	- kr	100%	Treatment: 921 kr Administration: 0 kr
Abiraterone	Zytiga	2 tablets of 500 mg	Daily	21,615 kr	56 tablets	- kr	100%	Treatment: 5,406 kr (abi 5,404 kr + pred 2 kr) Administration: 0 kr
Enzalutamide	Xtandi	4 tablets of 40 mg	Daily	22,088 kr	112 tablets	- kr	100%	Treatment: 5,522 kr Administration: 0 kr
Docetaxel	Accord	75 mg/m2 (2 vials of 80 mg)	Every 3 weeks for 10 cycles (95%) [48]	150 kr	per 80 mg vial	3,235 kr	100%	Treatment: 114 kr Administration: 1,078 kr
Cabazitaxel	Jevtana	25 mg/m2 (1 vial of 60 mg)	Every 3 weeks for 10 cycles (60%) [49]	29,035 kr	per 60 mg vial	3,235 kr	100%	Treatment: 10,599 kr Administration: 1,078 kr
Radium-223	Xofigo	55 kBq/kg (1 vial of 6,600 kBq)	Every 4 weeks for 6 cycles (58%) [50]	38,600 kr [32]	6600 kBq	3,235 kr	100%	Treatment: 9,650 kr Administration: 809 kr

ADT	Brand name [25]	Dosage [25]	Frequency [25]	Package cost [24]	Package size [25]	Admin. cost per dose [33, 34]	Market shares*	Compliance (assumption)	Weighted annual cost
Goserelin	Zoladex	1 vial of 10.80 mg	Every 3 months	3,174 kr	10.80 mg vial	3,235 kr	25.00%	100%	Treatment: 10,134 kr Administration: 9,705 kr
Leuprorelin	Eligard	1 vial of 22.50 mg	Every 3 months	3,424 kr	22.50 mg vial	3,235 kr	25.00%		
Triptorelin	Pamorelin	1 vial of 11.25 mg	Every 3 months	3,194 kr	11.25 mg vial	3,235 kr	25.00%		
Bicalutamide	Sandoz	3 tablets of 50.00 mg	Daily	125 kr	100 tablets	- kr (oral)	25.00%		

ADT= Androgen deprivation therapy; mCRPC= Metastatic castration resistant prostate cancer; Abi = Abiraterone; pred = prednisone
*The market shares for ADT waswere assumed to be equally divided over the four ADT regimens

Patients receive subsequent treatment costs once they progress from nmCRPC to mCRPC health state. The subsequent treatment mix was modelled to be dependent on the treatment that patients received in nmCRPC state. Patients can receive up to 3 lines of treatment in mCRPC health state. The considered treatments reflect the expected clinical practice of Denmark where patients are assumed to receive either abiraterone, enzalutamide, docetaxel, cabazitaxel, or radium-223 [51].

The distribution of subsequent treatments in each line, was based on assumed Danish market shares. It is assumed that regardless of the treatment in nmCRPC, the treatment pathway in mCRPC is similar for all patients. Also, the distribution of patients on each subsequent treatment in the Danish setting is presented in Table 10.

Table 10: Distribution of subsequent treatments based on assumed Danish market shares [51]

Treatment in nmCRPC	Treatment line	Abiraterone	Enzalutamide	Docetaxel	Cabazitaxel	Radium-223
Apalutamide + ADT	1st line	10.0%	30.0%	52.0%	7.0%	1.0%
	2nd line	16.0%	12.0%	40.0%	25.0%	7.0%
	3rd line	40.0%	13.0%	18.0%	19.0%	10.0%
ADT alone	1st line	20.0%	60.0%	12.0%	7.0%	1.0%
	2nd line	50.0%	30.0%	10.0%	5.0%	5.0%
	3rd line	20.0%	20.0%	30.0%	20.0%	10.0%

ADT= Androgen deprivation therapy; nmCRPC= Non-metastatic castration resistant prostate cancer

2.12.1.1.1 Treatment duration of subsequent treatments

As the progression on each subsequent treatment was not measured in the SPARTAN trial, external data sources were used to define the duration of each subsequent line. The treatment duration of the subsequent treatment was derived from the International Prostate Cancer Registry (NCT02236637) (Table 11) [52]. The duration of each subsequent treatment line is assumed to be the same regardless of the treatment in nmCRPC (apalutamide + ADT or ADT alone).

Table 11: Treatment duration in each treatment line in mCRPC (Prostate Cancer Registry) [52]

Treatment line	Active treatment duration
1st line	10.0 months
2nd line	8.3 months
3rd line	6.6 months
Total mCRPC treatment duration	24.9 months

mCRPC= Metastatic castration resistant prostate cancer

The duration of the line was considered as a progression to the next line treatment. The duration of each subsequent treatment was defined as follows:

- Treat-to-progression (abiraterone and enzalutamide): the treatment costs are applied continuously for the active treatment duration.
- Fixed-duration drugs (docetaxel, cabazitaxel and radium-223): the treatment costs are applied based on a fixed duration of treatment in line with the clinical practice in Denmark (see Table 12) [48–50].
- Other treatments: the treatment cost of ADT is applied continuously.

For the treatments with fixed duration, the average treatment durations are presented in Table 12.

Table 12: Treatment duration in mCRPC of treatments with fixed duration

Treatment	Mean percentage completion of the full course of fixed duration drugs	Dosing schedule	Number of administrations per year	Frequencies	Treatment duration in all lines	Source
Docetaxel	95% [48]	Max of 10 cycles	9.50 cycles	1 every 3 weeks	28.50 weeks	Calculated based on the frequency and the maximum cycle of treatment mulitplied by the proportion of patients that complete the full course of the drug
Cabazitaxel	60% [49]	Max of 10 cycles	6.00 cycles	1 every 3 weeks	18.00 weeks	
Radium-223	58% [50]	Max of 6 cycles	3.48 cycles	1 every 4 weeks	13.92 weeks	

mCRPC= Metastatic castration resistant prostate cancer

In case the mean time in mCRPC is shorter than the sum of the maximum treatment durations of all lines, the duration of the second- and third-line treatments is limited based on the mean duration of mCRPC. This implies that the total duration of three lines of treatment cannot be longer than the mean duration of mCRPC. The adjustment of the total treatment duration in mCRPC was done to guarantee that the costs of subsequent treatments are not overestimated for any of the treatment arms. If the total duration of active treatments (e.g. 24.9 months) does not cover the total mCRPC phase, the active treatment duration in 1st, 2nd, and 3rd line is increased proportionally so patients receive active treatments during the whole mCRPC phase (see Table 13). The treatment duration of subsequent lines (1L: 10.0 months, 2L: 8.3 months, 3L: 6.6 months) is decreased/increased proportionally to match mCRPC duration so patients are treated actively for 100% of the time.

Table 13: Treatment duration versus the time spend in mCRPC

	APA+ADT	ADT
1st line	14.3 months	18.3 months
2nd line	11.8 months	15.2 months
3rd line	9.4 months	12.1 months
Total actively treatment duration	35.5 months	45.6 months
Time spend in mCRPC	35.5 months	45.6 months
% of mCRPC duration that patients are actively treated	100%	100%
No. months non-actively treated	Patients are actively treated till death	Patients are actively treated till death

ADT= Androgen Deprivation Therapy; mCRPC= Metastatic castration resistant prostate cancer

2.12.2 Adverse event costs

Unit cost per AE were applied based on the frequency of each AE. The frequencies of AEs in the nmCRPC phase, for apalutamide + ADT and ADT alone, were taken from the SPARTAN trial, FA (CCO 01 February 2020) [14]. Adverse events grade 3-4 that occurred in at least 5% of the patients in any of the treatments in nmCRPC were included in the analysis.

The associated costs of each AE were derived from the DRG tariffs list [33]. Costs are applied once at the start of the treatment in nmCRPC stage and as a one-off cost at time of metastases. Unit cost of each AE are presented in Table 14.

Table 14: Grade 3 or 4 adverse event unit cost per event

Adverse event	Unit cost	
Hypertension	1,932 kr	DRG 2020: Group 11MA98 [33]
Rash	1,932 kr	DRG 2020: Group 11MA98 [33]

2.12.3 Patient costs

Transportation and patient time costs were considered for the patients when hospital visits were needed. These patient costs were included for patients that received intravenous treatments (ADT or subsequent treatments (docetaxel, cabazitaxel and radium-223)) and therefore had to travel to the hospital. The transportation costs and the patient costs per hour were derived from the Medicines Council [36]. It was assumed that a hospital visit would take one hour (excluding the travel time).

2.12.3.1 Intravenous ADT

Transportation and patient time costs were included for the administration of intravenous ADT. Table 15 presents the annual transportation and patient time costs in nmCRPC and mCRPC. The total patient costs for ADT in nmCRPC and mCRPC were calculated by multiplying the number of visits per year with the transportation and patient time cost per year, while taking into account the market shares of intravenous ADT treatments and compliance rate of ADT.

Table 15: Transportation and patient time costs for intravenous ADT

		Number of visits per year	Unit cost	Sum of intravenous ADT market shares	Compliance rate	Cost per year	Total patient costs per year
nmCRPC	**Transportation cost of ADT in nmCRPC**	4 visits of 1 hour	100 kr per administration	75.00%	96.67%	290 kr	809 kr
	Patient time cost of ADT in mCRPC		179 kr per hour			519 kr	
mCRPC	**Transportation cost of ADT in nmCRPC**	4 visits of 1 hour	100 kr per administration		100.00%	300 kr	837 kr
	Patient time cost of ADT in nmCRPC		179 kr per hour			537 kr	

ADT= Androgen deprivation therapy; nmCRPC= non-metastatic castration resistant prostate cancer; mCRPC= metastatic castration resistant prostate cancer

2.12.3.2 *Intravenous subsequent treatments*

Transportation and patient time costs were included for the administration of intravenous subsequent treatments. Table 16 presents the annual transportation and patient time costs in mCRPC. The total patient costs were calculated by multiplying the number of visits of each intravenous subsequent treatment regimen with the transportation and patient time cost per year.

Table 16: Transportation and patient time costs for intravenous subsequent treatments

		Number of visits (see paragraph 2.12.1.1.1)	Unit costs	Treatment duration	Total costs	Total patient costs per treatment
mCRPC - Docetaxel	**Transportation cost of docetaxel in mCRPC**	9.50 visits of 1 hour	100 kr per administration	28.50 weeks	950 kr	2,651 kr
	Patient time cost of docetaxel in mCRPC		179 kr per hour		1,701 kr	
mCRPC - Cabazitaxel	**Transportation cost of cabazitaxel in mCRPC**	6.00 visits of 1 hour	100 kr per administration	18.00 weeks	600 kr	1,674 kr
	Patient time cost of cabazitaxel in mCRPC		179 kr per hour		1,074 kr	
mCRPC – Radium-223	**Transportation cost of radium-223 in mCRPC**	3.48 visits of 1 hour	100 kr per administration	13.92 weeks	348 kr	971 kr
	Patient time cost of radium-223 in mCRPC		179 kr per hour		623 kr	

ADT= Androgen deprivation therapy; nmCRPC= non-metastatic castration resistant prostate cancer; mCRPC= metastatic castration resistant prostate cancer

2.12.4 End-of-life costs

End-of-life costs were estimated based on a study from the UK due to a lack of more accurate Danish specific tariffs or studies. The UK study focused on end-of-life costs and included patients with advanced cancer, including prostate cancer patients [35]. Based on 2013-2014 prostate cancer-related UK tariffs, the study found that prostate cancer patients had an expected mean end-of-life cost of £14,859 per patient (including health care, social care, charity care and informal care cost). Excluding informal care and charity care, the end-of-life cost per patient was £9,415 (2014 pounds). Applying a simplified approach, the £9,415 accounts to 80,115.44 kr based on the average exchange rate for 2019 which is the most recent average annual exchange rate available [53]. The exchange rate was lower in 2019 compared to 2014, can therefore be considered more conservative (as higher end-of-life costs reduce the incremental cost per patient). The cost has been adjusted for inflation based on a Danish constant inflation rate of 0.7% from 2014-2019 per year [54]. 2020 was not applied as inflation data for 2020 is not available yet. Danish inflation rates were selected as these are lower than inflation rates in the UK providing the most conservative estimate. After adjusting for inflation, the 80,115.44 kr accounted to 82,895 kr End-of-life costs of 82,895 kr were applied as a one-time cost in the mCRPC stage for each patient that dies. A scenario analysis with a lower end-of-life cost has also been conducted.

2.13 Base case analysis

Table 17 presents an overview of all the base case settings applied in the Danish model. The uncertainty of the base case results is considered in the next section.

Table 17: Overview of the baseline settings

Category	Parameter	Base case	Justification
Model settings	Patient population	High-risk non-metastatic castration resistant prostate cancer patients	Per SPARTAN population [12]
	Country	Denmark	Not applicable
	Model perspective	Societal	As recommended by the Medicines Council [15]
	Time horizon	Lifetime (30 years)	Given the mean age of patients at baseline (73.9 years) and survival projections, 30 years is a sufficient time horizon to capture all potential costs and benefits associated with each comparator
	Cycle length	One week	This cycle length is short enough to capture all relevant events.
	Annual discount rate	Costs: 4.0%	As recommended by the Medicines Council [15] based on the Ministry of Finance [18]
	Comparators	ADT alone	Comparator stated in the protocol [17]
Clinical inputs	MFS (IA1) [12]	Apalutamide + ADT /ADT alone: Weibull distribution	The Weibull curves as they had a good fit to the data (best fit on OS) and might be more clinically plausible compared to lognormal, exponential, generalized gamma or loglogistic curves.
	OS (FA) [14]	Apalutamide + ADT/ADT alone: Weibull distribution	
Treatment duration	TTTD (FA) [14]	Apalutamide + ADT: Weibull distr bution	The Weibull fit was selected to be consistent with the MFS curve selection.
		ADT alone	Lifetime treatment duration [17]
Cost inputs	Wastage	Considered for intravenous treatments	It is assumed vial-sharing is not applied. Therefore, the costs of wastage need to be included.
	Subsequent treatments	Distr bution of 1L, 2L and 3L treatments are based on assumed Danish market shares	The subsequent treatment use in the SPARTAN trial is related to the efficacy outcomes observed in the SPARTAN trial [14]

ADT= Androgen deprivation therapy; nmCRPC= non-metastatic castration resistant prostate cancer; mCRPC= metastatic castration resistant prostate cancer; MFS= metastasis-free survival; OS= overall survival; RMME= Repeated Measures Mixed-Effect; TTTD= time-to-treatment discontinuation

2.14 Scenario analyses

The sensitivity of the base case settings was assessed within several scenario analyses. These analyses are summarized in Table 18.

Table 18: Overview of the base case analysis and scenario analysis (one-way scenario analysis)

Parameter	Base case	Scenario	Scenario analysis conducted for
Annual discount rate	4.0% for cost	0% for costs	Incremental costs per patient
		5% for costs	
Time horizon	30 years	10 years	Incremental costs per patient
		15 years	
Methods SPARTAN FA OS & TTTD	ITT analysis	Adjusted for crossover (RPSFTM)	Incremental costs per patient & budget impact
Parametric distribution	TTTD (FA) [14]: Weibull MFS (IA1) [12]: Weibull OS (FA) [14] : Weibull	TTTD (FA) [14]: Gompertz MFS (IA1) [12]: Gompertz OS (FA) [14] : Gompertz	Incremental costs per patient & budget impact
Use MFS or PFS curves	MFS curves are used to define patients in nmCRPC state	PFS curves are used to define patients in nmCRPC state	Incremental costs per patient & budget impact
Joined/Individual curve to OS	Combinedly fitted models are used to model OS	Individually fitted models to each treatment arm are fitted to OS	Incremental costs per patient & budget impact
Treatment duration	Weibull TTTD curve	Median TTTD from SPARTAN	Incremental costs per patient & budget impact
Wastage	Wastage is included	Wastage is excluded	Incremental costs per patient & budget impact
End-of-life cost	82,895 kr	41,447.50 kr (assumption: half of the end-of-life costs applied in the base case)	Incremental costs per patient & budget impact
New patients per year (scenario for budget impact)	100	70	Budget impact

FA= final analysis; MFS= metastasis-free survival; nmCRPC= non-metastatic castration resistant prostate cancer; OS= overall survival; PFS: progression-free survival; TTTD= time-to-treatment discontinuation.

2.15 Budget Impact Model

2.15.1 Input and data sources BIM

As per communication from the Medicines Council [15], the budget impact model should be in the same Excel file as the calculation for incremental costs per patient and the budget impact model should cover five years. Based on the guidance, a budget impact model was implemented into the model accounting for incremental costs per patient allowing one single Excel file to be delivered.

The budget impact model is based on the model inputs described in the previous section. It is stated in the guidance by the Medicines Council that, in addition to drug costs, other cost should also be included if possible. These costs have also been included in the budget impact analysis based on the output from the model. The budget impact calculation is excluding patient costs and is not discounted as per guidance. The budget impact model consists of a reference scenario where apalutamide + ADT is not recommended for standard treatment and an alternative scenario where apalutamide + ADT is recommended for standard treatment.

For the model input, it is possible to enter number of patients starting treatment per year as well as the expected market share in the reference scenario and the alternative scenario.

In the protocol for apalutamide + ADT, it is stated that 100 patients with nmCRPC are expected to start treatment annually [17]. The base case has been conducted with 100 patients due to the statement in the protocol, but it is expected that the number patients starting treatment annually is lower due to recently established scanning techniques which will be elaborated on in paragraph 3.2.1.

Table 19 shows the reference case where it is assumed that 100% of patients can be treated with ADT.

Table 19. Reference case – Shares and number of patients

Reference scenario (negative recommendation) - patient share and number of patients					
Reference scenario (no recommendation)	Year 1	Year 2	Year 3	Year 4	Year 5
APA + ADT share	0%	0%	0%	0%	0%
APA + ADT patients	0	0	0	0	0
ADT share	100%	100%	100%	100%	100%
ADT patients	100	100	100	100	100

In case of a negative recommendation, 0% market share has been assumed for apalutamide + ADT. This will serve as a conservative estimate since the cost of treatment with the apalutamide + ADT sequence is estimated to be more expensive than ADT alone (presented in the results section). In case market shares were assigned to apalutamide + ADT in the reference case, it would have had to be deducted from the alternative scenario. In the case of a negative recommendation, selected patients may start apalutamide treatment. In addition, serving as another conservative estimate, it is also assumed that all patients will receive apalutamide + ADT or ADT alone. It might be the case that some patients are not eligible for any of the treatments and neither apalutamide + ADT which would decrease the overall patient population and the estimated budget impact.

Although apalutamide + ADT demonstrates superior efficacy and a manageable safety profile, it should be noted that in Danish Clinical practice, there is likely specific preferences for the nmCRPC treatment depending on the treating physician as well as patient preferences. Some physicians may prefer treating with an ADT alone regimen as the treatment for nmCRPC which will naturally decrease the patient population for apalutamide + ADT if this preference is evident after a recommendation of apalutamide + ADT. Table 20 presents the market shares for apalutamide + ADT over five years. Table 21 presents the assumed number of new patients entering the model over time based on the market shares.

Table 20. Market share per year for APA +ADT in recommendation scenario

Estimated market share per year for APA + ADT in recommendation scenario					
	Year 1	Year 2	Year 3	Year 4	Year 5
APA + ADT recommended vs. ADT	40.0%	60.0%	70.0%	70.0%	70.0%

Table 21. Number of patients per year starting APA + ADT treatment in recommendation scenario

Estimated number of patients per year starting APA + ADT treatment in recommendation scenario					
	Year 1	Year 2	Year 3	Year 4	Year 5
APA + ADT recommended vs. ADT	40	60	70	70	70

2.15.2 Budget impact model – methodology

In short, the budget impact model is multiplying the cost per patient each week, estimated in the health economic model by the number of patients treated each week and the assigned market share.

The budget impact model assumes that a new cohort of patients are starting nmCPRC treatment every 4th week. The number of patients starting treatment is assumed to be evenly distributed throughout the year based on an entered number of patients expected to start annually.

Patients starting in a given week is tracked throughout the modelled period. Serving as examples, the patient cohort starting first-line treatment in week 1 (year one of budget impact period) will continue to be tracked on a weekly basis until the end of 5-year budget impact period (and accumulate the relevant cost for the given week they are in). A patient cohort starting treatment in week 53 (year two of the budget impact period) will continue to be tracked until end of the 5-year budget impact period. Since this specific patient cohort started treatment in the second year of the budget impact period, these patients will be tracked for a total of 4 years in the budget impact model which in turn will be year 5 for the budget impact period. The patient cohort starting in week 53 (year 2 of the budget impact period but the first year of treatment for these patients) will accumulate the week 1 costs from the model. Once this patient cohort entered week 54, they will accumulate the costs based on week 2 from the model.

The costing per week of the specific cohort is connected to the cost output from the model where the cost input and output was described in the previous section (however excluding patient costs and not discounted). For each regimen in the model (in the reference case, ADT alone; in the alternative case, apalutamide + ADT, ADT alone), the number of patients for a specific week is multiplied by the entered market share (reference scenario and alternative scenario) for the different regimens and then multiplied by the cost of each comparator in the model based where the patient cohort is in the treatment cycle. This approach ensures the costs over time of patients starting on apalutamide + ADT or ADT alone are captured accurately in the BIM. In nmCRPC, the patients will receive the costs of apalutamide + ADT or ADT alone (and the corresponding adverse event costs). In mCRPC, the costs of three lines of subsequent treatments were included in the cost output as follows; when a patient progresses to mCRPC, a one-off cost for the first line subsequent treatment was applied. After the duration of the first line mCRPC treatment (apalutamide + ADT 14.3 months; ADT alone 18.3 months), the one-off cost for the second subsequent treatment was applied. The one-off cost of the third line subsequent treatment was applied after the duration of first- and second line subsequent treatment (apalutamide + ADT 26.1 months; ADT alone 33.5 months). End-of-life costs were applied for patients who died.

2.15.3 Model outcomes

A budget impact estimate per year for a five-year period is provided for the different recommendation scenarios.

Based on the number of patients starting treatment and the market shares for the given scenario (reference scenario and alternative scenario), the model will provide an estimate of the incremental costs per treatment regimen per year (for a five-year period) as well as a total.

3. Results

3.1 Incremental costs per patient

Over a 10-year time horizon, the incremental cost of apalutamide + ADT versus ADT alone is 386,733 kr (discounted) per patient.

Table 22 presents the discounted costs for apalutamide + ADT and ADT alone. The total discounted cost for apalutamide + ADT is 1,305,515 kr and 910,646 kr for ADT alone (costs discounted at 4.0%). Most of the costs in the apalutamide + ADT group are generated in the nmCRPC phase (main treatment cost) as the time spent in this health state is longer compared to the time that patients on ADT are in nmCRPC and as the drug costs of apalutamide + ADT are higher than those of ADT alone. These increased costs in nmCRPC are offset by the costs of subsequent treatments in mCRPC. The ADT costs in mCRPC are higher versus those of apalutamide + ADT as the duration of mCRPC is longer for patients treated with ADT and it is expected more patients will be treated with enzalutamide and abiraterone after ADT.

Table 22: Costs per patient over a 10-year time horizon, discounted (4.0%)

	Type of cost	Apalutamide + ADT	ADT alone	Incremental
nmCRPC	Main treatment cost	777,072 kr	14,639 kr	762,433 kr
	Drug administration cost	26,615 kr	14,018 kr	12,597 kr
	Adverse events	416 kr	243 kr	174 kr
	Total patient costs	2,370 kr	1,209 kr	1,161 kr
mCRPC 1L	Main treatment cost	130,879 kr	343,189 kr	- 212,310 kr
	Drug administration cost	23,033 kr	18,009 kr	5,024 kr
	Total patient costs	1,986 kr	1,553 kr	433 kr
mCRPC 2L	Main treatment cost	111,513 kr	269,711 kr	- 158,198 kr
	Drug administration cost	20,862 kr	14,350 kr	6,512 kr
	Total patient costs	1,799 kr	1,238 kr	562 kr
mCRPC 3L	Main treatment cost	128,453 kr	143,537 kr	- 15,084 kr
	Drug administration cost	13,098 kr	19,389 kr	- 6,291 kr
	Total patient costs	1,130 kr	1,672 kr	- 543 kr
	End of life costs	66,289 kr	67,889 kr	- 1,600 kr
Total cost		**1,305,515 kr**	**910,646 kr**	**394,869 kr**

ADT= Androgen deprivation therapy; AE= Adverse Event; mCRPC= Metastatic Castration Resistant Prostate Cancer; nmCRPC= non-metastatic castration resistant prostate cancer

3.1.1 Results scenario analyses

The results of the scenario analysis are shown in Table 23. In most of the performed scenario analyses, the results are close to those found in the base case.

Table 23: Scenario analysis results: apalutamide + ADT versus ADT alone

Scenario	Incremental Costs
Reference case	394,869 kr
Discount rate 0%	458,339 kr
Discount rate 5%	381,591 kr
Time horizon - 10 years	385,962 kr
Time horizon – 15 years	394,634 kr
Methods SPARTAN FA OS & TTTD – adjusted for crossover (RPSFTM)	459,404 kr
MFS, TTTD and OS: Gompertz	363,595 kr
Individually fitted models to each treatment arm are fitted to OS	387,333 kr
Treatment duration based on median treatment duration	411,089 kr
Use PFS instead of MFS curves	412,524 kr
Exclude wastage	390,527 kr
End-of-life cost (assumption, 41,447.50 kr)	395,669 kr

MFS= metastasis-free survival; OS= overall survival; PFS: progression-free survival; TTTD= time-to-treatment discontinuation
There has been made no attempt to make a scenario analysis excluding subsequent treatments since nmCRPC patients are expected to receive subsequent treatments after primary treatment in Danish clinical practice and such scenario would be unrealistic. Also, it would be incorrect to exclude the subsequent treatments because the OS results of the SPARTAN trial are dependent on the use of subsequent treatments during the trial.

3.2 Budget impact model

Results are presented for the recommendation versus the no recommendation scenarios (Table 24). The reference case assumes the market shares stated in section 2.15.1. The budget impact results are undiscounted and excluding patient costs.

The tables below show the budgetary consequences of apalutamide + ADT recommended versus not recommended. A gradual market share uptake is assumed up to the end of year 2 and then a stable market share from year 3. A gradual uptake is expected due to regional implementation, update of treatment guidelines, and physicians gradually adapting to new treatment strategies. The below scenario takes a conservative approach assuming that no other new nmCRPC treatments in the first-line setting will be recommended for standard treatment for the budget impact period ("competing regimens"). In case this would have been included, it could have decreased the assumed market share.

Table 24. Base case scenario – APA + ADT recommended vs. ADT

Estimated budget impact per year for APA + ADT					
	Year 1	Year 2	Year 3	Year 4	Year 5
New patients treated with APA + ADT	40	60	70	70	70
APA + ADT % uptake	40%	60%	70%	70%	70%
***ADT share* (if APA + ADT is recommended)**	60%	40%	30%	30%	30%
Reference scenario (no recommendation)	8,457,427 kr	25,721,524 kr	47,289,438 kr	68,450,550 kr	84,113,848 kr
Alternative scenario (recommendation)	11,277,682 kr	33,567,186 kr	58,811,186 kr	82,275,401 kr	100,037,432 kr
Incremental costs	2,820,255 kr	7,845,662 kr	11,521,748 kr	13,824,852 kr	15,923,583 kr

3.2.1 Results scenario analyses

The results of the scenario analysis are shown in Table 25. In most of the performed scenario analyses, the results are close to those found in the base case. The scenario that was most sensitive to changes was the number of patients starting per year. The reason for running this scenario is that previously, ^{99}mTc-Bone scan has been the most widely used method for evaluating bone metastases of prostate cancer [55]. Recently, ^{68}Ga- or ^{18}F-labelled prostate-specific membrane antigen (PSMA) positron-emission tomography (PET)/CT is increasingly used, because it provides excellent contrast-to-noise ratio, thereby improving the detectability of lesions [56]. As a consequence of the increased use of PSMA-PET for evaluating bone metastases and hence improved detectability, a portion of the nmCRPC patient group will be transferred to the mCRPC patient group and the size of nmCRPC patient group will decrease [57]. To reflect the recently established scanning techniques which may result in a lower patient population than stated in the protocol for apalutamide, this scenario analysis has been conducted.

Table 25: Scenario analysis results: apalutamide + ADT versus ADT alone

Scenario	Estimated budget impact per year for APA + ADT				
	Year 1	Year 2	Year 3	Year 4	Year 5
Reference case	2,820,255 kr	7,845,662 kr	11,521,748 kr	13,824,852 kr	15,923,583 kr
Methods SPARTAN FA OS & TTTD – adjusted for crossover (RPSFTM)	3,114,700 kr	8,471,287 kr	12,488,742 kr	15,301,569 kr	18,553,647 kr
MFS, TTTD and OS: Gompertz	2,952,620 kr	8,575,002 kr	13,094,918 kr	16,405,703 kr	19,497,598 kr
Individually fitted models to each treatment arm are fitted to OS	2,798,308 kr	7,753,855 kr	11,343,880 kr	13,602,062 kr	15,621,332 kr
Treatment duration based on median treatment duration	2,887,870 kr	8,169,536 kr	12,227,086 kr	14,860,859 kr	17,099,816 kr
Use PFS instead of MFS curves	2,580,361 kr	7,328,367 kr	10,694,513 kr	12,517,356 kr	14,273,830 kr
Exclude wastage	2,836,507 kr	7,886,690 kr	11,555,264 kr	13,857,453 kr	15,957,236 kr
End-of-life cost (assumption, 41,447.50 kr)	2,823,691 kr	7,869,316 kr	11,587,090 kr	13,946,559 kr	16,102,035 kr
New patients per year (70 patients)	1,974,179 kr	5,491,963 kr	8,065,223 kr	9,677,396 kr	11,146,508 kr

MFS= metastasis-free survival; OS= overall survival; PFS: progression-free survival; TTTD= time-to-treatment discontinuation

4. Conclusion

The aim of the analyses was to evaluate the incremental cost per patient and budget impact of apalutamide + ADT versus ADT alone for the treatment of men with high-risk nmCRPC from the Danish perspective. For that purpose, a partition survival model has been developed.

There is clear need for an effective treatment option for patients with nmCRPC that is able to delay progression, extend survival, maintain health-related quality of life of these patients. The model suggests that the incremental costs are 394,869 kr per patient treated with apalutamide + ADT instead of ADT alone.

The budget impact estimated over 5 years resulted in higher incremental costs for apalutamide + ADT compared to ADT alone, with 2,820,255 kr, 7,845,662 kr, 11,521,748 kr, 13,824,852 kr, and 15,923,583 kr in year 1, year 2, year 3, year 4 and year 5, respectively. The results of the economic analyses should be considered part of a broader assessment of apalutamide + ADT that does not solely focus on its higher incremental costs per patient versus ADT over a treatment sequence. The findings in this report should be assessed in parallel with the clinical benefit that apalutamide + ADT delivers to patients versus ADT.

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Appendix 1. SPARTAN Final analysis – Adjusted for crossover

In the base case analysis, the OS and TTTD of the SPARTAN ITT population (FA, CCO 01 February 2020 [14]) unadjusted for crossover was used. In a scenario analysis, the OS and TTTD adjusted for crossover were applied. The description of the OS and TTTD extrapolations adjusted for crossover is provided in the paragraphs below.

5.1.1 Overall survival FA

5.1.1.1 Proportional hazard assumption

Figure 17 and Figure 18 present the log-cumulative hazard plots and Schoenfeld plots of OS with crossover adjustment. The log-cumulative hazard plots show that the curves were relatively parallel over time but seemed to cross at multiple time points given the curves are very close to each other. Based on the Schoenfeld test, for OS adjusted for crossover, the Schoenfeld test p-value was not significant (p= 0.5478). As the PH assumption holds, and to make efficient use of the data, it was considered more appropriate to apply combinedly fitted models within the base case, using the ADT alone arm as the reference curve and the apalutamide + ADT arm as a covariate.

[redacted]

[redacted]

[redacted]

5.1.1.2 Combinedly fitted models

The goodness-of-fit statistics are presented in Table 26. The Weibull model has the best statistical fit; but the loglogistic model has very comparable fits (AIC/BIC scores lie within 5 points from the distribution with the lowest scores). The long-term projections are presented in Figure 19. The exponential, lognormal, and loglogistic curves are characterized by long, potentially infeasible tails for both the apalutamide + ADT arm and ADT arms.

[redacted]

[redacted]

[redacted]

[redacted]

5.1.2 Time to treatment discontinuation FA

Six parametric distributions were fitted on the FA apalutamide + ADT TTTD data from the SPARTAN trial [14] (Figure 20). Based on the statistical fit, if AIC and BIC are summed, the exponential distribution has the lowest AIC/BIC score and therefore is the best fitting model for apalutamide + ADT (Table 27).

[redacted]

[redacted]

[redacted]

Medicinrådet

Medicinrådets protokol for vurdering af apalutamid til behandling af højrisiko ikke-metastaserende kastrationsresistent prostatakræft

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

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

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

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

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

Om protokollen

Protokollen er grundlaget for Medicinrådets vurdering af et nyt lægemiddel. Den indeholder et eller flere kliniske spørgsmål, som den ansøgende virksomhed skal besvare i den endelige ansøgning, og som Medicinrådet skal basere sin vurdering på.

Lægemidlet vurderes efter Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser – version 2. Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	2. januar 2020
Ikrafttrædelsesdato	2. januar 2020
Dokumentnummer	64964
Versionsnummer	1.0

Fremkommer der nye og væsentlige oplysninger i sagen af betydning for protokollens indhold, kan Medicinrådet tage protokollen op til fornyet behandling. Det samme gælder, hvis der er begået væsentlige fejl i forbindelse med sagsbehandlingen vedrørende protokollen. Hvis Medicinrådet foretager ændringer i protokollen, vil ansøgende virksomhed få besked.

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
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1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	ERLEADA
Generisk navn	Apalutamid
Firma	Janssen-Cilag A/S
ATC-kode	L02BB05
Virkningsmekanisme	Apalutamid er et antiandrogen, som virker ved at hæmme signalering fra androgenreceptorer, hvorved aktiviteten af androgener blokeres. Apalutamid gives i kombination med androgen deprivationsbehandling (ADT).
Administration/dosis	Apalutamid er tilgængelig som 60 mg tabletter til oral brug. Apalutamid administreres som en daglig dosis á 240 mg (fire tabletter). Behandlingen fortsættes indtil første tegn på fjernmetastaser.
EMA-indikation	Apalutamid er indiceret til behandling af voksne mænd med ikke-metastatisk kastrationsresistent prostatacancer (nmCRPC), som har høj risiko for at udvikle metastatisk sygdom.

2 Forkortelser

ADT:	Androgen deprivationsterapi
AE:	Uønsket hændelse (*adverse event*)
CI:	Konfidensinterval
CRPC:	Kastrationsresistent prostatakræft
EMA:	*European Medicines Agency*
EPAR:	*European Public Assessment Report*
GRADE:	*Grading of Recommendations Assessment, Development and Evaluation System*
HR:	*Hazard ratio*
ITT:	*Intention-to-treat*
LHRH:	*Luteinising Hormone Releasing Hormone*
mCRPC:	Metastaserende kastrationsresistent prostatakræft
MFS:	Metastasefri overlevelse (*metastasis free survival*)
nmCRPC:	Ikke-metastaserende kastrationsresistent prostatakræft
OR:	*Odds ratio*
OS:	Samlet overlevelse (*overall survival*)
PCWG2:	*Prostate Cancer Working Group 2*
PSA:	Prostataspecifikt antigen
RECIST:	*Response Evaluation Criteria in Solid Tumors*
RR:	Relativ risiko
SRE:	Skeletrelateret hændelse (*skeletal-related event*)
TUR-P	Transurethral resektion af prostata

3 Formål

Protokollen har til formål at definere de kliniske spørgsmål, der ønskes belyst i vurderingen af apalutamid som mulig standardbehandling af patienter med højrisiko ikke-metastaserende kastrationsresistent prostatakræft (nmCRPC). I protokollen angives en definition af population(er), komparator(er) og effektmål, der skal præsenteres i den endelige ansøgning, samt de metoder der ønskes anvendt til den komparative analyse. Arbejdet med protokollen er igangsat på baggrund af den foreløbige ansøgning vedrørende apalutamid modtaget den 2. oktober 2019.

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

4 Baggrund

Prostatakræft er den hyppigste kræftform hos mænd i Danmark. Prostatakræft manifesterer sig især efter 60-års alderen [1]. I 2017 og i 2018 blev der registreret henholdsvis 4.362 og 4.620 nye sygdomstilfælde [1,2]. Ved udgangen af 2017 var antallet af mænd med prostatakræft i Danmark 40.116 [1]. I perioden 2014-2016 var overlevelsen 98 % efter 1 år og 88 % efter 5 år [3].

Patienter med prostatakræft, der endnu ikke har modtaget kastrationsbehandling (androgen deprivationsterapi (ADT)) eller responderer på behandling med ADT, kaldes kastrationssensitive. De fleste kastrationssensitive prostatakræfttilfælde vil over tid udvikle sig til kastrationsresistente. Kastrationsresistent prostatakræft (CRPC) defineres ved serum testosteron i kastrationsniveau (< 0,5 ng/mL eller 1,7 nmol/L) og progression enten biokemisk eller radiologisk [4]. Fagudvalget estimerer, at ca. 1.500 udvikler CRPC årligt [5].

Patienter med CRPC opdeles i to grupper i forhold til tilstedeværelse af metastaser. Ikke-metastaserende CRPC (nmCRPC) defineres som CRPC uden påviste fjernmetastaser. De fleste patienter med nmCRPC er asymptomatiske og har forholdsvis god livskvalitet. Sygdommen betegnes som højrisiko nmCRPC i de tilfælde, hvor fordoblingstiden af prostata specifikt antigen (PSA) er på 10 måneder eller mindre. PSA er en af de mest betydende faktorer for prognose før igangsættelse af behandling samt monitorering af behandlingseffekt. PSA-fordoblingstid på 10 måneder eller mindre er forbundet med en øget risiko for udvikling af metastaser [6]. Fagudvalget vurderer, at 100 patienter årligt vil være kandidater til behandling med apalutamid.

Median metastasefri overlevelse blandt mænd med højrisiko nmCRPC er mellem 16-18 måneder [6]. Fagudvalget estimerer, at medianoverlevelsen for patienter med højrisiko nmCRPC er ca. 3 år. Det anslås, at 5-års-overlevelsen er ca. 20 % [6].

4.1 Nuværende behandling

I udgangspunktet tilbydes patienter med højrisiko nmCRPC behandling med livsforlængende sigte. Patienterne behandles med ADT, enten ved bilateral orkiektomi (kirurgisk fjernelse af testikler) eller medicinsk kastration med Luteinising Hormone Releasing Hormone (LHRH)-analoger [4].

Der findes på nuværende tidspunkt ikke nogen anden standardbehandling til patienter med højrisiko nmCRPC, hvor eneste tegn på sygdomsprogression er stigende PSA-niveau uden radiologisk bevis for fjernmetastaser.

4.2 Apalutamid

Apalutamid er et antiandrogen, som virker ved at hæmme signalering fra androgenreceptorer, hvorved aktiviteten af androgener blokeres. Apalutamid gives i kombination med ADT. ADT virker ved at reducere androgenproduktionen i testiklerne, men påvirker ikke androgenproduktionen i binyrerne eller i tumoren i prostata, hvorfor testosteron stadig kan detekteres i serum. Behandling med apalutamid i kombination med ADT vil resultere i, at effekten af tilstedeværende androgener reduceres.

Apalutamid er godkendt af EMA som førstelinjebehandling i kombination med ADT til voksne patienter med højrisiko nmCRPC [7].

Apalutamid gives som 60 mg tabletter i en daglig dosis á 240 mg (fire tabletter). Behandlingen fortsættes indtil første tegn på fjernmetastaser. Apalutamid gives i kombination med ADT [7].

5 Kliniske spørgsmål

5.1 Klinisk spørgsmål 1

Hvad er værdien af apalutamid i kombination med androgen deprivationsterapi (ADT) sammenlignet med ADT alene til patienter med højrisiko ikke-metastaserende kastrationsresistent prostatakræft?

Population
Patienter med højrisiko ikke-metastaserende kastrationsresistent prostatakræft (nmCRPC). Højrisiko defineres som PSA-fordoblingstid på eller under 10 måneder.

Intervention
Apalutamid i kombination med ADT, jf. afsnit 4.2.

Komparator
ADT.

Effektmål
Tabel 1 summerer de valgte effektmål.

5.2 Valg af effektmål

Tabel 1 summerer de valgte effektmål, deres vigtighed, den retningsgivende mindste klinisk relevante forskel, en evt. justeret mindste klinisk relevant forskel og effektmålsgruppe. I forbindelse med justeringen af Medicinrådets metodehåndbog, som trådte i kraft pr. 1. januar 2019, vil absolutte effektforskelle fremover blive kategoriseret ud fra konfidensintervaller (tabel 3, side 29 i metodehåndbogen). Det er derfor nødvendigt at foretage en justering af den mindste klinisk relevante forskel. Den retningsgivende mindste klinisk relevante forskel er fremkommet på samme måde som under den gamle metode og afspejler den mindste forskel, fagudvalget vurderer, er klinisk relevant. Når lægemidlets værdi for det enkelte effektmål skal kategoriseres, vil grænsen for konfidensintervallet blive sammenholdt med den justerede mindste klinisk

relevante forskel. Den justerede værdi vil være det halve af den retningsgivende værdi i de tilfælde, hvor et konfidensinterval forventes at være tilgængeligt. Rationalet for denne tilgang er at sikre, at alle værdier i konfidensintervallet ligger tættere på den *retningsgivende MKRF* end på 'ingen forskel' (absolut effektforskel på 0). Eller sagt på en anden måde – alle de sandsynlige værdier for effekten er tættere på en klinisk relevant effekt end på 'ingen effekt'.

For alle effektmål ønskes både absolutte og relative værdier, jf. ansøgningsskemaet. Der ønskes både punktestimater og konfidensintervaller (for de absolutte værdier ønskes dog ikke konfidensintervaller, hvor metoderne til beregning af disse ikke er veldefinerede). For de absolutte værdier, hvor der kan beregnes konfidensintervaller efter veldefinerede metoder, vurderes den kliniske relevans (værdi), jf. tabel 3 i Medicinrådets håndbog for vurdering af nye lægemidler. For de relative værdier vurderes den kliniske relevans (værdi), jf. væsentlighedskriterierne beskrevet i Medicinrådets håndbog. De relative effektestimater skal angives i relativ risiko (RR) eller hazard ratio (HR). Hvis studierne resulterer i en odds ratio (OR), skal denne transformeres til relativ risiko, jf. appendiks 2 i Medicinrådets håndbog. Det skal begrundes i ansøgningen, hvis der afviges fra de ønskede effektmål.

Fagudvalget har i valg af effektmål og fastsættelse af MKRF taget udgangspunkt i Medicinrådets protokol for vurdering af enzalutamid til samme indikation [8].

Tabel 1. Oversigt over valgte effektmål. For hvert effektmål er angivet deres vigtighed. For kritiske og vigtige effektmål er desuden angivet den mindste klinisk relevante forskel (retningsgivende og evt. justeret) samt indplacering i de tre effektmålsgrupper ('dødelighed', 'livskvalitet, alvorlige symptomer og bivirkninger' og 'ikkealvorlige symptomer og bivirkninger').

Effektmål*	Vigtighed	Effektmålsgruppe	Måleenhed	Retningsgivende mindste klinisk relevante forskel	Justeret mindste klinisk relevante forskel
Samlet overlevelse (OS)	Kritisk	Dødelighed	Median OS i antal måneder	6 måneder	-
			OS-rate ved 3 år	5 %-point	2,5 %-point
Bivirkninger / uønskede hændelser (AE'er)	Kritisk	Livskvalitet samt alvorlige symptomer og bivirkninger	Andel patienter med grad 5 bivirkninger Derudover en kort beskrivelse af hændelserne	2 %-point	1 %-point
	Vigtig		Andel patienter med grad 3-4 AE'er	5 %-point	2,5 %-point
			Kvalitativ gennemgang af hændelsestyperne	Narrativ vurdering	-
Metastasefri overlevelse (MFS)	Vigtig	Livskvalitet samt alvorlige symptomer og bivirkninger	Median MFS i antal måneder	12 måneder	-
			MFS-rate ved 3 år	20 %-point	10 %-point
Skeletrelaterede hændelser (SRE'er)	Vigtig	Livskvalitet samt alvorlige symptomer og bivirkninger	Andel af patienter, der er fri for skeletrelaterede hændelser efter 3 år	5 %-point	2,5 %-point
Tid til kræftrelaterede procedurer	Vigtig	Livskvalitet samt alvorlige symptomer og bivirkninger	Median tid for udsættelse til kræftrelaterede procedurer	6 måneder	-
Livskvalitet målt ved FACT-P	Vigtig	Livskvalitet samt alvorlige symptomer og bivirkninger	Andelen af patienter, som oplever en ≥ 10 points reduktion fra	10 %-point	5 %-point

			baseline ved 2, 6, 12 og 24 måneder		

* For alle effektmål ønskes data med længst mulig opfølgningstid, med mindre anden grænse er indikeret.

Kritiske effektmål

Samlet overlevelse (OS)

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 kastrationsresistent prostatakræft er en dødelig sygdom. Fagudvalget estimerer, at medianoverlevelsen for den pågældende patientgruppe i den eksisterende behandling er 3 år, og det anslås, at 5-års-overlevelsen er ca. 20 % [6]. Fagudvalget vurderer derfor, at en forskel på 6 måneder i median OS og en forskel på 5 procentpoint i andelen af patienter, der er i live efter 3 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. Fagudvalget vil kun acceptere en lav forekomst af grad 5 bivirkninger i denne patientpopulation, da de i udgangspunktet er asymptomatiske, metastasefri og har lang forventet overlevelse. Den mindste klinisk relevante forskel er derfor sat til 2 procentpoint.

Vigtige effektmål

Uønskede hændelser (AE'er) 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 grad 3-4 uønskede hændelser (AE'er). Da der typisk er tale om asymptomatiske patienter, betragter fagudvalget selv få tilfælde af grad 3-4 AE'er som alvorlige. Fagudvalget vil derfor kun acceptere en lille forskel i forekomsten af grad 3-4 AE'er, og den mindste klinisk relevante forskel er sat til 5 procentpoint.

Fagudvalget ønsker derudover en kvalitativ gennemgang af hændelsestyperne for apalutamid 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 produktresuméet.

Metastasefri overlevelse (MFS)

Metastasefri overlevelse (MFS) anvendes til vurdering af sygdomsprogression. MFS defineres som tiden fra randomisering til radiologisk progression eller død uanset årsag. Radiologisk progression er defineret ved

forekomst af en eller flere knoglemetastaser bestemt ved knogleskanning [9] eller forekomst af bløddelsmetastaser bestemt ved CT- eller MR-skanning i henhold til Response Evaluation Criteria in Solid Tumors (RECIST) [10]. Enkelte undersøgelser indikerer, at der er en positiv korrelation mellem MFS og OS hos patienter med nmCRPC, men fagudvalget anser endnu ikke en sådan sammenhæng for veldokumenteret [11,12].

Fagudvalget betragter MFS som et vigtigt effektmål, da det belyser perioden under sygdomsforløbet, hvor sygdommen er i ro. Udvikling af metastaserende sygdom er forbundet med kræftrelaterede komplikationer og øget risiko for død. Median MFS blandt mænd med højrisiko nmCRPC er 16-18 måneder [6]. Fagudvalget vurderer, at den mindste klinisk relevante forskel for median MFS er 12 måneder. Herudover vurderer fagudvalget, at en absolut forskel på 20 procentpoint i MFS-rate ved 3 år sammenlignet med komparator er klinisk relevant.

Skeletrelaterede hændelser (SRE'er)

En skeletrelateret hændelse (SRE) er en selvstændig alvorlig begivenhed, som kan være relateret til knoglemetastaser. SRE'er defineres som patologiske frakturer, tværsnitssyndrom, behov for pallierende strålebehandling eller ortopædkirurgisk intervention. Effekt på udviklingen af SRE'er kan angives som en reduktion i antallet af patienter med SRE'er på et givet tidspunkt eller tiden fra randomisering til første SRE.

En stor del af de patienter, som dør af CRPC, vil have knoglemetastaser, hvilket kan resultere i, at patienten får SRE'er. Fagudvalget vurderer, at SRE'er er et vigtigt effektmål, da det er særligt invaliderende for patienten, påvirker patientens velbefindende betydeligt og er behandlings- eller indlæggelseskrævende. Fagudvalget ønsker derfor en opgørelse over andelen af patienter, der er fri for SRE'er efter 3 år og finder, at en forskel på 5 procentpoint er klinisk relevant.

Tid til kræftrelaterede procedurer

Kræftrelaterede procedurer defineres som pallierende indgreb imod tilstande forårsaget af lokoregional progression af sygdommen (transurethral resektion af prostata (TUR-P), nefrostomi/JJ-kateter, stomi, palliativ strålebehandling etc.). Tid til kræftrelaterede procedurer defineres som tiden fra randomisering til første kræftrelaterede procedurer.

Fagudvalget vurderer, at dette effektmål er vigtigt, idet det beskriver lokalvækst af prostata og er et udtryk for klinisk betydende sygdomsprogression, som har direkte indflydelse på patientens livskvalitet. Fagudvalget ønsker en opgørelse over median tid til kræftrelaterede procedurer og finder, at en median forskel på 6 måneder mellem intervention og komparator er klinisk relevant.

Livskvalitet

Fagvalget betragter livskvalitet som et vigtigt effektmål, idet behandling med apalutamid er livsforlængende og ikke-kurativ. De fleste nmCRPC-patienter er asymptomatiske og har forholdsvis god livskvalitet. Fagudvalget mener derfor, at det er vigtigt at sikre, at patienternes livskvalitet ikke påvirkes i negativ retning ved behandling med apalutamid. 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 [13]. 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 2, 6, 12 og 24 måneder baseret på Basch et al. 2013, som benytter en mere konservativ grænse [14]. Fagudvalget vurderer, at den mindste klinisk relevante forskel er 10 procentpoint.

6 Litteratursøgning

Vurderingen af klinisk værdi baseres som udgangspunkt på data fra peer-reviewede publicerede fuldtekstartikler og data fra EMAs EPAR – public assessment report(s). Data skal derudover stemme overens med protokollens beskrivelser.

Sekretariatet har på baggrund af den foreløbige ansøgning undersøgt, om der findes et eller flere peer-reviewede publicerede fuldtekstartikler, hvor apalutamid og ADT er sammenlignet direkte med ADT alene.

Sekretariatet fandt følgende artikler fra et relevant klinisk studie (SPARTAN), som kan anvendes til direkte sammenligning af samtlige definerede effektmål:

- Apalutamide Treatment and Metastasis-Free Survival in Prostate Cancer. Smith, M. et al. The New England Journal of Medicine, 2018.
- Effect of apalutamide on health-related quality of life in patients with non-metastatic castration-resistant prostate cancer: an analysis of the SPARTAN randomised, placebo-controlled, phase 3 trial. Saad, F. et al. Lancet Oncology, 2018.
- Apalutamide and overall survival in non-metastatic castration-resistant prostate cancer. Small, E. J. et al. Annals of Oncology. 2019.

Virksomheden skal derfor ikke søge efter yderligere studier. Dog skal EMAs European public assessment reports (EPAR) konsulteres for både det aktuelle lægemiddel og dets komparator(er).

7 Databehandling og analyse

De inkluderede studier og baselinekarakteristikken af studiepopulationerne beskrives i Medicinrådets ansøgningsskema. Det skal angives, hvilke studier der benyttes til at besvare hvilke kliniske spørgsmål.

Al relevant data skal som udgangspunkt ekstraheres ved brug af Medicinrådets ansøgningsskema. Der skal udføres en komparativ analyse for hvert enkelt effektmål på baggrund af relevant data fra inkluderede studier. For hvert effektmål og studie angives analysepopulation (f.eks. intention-to-treat (ITT), per-protocol) samt metode. Resultater for ITT-populationen skal angives, hvis muligt, hvis komparative analyser ikke i udgangspunktet er baseret på denne population. Alle ekstraherede data skal krydstjekkes med de resultater, der beskrives i EPAR'en. Findes uoverensstemmelser, gives en mulig grund herfor.

Hvis ekstraherede data afviger fra de forhåndsdefinerede PICO-beskrivelser, specielt i forhold til præspecificeret population og effektmål, begrundes dette.

Hvis data for et effektmål ikke er tilgængelige for alle deltagere i et studie, vil der ikke blive gjort forsøg på at erstatte manglende data med en meningsfuld værdi. Det vil sige, at alle analyser udelukkende baseres på tilgængelige data på individniveau.

For effektmål (ORR, SAE, behandlingsstop pga. bivirkninger og ikkealvorlige bivirkninger), hvor det er naturligt at beregne både absolut og relativ forskel, vil den relative forskel være basis for statistiske analyser. Den absolutte forskel vil derefter blive beregnet, baseret på den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen. Det antagne niveau vil afspejle det forventede niveau i Danmark ved behandling med komparator (hvis relativ risiko (RR) = 0,5 og antaget andel med hændelse i komparatorgruppen er 30 %, da er den absolutte risikoreduktion (ARR) = 30 – 30 x 0,5 = 15 %-point).

Hvis der er mere end ét sammenlignende studie, foretages en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt. Hvis der ikke foreligger sammenlignende studier, kan data eventuelt syntetiseres indirekte (evt. i form af formelle netværksmetaanalyser eller ved brug af Buchers metode), hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Medicinrådet forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans.

For effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, vil eventuelle metaanalyser blive baseret på standardized mean difference (SMD). Den estimerede SMD vil blive omregnet til den foretrukne skala for effektmålet. Til dette formål anvendes medianen af de observerede standardafvigelser i de inkluderede studier.

Hvis det ikke er en mulighed at udarbejde metaanalyser (herunder netværksmetaanalyser), syntetiseres data narrativt. Studie- og patientkarakteristika samt resultater fra de inkluderede studier beskrives narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er). Forskelle i patientkarakteristika og studiekontekst (f.eks. geografi og årstal) mellem studier skal beskrives og vurderes for at afgøre, hvorvidt resultaterne er sammenlignelige.

Valget af syntesemetode (metaanalyse eller narrativ beskrivelse) begrundes, og specifikke analysevalg truffet i forhold til metoden skal fremgå tydeligt.

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9 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende kræft i blærehalskirtlen

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10 Versionslog

Version	Dato	Ændring
1.0	2. januar 2020	Godkendt af Medicinrådet.