Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende apalutamid til metastatisk hormonfølsom kræft i blærehalskirtlen

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. apalutamid
2. Forhandlingsnotat fra Amgros vedr. apalutamid
3. Ansøgers endelige ansøgning vedr. apalutamid

Janssen-Cilag A/S

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29. August 2022

Til Medicinrådet

Hermed Janssen-Cilags tilbagemelding på Medicinrådets udkast til vurdering vedrørende apalutamid til behandling af metastatisk hormonfølsom kræft i blærehalskirtlen

Janssen imødeser Medicinrådets anbefaling vedr. behandling med apalutamid af metastatisk hormonfølson kræft i blærehalskirtlen (mHSPC), planlagt til den 28. september 2022, med nedenstående kommentarer in mente.

Validiteten af datagrundlaget

Janssens oprindelige ansøgning til Medicinrådet viste apalutamids effekt i den fulde mHSCP patientpopulation i overensstemmelse med EMA indikationen (OS HR:0.85 (95% CI 0.67-1.09) Apalutamid vs. Docetaxel; OS HR:0.71 (95% CI 0.56-0.9) Apalutamid vs. Strålebehandling). Medicinrådet anmodede imidlertid Janssen om en ny ansøgning, opdelt på sygdomsvolumen, hvor apalutamid sammenlignes med docetaxel for højvolumen patienter og strålebehandling for lavvolumen patienter. For at imødekomme Medicinrådet, udarbejdede Janssen en ny ansøgning og model, der baserer sig på den evidens, der foreligger på området.

Janssen stiller sig derfor undrende over, at Medicinrådet anfægter validiteten af det efterspurgte og accepterede datagrundlag. Medicinrådet skriver, at resultaterne af netværksmetanalysen (NMA) er "yderst tvivlsomme" begrundet med "forskelle i studiedesign, umodne data og uvished om, hvor sammenlignelige populationerne er, når de opdeles i forhold til sygdomsvolumen". Janssen anerkender de generelle metodiske usikkerheder, der er forbundet med enhver NMA, men er ikke enig i Medicinrådets samlede vurdering af datagrundlaget som yderst tvivlsomt. Janssens NMA er udarbejdet efter internationale anerkendte principper, beskrevet i bl.a. NICE's Decision Support Unit guidelines. I fraværet af et RCT, er en NMA den bedste metodik til at besvare Medicinrådets ønske til PICO. Alternativet ville være en unanchored MAIC analyse og tilhørende større confounding problematikker.
Janssen anerkender, at en NMA aldrig bliver bedre end de enkeltundersøgelser (N=400 til 1000 patienter), som den består af. Hvis Medicinrådet mener, at de fulde patientpopulationer er sammenlignelige, så har Janssen svært ved at forstå argumentationen for, hvorfor det skulle afvige væsentligt, når der opdeles i sygdomsvolumen. Den største trussel for NMA'ens validitet er effektmodifikatorer, hvor sygdomsvolumen må forventes at være den primære kandidat, hvilket der er taget højde for ved opdelingen af analysen i høj- og lavvolumen.

Janssen konstaterer ydermere, til perspektivering af kritikken, at Medicinrådet inden for ikke-metastaserende kastrationsresistent prostatakræft (nmCRPC) har ligestillet lægemidlerne apalutamid, darolutamid, enzalutamid, trods den usikkerhed, som er forbundet med en naiv indirekte sammenligning af studierne.

HR =1 og ekstrapolering af rPFS i højvolumen patienter

For højvolumen mHSPC viser resultaterne en HR på 0,95 (95% CI 0,72-1,26) for OS og 0,81 (95 % CI 0,61-1,10) for PFS, når apalutamid sammenlignes med docetaxel. Medicinrådet vurderer på denne baggrund, at der ikke er dokumenteret forskel på behandling med docetaxel og apalutamid, og vælger at ændre HR til 1 for både OS og PFS. Janssen stiller sig uforstående overfor denne forsimplede vurdering og tilgang.

Medicinrådet vurderer endvidere, at der ikke kan antages at være proportional hazard i estimaterne for rPFS mellem apalutamid + ADT og ADT alene for patienter med højvolumen mHSPC, og ændrer ekstrapoleringen til en gamma-fordeling. At p-værdien for testen er statistisk signifikant skyldes kunstige fald ved hver måling. I virkeligheden er rPFS opstået allerede før målingen. Hvis man kunne kontinuerligt observere rPFS (som ved OS), ville man se en mere jævn faldende kurve. Hazarden er således ikke 0 og PH antagelserne er valide, hvilket de visuelle plots understøtter (kurverne er nærmest parallelle). Janssen er således ikke enig med Medicinrådet i, at der er problemer med antagelsen om proportional hazards i TITAN-studiet og i at have anvendt en forkert tilgang til at ekstrapolere rPFS data for apalutamid + ADT for patienter med højvolumen mHSPC.

Apalutamids værdi til patienter med metastatisk hormonsensitiv prostatakræft

Det er velkendt, at de fleste patienter med mHSPC har gavn af maksimal anti-androgen behandling uanset sygdomsvolumen. Apalutamid er en veltolereret og velegnet behandling til patienter med mHSPC, med dokumentation for at forsinke sygdomsprogression, øge overlevelsen og ikke mindst bevare patientens livskvalitet under behandling. Det samme gælder ikke behandling med docetaxel, og for strålebehandling er det fortsat usikkert for denne patientgruppe.

Det er velkendt at docetaxel er en bivirkningstung behandling, hvor patientens livskvalitet nedsættes væsentligt op til, i hvert fald, 1 år efter behandlingsstart. Derfor værdsætter Janssen også, at Medicinrådet fremhæver, at behandling med apalutamid vil være bedre tolereret end behandling med docetaxel, med fokus på særligt febril neutropeni og kronisk neuropati.

Frekvensen af betydelige bivirkninger ved behandling med apalutamid og strålebehandling vurderes af Medicinrådet lav og sammenlignelig med placebo. Til dette gør Janssen opmærksom på, at der for strålebehandling foreligger meget lidt viden om mulige langtidsbivirkninger, herunder kroniske senfølger hos denne patientgruppe, og at der ikke foreligger studier inden for mHSPC af indvirkningen på livskvalitet. En patient i strålebehandling skal dagligt møde ind på et hospital og kan ikke varetage et normalt liv under behandlingens forløb.
Janssen vil gerne fremhæve, at strålebehandling er en højtspecialiseret og kompleks behandling, der involverer mange forskellige specialer og forberedelsestid hos de forskellige funktioner. Det er derfor relevant at inddrage forberedelsestid for flere kliniske specialer i omkostsningsanalysen. Janssen mener også, at det er lavt sat, når Medicinrådet sætter patienttiden til 15 minutter.

Endvidere bemærker Janssen at Medicinrådet har øget patientoptaget til 80% i år 1 og 95% fra år 2 for højvolumen patienter og et markedsoptag på 80% allerede fra år 1 og frem for

lavvolumen patienter, med afledte store budgetmæssige konsekvenser. Janssen værdsætter at Medicinrådet anerkender, at behandlingen forventes at være mere efterspurgt.

Prostatakræft er den 2. hyppigste kræftdødsårsag i Danmark og den hyppigste kræftform blandt danske mænd. Der er ingen kendt forebyggelse, og det er vanskeligt at diagnosticere i tidlige stadier.
Behandlingsvinduet bør holdes åbent i så lang tid som muligt. Ved at indføre apalutamid kan patienterne ved recidiv behandles med kemoterapi, strålebehandling og abiraterone og derved opretholdes et åbent behandlingsvindue.

Med ovenstående kommentarer in mente ser vi frem til en afgørelse den 28. september, så vi sammen kan sikre, at der også kan tilbydes apalutamid til patienter med mHSPC i Danmark.

Janssen takker Medicinrådets sekretariat for en konstruktiv dialog i processen.

Med venlig hilsen

Madina Saidj
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01.09.2022

DBS, SNI

Forhandlingsnotat

Dato for behandling i Medicinrådet	28.09.2022
Leverandør	Janssen-Cilag A/S
Lægemiddel	Erleada (apalutamid)
Ansøgt indikation	Metastatisk hormonfølsom prostatakræft

Forhandlingsresultat

Amgros har opnået følgende betinget pris på Erleada (apalutamid):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP	Nuværende SAIP	Forhandlet SAIP	Rabatprocent ift. AIP
Erleada (Apalutamid)	60 mg	112 stk.	21.810,60 kr.	[redacted]	[redacted]	[redacted]

Prisen vil være gældende fra 01.11.2022 såfremt indikationen anbefales fuldt eller delvist.

Prisen er betinget af en godkendelse en fuld eller en delvis anbefaling til en af populationerne, som fx alle lavvolume patienterne og/eller alle lav- og højvolume patienter, der ikke kan tåle docetaxel.

Erleada (Apalutamid) er allerede anbefalet til ikke-metastaserende kastrationsresistent prostatakræft og indgår i Medicinrådets kliniske sammenligningsgrundlag af lægemidler til denne indikation. Disse er Erleada (apalutamid), Nubega (darolutamid) og Xtandi (enzalutamid).

Der er aktuelt en prisreguleringsmekanisme i gang pga. patentudløb på Zytiga (abirateron), som påvirker ovenstående lægemidler og derfor får leverandørerne mulighed for at byde ind med nye priser. De eventuelle nye priser som følge af prisreguleringsmekanismen vil Amgros kende 30.09.2022 og vil være gældende fra 01.11.2022 - 31.03.2023, hvorefter der vil komme en ny aftale baseret på et udbud for alle lægemidlerne pr. 01.04.2023 med mulighed for forlængelse indtil 31.03.2025.

Konkurrencesituationen

Udover Erleada (apalutamid) har medicinrådet i juni 2021 modtaget en anmodning om vurdering af Xtandi (enzalutamid) til indikationen metastatisk hormonfølsom prostatakræft.

Nedenstående priser er medtaget for at vise den nuværende konkurrencesituation blandt indikationen ikke-metastaserende prostatakræft, som med den aktuelle prisreguleringsmekanisme kan få betydning for markedsandelen for Erleada (apalutamid).

Tabel 2: Sammenligning af lægemiddelpriser

Lægemiddel	Styrke/dosis/form	Pakningsstørrelse	Pakningspris SAIP (DKK)	Antal pakninger/år	Årlig lægemiddelpris SAIP pr. år (DKK)
Erleada (apalutamid)	60 mg / tablet *240 mg én gang dagligt*	112 stk.	[redacted]	13,04	[redacted]
Nubega (darolutamid)	300 mg / tablet *600 mg to gange dagligt*	112 stk.	[redacted]	13,04	[redacted]
Xtandi (enzalutamid)	40 mg / tablet *160 mg én gang dagligt*	112 stk.	[redacted]	13,04	[redacted]
Zytiga (abirateron acetat)	500 mg / tablet *1000 mg én gang dagligt*	56 stk.	[redacted]	13,04	[redacted]
Docetaxel "Kabi"*	80 mg / IV *75 mg/m2 hver 3. uge i 6 serier*	4 ml	[redacted]	30,54	[redacted]

*Ved gennemsnitligt BSA på 1,81 m^2 **Pris for behandling hver 3. uge i 6 serier.

** Her er mulighed for nye priser ifm prisreguleringen samt patentudløbet på abiratone.

Status fra andre lande

Norge: Erleada (apalutamid) i kombination med androgen deprivationsbehandling er indført til behandling af metastatisk hormonfølsom prostatakræft som ikke er kandidater til kemoterapi[1]
Sverige: Godkendt til hele populationen (høj/lav volumen)[2]

[1] https://nyemetoder.no/metoder/apalutamid-erleada-indikasjon-ii
[2] https://janusinfo.se/nationelltinforandeavlakemedel/avtal.4.728c0e316219da813569b23.html

England: Godkendt til behandling af metastatisk hormonfølsom prostatakræft hos voksne, der ikke er kandidater til docetaxel[3]

Konklusion

Det er ikke muligt at få en bedre pris på dette lægemiddel i denne omgang. Tilbagemeldingerne fra alle firmaerne på disse indikationer er at prisniveauet i Danmark er utroligt lavt sammenlignet med de andre lande i Europa og derfor er det meget svært for leverandørerne at få tilladelse til at give ekstra rabat.

[3] https://www.nice.org.uk/guidance/ta741/chapter/1-Recommendations

Application for the assessment of Erleada for metastatic hormone sensitive prostate cancer

Instructions for companies

This is the template for submission of evidence to the Danish Medicines Council (DMC) as part of the appraisal process for a new pharmaceutical or new indication for an existing pharmaceutical. The template is not exhaustive; companies must adhere to the current version of the guidelines alongside using this template when preparing their submission.

Headings and subheadings are not to be removed. Additional subheadings can be added when appropriate. All sections in the template must be filled in. If a section is not applicable, state "not applicable" and explain why. Examples of texts and tables are provided in the template. These can be edited or removed. The company can provide different table layouts to accommodate data, as long as the required information is provided.
The submission should be as brief and informative as possible. The main body of submission must not be longer than 100 pages, excluding the appendices. Submissions in Danish and English are accepted.

In addition to this template, the company must submit a health economic model in Excel, with full access to the programming code. All the information requested in this template and described in the guidelines must be presented in the application. The model can be accompanied by a technical document. The information in the technical document will, however, not be considered as part of the application. Hence, all relevant information for the application must also be described in the application (including appendices) itself. This can be done by copying the relevant information from the technical document into the application, and by presenting it as described in this template and in the guidelines. Companies are encouraged to provide the European Public Assessment Report (EPAR) including the scientific discussion as an appendix to the submission (draft versions will be accepted).
When making an evidence submission, companies must ensure that all confidential information is highlighted in yellow and provide the expected date of publication. If confidential appendices are provided, these must be watermarked as "confidential".

Version 1.0

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Information marked with yellow represents confidential information. For appendix G and J, the title of the appendix is marked with a yellow color, but the full appendix is considered confidential.

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1. Basic information

Contact information	
Name	**Madina Saidj**
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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 (AR) 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 metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT)
Other approved therapeutic indications	Adult men for the treatment of non-metastatic castration-resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease.

Overview of the pharmaceutical	
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

Abbreviation	Definition
ADT	androgen-deprivation therapy
AE	adverse event
AR	androgen receptor
BICR	blinded independent central review
BSA	body surface area
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CRPC	castration resistant prostate cancer
CSPC	castration sensitive prostate cancer (see also HSPC)
CT	computed tomography
EBRT	external beam radiation therapy
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC-QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D	EuroQol five dimensions questionnaire
EWB	emotional well-being
FACT-G/P	Functional Assessment of Cancer Therapy - General/Prostate
FDA	US Food and Drug Administration
FWB	functional well-being
HR	hazard ratio
HRQoL	Health-Related Quality of Life
HSPC	hormone sensitive prostate cancer (see also CSPC)
HVD	high volume disease
ITT	intent-to-treat
LVD	low volume disease
mCRPC	metastatic castration resistant prostate cancer
MD	physician
MRU	medical resource utilisation

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nmCRPC	non-metastatic castration resistant prostate cancer
OS	overall survival
PCWG	Prostate Cancer Working Group
PFS	progression-free survival
PFS2	progression-free survival with the first subsequent therapy
PRO	patient-reported outcome
PSA	prostate-specific antigen
PSADT	prostate-specific antigen doubling time
PWB	physical well-being
rPFS	radiographic progression free survival
SE	standard error
SFWB	Social and family well-being
SRE	skeletal-related event
TOI	trial outcome index
US	United States
VAS	Visual Analogue Scale

3. Tables and Figures

Tables

[redacted]

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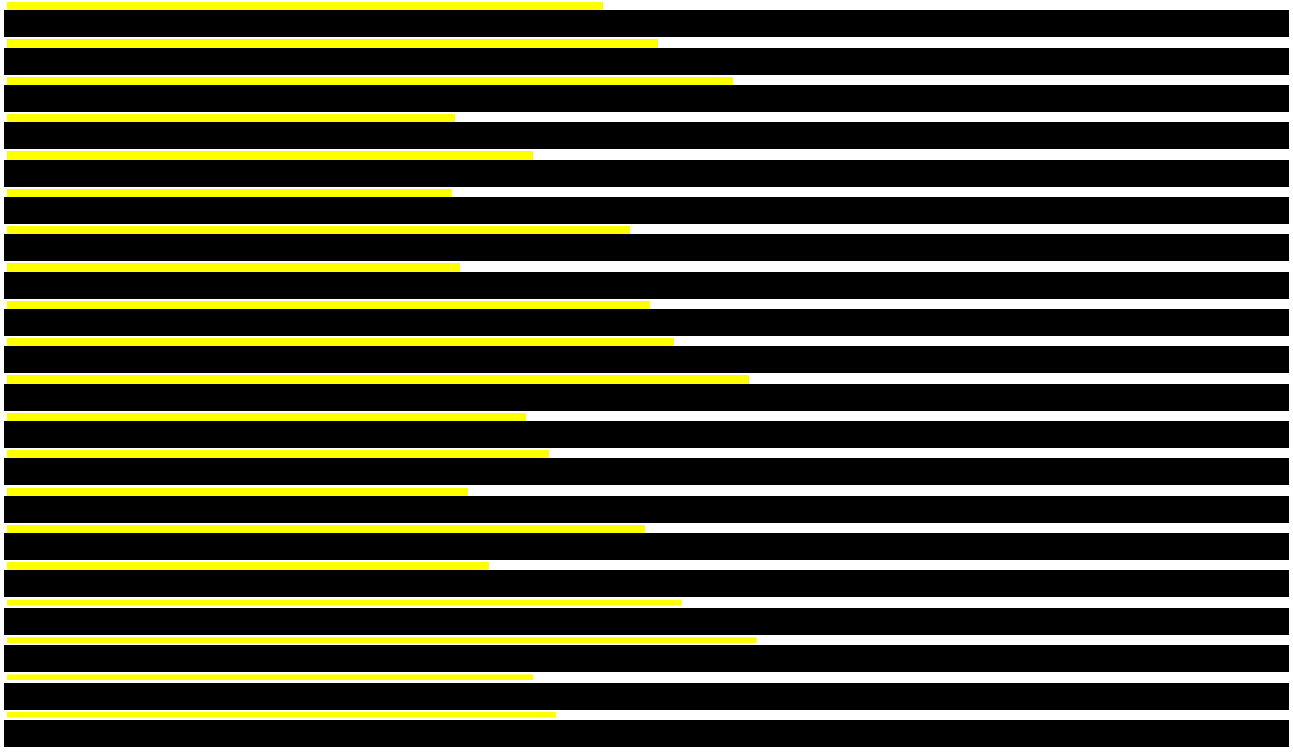

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Figures

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4. Summary

This submission presents efficacy and safety of Erleada (apalutamide) for adult men with metastatic hormone sensitive prostate cancer (mHSPC).

Upon Janssens initial submission based on the full population, DMC has requested Janssen to submit data separately for patients with high volume disease (HVD) and low volume disease (LVD), comparing apalutamide to docetaxel (DOC) + androgen deprivation therapy (ADT), and radiation therapy (RT) + ADT, respectively. Janssen has sought to

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accommodate the DMC request in this application version 2, though the evidence is less certain and the available data more sparse than for the total population, as these subgroup analyses were not powered for statistical significance.

Janssen request DMC to consider Erleada for reimbursement for the full mHSPC population. Apalutamide is already approved for reimbursement in Denmark for non-metastatic castration resistant prostate cancer (DMC recommendation January 21, 2021).

Patient population
The mHSPC patient population is heterogeneous, and its management can be complex. The population includes men with metastasis at the time of prostate cancer diagnosis (newly diagnosed/ND) and men diagnosed with local prostate cancer and a later development of metastasis. Metastases are the primary source of morbidity and mortality in patients with prostate cancer. Hence, all patients with mHSPC are living with a serious and life-threatening disease and are in urgent need of treatment. Based on the number of visceral metastases and/or bone metastases, patients are categorized as having either high (HVD) or low volume disease (LVD). In Denmark approximately 500 men are diagnosed with mHSPC yearly, including both HVD + LVD patients.

Intervention
Erleada is an oral second generation non-steroidal anti-androgen with the approved indication: "treatment of mHSPC in combination with ADT". This means, Erleada is approved for treatment in all men with mHSPC, irrespective of high or low volume disease, both newly diagnosed as well as those progressing from localized disease.

The goal of treatment in mHSPC is to delay disease progression and thereby prolong survival and maintain health-related quality of life (HRQoL) by delaying debilitating symptoms. Apalutamide represses the expression of genes crucial for prostate tumor viability and growth and consequently inhibits tumor progression. Apalutamide has an immediate, meaningful and durable impact on PSA levels when used in combination with ADT in patients with mHSPC. Dosing of apalutamide is 240mg (4x 60mg tablets) taken orally once daily. Treatment continues until progression or death.

Comparators
According to current Danish clinical guidelines from DAPROCA, mHSPC patients with HVD can receive treatment with DOC+ADT, while patients with LVD can receive treatment with RT+ADT. Hence apalutamide will be compared to these treatment options, as specifically requested by DMC.

Outcomes
Although most patients with mHSPC initially respond to ADT, most patients will develop progressive disease that is resistant to further hormone manipulation (metastatic castration resistant prostate cancer [mCRPC]) within 10–24 months of being diagnosed with mHSPC. By introducing apalutamide into the prostate cancer treatment pathway early, patients benefit by prolonged survival.

This submission includes the following main efficacy outcomes: overall survival (OS), (radiographic) progression free survival ((r)PFS) and time to prostate specific antigen (PSA) progression; Quality of Life (QoL) and the following safety outcomes: adverse events (AEs) of any grade, treatment discontinuations due to AEs and serious AEs (SAEs).

Methods

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As there exists no direct comparisons between APA+ADT and comparators, indirect comparisons are applied. A network meta analyses (NMA) was performed for available efficacy endpoints based on trials identified in a systematic literature review (SLR).
Four trials (CHAARTED, GETUG-AFU15, HORRAD and STAMPEDE15) were identified for inclusion in the NMA alongside the TITAN trial. The NMA evaluated the relative efficacy of APA + ADT, DOC + ADT (with or without prednisone/prednisolone), radiotherapy + ADT and ADT alone based on the available data from the identified trials. To ensure a homogeneous comparison, data-cut closest possible to TITAN was selected for the analyses.
Due to limited available safety data for the comparisons an NMA was not feasible, hence available safety data from the trials and SmPC are reported in a narrative manner.

Results
NMA results show that combination treatments all offered an advantage over ADT alone in terms of improved OS, rPFS, and time to PSA progression outcomes. Treatment with APA + ADT resulted in the best outcomes for all efficacy analyses. Treatment is efficacious in all patients, irrespective of high or low volume disease. No analysis was possible on time to next skeletal-related event endpoint due to data limitations.

In terms of safety, the available data for comparison is limited. Results from TITAN show that APA + ADT is well tolerated and associated with a manageable safety profile. The safety/tolerability profile of APA + ADT in patients with mHSPC is consistent with the results of the SPARTAN study in nonmetastatic castration-resistant prostate cancer (nmCRPC).

Health economy
In this application version 2.0 two separate cost-effectiveness models (CEM) have been developed in Microsoft Excel®: one to assess the cost-effectiveness of APA+ADT vs DOC+ADT for the treatment of mHSPC HVD, and one to assess the cost-effectiveness of APA+ADT vs. RT+ADT for the treatment of mHSPC LVD. Separate models for HVD and LVD was chosen as the best approach, as it would otherwise be necessary to re-run the analysis when altering between subgroups. The model structure is the same.

The CEM models captures the associated costs, quality of life, and treatment effects on disease stages recognized in clinical practice (including mHSPC and mCRPC), whilst maintaining a simple, easy-to-understand structure. For these reasons, the models uses a partitioned survival analysis approach to estimate the time in each state. Furthermore, partitioned survival models (PSM) represent the standard and well-accepted approach for oncology models for health technology assessment (HTA)/payer submissions.
The models considers three health states: rPFS, post-progression survival (PPS), and death. Patients who are eligible for treatment enter the model, initiate frontline treatment, and experience an interval of rPFS. Within the rPFS health state, patients were further partitioned according to whether they were on- and off-treatment to more accurately estimate treatment costs.
Patients who experience disease progression and do not die during frontline treatment continue to the mCRPC/post-progression setting. Within the mCRPC setting, patients could receive subsequent treatment.
The analysis take a restricted societal perspective, using the best available clinical and economic evidence. Local Danish data inputs are used when available. The model is based on results from TITAN and the NMA results.

For low volume disease the base case analysis showed that APA+ADT yielded better survival outcomes and was associated with more LYs and QALYs vs. RT+ADT. Incremental QALYs for APA+ADT vs. RT+ADT +0.66 and incremental LYs +0.85. Based on list prices the ICER for APA+ADT vs. RT+ADT was 937,482 DKK/QALY. The budget impact results of recommending APA+ADT for low volume disease range from 4,922,569 DKK in year 1 to 64,609,853 DKK in year 5.

For high volume disease the base case analysis showed that APA+ADT yielded better survival outcomes and was associated with more LYs and QALYs vs. DOC+ADT. Incremental QALYs for APA+ADT vs. DOC+ADT +0.19 and incremental LYs +0.20. Based on list prices the ICER for APA+ADT vs. DOC+ADT was 2,170,696 DKK/QALY. The budget impact results of recommending APA+ADT for low volume disease range from 8,910,790 DKK in year 1 to 68,429,399 DKK in year 5.

Discussion

Apalutamide is efficacious in all patients with mHSPC and is well tolerated. Apalutamide fulfills an unmet medical need as it delays progression to metastases, extends time to symptomatic progression and allows patients to maintain their quality of life at a level similar to the general population. By introducing apalutamide into the prostate cancer treatment pathway early, patients benefit of an additional treatment option improving their chances of survival while retaining additional treatment options for the metastatic CRPC disease stage.

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

5.1 The medical condition and patient population

Prostate cancer is the most common form of cancer among men in Denmark, and it can be divided in three categories: localized, locally advanced and metastatic. Furthermore, metastatic prostate cancer can be divided into low and high volume disease depending on spread and localization of the metastases:

- **High volume disease**: Visceral metastases AND/OR bone metastases (at least 4 or more bone lesions one of which must be outside the vertebral column or pelvis
- **Low volume disease**: Patients who do not have high volume disease

Patients with metastatic prostate cancer who have yet to receive androgen-deprivation therapy (ADT) or who respond to ADT are referred to as hormone/castration sensitive (mHSPC or mCSPC, the terms are used interchangeably) and most of these prostate cancer patients will eventually progress to castration resistant prostate cancer (mCRPC). As patients progress and develop castration resistance, they experience further disease-related symptoms which are associated with a considerable emotional burden and lead to a decline in HRQoL and poor prognosis (1–3). While, on average, HRQoL in the mHSPC stage may be comparable to the general population, progression to mCRPC is associated with the development of a range of physical and mental health issues (2,4).
The development of castration resistance affects the survival prognosis in patients with prostate cancer. Deferring treatment of metastatic prostate cancer increases the risk of developing debilitating symptoms and complications (5). A randomized study conducted by the Medical Research Council compared the effect of immediate versus deferred treatment for advanced prostate cancer (5). Of 261 patients with metastatic prostate cancer included in the study (hormone sensitivity not reported), 130 received immediate treatment with orchiectomy or an LHRH analogue, while treatment was deferred in 131 patients until an indication for treatment had occurred (e.g. disease progression, complications, patient preference). Pathological fracture, spinal cord compression, ureteric obstruction and development of extra-skeletal metastases were more common in patients receiving deferred treatment, compared with those who received immediate treatment. Additionally, patients whose treatment was deferred developed metastatic pain faster than those who received immediate treatment (5).

Despite suffering from metastatic disease, patients with mHSPC often have low levels of symptomatology. Therefore, delaying progression to mCRPC for as long as possible is a key goal of treatment in order to maintain quality of life and

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prevent complications. Furthermore, progression to mCRPC is associated with a substantial increase in healthcare costs and medical resource use compared with mHSPC, including increased number of hospitalisations and outpatient prescriptions (6).

Patient population

In 2019 4.449 new cases of prostate cancer was registered in Denmark at an incidence of 194/100.000 and the prevalence was approximately 40.00 (7). At the time of diagnosis most patients present as non-metastatic, however a proportion of the patients will have metastatic disease at diagnosis (8). In a Danish context the incidence has been estimated to approximately 10-15% or about 500 patients per year and this includes both high and low volume mHSPC (7,9). In support of this assumption, a Danish registry study of 47,024 prostate cancer cases diagnosed between 1995 and 2011 reported that 6,874 patients in the cohort had metastatic disease at diagnosis. The study showed that between 1995 and 2011 the proportion of patients with newly diagnosed mHSPC in the cohort decreased from 20.3% to 11.3% (10). There is unfortunately no recorded prevalence data for mHSPC in Denmark. A recent review of real-world prevalence of mHSPC also found no studies reporting reliable data (11). The prevalence estimates presented in Table 1 are rough and uncertain estimates based on available data from NORDCAN (https://www-dep.iarc.fr/nordcan/dk/frame.asp).

Table 1: Incidence and prevalence of patients with mHSPC in the past 5 years (7)

Year	2017	2018	2019	2020	2021
Incidence in Denmark*	496 HVD: 298 LVD: 198	575 HVD: 345 LVD: 230	629 HVD: 377 LVD: 252	578 HVD: 347 LVD: 231	NR
Prevalence in Denmark¤	4471	4777	5427	5197	NR

*based on DAPROCA data (7) ¤ these are estimates based on available data from NORDCAN. HVD = high volume disease; LVD = low volume disease. HVD and LVD estimates based on assumption that approximately 60% patients have HVD and 40% patients have LVD. NR = not reported

Table 2: Estimated number of patients eligible for treatment

Year	2022	2023	2024	2025	2026
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years	500 HVD: 300 LVD: 200	500 HVD: 300 LVD: 200	500 HVD: 300 LVD: 200	500 HVD: 300 LVD: 200	500 HVD: 300 LVD: 200

Estimates in table 2 are based on assumptions from DMC expert committee (9) .

5.1.1 Patient populations relevant for this application

All adult men (≥18 years) with mHSPC in subgroups of high and low volume disease, as requested by DMC.

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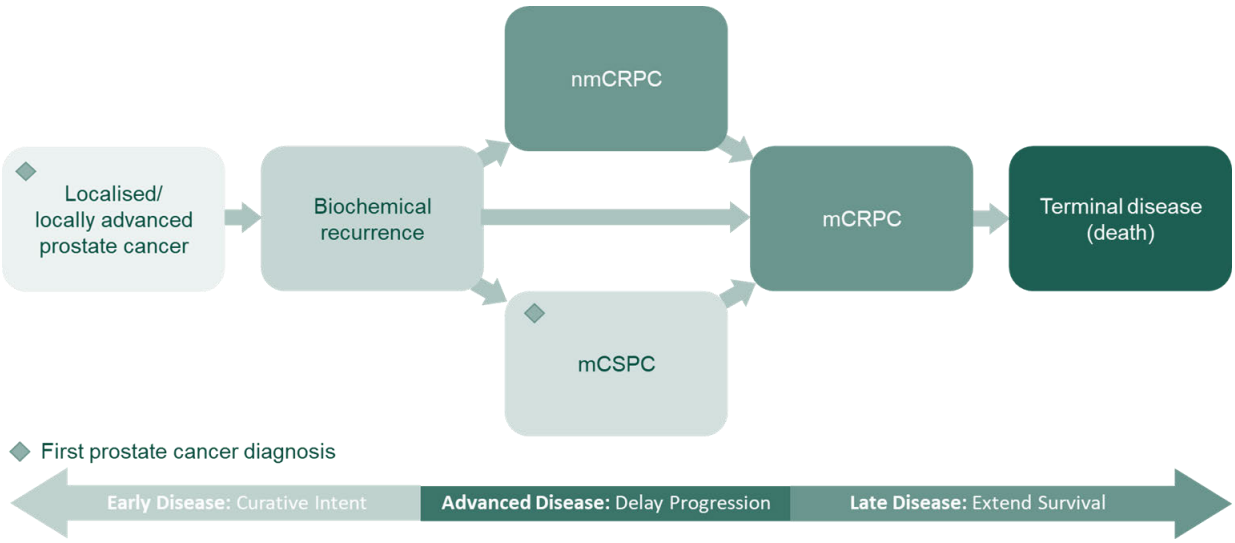
5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

When prostate cancer is detected early and is still confined within the prostate, eligible patients are initially treated with curative intent by surgery (radical prostatectomy) or radiation (12,13). For many patients, treatment with curative intent results in a cure or delays disease progression so that no further treatment is required. However, between 27% to 53% of patients develop recurrent disease, identified as rising prostate specific antigen (PSA) levels after primary treatment (termed biochemical recurrence) (12). Many men facing biochemical recurrence receive androgen deprivation therapy (ADT) in the form of surgical or medical castration (13). The majority of men treated for recurrent prostate cancer stop responding to ADT and, sooner or later, become castration resistant (13–15). Patients progress to metastatic hormone sensitive prostate cancer (mHSPC) or non-metastatic castrate-resistant prostate cancer (nmCRPC) and eventually mCRPC (Figure 1). The mainstay of treatment of mHSPC has been to achieve castrate levels of testosterone by surgical means, such as bilateral orchidectomies, or by medical castration with androgen deprivation therapy (ADT), such as gonadotropin-releasing hormone (GnRH) analogues. ADT decreases testicular production of testosterone (accounting for 90–95% of androgen production) by its effects on the hypothalamic–pituitary axis. The most widely employed strategy is continuous treatment with a GnRH agonist, which suppresses luteinizing hormone production and therefore the synthesis of testicular androgens. Unfortunately, mHSPC treated with ADT often transitions into a metastatic castrate-resistant state (mCRPC), defined by disease progression despite ADT with castrate testosterone levels. This may present in a variety of ways, including a continuous rise in serum prostate specific antigen (PSA) levels, progression of pre-existing disease and/or appearance of new metastatic deposits (16).

Figure 1: Prostate cancer disease progression



mCRPC = metastatic castration-resistant prostate cancer; mCSPC = metastatic castration-sensitive prostate cancer (equivalent to mHSPC = metastatic hormone-sensitive prostate cancer); nmCRPC = non-metastatic castration-resistant prostate cancer

Current treatment guidance in Denmark for mHSPC should be given by RADS guidance from 28. September 2016 "*Tidlig kemoterapi til patienter som påbegynder kastrationsbehandling for metastaserende prostatacancer – Tillæg til Baggrundsnotat for medicinsk behandling af metastaserende kastrationsreistent prostatacancer, mCRPC*" (15).

The RADS recommendation divides the mHSPC group in two subpopulations.

- Patients with high volume disease, defined as: At least 4 bone metastases, of which at least one should be outside the spine and pelvis or by visceral metastasis.
- Patients with low volume disease, defined as: Less than 4 bone metastases and no visceral metastases.

As standard treatment RADS guideline is recommending use of docetaxel in combination with ADT in both groups.

However Danish clinical guidelines from DaPROCA (18) are more recent and these recommend that patients with *low volume mHSPC* should be offered local radiation treatment, normally 60 GY over 20 fractions in 4 weeks, in combination with ADT. Only patients with high volume mHSPC should be offered docetaxel, in combination with ADT.

Treatment with docetaxel is associated with severe adverse events and reductions in health-related quality of life and is therefore not suitable for all patients due to their eligibility, fitness and/or treatment preference. Patients ineligible for treatment with docetaxel, can be treated with abiraterone acetate (DMC recommendation June 2018) (18).

While radiotherapy itself is painless it is associated with a number of side effects, such as fatigue and tiredness, as well as 'radiation disease' which includes urinary, bowel, erection and fertility problems. No recommendations regarding patients ineligible for radiation therapy exists (18), but in clinical practice radiation therapy is generally not recommended by doctors in patients with metastases in lymph nodes, patients prior RT treatment, ECOG score >2, patients with high pelvis tumor burden.

5.2.2 Choice of comparator(s)

As requested by DMC the selected comparators for this application are:

Docetaxel (DOC) in combination with ADT. Docetaxel has been used in clinical practice for an extended period and assessed to be an established treatment option in Danish clinical practice for patients with high volume disease (HVD).

Radiotherapy (RT) in combination with ADT. Radiotherapy is a localized treatment used to deliver ionizing radiation to the location of the cancer. It has traditionally been considered a palliative treatment for patients with metastatic prostate cancer, recommended by guidelines for symptom control only. In Danish clinical practice it is considered an established treatment option for patients with low volume disease (LVD).

DMC has in the 2nd validation round asked for justification for not comparing to placebo: As explained in 5.2.1, with reference to DAPROPA guidelines, and as the DMC expert committee has described in an earlier protocol for this assessment (9), treatment with DOC and RT are considered as the established standard Danish treatment practices.

5.2.3 Description of docetaxel, DOC

- **Generic name(s) (ATC-code):** Docetaxel (L01CD02)
- **Mode of action:** Docetaxel is a cytotoxic agent, and the main mode of therapeutic action is the suppression of microtubule dynamic assembly and disassembly. Microtubules play a crucial role in mitotic spindle assembly, the mitotic checkpoint, and chromosome movement. As microtubules do not disassemble in the presence of docetaxel, they accumulate inside the cell which induces apoptosis. Additionally, docetaxel cause apoptosis by blocking of the apoptosis-blocking bcl-2 oncoprotein.
- **Pharmaceutical form:** Concentrate and solvent for solution for infusion. The concentrate is a clear viscous, yellow to brown-yellow solution. The solvent is a colorless solution.

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- **Posology:** The recommended dose of docetaxel is 75 mg/m^2 every 3 weeks for 6 cycles.
- **Method of administration:** Docetaxel is administered as a one-hour infusion every three weeks.
- **Dosing**: 75 mg/m^2 every 3 weeks for 6 cycles
- **Should the pharmaceutical be administered with other medicines?** Prednisone or prednisolone 5 mg orally twice daily may be administered continuously. For mHSPC patients docetaxel is used in combination with ADT, most commonly Luteinizing Hormone Releasing Hormone (LHRH) analogues.
- **Treatment duration/criteria for end of treatment:** 6 cycles is the recommended duration.
- **Necessary monitoring, both during administration and during the treatment period.** There are several situations were monitoring is relevant listed in the product information. For example, since neutropenia is the most common adverse reaction of docetaxel, frequent monitoring of complete blood counts should be conducted on all patients. For a complete overview we refer to section 4.4 of the product information (19).

5.2.4 Description of radiotherapy, RT

Template adjusted to reflect comparator

- **Mode of action:** External beam radiotherapy (EBRT) is a commonly used type of RT for prostate cancer. EBRT involves directing high-energy external X-ray beams at the prostate gland to destroy the cancerous cells in the area. Brachytherapy is another type of RT that involves implanting radioactive seeds into the prostate, thereby delivering radiation internally. In Denmark Brachytherapy is the main RT option. RT treatment is in Denmark given in accordance with STAMPEDE RT protocol.
- **Dosing and treatment duration**: RT involves the delivery of 1 fraction, 3 Gy per fraction, during 20 days. 4 x5 day regime (Mon-Fri). Amounting to total dose of 60 GY.
- **Should RT be administered with other medicines?** RT treatment is given in combination with ADT, most commonly Luteinizing Hormone Releasing Hormone (LHRH) analogues.
- **Necessary monitoring, during administration, during the treatment period, and after the end of treatment**? RT is given in hospital and requires multiple visits to the hospital per week. Patients usually have to arrive at the treatment with an empty bowel and bladder, or receive an enema or suppository on site, which may cause discomfort in preparation for the treatment. While the treatment itself is painless it is associated with a number of side effects, such as fatigue and tiredness, as well as 'radiation disease' which includes urinary, bowel, erection and fertility problems.

5.2.5 Description of ADT

Template adjusted to reflect comparator

In Denmark several ADT medicines are on the market. LHRH agonists, hormone treatment suppressing production of testosterone, are injected or placed as small implants under the skin. Some known LHRH agonists available in Denmark are goserelin, triptorelin and leuprorelin. Depending on drug used they are given anywhere from once a month to once a year.
Anti-androgens are taken as pills and works by binding to an androgen receptor (protein in the prostate cell) so that androgens cannot work. Anti-androgen treatment is usually added to treatment if patients are progressing after orchiectomy or while on LHRH agonist or antagonist therapy. Anti-androgens are also given initially to mHSPC before starting LHRH agonist to prevent a tumor flare.
ADT treatment is recommended to continue after castration resistance is developed and is considered a

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life-long treatment. ADT treatment options included in the model is goserelin, leuprorelin, triptorelin and bicalutamide (each 25% market share). Treatment with ADT is lifelong.

There is currently no treatment guideline for ADT. The existing RADS guideline is outdated and therefore cancelled (https://medicinraadet.dk/anbefalinger-og-vejledninger/laegemiddelrekommandationer/kraeftsygdomme/prostatakraeft/prostatakraeft-3-2-rads).

5.3 The intervention (Erleada)

- **Dosing:** The recommended dose is 240 mg (four 60 mg tablets).
- **Method of administration**: Oral single daily dose.
- **Treatment duration/criteria for treatment discontinuation:** Treat to progression.
- **Should the pharmaceutical be administered with other medicines?** ADT
- **Need for diagnostics or other tests**? No

EMA indications for Erleada are “in adult men for the treatment of non-metastatic castration resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease”, and relevant to this submission: “in adult men for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT)”.

Erleada is EMA approved for all men with mHSPC, irrespective of high or low volume disease, both newly diagnosed as well as those progressing from localized disease, and enables these patients to benefit from an effective treatment and simplifies clinical practice for physicians and patients. Erleada does not require risk stratification testing or tumor burden assessments to be undertaken.
Erleada is an oral treatment that can be taken at home without food restrictions, and treatment with Erleada does not require co-administration of steroids or additional monitoring which further reduces time spent in and hospitals and thereby minimizes the patient burden.

Erleada fulfills an unmet medical need as it delays progression to metastases, extends time to symptomatic progression and allows patients to maintain their HRQoL at a level similar to the general population. In a complex treatment landscape, treating with apalutamide is simpler for physicians and more convenient for patients than docetaxel and radiation therapy. By introducing Erleada into the prostate cancer treatment pathway early, patients benefit of an additional treatment option improving their chances of survival while retaining additional treatment options for the metastatic CRPC disease stage.

Because of the benefits outlined above, Erleada would ideally replace both docetaxel and radiotheraphy in the treatment algorithm as first line treatment for mHSPC.

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6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

The first systematic search was conducted on 18th December 2018 followed by five updates (1st update: 2nd July 2019, 2nd update: 12th November 2019, 3rd update: 2nd June 2020, 4th update: 26th October 2020) with the latest and 5th update on 17th June 2021.

All searches were conducted to identify primary intervention trials (RCTs and non-RCTs) assessing the efficacy and safety of APA or other potentially relevant treatments in men with mHSPC. Embase, MEDLINE, MEDLINE In-process, and the Cochrane Library databases were searched for any RCTs published in English using words synonymous for "metastatic hormone sensitive prostate cancer" combined with filters for study designs of interest without geographic or time restrictions. Separate searches were conducted for prospective, non-randomised interventional trials reporting on the use of APA in mHSPC. Bibliographies of SLRs and/or meta-analyses identified by the searches and published in the last three years were manually reviewed for any additional relevant publications. The most recent three editions of selected conferences were also searched for supplemental evidence. Data were extracted into a piloted data extraction template, and the Cochrane Risk of Bias tool was used to determine the quality of included studies.

During the first level of screening, title and abstracts of 7,414 unique records were reviewed. At the second level of screening, 707 full-text records were reviewed, of which 130 publications met the inclusion criteria. Grey literature searches, the manual bibliography review, and searches of www.clinicaltrials.gov identified an additional 32 citations. In the most recent update (5th SLR update, 17th June 2021), a total of 130 publications reporting on 40 unique RCTs were included. Quality assessment found that most studies (n= 24) had a low risk of bias. 8 studies had a high risk of bias and 8 studies has an unclear risk of bias.

Furthermore, we have searched for active or unpublished studies that include apalutamide and comparators (docetaxel; radiotherapy/radiation therapy) on the intended patient population (irrespective of HVD or LVD disease) in Clinicaltrials.gov and the EU Clinical Trials Register. Search list results are included in Appendix A.

6.2 List of relevant studies

The NMA scenario relevant for this submission is based on studies identified at the 4th SLR update (October 2020) which identified 38 relevant studies. 2 additional studies were identified in SLR 5th update (June 2021): Dai 2020 (20) and Fizazi 2021 (21), both not relevant in the context of this submission.

All studies identified in SLR underwent a feasibility assessment of whether the studies:

1. Contributed data to the NMA of APA + ADT vs. other relevant comparators approved and recommended for patients with mHSPC
2. Reported comparable outcomes of interest
3. Were sufficiently comparable with regards to study design, treatment and patient-level characteristics

A summary of the feasibility assessment results is presented in Figure 2, including the number of studies included/excluded and reasons for exclusion. A total of five trials (CHAARTED(22), GETUG-AFU 15(23), HORRAD(24), STAMPEDE(25–28), and TITAN(29)) were deemed eligible for inclusion in the network of evidence for the efficacy NMA. The key considerations and findings from the feasibility assessment are briefly described below.

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The inclusion criteria applied to the studies reviewed for the NMA are summarized in Table 3 below:

Table 3 PICOS-T Inclusion Criteria

Domain	Inclusion Criteria
Population	Men (≥ 18 years) with mHSPC
Interventions	APA, DOC, EBRT, Radiotherapy
Comparisons	ADT or Placebo + ADT
Outcomes	**Efficacy** • PFS • OS • Time to next skeletal-related event • Time to PSA progression • Time to subsequent therapy for PC • Time to clinical progression **Safety** • Incidence of AEs • Incidence of SAEs • Treatment-related AEs/SAEs • Treatment withdrawal/discontinuation **PRO** • Generic HRQoL– e.g. EQ-5D, SF-36/SF-12 • Disease specific HRQoL – e.g. FACT-G, FACT-P, BFI, BPI-SF)
Study designs	The review will be limited to publications of studies with the following designs: • RCTs
Duplicate	N/A
Publication types	N/A
Other criteria	Only English-language articles/conference abstracts will be included

Abbreviations: ADT = androgen deprivation therapy; AE = adverse event; APA = apalutamide; BFI = Brief Fatigue Inventory; BPI-SF = Brief Pain Inventory-Short Form; DOC = docetaxel; EBRT = external beam radiation treatment; EQ-5D = EuroQol Questionnaire, Five Dimensions; FACT-G = Functional Assessment of Cancer Therapy-General; FACT-p = Functional Assessment of Cancer Therapy-Prostate; HRQoL = health-related quality of life; mHSPC = metastatic hormone-sensitive prostate cancer; N/A = not applicable; OS = overall survival; PC = prostate cancer; PFS = progression-free survival; PICOS-T = Population, intervention, comparison, outcome, study design, time period; PRO = patient-reported outcome; PSA = prostate-specific antigen; RCT = randomised controlled trial; SAE = serious adverse event; SF-12 = Short Form Survey, 12 items; SF-36 = Short Form Survey, 36 items

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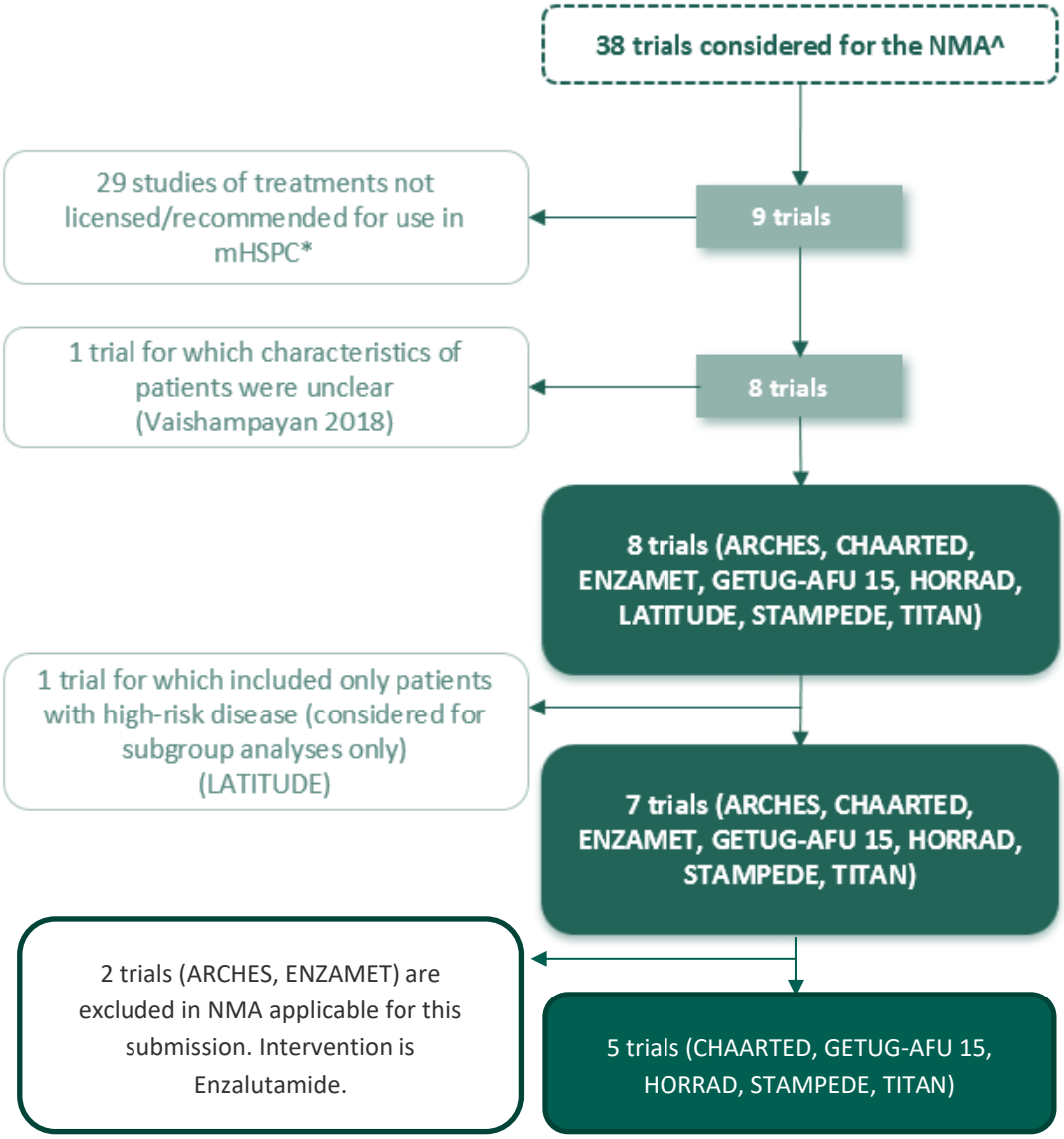
Figure 2: Attrition Diagram of Studies Considered for the NMA (Extended Network)¤



¤ The NMA scenario relevant for this submission is based on studies identified at the 4th SLR update (October 2020) which identified 38 relevant studies. 2 additional studies were identified in SLR 5th update (June 2021): Dai 2020 and Fizazi 2021, both not applicable to the NMA for this submission.

^ STAMPEDE data identified by the review involved five different sets of comparisons.

* Two STAMPEDE comparisons were included in the scenario NMA for this submission – arm C vs. A; arm C vs. G

Abbreviations: mHSPC = metastatic hormone-sensitive prostate cancer; NMA = network meta-analysis

Table 4: Relevant studies considered for the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of*
Primary: Sweeney, CJ., et al., 2015 (22)	CHAARTED	NCT00309985	July 28, 2006 December 2022	Docetaxel + ADT vs. ADT alone
Primary: Gravis G, 2013 (30)	GETUG-AFU 15	NCT00104715	October 18, 2004 December 15, 2015	Docetaxel + ADT vs. ADT alone
Boeve, LM., et al., 2019 (24)	HORRAD	NA (ISRCTN06890529)		Radiotherapy + ADT vs. ADT + Placebo
Primary: Chi, KN., et al., 2019 (31)	TITAN	NCT02489318	November 27, 2015 March 1, 2024	ADT + Apalutamide vs. ADT + Placebo
Parker, CC, et al., 2018 (27)	STAMPEDE (STAMPEDE-HA)	NCT00268476	July 8, 2005 December 2030	Radiotherapy + ADT vs. ADT
Clarke, NW, et al., 2019 (32)) ; James, ND., et al., 2016 (26)	(STAMPEDE-CA)			Docetaxel + ADT vs. ADT

For detailed information about included studies, refer to Appendix B Main characteristics of included studies.

7. Efficacy and safety

In the following sections two comparisons will be presented:

1. Comparison of apalutamide + ADT (AAP+ADT) and docetaxel + ADT (DOC+ADT) for mHSPC patients
2. Comparison of apalutamide + ADT (AAP+ADT) and radiotherapy + ADT (RT+ADT) for mHSPC patients

When available, data is presented separately for patients with high volume disease (HVD) and patients with low volume disease (LVD).

First the relevant studies will be introduced, then the results per study and lastly the results of the NMA which the comparative analyses are based upon will be presented.

7.1 Efficacy and safety of apalutamide + ADT compared to docetaxel + ADT or radiotherapy + ADT for men with mHSPC

7.1.1 Relevant studies

This section presents the network of evidence comparing APA+ADT with DOC+ADT (with or without prednisone/prednisolone), RT + ADT and ADT alone

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To be included in the network, trials with a common comparator to TITAN or those involving treatments that are either recommended or in development were considered. In the TITAN trial, the addition of APA to ADT was compared to placebo + ADT. Since the network could only contain trials with a common comparator to TITAN, trials that contained comparisons to placebo + ADT were considered, specifically:

1. Surgical castration (alone or combined with non-steroidal anti-androgens [NSAAs])
2. LHRH agonists (alone or combined with NSAAs)

Variability in the definition of ADT was seen within and across studies. Although ADT involved either surgical or medical castration, the definition of medical castration also varied. In addition, the duration of DOC administration for studies involving that intervention differed with patients being treated for six cycles in one trial and nine cycles in another trial. Table 5 summarizes the details of interventions in the trials considered, as well as providing a specific breakdown of ADT types received in each one of the included trials. Radiotherapy comprised EBRGT in both HORRAD and

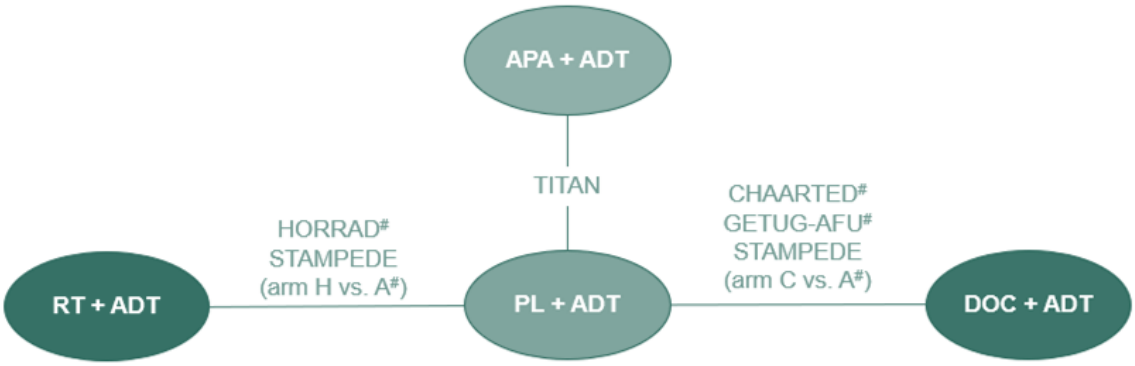
Table 5: Interventions Evaluated in Studies Considered for the NMA

Name of Trial	Intervention	Comparator Intervention	Type of ADT Received During Study
CHAARTED	DOC + ADT	ADT	ADT administration comprised surgical castration or LHRH agonists, alone or in combination with non-steroidal anti-androgens
GETUG-AFU 15	DOC + ADT	ADT	ADT administration comprised surgical castration or LHRH agonists, alone or in combination with non-steroidal anti-androgens
HORRAD	EBRT+ADT	ADT	ADT administration comprised LHRH agonist
STAMPEDE	DOC + ADT (STAMPEDE-CA)	ADT	ADT administration comprised hormone therapy for at least two years with gonadotropin-releasing hormone agonists or antagonists. Orchiectomy was an allowable alternative to drug therapy. Patients received orchiectomy, LHRH-based therapy, or bicalutamide (anti-androgen).
	Radiotherapy + ADT (STAMPEDE-HA)	ADT	ADT administration comprised gonadotrophin-releasing hormone agonists/antagonists or orchidectomy
TITAN	APA + ADT	Placebo + ADT	ADT administration comprised gonadotropin releasing hormone analog or surgical castration

Abbreviations: ADT = androgen deprivation therapy; APA = apalutamide; DOC = docetaxel; EBRT = external beam radiation treatment; LHRH = luteinizing hormone-releasing hormone

From the trials included in the extended network those examining APA+ADT, DOC+ADT or RT+ADT were included in this assessment (listed above in Table 5), i.e. following five trials: TITAN, CHAARTED, GETUG-AFU15, HORRAD, and STAMPEDE (two comparisons: arm C vs. A = STAMPEDE-CA; and arm H vs. A = STAMPEDE-HA). This network contains both relevant comparators (DOC+ADT and RT+ADT) as defined above (Section 7), and will be used in both scenarios. Figure 3 illustrates the evidence network diagram.

Figure 3: Evidence Network Diagram (ITT All-comer Populations)



Abbreviations: ADT = androgen deprivation therapy; APA = apalutamide; DOC = docetaxel; PL = placebo, RT = radiotherapy.
This network depicts the greatest number of trials that can be included in the analyses.
#Note that the control arm in CHAARTED, GETUG-AFU, STAMPEDE and HORRAD trials is ADT alone and not PL+ADT.

Patient populations

All included studies were conducted in patient populations of adult (aged ≥18 years) men with mHSPC. The population definitions based on the enrolment criteria were generally similar across the five studies with minor differences in terms of exceptions the trials permitted related to the previous treatment. Population definitions based on the enrolment criteria of the trials identified are summarized in Table 6, while the patient characteristics are presented in Table 7. HORRAD subgroup data for HVD and LVD is not available.

Table 6: Summary of Enrolment Criteria for Studies Included in the NMA

Trial	Previous Treatment
CHAARTED	Patients who were receiving ADT for metastatic disease were eligible if there was no evidence of progression and treatment had commenced within 120 days before randomisation.
GETUG-AFU 15	Patients who had received previous chemotherapy for metastatic disease were excluded, but ADT for patients with metastatic disease could have been initiated no more than two months before enrolment.
HORRAD	Patients who had received previous treatment for prostate cancer were not included
STAMPEDE	Not clear on previous treatment - previous local therapy were also permitted if they had PSA>20 ng/ml or PSA>4 ng/ml with a PSA doubling time<6 months or those who developed loco-regional or metastatic spread while not on hormone therapy. (publications evaluating AAP) Patients who were previously treated with radical surgery, radiotherapy, or both and relapsing with high-risk features (publication evaluating DOC)
TITAN	Maximum of one course of radiation or surgical intervention; radiation therapy for metastatic lesions must be completed prior to randomisation; less than or equal to six months of ADT prior to randomisation

Abbreviations: AAP = abiraterone acetate + prednisone; ADT = androgen deprivation therapy; DOC = docetaxel; PSA = prostate-specific antigen

Table 7: Summary of Patient Characteristics

Trial	CHAARTED	GETUG-15	HORRAD	STAMPEDE	TITAN

Only de novo metastatic?	No	No	No	No	No
HVD/LVD subgroup data?	Yes	Yes	No	Yes	Yes
All metastatic?	Yes	Yes	Yes	Yes	Yes
Prior ADT?	Patients received ADT for M1 disease eligible if there was no evidence of progression and treatment commenced ≤120 days before randomisation. Prior adjuvant ADT allowed if the duration of treatment was ≤24 months and progression had occurred >12 months after completion of therapy	ADT for metastatic disease initiated ≤2 months before enrolment Neoadjuvant and adjuvant settings or in context of isolated PSA increase, previous ADT, allowed: treatment discontinued ≥ 12 months before inclusion in the study and no metastases or PSA increase documented during this period.	No: Previously untreated	If ADT started prior to randomisation, must be ≤12 weeks. Relapsing patients treated with adjuvant or neo adjuvant ADT alongside their RP or RT must have completed ≥12 months before and be ≤12 months in duration.	If started, ≤6 months of ADT prior to randomisation. ADT must have been started ≥14 days prior to randomisation. For localised PC: ≤3 years total of ADT and completed ≥1 year prior randomisation
Previous treatment for localised PC?	Yes, RT and RP both allowed	Neo adjuvant and adjuvant settings or in context of isolated PSA increase, previous CT or ADT, or both, were allowed: treatment discontinued ≥12 months before inclusion in the study and no metastases or PSA increase documented during this period.	No: Previously untreated	Allowed: previously radically treated, now relapsing (prior radical surgery and/or RT)	Allowed but must have been completed ≥1 year prior to randomisation
Previous DOC use?	No	Not allowed for metastatic disease	No: Previously untreated	Excluded: prior CT for PC (excluding patients receiving DOC as a part of new SOC)	In case of prior DOC, ≤6 cycles, last dose ≤2 months before randomisation and maintained a response to DOC of stable disease or better

Abbreviations: ADT = androgen deprivation therapy; CT = chemotherapy; DOC = docetaxel; M1 = metastatic disease; PC = prostate cancer; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiotherapy; SOC = standard of care

Study duration and outcomes

Available efficacy outcomes are presented in Table 8. In general there were no notable differences in the definition of available efficacy outcomes, however PFS in the CHAARTED study was defined differently from other included studies, and not included in the NMA.

Table 8: Summary of Efficacy Outcome Definitions from Studies Included in the NMA

Trial	INV/IRC	OS	rPFS	PFS	Time to Next SRE	Time to PSA Progression	Time to Next Subsequent Treatment for PC
CHAARTED	INV*	Time from randomisation to death from any cause	*Outcome NR*	*Outcome NR*	*Outcome NR*	*Outcome NR*	*Outcome NR*
GETUG-AFU 15	INV*	Time from randomisation to death from any cause	Time from randomisation to the occurrence of radiographic progression or death from any cause	*Outcome NR*	*Outcome NR*	*Outcome NR*	Median time to subsequent treatment
HORRAD	INV*	Time between date of diagnosis at prostatic biopsy and date of death	*Outcome NR*	*Outcome NR*	*Outcome NR*	Time between diagnosis and a PSA increase after initiation of ADT of more than 50% of the lowest PSA value after start of treatment (PSA-nadir), with a minimum of 1 ng/ml.	*Outcome NR*
STAMPEDE	INV	Time from randomisation to death from any cause	*Outcome NR*	Progression-free survival including death from prostate cancer	Freedom from symptomatic skeletal events	*Outcome NR*	*Outcome NR*
TITAN	INV	Time from randomisation to death from any cause	Time from randomisation to the occurrence of radiographic progression or	*Outcome NR*	Skeletal-related events were defined as the occurrence of	Time to PSA progression as date of random assignment	Time to initiation of cytotoxic chemotherapy

		death from any cause		symptomatic pathologic fracture, spinal cord compression, radiation to bone, or surgery to bone	to date of PSA progression, based on PCWG2 criteria

Abbreviations: ADT = androgen deprivation therapy; INV = investigator assessed; IRC = independent review committee; NR = not reported; OS = overall survival; PC = prostate cancer; PFS = progression-free survival; PSA = prostate-specific antigen; rPFS = radiographic progression-free survival; SRE = skeletal-related event
*Assumed to be INV

Additional details on the population, outcomes of interest, and data cut-off for the analyses are listed below:

- Population: the all-comers mHSPC population was used as a base-case analysis.
- Outcomes: variability was observed for definitions of PFS across studies and therefore, a strict rPFS definition (specific to radiographic progression) was used as base-case and an additional analysis of PFS was used as a sensitivity analysis (using the definition applied in the STAMPEDE trial). Use of this definition allowed the network to be expanded to include comparisons to DOC + ADT, and radiotherapy + ADT on this endpoint. This analysis should be interpreted with caution as there were differences in the definitions of death for PFS. Specifically, the STAMPEDE trial reported prostate cancer related deaths while other trials were inclusive of death from all-causes. Nevertheless, to ensure a comparison could be made, analyses including a broader PFS definition based on STAMPEDE trial were also conducted and results were reported separately for both rPFS and PFS outcomes.
- Cut-off date: to ensure a homogeneous comparison, data-cut close to TITAN was selected for the analyses.

Information from the five trials considered for the NMA are reported in Table 9. While the median overall follow-up durations of studies are described in the table below, studies also reported outcomes of interest at interim follow-up durations.

Table 9: Overview of trials considered for the comparative analyses

	CHAARTED	GETUG-AFU 15	HORRAD	STAMPEDE	TITAN
NCT number	NCT00309985	NCT00104715	ISRCTN06890529	NCT00268476	NCT02489318
Patient population	Patients with mHSPC	Patients with metastatic non-castrate PC	Primary bone metastatic prostate cancer	Patients with PC that was newly diagnosed as metastatic, node positive, or high risk locally advanced (with at least two of T3/4, Gleason score of 8–10, and PSA ≥40ng/ml); or previously treated with radical surgery, RT, or both and relapsing	Patients with mCSPC

				with high risk features	
Therapy	DOC + ADT (75mg/m^2 every 3 weeks for six cycles) ADT alone	DOC + ADT (75mg/m^2 every 3 weeks for up to nine cycles) ADT alone	EBRT + ADT (EBRT regime either 70 gy 35 fractions of 2 Gy during overall treatment of 7 weeks (82%) OR 66.76 Gy in 19 fractions of 3.04 Gy, 3 times a week for 6 weeks (12%)) ADT alone	**STAMPEDE-CA (arm C):** SOC (hormone therapy with gonadotropin-releasing hormone agonists or antagonists or oral anti-androgens) SOC + DOC (75mg/m^2 every 3 weeks for six cycles) + Prednisolone (10mg daily) **STAMPEDE-HA (arm H)**: SOC (ADT as either gonadotrophin-releasing hormone agonists or antagonists or orchidectomy) SOC+ radiotherapy (EBRT) 33 Gy/6 fractions/6 weeks or 55 GY/20 fractions/4 weeks	APA + ADT (240 mg oral, once daily) Placebo + ADT
Number of patients with mHSPC	790	385	432	1,817[a]	1,052
Patients with newly diagnosed mHSPC	75%	71%	NR	100%	81%
Patients with high volume disease[b]	65% (514/790)	52% (202/385)[c]	NR[g]	**STAMPEDE-CA (arm C, DOC):** 56% (468/1086) **STAMPEDE-HA (arm H, RT):** 54% (553/1032)[d]	62.7%
Median age, years (range)	64 (36–91)	64 (57–70)	NR	65 (42–84)	68 (43–94)
Gleason score of 8–10	61%	56%	66% (286/432)	70%	67.4%
Performance status of 0–1	98%	NR	96% (416/432)	99%	NR

Prior adjuvant hormonal therapy	Permitted if ADT was ≤24 months in duration and progression had occurred >12 months after completion of therapy	Permitted if ADT discontinued 12 months before study entry	No prior treatment permitted	Permitted if ADT discontinued 12 months before study entry and ≤12 months in duration	<= 6 months of ADT prior to randomisation; Allowed prior treatments for localised PC (all treatments must have been completed >= 1 year prior to randomisation) a) <= 3 years total of ADT; b) All other forms of prior therapies including RT, prostatectomy, lymph node dissection, and systemic therapies
Median follow-up	53.7 months	83.9 months	47 months	40 months[e] – 73.5 months	22.7/44 months[f]
Primary endpoint	Median OS	Median OS	Median OS	Median OS	Median OS and rPFS

Abbreviations: AAP = abiraterone acetate + prednisone; ADT = androgen deprivation therapy; APA = apalutamide; DOC = docetaxel; EBRT = external beam radiation treatment; mCSPC = metastatic castration-sensitive prostate cancer; mHSPC = metastatic hormone-sensitive prostate cancer; NCT = National Clinical Trial; NMA = network meta-analyses; NR = not reported; NSAA = non-steroidal anti-androgen; OS = overall survival; PC = prostate cancer; PSA = prostate-specific antigen; rPFS = radiographic progression-free survival; RT = radiotherapy; SOC = standard of care.

[a]Number of patients in the subgroup with metastatic prostate cancer at randomisation

[b]High volume disease defined as visceral metastases and/or ≥4 bone metastases with at least one metastasis beyond the pelvis or vertebral column

[c]High volume disease was retrospectively defined in the GETUG-AFU 15 trial following the CHAARTED definition (visceral metastases and/or ≥4 bone metastases with at least one metastasis beyond the pelvis or vertebral column)

[d]The metastatic burden was unknown for 122 (6%)

[e]Median follow-up reported for all randomised patients (standard of care [SoC], DOC + SoC, zoledronic acid [ZA] + SoC, DOC + ZA + SoC). For RT comparison (arm H) median follow-up was 37 months..

[f]Median follow up at interim analysis 1 (IA1) was 22.7 months (used for rPFS and PFS analyses), median follow-up at final analysis (FA) was 44 months (used for OS, TTNSRE, TTPSA and safety analyses).

[g]The metastatic burden (high/low) was not classified according to the definition used in the CHAARTED and STAMPEDE trials.

7.1.2 Efficacy and safety – results per study

A feasibility assessment was performed based on the outcomes available in the relevant trials. The efficacy outcomes deemed feasible to analyze were the following:

- Overall survival (OS) (hazard ratio [HR]; 95% confidence intervals [CIs])
- Radiographic progression-free survival (rPFS) (HR; 95% CIs)
- Progression-free survival (PFS) (HR; 95% CIs)
- Time to PSA Progression (TTPSA) (HR; 95% CIs)

Table 10 summarizes the available outcome data for all-comer efficacy analyses from the trials included in this network scenario. These outcomes were analyzed based on the availability of data from comparable timepoints, and the impact of follow-up duration was tested as an effect modifier by conducting sensitivity analyses using data from final data cuts where available. All time-to-event outcomes listed above were meta-analysed using HRs.

The safety outcomes deemed relevant to be analyzed included:

- Adverse Events (AEs)
    - Any grade

- Treatment discontinuations due to AEs
- Serious AEs

Limited data are available for safety comparisons. Table 11 summarizes the available outcome data for all-comer safety analyses.

Upon feasibility assessment of the available patient reported outcome (PRO) data (including quality of life data) it was determined that a comparison on PROs was not feasible. A brief summary of the PRO data from the TITAN trial will be presented.

In the following sections, the outcomes deemed feasible to analyze will be summarized on a per study basis.

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Table 10: Efficacy Outcome Data Available for Analysis

			OS				rPFS			PFS			TTPSA			TTNSRE		
Trial	**Treatment**	**Comparator**	**N**	**Publ.**	**Time**	**HR [95%CI]**	**Publ.**	**Time**	**HR [95%CI]**	**Publ.**	**Time**	**HR [95%CI]**	**Publ.**	**Time**	**HR [95%CI]**	**Publ.**	**Time**	**HR [95%CI]**
TITAN	APA + ADT	PL + ADT	525	Chi K et al 2021	44M	All: 0.651 [0.534; 0.793]	Chi K, 2019/ CSR	22.7 M	0.484 [0.391; 0.600]	Chi K, 2019/ CSR	22.7M	0.484 [0.391; 0.600]	Chi K et al 2021	44M	0.266 [0.218; 0.325]	Chi K et al 2021	44M	0.857 [0.615; 1.194]
						Cross over adjusted: [redacted]												
			HVD: 325			**HVD**: 0.700 [0.560; 0.880]			**HVD**: 0.530 [0.410; 0.670]			**HVD**: 0.530 [0.410; 0.670					
						Cross over adjusted: [redacted]												
			LVD: 200			**LVD**: 0.520 [0.350; 0.790]			**LVD**: 0.360 [0.220; 0.570]			**LVD**: 0.360 [0.220; 0.570]					
						Cross over adjusted: [redacted]												
CHAARTED	DOC + ADT	PL + ADT	397	Sweeney C, 2015	28.9 M	0.610 [0.470; 0.800]												
			HVD: 263			**HVD**: 0.600 [0.450; 0.810]												
			LVD: 134			**LVD**: 0.600												

						[0.320; 1.130]											
GETUG-AFU 15	DOC + ADT	PL + ADT	192	Gravis G, 2013	50M	1.010 [0.750; 1.360]	Gravis G, 2016	83.9 M	0.690 [0.550; 0.870]	Gravis G, 2016	83.9M	0.690 [0.550; 0.870]					
			HVD: 92	Gravis G, 2016	83.9 M	**HVD**: 0.780 [0.560; 1.090]			**HVD**: 0.610 [0.440; 0.830]			**HVD**: 0.610 [0.440; 0.830]					
			LVD: 100			**LVD**: 1.020 [0.670; 1.550]			**LVD**: 0.810 [0.570; 1.140]			**LVD**: 0.810 [0.570; 1.140]					
STAMPEDE-CA (arm C with DOC vs. arm A)	DOC + ADT	PL + ADT	362[¤]	James N, 2016	43M	0.760 [0.620; 0.920]				Clarke N, 2019	78,2 M	0.690 [0.590; 0.810]					
			HVD: 148	Clarke N, 2019	78,2 M	**HVD**: 0.810 [0.640; 1.020]						**HVD**: 0.680 [0.540; 0.850]					
			LVD: 124			**LVD**: 0.760 [0.540; 1.070]						**LVD**: 0.620 [0.450; 0.850]					
HORRAD	RT + ADT	PL + ADT	216	Boevé L M, 2018	47M	0.900 [0.700; 1.140]							Boevé L M, 2018	47M	0.780 [0.630; 0.970]		
			HVD: NR			*HVD: NR*											
			LVD: NR			*LVD: NR*											
STAMPEDE-HA (arm H with RT vs. arm A)	RT + ADT	PL + ADT	1032[#]	Parker C, 2018	37M	0.920 [0.800; 1.060]				Parker C, 2018	37M	0.960 [0.850; 1.080]					
			HVD: 553			**HVD**: 1.070 [0.900; 1.280]						**HVD**: 1.090 [0.940; 1.260]					
			LVD: 410			**LVD**: 0.680 [0.520; 0.900]						**LVD**: 0.780 [0.630; 0.980]					

Abbreviations: ADT = androgen deprivation therapy; APA = apalutamide; CI = confidence interval; DOC = docetaxel; HVD = High Volume Disease; HR = hazard ratio; LVD = Low Volume Disease; OS = overall survival; PSA = prostate-specific antigen; rPFS = radiographic progression-free survival; RT = radiotherapy; TTNSRE = time to next skeletal-related event; TTPSA = time to PSA progression. Note TITAN: rPFS was measured in TITAN and is used as proxy for PFS in the NMA. Considerable variability was observed for definitions of PFS across studies and therefore, the analyses were conducted and reported separately for both the rPFS and PFS outcomes.

*A scenario analysis based on cross over adjusted OS for TITAN was conducted to estimate the effect of treatment on OS with the adjustment for the potential confounding effect in the presence of crossover. The crossover correction was performed using the rank-preserving structural failure time model (RPSFTM).

¤90 patients unassigned for metastatic burden.

¤69 patients not classified for metastatic burden.

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Table 11: Safety Outcome Data Available for Analysis

			AE			AE_DISC			SAE		
Trial	**Treatment**	**N**	**Publ.**	**Time**	**% (events/N)**	**Publ.**	**Time**	**% (events/N)**	**Publ.**	**Time**	**% (events/N)**
TITAN	APA+ ADT	525	Chi K et al 2021	44M	97.3% (510/524)	Chi K et al 2021	44M	11.8% (62/524)	Chi K et al 2021	44M	29.2% (153/524)
	PL+ ADT	527		44M	96.8% (510/527)		44M	5.7% (30/527)		44M	21.8% (115/527)
GETUG-AFU 15	PL+ ADT	186							Gravis G, 2013	50M	0.5% (1/187)
	DOC+ ADT	189								50M	38,2% (73/190)

Abbreviations: ADT = androgen deprivation therapy; AE = adverse event; AE_DISC = discontinuation due to AEs; APA = apalutamide; DOC = docetaxel; PL = placebo; SAE = serious adverse event. Note TITAN: safety population APA+ADT is n=524; Note GETUG-AFU 15: A continuity correction has been applied here because otherwise you have 0 events in one group and that cannot be analysed, therefore 0.5 is added to every cell of the two by two table (0.5 pat with no event; 0.5 pat with the event) and thus 1 is added to the total.

TITAN

Overall survival

The TITAN trial evaluated the addition of APA to ADT compared to the addition of placebo to ADT in patients with mCSPC. The median follow-up duration was 22.7 months. The OS rates at 24 months were 82% and 74% in the APA + ADT and placebo + ADT arms, respectively. Treatment with APA + ADT resulted in significantly longer OS compared to placebo + ADT at median follow-up of 22.7 months (HR: 0.67 [95% CI: 0.51, 0.89], p=0.005 and 44 months (HR: 0.65 [95% CI: 0.53, 0.79]. At 44 months, the median OS for the ADT + placebo treatment arm was 52.2 months, but was not reached in the ADT + APA arm (33).

TITAN showed OS benefit consistently in both high and low-volume subgroups: HR HVD: 0.700 [0.560; 0.880]; HR LVD: 0.520 [0.350; 0.790] at 44 months. This taking into account that the study was not powered to these subgroups.

Cross-over adjusted OS

Upon unblinding of the study at first interim analysis (IA1; median survival follow-up 22.7 months), 96/192 of low-volume disease patients (50%) and 112/335 of high-volume disease patients (33.4%) in the control (ADT alone) arm were allowed to cross over to the open-label extension phase and received apalutamide. As such, these patients in the control arm received active treatment as of this time point onwards. Patients switching from ADT alone to apalutamide + ADT 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 the analysis 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 national institute for health and care excellence (NICE) decision support

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unit (DSU) guidelines (http://nicedsu.org.uk/wp-content/uploads/2016/03/Crossover-and-survival-final-DSU-report.pdf). Rank Preserving Structural Failure Time Model (RPSFTM) with no recensoring was used in order to reconstruct the survival duration of ADT patients that crossed over to apalutamide, as if they had never received apalutamide. The adjusted ADT alone Kaplan Meier data will be presented in the upcoming sections (along with the censor at switch analysis and unadjusted curves). The apalutamide + ADT and ADT alone RPSFTM-adjusted curves were used in the base case analysis to predict OS. The resulting hazard ratio of the OS RPSFTM-adjusted curves are:

The crossover correction can however only be performed on TITAN data, and the result will hence not be included in the NMA.

Progression-free survival

The TITAN trial evaluated the addition of APA to ADT compared to adding placebo to ADT in patients with mCSPC. The median follow-up duration was 22.7 months for these analyses. Radiographic progression free survival (rPFS) was measured in the TITAN study. The rPFS rate was found to be greater in the APA arm (68%) compared to the placebo arm (48%) at 24 months. The HR for rPFS (0.48 [95% CI: 0.39, 0.60], p<0.0001) showed that APA + ADT significantly delayed the onset of radiographic progression in comparison to placebo + ADT as of the time of the correct data cut-off. The HR for PFS and rPFS showed that the benefit was consistent in high and low-volume subgroups: HVD: 0.530 [0.410; 0.670] and LVD: 0.360 [0.220; 0.570]. This taking into account that the study was not powered to these subgroups.

Time to PSA Progression

The TITAN trial reported time to PSA progression for patients with mCSPC, and indicated a statistical difference between APA + ADT compared to ADT alone at median follow up of 22.7 months (HR: 0.26 [95% CI: 0.21, 0.32], p<0.0001) (88) and 44 months (HR: 0.27 [95% CI: 0.22, 0.33); p<0.0001).(1) The median time to PSA progression was not reached in ADT + APA treatment arm, and was 12.9 months in the ADT + placebo arm (35). No data are available for HVD and LVD subgroups.

CHAARTED

Overall survival

In the CHAARTED trial (N=790), a statistically significant difference was observed in OS between treatment comparisons; DOC + ADT was found to be superior to ADT alone (23,36–39). This trial found that men with mHSPC who were treated with DOC + ADT had a statistically longer median OS (57.6 months) compared with those who were treated with ADT alone (44.0 months) at 28.9 months of median follow-up (HR: 0.61 [95% CI: 0.47 to 0.80], p<0.001) (23,36–39). This difference was preserved at a longer median follow-up of 53.7 months (HR: 0.73 [95% CI: 0.59, 0.89], p = 0.0018), where median OS remained statistically longer in men treated with DOC + ADT (57.6 months) compared with those who were treated with ADT monotherapy (47.2 months). At a median follow up of 54 months, the results remained similar (HR: 0.73 [95%CI: 0.59, 0.89], p = 0.0018) (23,36–39).

At 28.9 months of median follow-up HR for HVD and LVD subgroups are both 0.600, wider confidence intervals for LVD disease [0.320; 1.130], compared to HVD disease [0.450; 0.810].

Progression-free survival
Not reported.

Time to PSA Progression
Not reported.

STAMPEDE-CA
Overall survival
The STAMPEDE study, which used an adaptive multi-arm methodology, compared SoC only (ADT) in arm A to SoC + Docetaxel in arm C (40). SoC was hormone therapy for at least 2 years. Median follow-up was 43 months. Pre-planned subset analyses in all 1817 patients with metastatic disease at randomization. There were 350 deaths in patients on SoC-only and 144 deaths on SOC + DOC (HR: 0.760 [95% CI 0.620; 0.920], p:0.005(40).

There was no evidence of heterogeneity of docetaxel effect between metastatic burden sub-groups. In patients with low metastatic burden: HR:0.760 [0.540; 1.070], in patients with high metastatic burden: HR: 0.810 [0.640; 1.020] (42).

Progression-free survival
In the Clarke publication of STAMPEDE trial, PFS is time reported – defined as time from randomization to the first PFS event, not including biochemical progression. Analysis found evidence of benefit for docetaxel over SOC in progression-free survival (HR=0.69, 95% CI 0.59–0.81, P < 0.001) with no evidence of heterogeneity of docetaxel effect. In patients with low metastatic burden: HR:0.62 [0.45; 0.85], in patients with high metastatic burden: HR: 0.68 [0.54; 0.85] (32).

Time to PSA Progression
Not reported.

STAMPEDE-HA
Overall survival
In this part of the multi-arm STAMPEDE study, SoC only (ADT) in arm A (N=1029) was compared to SoC + Radiotherapy (EBRG) in arm H (N=1032) (43). Median follow-up was 37 months. There was not found evidence of an overall treatment effect of radiotherapy. There was evidence of an effect in patients with low metastatic burden (N=819) (HR: 0.680 [95% CI: 0.520; 0.900]), but not in patients with high metastatic burden (N=1120) (HR: 1.070 [95% CI: 0.900; 1.280]). A significant interaction was seen between treatment effect and metastatic burden (p = 0.007).

Progression-free survival
In the STAMPEDE trial, a treatment effect of radiation therapy was only found in patients with a low metastatic burden (HR 0·78, 95% CI 0·63–0·98; p=0·033) (43)

Time to PSA Progression
Not reported.

GETUG AFU15
Overall survival
The GETUG-AFU 15 trial compared DOC + ADT to ADT monotherapy in a population of patients with mHSPC (N=385) (24,44). Although longer OS durations were observed for DOC + ADT at median follow-up times of 50 months and 83.9 months, these differences were not statistically different (HR: 1.01 [95%CI: 0.75,1.36], p=0.955 and 0.90 [0.7,1.1], p=0.3, respectively) (24,44).

Progression-free survival
Over a median of 50 months follow-up in the GETUG-AFU 15 trial, longer PFS was reported in s mHSPC patients receiving DOC + ADT versus ADT alone (HR: 0.75 [95%CI: 0.59, 0.94], p=0.015) (24,31,44). Additionally, DOC + ADT in the GETUG-AFU15 trial showed a significantly longer median radiographic PFS (22 months) compared to ADT alone (15.3 months; HR: 0.69 [95% CI: 0.55, 0.87], p=0.002) (24,31,44).

Time to PSA Progression
Not reported.

HORRAD
Overall survival
The HORRAD trial evaluated the addition of external beam radiation treatment (EBRT) to ADT compared to the addition of placebo to ADT in patients with mCSPC (24). The median follow-up duration was 47 months. Treatment with EBRT + ADT did not result in significantly longer OS compared to placebo + ADT at median follow-up of 47 months (HR: 0.90 [95% CI: 0.70, 1.14], p=0.4. The median OS for the ADT + placebo treatment arm was 43 months, and 45 months in the EBRT + ADT arm. (24).

Progression-free survival
Not reported.

Time to PSA Progression
The HORRAD trial reported median time to PSA progression in the EBRT+ADT group was 15 months (95% CI: 11.8-18.2), compared with 12 months (95% CI: 10.6-13.4) in the placebo + ADT group. While a statistical difference was indicated from the crude HR (HR: 0.78 [95%CI: 0.63, 0.97], p=0.02), after adjustment, the statistical difference was not maintained (HR: 0.86 [95%CI: 0.69, 1.08], p=0.20) (24).

7.1.3 Comparative analyses of efficacy and safety

Method of synthesis

NMA Methods
Bayesian Approach

Bayesian NMA models were used to simultaneously synthesize the results of the included trials for each outcome of interest to obtain the relative treatment effects for all treatments included in the network. All analyses were conducted according to the methods described in the NICE Decision Support Unit (NICE DSU) Technical Support Documents (TSD) (45).

All analyses were conducted within a Bayesian framework using WinBUGS (version 1.4.3). All Bayesian NMA analyses were performed using three chains with a 50,000 run-in iteration phase and a 50,000 iteration phase for parameter estimation. Convergence was confirmed by evaluating the three-chain convergence plots. In order to avoid prior beliefs influencing the results of the model, non-informative prior distributions were used for the baseline effects and treatment effects and in RE models, a Uniform(0,1) distribution was used for the between-study standard deviation.

Model Fitting

In the analyses, fixed-effects models were fitted due to the limitations of the networks i.e., the presence of only one or few studies per treatment comparison.
Results were also run using random-effects models (provided as requested in appendix F). Differences were noted between the fixed- and random effect models. Specifically, larger credible intervals were seen in the random-effects analyses versus in the fixed-effect models.

Model Convergence

Convergence (which is required in Bayesian models for the estimates to be valid) was confirmed by visual inspection of the trace-plots of three independently run chains, with different starting values for the parameters to be estimated.

Additionally, the Brooks-Gelman-Rubin (BGR) diagnostic statistic was calculated. The BGR statistic is an ANOVA-type diagnostic that compares within- and among-chain variance. Values around 1 indicate convergence. For all analysis, the BGR statistic was very close to 1 (always below the commonly used threshold of 1.05).

Interpretation of NMA Results

The output of a Bayesian NMA is a joint posterior distribution of all relative treatment effects between interventions included in the network, which are typically reported as a “point estimate” or “effect estimate”. These point estimates present the median value of the three times 50,000 iterations performed and are accompanied with both CrIs and a Bayesian pairwise probability for the treatment of interest being more effective than the other comparators assessed in the network. Using the posterior distributions, we can also determine the probability that a given regimen was the best among all treatments within a given network. Results using frequentist methods were similar to the Bayesian approach results.

All analyses were conducted by Janssen.

Results from the comparative analysis

This section summarizes the results from the NMA for all-comer populations using fixed-effects models.

Efficacy

OS

Table 12 presents the OS results from the fixed-effects NMA for each treatment including the pooled median HRs and 95% CrIs and the probability that the treatment is better than placebo, using the final datacut from TITAN and

the closest datacut from other trials. Treatments from the five included trials were APA + ADT, DOC + ADT (three trials), and radiotherapy + ADT (two trials), all compared to placebo + ADT. Results from the NMA suggest that APA + ADT results in the best OS outcomes. Results from the NMA suggest that combination treatment with APA + DOC and DOC + ADT offer an advantage over placebo + ADT in terms of improved OS, with APA + ADT being ranked as the best treatment option for OS. The median HR (95% CrI) for for APA + ADT vs. placebo + ADT, DOC + ADT vs. placebo + ADT and radiotherapy + ADT vs. placebo + ADT were 0.651 (0.534; 0.793); 0.762 (0.662; 0.876); and 0.915 (0.811; 1.034) respectively (Table 12). The benefit of APA+ADT is consistent in both high and low-volume subgroups (Table 12).

Table 12 also presents the surface under the cumulative ranking curve (SUCRA) results that emerge from these data. The SUCRA rankings also suggest that APA+ADT is the treatment with the highest probability of improving OS for all comers mHSPC patients. The matrixes presented in Figure 4 for total population, HVD (Figure 5) and LVD (Figure 6), show that APA + ADT has favourable OS vs. DOC + ADT and radiotherapy + ADT.

Table 12: OS All-comer Populations (FE), Comparisons vs. Placebo + ADT, Datacut closest to TITAN-FA

Trial	Treatment	Median HR (95% CrI)	Probability HR<1	Rank 1	SUCRA
TITAN	APA + ADT	0.651 [0.534; 0.793] **HVD**: 0.700 [0.560; 0.880] **LVD**: 0.520 [0.350; 0.790]	100.0%	89.7%	96.5%
CHAARTED GETUG-AFU STAMPEDE-CA (arm C vs. A)	DOC + ADT	0.762 [0.662; 0.876] **HVD**: 0.735 [0.626; 0.862] **LVD**: 0.811 [0.635; 1.035]	100.00%	10.3%	69.2%
HORRAD STAMPEDE-HA (arm H vs. A)	Radiotherapy + ADT	0.915 [0.811; 1.034] **HVD (only STAMPEDE data)**: 1.070 [0.897; 1.276] **LVD (only STAMPEDE data)**: 0.680 [0.517; 0.895]	92.36%	0.0%	31.7%

Abbreviations: ADT = androgen deprivation therapy; APA = apalutamide; CrI = credible interval; DOC = docetaxel; FA = final analysis; FE = fixed effects; HVD = high volume disease; HR = hazard ratio; LVD = low volume disease; OS = overall survival; SUCRA = surface under the cumulative ranking curve

Figure 4: OS Matrix total population: HR [95% Confidence intervals], p(HR<1), fixed effects

OS	APA+ADT	DOC+ADT	Radioth+ADT	PL+ADT
APA+ADT		0.85 [0.671; 1.09] 90%	0.71 [0.565; 0.90] 100%	0.65 [0.534; 0.79] 100%
DOC+ADT	1.17 [0.918; 1.49] 10%		0.83 [0.691; 1.00] 97%	0.76 [0.662; 0.88] 100%
Radioth+ADT	1.41 [1.115; 1.77] 0%	1.20 [0.998; 1.45] 3%		0.92 [0.811; 1.03] 92%
PL+ADT	1.54 [1.261; 1.87] 0%	1.31 [1.141; 1.51] 0%	1.09 [0.967; 1.23] 8%	

Comparators are ordered according to the SUCRA. Cells contain HR with [95% Confidence intervals], and P(HR<1) (row vs column). Abbreviations: ADT = androgen deprivation therapy; APA = apalutamide; DOC = docetaxel; HR = hazard ratio; OS = overall survival; P = probability; PL = placebo; Radioth = Radiation therapy.

Figure 5: OS Matrix HVD patients: HR [95% Confidence intervals], p(HR<1), fixed effects

OS	APA+ADT	DOC+ADT	PL+ADT	Radioth+ADT
APA+ADT		0.95 [0.723; 1.26] 63%	0.70 [0.559; 0.88] 100%	0.65 [0.492; 0.87] 100%
DOC+ADT	1.05 [0.795; 1.38] 37%		0.73 [0.626; 0.86] 100%	0.69 [0.542; 0.87] 100%
PL+ADT	1.43 [1.139; 1.79] 0%	1.36 [1.159; 1.60] 0%		0.93 [0.783; 1.11] 77%
Radioth+ADT	1.53 [1.148; 2.03] 0%	1.45 [1.148; 1.85] 0%	1.07 [0.898; 1.28] 23%	

Comparators are ordered according to the SUCRA. Cells contain HR with [95% Confidence intervals], and P(HR<1) (row vs column). Abbreviations: ADT = androgen deprivation therapy; APA = apalutamide; DOC = docetaxel; HR = hazard ratio; HVD = high volume disease; OS = overall survival; P = probability; PL = placebo; Radioth = Radiation therapy.

Figure 6: OS Matrix LVD patients: HR [95% Confidence intervals], p(HR<1), fixed effects

OS	APA+ADT	Radioth+ADT	DOC+ADT	PL+ADT
APA+ADT		0.77 [0.469; 1.25] 86%	0.64 [0.399; 1.03] 97%	0.52 [0.346; 0.78] 100%
Radioth+ADT	1.31 [0.802; 2.13] 14%		0.84 [0.581; 1.21] 82%	0.68 [0.518; 0.90] 100%
DOC+ADT	1.56 [0.967; 2.50] 3%	1.19 [0.826; 1.72] 18%		0.81 [0.634; 1.04] 95%
PL+ADT	1.92 [1.280; 2.89] 0%	1.47 [1.117; 1.93] 0%	1.23 [0.965; 1.58] 5%	

Comparators are ordered according to the SUCRA. Cells contain HR with [95% Confidence intervals], and P(HR<1) (row vs column). Abbreviations: ADT = androgen deprivation therapy; APA = apalutamide; DOC = docetaxel; HR = hazard ratio; LVD=low volume disease; OS = overall survival; P = probability; PL = placebo; Radioth = Radiation therapy.

rPFS

Table 13 presents the rPFS results from the fixed-effects NMA for each treatment including the pooled median HRs and 95% CrIs and the probability that the treatment is better than placebo, using the first interim analysis (IA1) datacut from TITAN and the closest datacut from the other trials. Treatments from the included trials were APA + ADT and DOC + ADT vs. placebo + ADT. Results from the NMA suggest that APA + ADT results in the best rPFS outcomes. The results suggest that both combination treatments are superior to placebo + ADT in terms of improved rPFS with median HR (95% CrI) of 0.484 (0.391; 0.600) for APA + ADT vs. placebo + ADT; and 0.690 (0.548; 0.868) for DOC + ADT vs. placebo + ADT. The SUCRA rankings in Table 13 suggest that all treatments are superior to placebo + ADT, with APA + ADT ranked as the preferred treatment option. The comparison of APA + ADT to the other treatments is presented in Figure 7 for the total population (Figure 8 for HVD, Figure 9 for LVD), showing that APA + ADT is better than DOC + ADT (HR: 0.702 [0.512; 0.960]).

Table 13: rPFS All-comer Populations (FE), Comparisons vs. Placebo + ADT, Datacut closest to TITAN-IA1

Trial	Treatment	Median HR (95% CrI)	Probability HR<1	Rank 1	SUCRA
TITAN	APA + ADT	0.484 [0.391; 0.600] **HVD**: 0.530 [0.415; 0.678] **LVD**: 0.360 [0.224; 0.579]	100.00%	98.7%	99.3%
GETUG-AFU	DOC + ADT	0.690 [0.548; 0.868] **HVD**: 0.610 [0.444; 0.838] **LVD**: 0.810 [0.573; 1.146]	99.93%	1.3%	50.6%

Abbreviations: ADT = androgen deprivation therapy; APA = apalutamide; CrI = credible interval; DOC = docetaxel; FE = fixed effects; HR = hazard ratio; HVD = high volume disease; IA1 = first interim analysis; LVD = Low volume disease; rPFS = radiographic progression-free survival; SUCRA = surface under the cumulative ranking curve.

Figure 7: rPFS Matrix total population: HR [95% Confidence intervals], p(HR<1), fixed effects

rPFS	APA+ADT	DOC+ADT	PL+ADT
APA+ADT		0.70 [0.513; 0.96] 99%	0.48 [0.391; 0.60] 100%
DOC+ADT	1.42 [1.041; 1.95] 1%		0.69 [0.548; 0.87] 100%
PL+ADT	2.06 [1.668; 2.56] 0%	1.45 [1.152; 1.82] 0%	

Comparators are ordered according to the SUCRA. Cells contain HR with [95% Confidence intervals], and P(HR<1) (row vs column). Abbreviations: ADT = androgen deprivation therapy; APA = apalutamide; DOC = docetaxel; HR = hazard ratio; P = probability; PL = placebo; rPFS = radiographic progression-free survival.

Figure 8: rPFS Matrix HVD population: HR [95% Confidence intervals], p(HR<1), fixed effects

rPFS	APA+ADT	DOC+ADT	PL+ADT
APA+ADT		0.87 [0.582; 1.30] 75%	0.53 [0.415; 0.68] 100%
DOC+ADT	1.15 [0.770; 1.72] 25%		0.61 [0.444; 0.84] 100%
PL+ADT	1.89 [1.476; 2.41] 0%	1.64 [1.193; 2.25] 0%	

Comparators are ordered according to the SUCRA. Cells contain HR with [95% Confidence intervals], and P(HR<1) (row vs column). Abbreviations: ADT = androgen deprivation therapy; APA = apalutamide; DOC = docetaxel; HR = hazard ratio; HVD= high volume disease; P = probability; PL = placebo; rPFS = radiographic progression-free survival.

Figure 9: rPFS Matrix LVD population: HR [95% Confidence intervals], p(HR<1), fixed effects

rPFS	APA+ADT	DOC+ADT	PL+ADT
APA+ADT		0.44 [0.246; 0.80] 100%	0.36 [0.224; 0.58] 100%
DOC+ADT	2.25 [1.249; 4.06] 0%		0.81 [0.573; 1.15] 88%
PL+ADT	2.78 [1.727; 4.47] 0%	1.23 [0.872; 1.75] 12%	

Comparators are ordered according to the SUCRA. Cells contain HR with [95% Confidence intervals], and P(HR<1) (row vs column). Abbreviations: ADT = androgen deprivation therapy; APA = apalutamide; DOC = docetaxel; HR = hazard ratio; LVD= low volume disease; P = probability; PL = placebo; rPFS = radiographic progression-free survival.

PFS

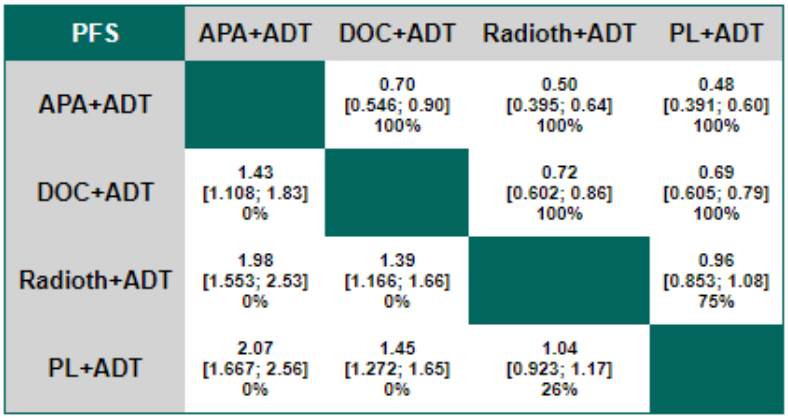
Table 14 presents the PFS results from the fixed-effects NMA (using the first datacut) for each treatment including the pooled median HRs and 95% CrIs and the probability that the treatment is better than placebo, using the IA1 datacut from TITAN and the closest datacut from the other trials. Treatments from the included trials were APA + ADT, DOC + ADT, and radiotherapy + ADT vs. placebo + ADT. Results from the NMA resulted in point estimates that favour the combination treatments over placebo + ADT in terms of improved PFS, with median HR (95% CrI) of 0.484 (0.391; 0.600) for APA + ADT vs. placebo + ADT; 0.690 (0.548; 0.868) for DOC + ADT vs. placebo + ADT; and 0.961 (0.852; 1.082) for radiotherapy + ADT vs. placebo + ADT . The SUCRA rankings in Table 14 and the matrix in Figure 6 below suggest that all treatments are superior to placebo + ADT, with APA + ADT ranked as the preferred treatment option. The comparison of APA + ADT to the other treatments is presented in Figure 10 (Figure 11 for HVD, Figure 12 for LVD), showing that APA + ADT is better than DOC + ADT (HR: 0.702 [0.512; 0.960]) and radiotherapy + ADT (HR: 0.504 [0.395; 0.644]) in improving PFS outcomes.

Table 14: PFS All-comer Populations (FE), Comparisons vs. Placebo + ADT, Datacut closest to TITAN-IA1

Trial	Treatment	Median HR (95% CrI)	Probability HR<1	Rank 1	SUCRA
TITAN	APA + ADT	0.484 [0.391; 0.600]	100.0%	98.64%	99.9%
GETUG-AFU **STAMPEDE-CA (arm C vs. A)**	DOC + ADT	0.690 [0.606; 0.786]	99.92%	1.358%	66.8%
STAMPEDE (arm H vs. A)	Radiotherapy + ADT	0.961 [0.853; 1.083]	74.50%	0.000%	25.0%

Abbreviations: ADT = androgen deprivation therapy; APA = apalutamide; CrI = credible interval; DOC = docetaxel; FE = fixed effects; HR = hazard ratio; IA1 = first interim analysis; PFS = progression-free survival; SUCRA = surface under the cumulative ranking curve.

Figure 10: PFS Matrix total population: HR [95% Confidence intervals], p(HR<1), fixed effects



Comparators are ordered according to the SUCRA. Cells contain HR with [95% Confidence intervals], and P(HR<1) (row vs column). Abbreviations: ADT = androgen deprivation therapy; APA = apalutamide; DOC = docetaxel; HR = hazard ratio; P = probability; PL = placebo; PFS = progression-free survival; Radioth = radiation therapy.

Figure 11: PFS Matrix HVD population: HR [95% Confidence intervals], p(HR<1), fixed effects

PFS	APA+ADT	DOC+ADT	PL+ADT	Radioth+ADT
APA+ADT		0.81 [0.595; 1.10] 91%	0.53 [0.415; 0.68] 100%	0.49 [0.366; 0.65] 100%
DOC+ADT	1.24 [0.908; 1.68] 9%		0.66 [0.545; 0.79] 100%	0.60 [0.475; 0.76] 100%
PL+ADT	1.89 [1.475; 2.41] 0%	1.53 [1.267; 1.84] 0%		0.92 [0.792; 1.06] 87%
Radioth+ADT	2.05 [1.545; 2.73] 0%	1.66 [1.313; 2.10] 0%	1.09 [0.942; 1.26] 13%	

Comparators are ordered according to the SUCRA. Cells contain HR with [95% Confidence intervals], and P(HR<1) (row vs column). Abbreviations: ADT = androgen deprivation therapy; APA = apalutamide; DOC = docetaxel; HR = hazard ratio; HVD = high volume disease; P = probability; PL = placebo; PFS = progression-free survival; Radioth = radiation therapy

Figure 12: PFS Matrix LVD population: HR [95% Confidence intervals], p(HR<1), fixed effects

PFS	APA+ADT	DOC+ADT	Radioth+ADT	PL+ADT
APA+ADT		0.51 [0.303; 0.88] 99%	0.46 [0.274; 0.78] 100%	0.36 [0.224; 0.58] 100%
DOC+ADT	1.95 [1.143; 3.30] 1%		0.90 [0.651; 1.24] 74%	0.70 [0.554; 0.89] 100%
Radioth+ADT	2.17 [1.283; 3.65] 0%	1.11 [0.807; 1.54] 26%		0.78 [0.626; 0.97] 99%
PL+ADT	2.78 [1.726; 4.47] 0%	1.43 [1.128; 1.81] 0%	1.28 [1.027; 1.60] 1%	

Comparators are ordered according to the SUCRA. Cells contain HR with [95% Confidence intervals], and P(HR<1) (row vs column). Abbreviations: ADT = androgen deprivation therapy; APA = apalutamide; DOC = docetaxel; HR = hazard ratio; LVD = low volume disease; P = probability; PL = placebo; PFS = progression-free survival; Radioth = radiation therapy

Time to PSA progression

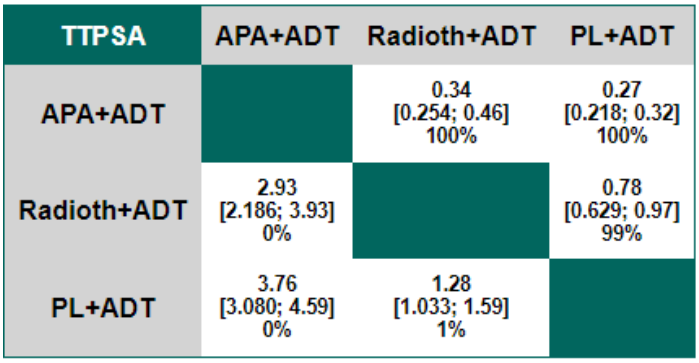
Table 15 presents the results for time to PSA progression from the fixed-effects NMA for each treatment including the pooled median HRs and 95% CrIs and the probability that the treatment is better than placebo, using the final datacut from TITAN and the closest datacut from other trials. Treatments from the included trials were APA + ADT and radiotherapy + ADT vs. placebo + ADT. Results from the NMA suggest that both treatments offer an advantage over placebo + ADT in terms of improved time to PSA progression with median HR (95% CrI) of 0.266 (0.218; 0.325) for APA + ADT vs. placebo + ADT; and 0.781 (0.629; 0.969) for radiotherapy + ADT vs. placebo + ADT. The SUCRA rankings in Table 15 and the matrix in Figure 7 below also suggest that both treatments are superior to placebo + ADT, wherein APA + ADT is ranked as the preferred treatment option on this endpoint. The comparison of APA + ADT to the other treatments, as presented in Figure 13, also demonstrate that APA + ADT is superior to radiotherapy + ADT (HR: 0.341 [0.254; 0.457]) in terms of delaying time to PSA progression. The scenarios for HVD and LVD have not been run because of no data available.

Table 15: Time to PSA Progression, All-comer Populations (FE), Comparisons vs. Placebo + ADT, Datacut closest to TITAN-FA

Trial	Treatment	Median HR (95% CrI)	Probability HR<1	Rank 1	SUCRA
TITAN	APA + ADT	0.266 [0.218; 0.325]	100.00%	100.0%	100.00%
HORRAD	Radiotherapy + ADT	0.781 [0.629; 0.969]	98.77%	0.0%	49.4%

Abbreviations: ADT = androgen deprivation therapy; APA = apalutamide; CrI = credible interval; FA = final analysis; FE = fixed effects; HR = hazard ratio; PSA = prostate-specific antigen; SUCRA = surface under the cumulative ranking curve.

Figure 13: Time PSA Progression Matrix total population: HR [95% Confidence intervals], p(HR<1), fixed effects



Comparators are ordered according to the SUCRA. Cells contain HR with [95% Confidence intervals], and P(HR<1) (row vs column). Abbreviations: ADT = androgen deprivation therapy; APA = apalutamide; HR = hazard ratio; P = probability; PL = placebo; PSA = prostate-specific antigen; Radioth = radiation therapy; TTPSA: time to PSA progression.

The scenarios for HVD and LVD have not been run because of no data available.

Safety

The safety outcomes deemed relevant to be analysed included:

- Adverse Events (AEs)
  - Any grade
- Treatment discontinuations due to AEs
- Serious AEs (SAEs)
- Death

Only the GETUG-AFU trial included data for a relevant outcome and only for SAE's (see Table 10). For the remaining outcomes the results of the TITAN study will serve as a comparison between APA+ADT and placebo+ADT (see Table 16). Furthermore, a narrative report of toxicity data for docetaxel and radiotherapy is also provided in appendix F.

Table 16: Data on Overall AEs (Any or Severe), Discontinuations and Death Reported in TITAN.

Study	Arm	AEs (overall)		Discontinuations			Death		
		Any	Serious	All cause	AEs	Loss of Efficacy	All cause	Treatment-related	Metastases-related
Chi et al 2019 (46)	APA+ADT	507/524 (96.8%)	153/524 (29.2%)	NR	42/524 (8%)	NR	18/524 (3.4%)	10/524 (1.9%)	8/524 (1.5%)

Chi et al 2021 (35)	Placebo+ADT	509/527 (96.6%)	115/527 (21.8%)	NR	28/527 (5.3%)	NR	23/527 (4.4%)	16/527 (3%)	7/527 (1.3%)

Abbreviations: ADT = androgen-deprivation therapy; APA = apalutamide; NR = not reported.

Overall AEs

The TITAN trial found similar rates of overall AEs for APA + ADT (96.8%) and placebo + ADT (96.6%) but a higher rate of drug-related AEs in the combination arm of APA + ADT (60%) compared to the placebo + ADT combination arm (41.6%) (35).

Treatment discontinuations due to AEs

The TITAN trial found a slightly elevated rate of discontinuations due to AEs in the APA+ADT arm (8%) compared to the placebo+ADT (5.3%) (35)

SAEs

The TITAN trial found an elevated rate of SAEs in the APA+ADT arm (29.2%) compared to the placebo+ADT (21.8%) (35). The GETUG-AFU trial reports 0 SAEs in the placebo+ADT arm and 73 (38.2%) in the DOC+ADT arm, making an indirect comparison impossible and redundant (31).

Safety comparison

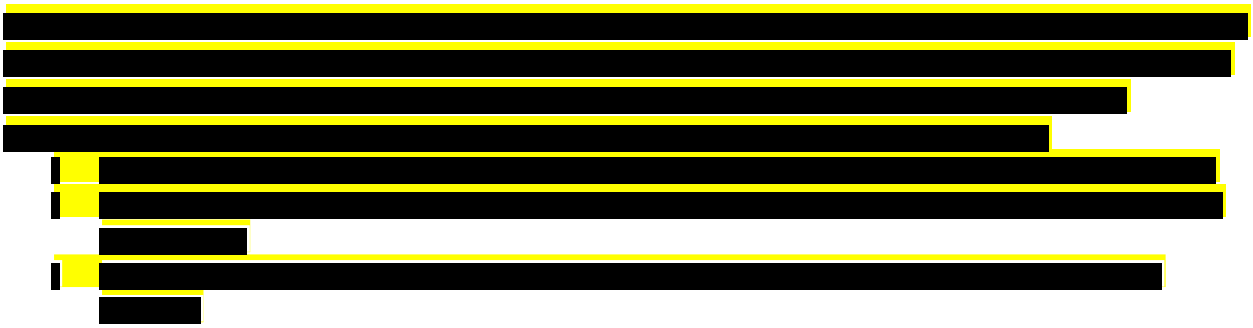
As comparable data is very limited for safety analyses and no indirect comparisons hence were possible, a narrative report of available toxicity data for docetaxel and radiotherapy is provided in appendix F. Hereunder we address some main points in comparison to apalutamide:

Docetaxel is associated with severe chemotherapy-related adverse events and is not suitable for all mHSPC patients who have varying eligibility, fitness and/or treatment preference. In the GETUG-AFU 15, CHAARTED and STAMPEDE trials, which compared docetaxel with ADT alone, toxicity associated with docetaxel was mainly haematologic, with approximately 12% to 15% of patients experiencing grade 3 to 4 neutropenia and 6% to 15% of patients experiencing grade 3 to 4 febrile neutropenia. Treatment-related deaths attributed to neutropenia led the GETUG-AFU 15 investigators to add prophylactic granulocyte colony-stimulating factor to the study protocol. Furthermore, treatment with docetaxel in patients with mHSPC requires pre-medication with steroids which can lead to additional side effects. Treatment with docetaxel requires frequent hospital visits for the initial infusion and ongoing patient monitoring related to the drug's safety profile including risk of neutropenia.

While **radiation therapy** itself is painless it is associated with a number of side effects, such as fatigue and tiredness, as well as 'radiation disease' which includes urinary, bowel, erection and fertility problems. In the STAMPEDE trial 48 (5%) adverse events (grade 3–4) were reported during radiotherapy and 37 (4%) after radiotherapy. The proportion reporting at least one severe adverse event (grade 3 or worse) was similar by treatment group in the safety population (398 [38%] with control and 380 [39%] with radiotherapy).
43 (5%) patients reported their worst acute bladder toxic effect as grade 3 or 4, and eight (1%) reported their worst acute bowel toxic effect as grade 3 or 4.
Urinary problems are usually caused by irritation to the urethra and bladder lining due to RT. Patients report needing to urinate frequently, night time incontinence and leaking, difficulty urinating or a sudden urge to urinate, a burning feeling while urinating and blood in the urine. RT may also result in a narrowing of the urethra which may cause additional problems with urination. Common bowel problems include flatulence, diarrhoea, abdominal

pain, a feeling of being unable to empty the bowel fully, bleeding and faecal incontinence. Patients who wish to have a family are generally advised to store semen samples before commencing RT as the cells that produce semen may be damaged during the treatment.

Apalutamide is well-tolerated and suitable for all patients with mHSPC. The safety profile of apalutamide is known from its use in non-metastatic castration-resistant prostate cancer (nmCRPC). APA + ADT is well tolerated and associated with a manageable safety profile. Rash and hypothyroidism have been reported and are manageable as assessed by DMC (45). The safety/tolerability profile of APA + ADT in patients with mHSPC is consistent with the results of the SPARTAN trial in nmCRPC. Similar rates of treatment-related AEs were observed with APA + ADT and placebo + ADT in patients with mHSPC, despite a longer median treatment duration on apalutamide (20.5 months) than placebo (18.3 months). The addition of apalutamide to ADT was associated with a low rate of treatment discontinuation due to TEAEs (8% with apalutamide + ADT vs 5% with placebo + ADT).



Patient-reported outcomes in the TITAN trial
Upon feasibility assessment of the available PRO data it was determined that a comparison on PROs was not feasible. Instead a brief overview of the PRO data from the TITAN study is presented below.

HRQoL was measured in TITAN using the Functional Assessment of Cancer Therapy-Prostate (FACT-P), EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) Visual Analog Scale (VAS), Brief Pain Index-Short Form (BPI-SF) interference subscale, and Brief Fatigue Inventory (BFI).

Patients maintained a HRQoL at a level similar to that observed in the general population in the TITAN trial (2,4,46). The majority of patients reported no or low levels of pain and fatigue, and were able to maintain their overall level of HRQoL, including functional, social and emotional well-being (31,46). Treatment with Apalutamide did not affect patients' ability to work or complete their normal daily activities and were not limited by lack of energy or pain (31,46).

Hereunder data from FACT-P and EQ-5D. FACT-P and EQ-5D-5L were completed during cycle one to cycle seven, then every other cycle until the end of treatment, and at months 4, 8, and 12 in follow-up. Because patient-reported outcome assessments were collected by treatment cycle, per the study protocol, the patient-reported outcome results over time are reported in the same manner, by treatment cycle.

FACT-P
Group mean total scores for HRQoL, as measured by the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire, were similar between the apalutamide + ADT and placebo + ADT treatment arms (no formal

statistical testing was performed) and were maintained from baseline to end of treatment (46). Group mean scores at baseline for FACT-G (apalutamide + ADT: 79.50; placebo + ADT: 78.81) were consistent with the FACT-G population norm for adult men (80.9 [SD: 17.4]), indicating that patients with mHSPC treated with apalutamide + ADT experienced similar HRQoL to the general population (4,46). Group mean scores for each of the FACT-G subscales were similar between treatment groups and maintained from baseline to end of treatment except for the physical well-being subscale, where patients in both treatment groups experienced a nominal decline (46). Results for the FACT-G subscales showed that treatment with apalutamide + ADT allowed patients to maintain their functional, social and emotional well-being (46).

EQ-5D

HRQoL was assessed in the TITAN trial using the EQ-5D-5L questionnaire. EQ-5D-5L comprise of five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and five levels (no problems, slight problems, moderate problems, severe problems and extreme problems). As opposed to EQ-5D-3L, the five levels improves the sensitivity of the analysis as well as reduces the ceiling effect.

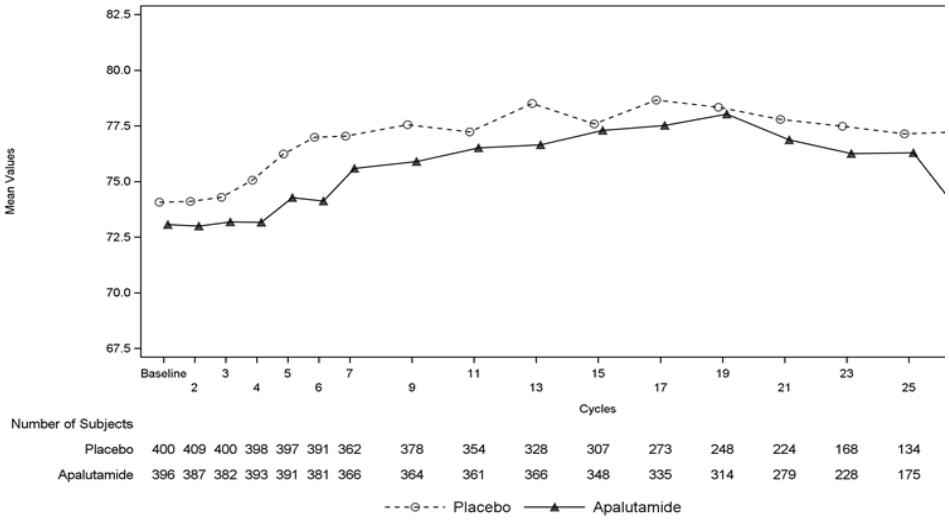
Group mean scores for HRQoL, as measured by EQ-5D-5L Visual Analogue Scale (VAS) and health utility index scores (HUI), were similar between the apalutamide + ADT and placebo + ADT treatment arms (no formal statistical testing was performed) and were maintained from baseline to end of treatment (46). For the repeated measures analysis of EQ-5D-5L scores, there were no statistically significant differences in EQ-5D-5L VAS and HUI scores between the apalutamide + ADT and placebo + ADT arms.

The group mean scores presented in Figure 14 and Figure 15, and the repeated measures analysis presented in Figure 16 and Figure 17 are from the interim analysis of the TITAN trial (clinical cut off: 23 November 2018; median follow-up ~22 months).
The group mean scores presented in Figure 18 and Figure 19, and the repeated measures analysis presented in Figure 20 and Figure 21 are from the final analysis of the TITAN (clinical cut off: 7 September 2020; median follow-up 44 months).

Results are reported for the total population, including high volume and low volume disease, previous docetaxel use, previous treatment for localized disease, and previously or newly diagnosed disease.

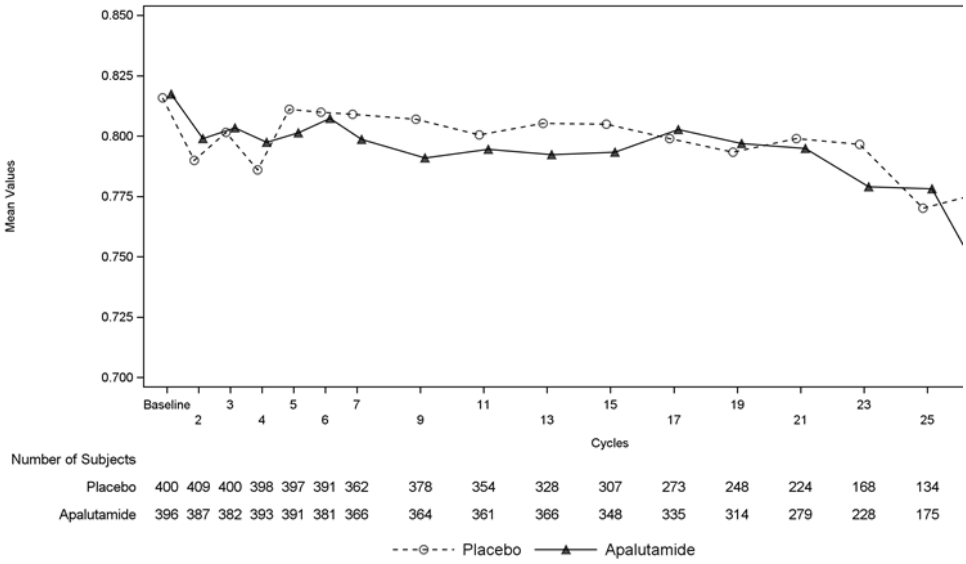
Results from interim analysis

Figure 14 Group mean EQ-5D-5L VAS scores over time (interim analysis); ITT population



EQ-5D = EuroQol five-dimensional questionnaire; ITT = intent to treat; VAS = visual analogue scale
Note: Higher EQ-5D-5L VAS scores indicate better health status. SOURCE: TITAN Review of PRO Results and Messages Slide deck (Data on file)

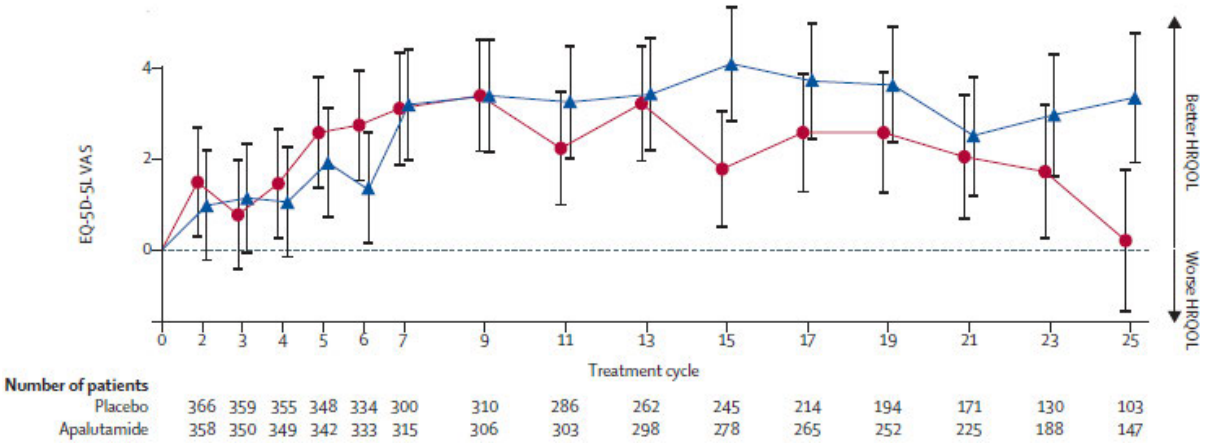
Figure 15 Group mean EQ-5D-5L HUI scores over time (interim analysis); ITT population



EQ-5D = EuroQol five-dimensional questionnaire; HUI = Health Utilities Index; ITT = intent to treat

Note: Higher EQ-5D-5L HUI scores indicate better health status. SOURCE: TITAN Review of PRO Results and Messages Slide deck (Data on file).

Figure 16 Mean change from baseline in EQ-5D-5L VAS scores (MMRM, interim analysis); ITT population

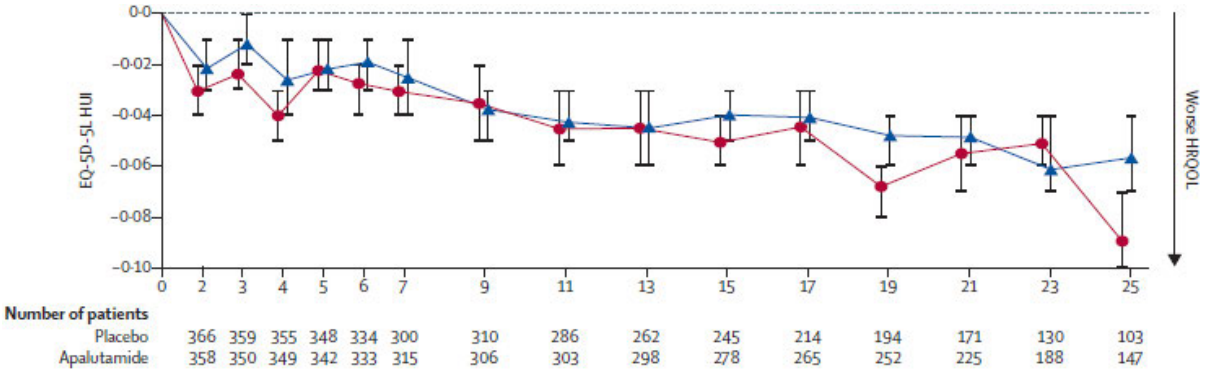


Red: PLACEBO, Blue: APALUTAMIDE.

EQ-5D = EuroQol five-dimensional questionnaire; ITT = intent-to-treat; MMRM = mixed models for repeated measures; VAS = visual analogue scale

Note: Higher EQ-5D-5L VAS scores indicate better health status.

SOURCE: Agarwal et al. 2019, Figure 5D



Red: PLACEBO, Blue: APALUTAMIDE.

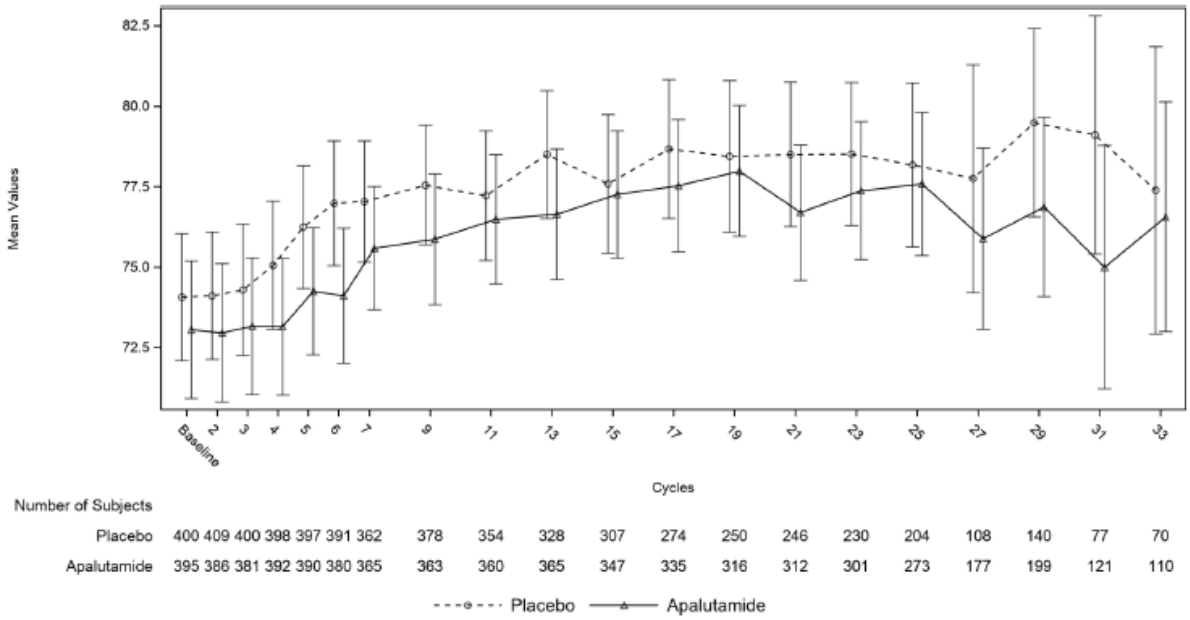
EQ-5D = EuroQol five-dimensional questionnaire; HUI = Health Utilities Index; ITT = intent-to-treat; MMRM = mixed models for repeated measures

Note: Higher EQ-5D-5L HUI scores indicate better health status.

SOURCE: Agarwal et al. 2019, Figure 5C

Results from final analysis

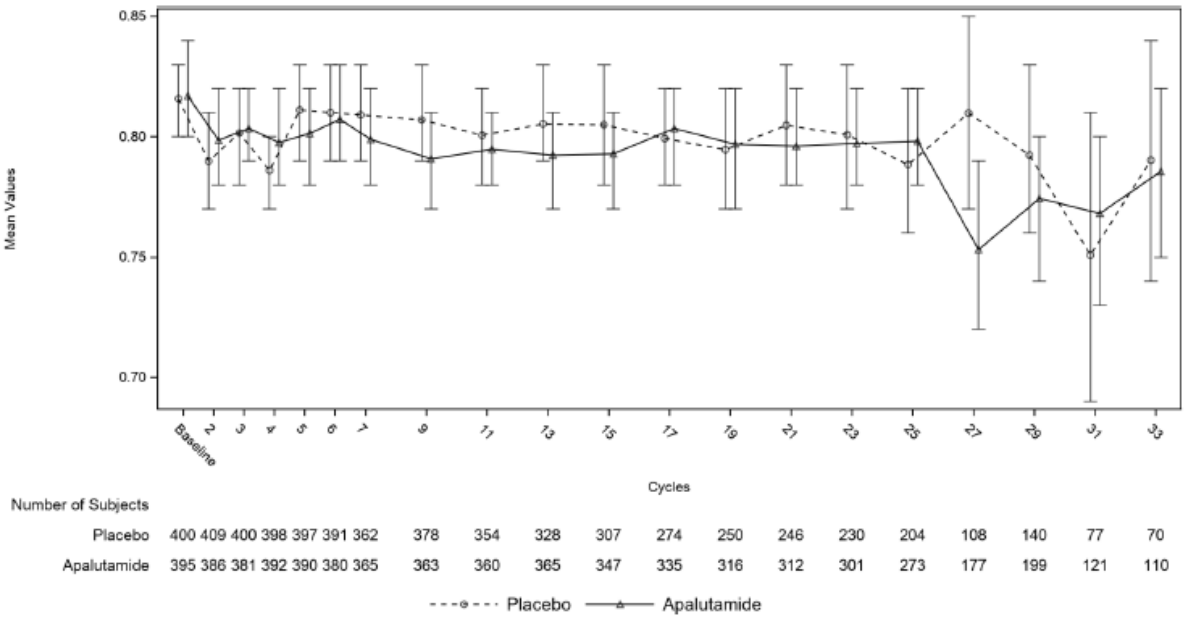
Figure 18 Group mean EQ-5D-5L VAS scores over time (final analysis); ITT population



EQ-5D = EuroQol five-dimensional questionnaire; ITT = intent to treat; VAS = visual analogue scale

Note: Higher EQ-5D-5L VAS scores indicate better health status. Note: Due to significant amount of missing data during final treatment cycles, truncation is applied for all subsequent visits at the first visit where 90% or more of the subjects are missing for each endpoint and from either arm. This truncation cycle is applied across both treatment arms. Note: Vertical bars represent 95% Confidence Intervals. SOURCE: GPRO02G1 – TITAN Final Analysis – Patient-reported outcomes (PRO) – Version 9.4 SAS System Output

Figure 19 Group mean EQ-5D-5L HUI scores over time (final analysis); ITT population

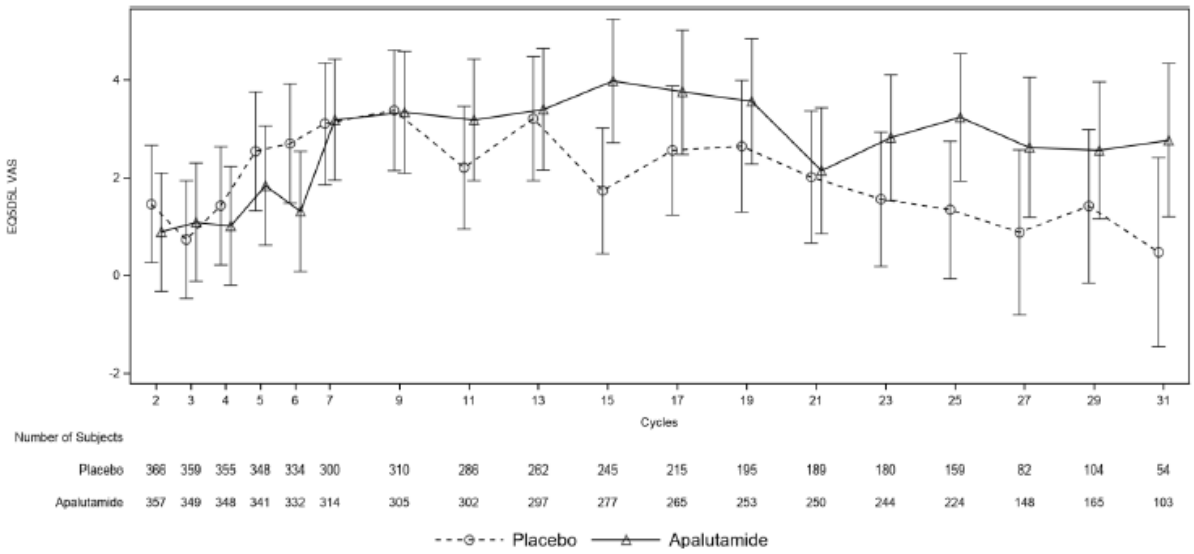


EQ-5D = EuroQol five-dimensional questionnaire; HUI = Health Utilities Index; ITT = intent to treat

Note: Higher EQ-5D-5L HUI scores indicate better health status

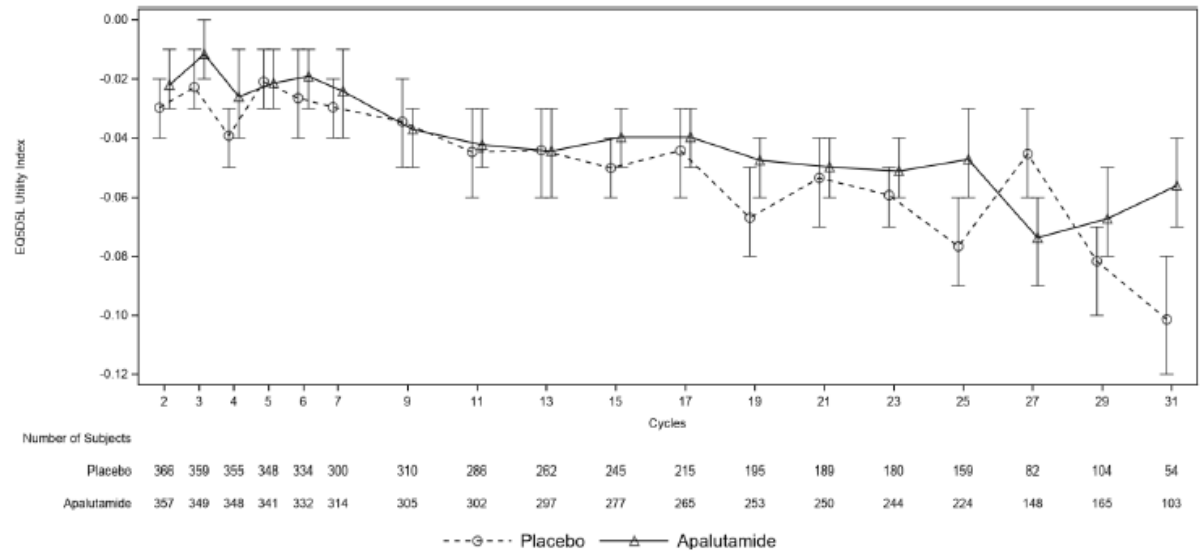
Note: Due to significant amount of missing data during final treatment cycles, truncation is applied for all subsequent visits at the first visit where 90% or more of the subjects are missing for each endpoint and from either arm. This truncation cycle is applied across both treatment arms. Note: Vertical bars represent 95% Confidence Intervals. SOURCE: GPRO02I1 – TITAN Final Analysis – Patient-reported outcomes (PRO) – Version 9.4 SAS System Output

Figure 20 Mean change from baseline in EQ-5D-5L VAS scores (MMRM, final analysis); ITT population



EQ-5D = EuroQol five-dimensional questionnaire; ITT = intent-to-treat; MMRM = mixed models for repeated measures; VAS = visual analogue scale
Note: Higher EQ-5D-5L VAS scores indicate better health status
Note: Due to significant amount of missing data during final treatment cycles, truncation is applied for all subsequent visits at the first visit where 90% or more of the subjects are missing for each endpoint and from either arm. This truncation cycle is applied across both treatment arms.
Note: LS means are derived based on the mixed effects model with baseline, visit, treatment, visit by treatment interaction as fixed effects and individual subject as random effect. The model includes stratification covariates. Note: Vertical bars represent standard error estimates. SOURCE: GPRO04M – TITAN Final Analysis – Patient-reported outcomes (PRO) – Version 9.4 SAS System Output

Figure 21 Mean change from baseline in EQ-5D-5L HUI scores (MMRM, final analysis); ITT population



EQ-5D = EuroQol five-dimensional questionnaire; HUI = Health Utilities Index; ITT = intent-to-treat; MMRM = mixed models for repeated measures
Note: Higher EQ-5D-5L HUI scores indicate better health status
Note: Due to significant amount of missing data during final treatment cycles, truncation is applied for all subsequent visits at the first visit where 90% or more of the subjects are missing for each endpoint and from either arm. This truncation cycle is applied across both treatment arms.
Note: LS means are derived based on the mixed effects model with baseline, visit, treatment, visit by treatment interaction as fixed effects and individual subject as random effect. The model includes stratification covariates. Note: Vertical bars represent standard error estimates.
SOURCE: GPRO04N – TITAN Final Analysis – Patient-reported outcomes (PRO) – Version 9.4 SAS System Output

Narrative comparison with HRQoL for Docetaxel (*no HRQoL outcomes have been reported for RT treatment)*

DOC+ADT is associated with reductions in HRQoL in patients with mHSPC. In GETUG-AFU trial, overall HRQoL was significantly worse in patients receiving DOC+ADT compared with ADT alone at 3 and 6 months, as reported in Gravis 2013 (47). At 12 months, HRQoL scores returned to baseline, with no significant difference observed between the two treatment groups (p=0.696).
Similarly, in the CHAARTED trial, overall HRQoL (as measured by the FACT-P questionnaire) was significantly worse in patients receiving D+ADT compared with those receiving ADT alone at 3 months (p=0.02) (48). Significant improvements in HRQoL with DOC+ADT compared with ADT alone were not seen in the overall mHSPC patient population until 12 months after the start of treatment (p=0.04), even though DOC+ADT was only administered for 18 weeks (48). HRQoL data comparing DOC+ADT with ADT alone from the STAMPEDE trial have not been reported; but they have for the comparison with abiraterone + ADT , showing that HRQoL was significantly worse for patients treated with DOC+ADT over 2 years (p=0.021) (49).

In a qualitative study of the real-world experience of patients with mHSPC who received DOC+ADT, most patients reported experiencing fatigue (68.9%), hair loss/thinning (73.3%) and nausea (60.2%). Patients reported limitations in daily activities that presented in difficulties in walking, pursuing sports and leisure activities and being able to work. Social interactions were also impacted due to risk of infection. Emotional and psychological impacts were reported, including anger and volatile moods due to treatment, as well as a changed outlook on life. Carers were also reported to be negatively affected by D+ADT treatment (50).

Unlike docetaxel, patients receiving apalutamide maintain a HRQoL similar to ADT alone. As shown in the prior figures (14-21), patients in TITAN maintained their HRQoL throughout treatment. Treatment with apalutamide + ADT resulted in a similar impact on fatigue intensity, fatigue interference and maintained functional, social and emotional well-being compared with ADT alone, allowing patients to continue with their daily activities and lives for longer irrespective of risk stratification or tumour burden (51). Apalutamide + ADT consistently showed favorable outcomes in pain-related PRO outcomes such as pain analysis, pain interference and change from baseline scores (51).
Based on patient preferences for treatment attributes from a discrete choice experiment (DCE), apalutamide displays more positive attributes that matter to patients than docetaxel. Patients with mHSPC in the DCE valued treatment effectiveness, pain control and the avoidance of nausea/vomiting as the most important treatment attributes(52). A time trade-off study also reported that patients value avoiding chemotherapy (53).

Summary of findings

The objective of this NMA was to gain an in-depth understanding of the clinical efficacy of APA in combination with ADT compared to approved or recommended therapies for the treatment of mHSPC. To this end, an SLR of RCTs that evaluated the therapies of interest in patients with mHSPC was conducted according to NICE guidelines (45), with respect to technology appraisal (TA) submissions, the PRISMA statement (54), and the Cochrane Handbook for Systematic Reviews of Interventions (55). Study populations, treatment characteristics, outcomes evaluated, and quality of the trials identified via the SLR were further assessed to determine whether there was sufficient, appropriate and comparable RCT evidence to proceed with NMAs for the clinical outcomes of interest. Following the completion of the feasibility assessment, and where deemed feasible, Bayesian NMAs were conducted to generate estimates of the comparative efficacy.

After the feasibility assessment, four trials (CHAARTED, GETUG-AFU15, HORRAD and STAMPEDE) were identified for inclusion in the NMA alongside the TITAN trial. The NMA evaluated the relative efficacy of APA + ADT, DOC + ADT (with or without prednisone/prednisolone), radiotherapy + ADT and ADT alone based on the available data from the identified trials. Where data is available, the relative efficacy was presented separately for high volume and low volume patients, as requested by DMC. Fixed-effects models were presented in this submission due to limitations of most of the outcome networks (i.e., the presence of only one or few studies per treatment comparison).
Based on the NMA results, the combination treatments all offered an advantage over ADT alone in terms of improved OS, rPFS, and time to PSA progression outcomes. Treatment with APA + ADT resulted in the best outcomes for all efficacy analyses, and was overall consistent for HVD and LVD.

The safety of DOC+ADT, APA + ADT, and ADT alone was explored based on the TITAN and GETUG-AFU 15 trials. In terms of safety, the results show that APA+ADT were similar to placebo for rates of overall AEs. Based also on a narrative report of adverse events, results shows that apalutamide plus ADT is well tolerated. Rash and hypothyroidism have been reported and are manageable. The safety/tolerability profile of APA + ADT in patients with mHSPC is consistent with the results of the SPARTAN trial in nmCRPC.

Lastly, HRQoL results shows that quality of life was maintained in all patients receiving treatment with apalutamide, with no substantial deterioration in HRQoL during treatment (opposed to DOC+ADT treatment). Apalutamide fulfills the main treatment goal of many physicians, being to maximize time to progression to mCRPC and the HRQoL of their patients.

8. Health economic analysis

As requested by DMC, we are submitting two models; one assessing the incremental cost-effectiveness of apalutamide + ADT compared with RT + ADT in low volume mHSPC patients and one assessing the incremental cost-effectiveness of apalutamide + ADT compared with DOC + ADT in high volume mHSPC patients.

The objective of the cost-effectiveness models (CEM) are to assess whether apalutamide + ADT is cost-effective versus current treatment options for mHSPC.

The CEM was developed in accordance with the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Good Modelling Practices (56), and in keeping with the requirements of HTA bodies such as UK's NICE.

8.1 Model

The models were developed in Microsoft Excel® 2010. The models were 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.

The same model structure was used for LVD and HVD models:

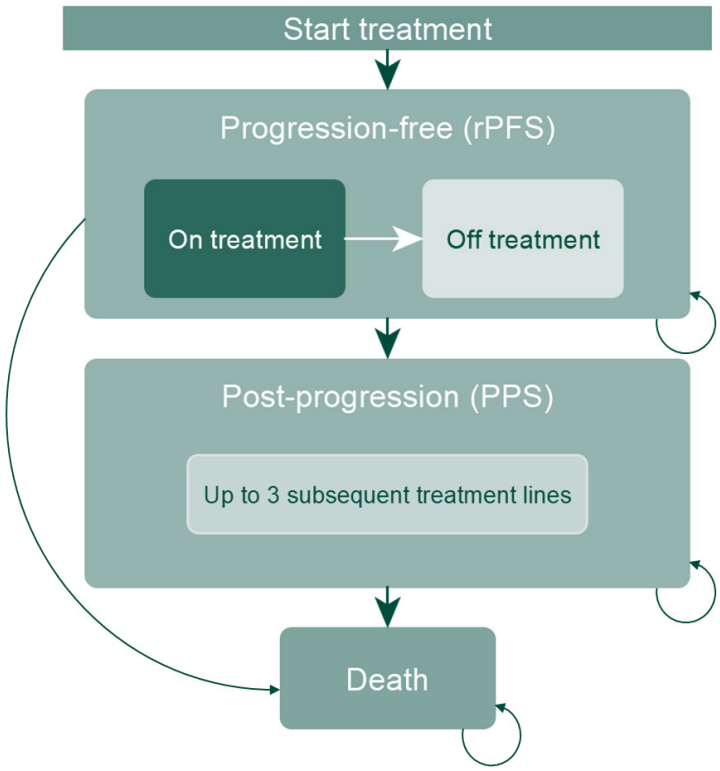
The model followed patients with mHSPC from initiation of treatment until disease progression or death (Figure 22). Thus, patients in this model were partitioned into three health states: progression-free (mHSPC), post-progression (mCRPC), and death.

Within the progression-free health state, it was important to track time on- and off-treatment, to accurately account for treatment costs. Within the mCRPC setting, patients could receive subsequent treatments, which were modeled as a market basket approach depending on the preceding mHSPC treatment.

An underlying assumption in this approach was that the impact of subsequent treatment as seen in the trial is already captured implicitly in the predicted OS, so only costs are considered specifically in the model.

Costs were assigned to each health state, and utilities were applied according to the patients' disease progression status and the type of treatment received. As the model progressed cycle by cycle for the duration of the time horizon, cost and utility data were summed per treatment arm, allowing for the calculation of differences in accumulated costs and effectiveness between comparators at model completion.

Figure 22: Model structure

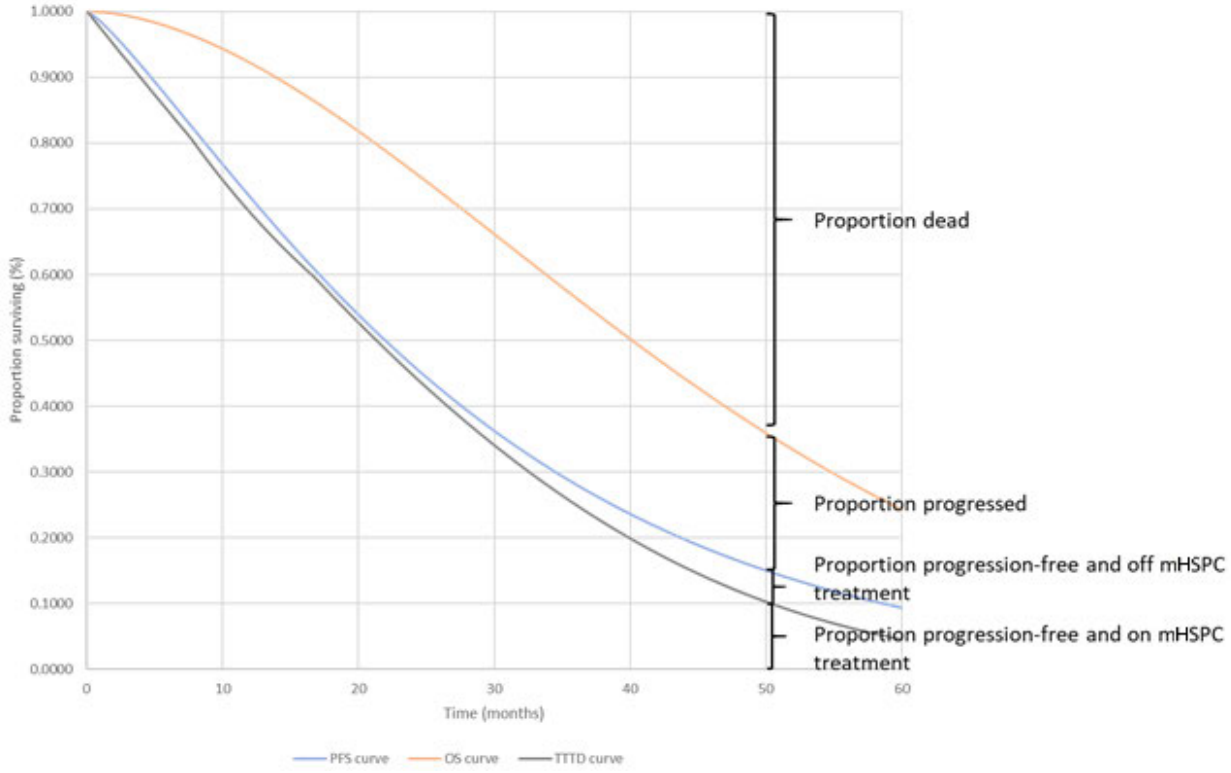


PFS= progression-free survival; PPS= post-progression survival

The CEM was programmed using a partitioned survival models (PSM) approach, which apportions patients to states of rPFS, PPS, and death based on the area under each curve. The time to treatment discontinuation (TTTD) curve was also used for treatment cost calculation purposes. The model assumed that time on treatment cannot exceed rPFS. Figure 23 presents the curves used in survival partition calculations. The model cycle length was set to 1 week to best capture the desired clinical outcomes.

The flexibility to pick different parametric survival models for TTTD, rPFS and OS was incorporated in the PSM to explore the reliability of the resulting extrapolations.

Figure 23: Curves Used in Survival Partition Calculations



mHSPC= metastatic hormone-sensitive prostate cancer; OS= overall survival; PFS= progression-free survival; TTTD= time to treatment discontinuation

8.1.1 Justification of the modelling approach

A thorough review of HTA submissions and associated criticisms in metastatic prostate cancer was conducted. No submissions specific to mHSPC were identified, so submissions specific to first-line treatment in mCRPC were reviewed instead. Table 17 presents the characteristics of these submissions, including two submissions to NICE, two to the pan-Canadian Oncology Drug Review (pCODR), and one to the Swedish Dental and Pharmaceutical Benefits Agency (TLV). The most common model types implemented were PSMs (57,58) and discrete event simulations (DESs) (59,60), incorporated in two studies each. The pCODR submissions for enzalutamide (61) was the only report that did not specify the model type used in their submitted analyses. Therefore, a PSM approach was determined to be the most widely acceptable for conducting this analysis.

Table 17: Characteristics of submitted HTA reports in first-line mCRPC

HTA body, Intervention	Comparator	Country	Study type	Model type, Health states, Cycle length
NICE (TA387), abiraterone	AAP vs. BSC (prednisolone plus placebo)	United Kingdom	CUA	DES NA – no explicit health states in an individual time-to-event simulation model NA

HTA body, Intervention	Comparator	Country	Study type	Model type, Health states, Cycle length
NICE (TA377), enzalutamide	Enzalutamide vs. AAP; Enzalutamide vs. BSC	United Kingdom	CUA	PSM 3 health states[a] (PF/PD/D) 1 week
pCODR, abiraterone	AAP vs. Prednisone	Canada	CUA	PSM 3 health states (PF/PD/D) NR
pCODR, enzalutamide	Enzalutamide vs. BSC (WW); Enzalutamide vs. WW followed by docetaxel; Enzalutamide vs. AAP	Canada	CUA	NR NR NR
TLV, abiraterone	AAP vs. BSC; AAP vs. Enzalutamide	Sweden	CUA	DES NA – no explicit health states in an individual time-to-event simulation model NA

AAP= abiraterone acetate plus prednisone, BSC= best supportive care, CUA= cost utility analysis, D= death, DES= discrete event simulation, NA= not applicable, NICE= National Institute for Health and Care Excellence, NR= not recorded, pCODR= pan-Canadian Oncology Drug Review, PD= progressive disease, PF= progression-free, PSM= partitioned survival model, TLV= Swedish Dental and Pharmaceutical Benefits Agency, WW= watchful waiting

8.1.2 Time Horizon

In order to capture the costs and benefits of each comparator, a 30 year time horizon was used. The impact of using an alternative time horizon on the model results was tested in the scenario analyses.

8.1.3 Annual Discount rate

In line with the Danish Ministers of Finance recommendations, costs and benefits were both discounted at a rate of 3.5% per year.

8.1.4 Cycle length

A weekly cycle length was applied to facilitate comparability with other treatments. Half-cycle correction was also adopted in the model.

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

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

Table 18: Included data in the economic model

Data	Data source
Clinical data for the economic model	The TITAN trial[2]: Clinical efficacy: • rPFS of apalutamide + ADT and ADT alone • OS of apalutamide + ADT and ADT alone • TTTD of apalutamide + ADT and ADT alone **Network meta-analysis (NMA):** Clinical efficacy – Low-volume disease: • RT+ADT o PFS (Hazard Ratio [HR] applied to APA+ADT) [PFS HR: 2.166 (95% CI 1.283-3.655; SE 0.267)] ▪ Assumed that PFS HR is a proxy for rPFS HR for LVD. rPFS comparison (RT+ADT vs APA+ADT) is not available in the NMA in LVD. o OS (HR applied to APA+ADT) [OS HR: 1.307 (95% CI 0.802-2.130; SE 0.249)] o Treatment duration = fixed duration (6 three-week courses) Clinical efficacy – High-volume disease: • DOC+ADT o rPFS (Hazard Ratio [HR] applied to APA+ADT) [rPFS HR: 1.151 (95% CI 0.770-1.717; SE 0.205)] o OS (HR applied to APA+ADT) [OS HR: 1.049 (95% CI 0.795-1.384; SE 0.141)] o Treatment duration = fixed duration (6 three-week courses)
	Safety: Frequency of AEs from TITAN trial (35) • TEAEs of grade 3/4, reported in ⩾1% frequency in apalutamide + ADT and ADT alone study cohorts Frequency of AEs from STAMPEDE trial[83] • TEAEs of grade 3/4, reported in ≥1% frequency in RT + ADT study cohort Frequency of AEs from STAMPEDE trial[29] • TEAEs of grade 3/4, reported in ≥1% frequency in DOC + ADT study cohort
Health-related quality of life	Individual patient data from the TITAN trial (EQ-5D-5L questionnaire with DK preference weights applied) and TITAN repeated measures mixed effect (RMME) analysis (see Appendix I Mapping of HRQoL data)

Treatment cost data	Dosing and frequency of apalutamide were derived from the European Medicines Agency (EMA) SmPC for apalutamide(62). The cost of apalutamide (Erleada) was derived from the Medicines price list of the Danish Medicines Agency (63). Dosing, frequencies and costs of ADT were derived from the Medicines price list and Product summaries of the Danish Medicines Agency (63). Dosing and frequencies for docetaxel and subsequent therapies were taken from EMA (64). The costs were derived from the Medicines price list of the Danish Medicines Agency. In case no costs in Denmark were available, costs were derived from FASS (65). The summaries of product characteristics that is published on the EMA website. Drug costs were derived from https://medicinpriser.dk/default.aspx and cost of RT was derived from the DRG tariffs list.
Market shares of ADT regimens and subsequent treatments	The market shares of ADT regimes were based on assumptions as no market share data for Denmark was readily available. The market shares were assumed to be the same for both mHSPC and mCRPC.
	The market shares of subsequent treatments were based on expected Danish market shares.
Administration costs	Administration costs were taken from the DRG tariffs list (66) based on Medicines Council guidelines.
Disease management costs	AE costs were derived from the DRG tariffs list. End-of-life cost are based on estimations from a UK study which included prostate-cancer patients (67).
Patient time costs	The patient time costs were derived from the Medicines Council. 1 hour of patient time per intravenous administration was assumed to be needed. Transportation costs were derived from the Medicines Council.

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

8.2.2.1 Patient population

The target population for the model is adult men with mHSPC. This population is in line with the population of the TITAN trial (29,31). Refer to section 5 for a description of the Danish population. 500 Danish patients are estimated to be eligible for apalutamide in mHSPC. The mean body weight and mean body surface area of the study population is presented in Table 19. The number are similar to expected in Danish clinical practice.

Table 19: Study population (n=1,052)

Mean age in years (SD)	Mean body weight in kg (SD)	Mean body surface area in m^2 (SD)
68.4 (8.28)	78.34 (16.16)	1.93 (0.23)

Abbreviations: SD= Standard deviation

8.2.2.2 Intervention

Intervention as expected in Danish clinical practice:
Refer to section 5.3.

Intervention in the clinical documentation submitted:
One clinical trial for apalutamide regarding the relevant indication is used as clinical documentation, the TITAN study. The submitted clinical documentation have previously been described in detail, refer to section 7.

Intervention as in the health economic analysis submitted:
Inputs regarding apalutamide in the model are informed by the clinical trial TITAN. The intervention is described below in Table 20.

Table 20: Intervention

Intervention: Apalutamide	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology	TITAN study, EMA SmPC apalutamide	Same as in clinical documentation	Expected to be similar in Danish clinical practice
Length of treatment		Same as in clinical documentation.	Expected to be similar in Danish clinical practice
Criteria for discontinuation	TITAN study, EMA SmPC apalutamide	Treat to progression	Expected to be similar in Danish clinical practice
Position in Danish clinical practice		Newly diagnosed as well as those progressing from localized disease	Newly diagnosed as well as those progressing from localized disease

8.2.2.3 Comparators

The current Danish clinical practice (as described in section 5):
In current Danish clinical practice DOC+ADT and RT+ADT is used in mHSPC. And these comparators were requested by DMC for high and low volume disease respectively.

Comparators in the clinical documentation submitted:

The comparators presented in the clinical documentation submitted are DOC+ADT and RT+ADT based on GETUG-AFU15 (30), CHAARTED (36), STAMPEDE (26) and HORRAD (24) trials. Refer to section 5 where these clinical trials has been described as well as related appendences.

Comparators in the health economic analysis submitted:
The comparators included in the model are DOC+ADT and RT+ADT. The clinical inputs are mainly collected from the same trials as in the clinical documentation.

8.2.2.4 Relative efficacy outcomes

The model inputs derived from the TITAN trial include the following:

- Efficacy outcomes:
    - rPFS: As a co-primary endpoint in the trial, evidence of rPFS was driven by investigator-reviewed radiographic assessment of progression by CT scan, bone scans, and MRI. An rPFS event was classified if either death or progression on the grounds of radiographic evidence occurred.
    - OS: Defined as the time from randomization to the date of death due to any cause.
    - TTTD: Defined as the time from randomization to the date of treatment discontinuation due to any cause
- Health-related quality of life (HRQoL)
- Incidence of AEs

The following data sources were included in the NMA for DOC+ADT specifically and are outlined below. These were used in the NMA (Section 7.1.3) to obtain HRs for including DOC+ADT as a comparator.
The model inputs for DOC+ADT derived from the CHAARTED trial include the following:

- Efficacy outcomes:
    - OS: Defined as the time until death from any cause

The model inputs for DOC+ADT derived from the GETUG-AFU 15 trial include the following:

- rPFS: Defined as the time between randomization and radiographic progression or death (rPFS)
- OS: Defined as the time between randomization and death from any cause.

8.2.2.5 Adjustment for crossover

Upon unblinding of the study at first interim analysis (IA1; median survival follow-up 22.7 months), 96/192 of low-volume disease patients (50%) and 112/335 of high-volume disease patients (33.4%) in the control (ADT alone) arm

were allowed to cross over to the open-label extension phase and received apalutamide. As such, these patients in the control arm received active treatment as of this time point onwards. Patients switching from ADT alone to apalutamide + ADT 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 the analysis 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 national institute for health and care excellence (NICE) decision support unit (DSU) guidelines. A Rank Preserving Structural Failure Time Model (RPSFTM) with no recensoring was used in order to reconstruct the survival duration of ADT patients that crossed over to apalutamide, as if they had never received apalutamide. The adjusted ADT alone Kaplan Meier data will be presented in the upcoming sections (along with the censor at switch analysis and unadjusted curves). The apalutamide + ADT and ADT alone RPSFTM-adjusted curves were used in the base case analysis to predict OS. The resulting hazard ratio of the OS RPSFTM-adjusted curves are:

8.2.2.6 Efficacy outcomes

This section summarizes the methods and inputs used to simulate the time patients spend in each model health state, which ultimately drives the aggregated costs, LYs, and QALYs.

Low-volume disease

The key effectiveness inputs in the model are rPFS (from IA1), OS (from FA), and TTTD (from FA), as shown in Table 21.

Table 21: Key clinical outputs – Low-volume disease

Measure	How used in model	Justification for use	How this is modelled
rPFS (IA1)	To inform time spent progression-free	Co-primary endpoint from TITAN; reported across trials	• Joint fits (apalutamide + ADT and ADT alone) • RT+ADT comparison – Low-volume disease: [PFS HR vs APA+ADT: 2.166 (95% CI 1.283-3.655; SE 0.267)]
OS (FA)	To inform time until death		• Joint fits (apalutamide + ADT and ADT alone) • RT+ADT comparison – Low-volume disease: [OS HR vs APA+ADT: 1.307 (95% CI 0.802- 2.130; SE 0.249)]
TTTD (FA)	To inform time on treatment	Best estimate of time on treatment	• Individual fits (apalutamide + ADT only; ADT is assumed to be applied continuously until death) • RT+ADT: fixed duration (20 RT fractions over 4 weeks)

ADT= androgen deprivation therapy; DOC= docetaxel; FA= final analysis (median follow-up 44 months); HR= hazard ratio; IA1= interim analysis 1 (median follow-up 22.7 months); OS= overall survival; rPFS= radiographic progression-free survival; RT= radiotherapy; TTTD= time to treatment discontinuation

A joint fits approach was used as the base case to model OS using a Weibull distribution. rPFS was used to define progression, since this was a co-primary endpoint of the TITAN trial. A joint fits approach was used as the base case to model rPFS using a Gompertz distribution. Joint fits were chosen since the proportional hazards assumption was not violated in the TITAN trial.

Modelling treatment duration is important in order for drug costs to be estimated in the model. TTTD curves from the TITAN trial were used to model treatment duration for apalutamide + ADT. ADT alone was assumed to be continued until death as determined by clinical experts. An individual fits approach was therefore applied to the apalutamide + ADT arm. Since RT+ADT is fixed duration therapy; the time on treatment was modelled as such.

High-volume disease

The key effectiveness inputs in the model are rPFS (from IA1), OS (from FA), and TTTD (from FA), as shown in Table 22.

Table 22: Key clinical outputs – High-volume disease

Measure	How used in model	Justification for use	How this is modelled
rPFS (IA1)	To inform time spent progression-free	Co-primary endpoint from TITAN; reported across trials	• Joint fits (apalutamide + ADT and ADT alone) • DOC+ADT comparison – High-volume disease: [rPFS HR vs APA+ADT: 1.24 (95% CI 0.908-1.680;)]
OS (FA)	To inform time until death		• Joint fits (apalutamide + ADT and ADT alone) • DOC+ADT comparison – High-volume disease: [OS HR vs APA+ADT: 1.049 (95% CI 0.795-1.384 ; SE 0.141)]
TTTD (FA)	To inform time on treatment	Best estimate of time on treatment	• Individual fits (apalutamide + ADT only; ADT is assumed to be applied continuously until death) • DOC+ADT: fixed duration (6 three-week courses)

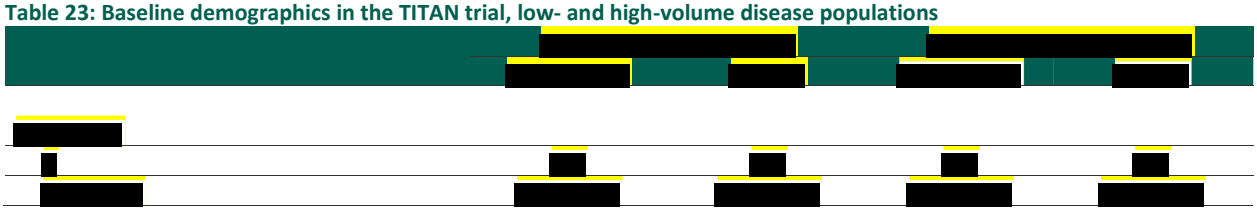
ADT= androgen deprivation therapy; DOC= docetaxel; FA= final analysis (median follow-up 44 months); HR= hazard ratio; IA1= interim analysis 1 (median follow-up 22.7 months); OS= overall survival; rPFS= radiographic progession-free survival; TTTD= time to treatment discontinuation

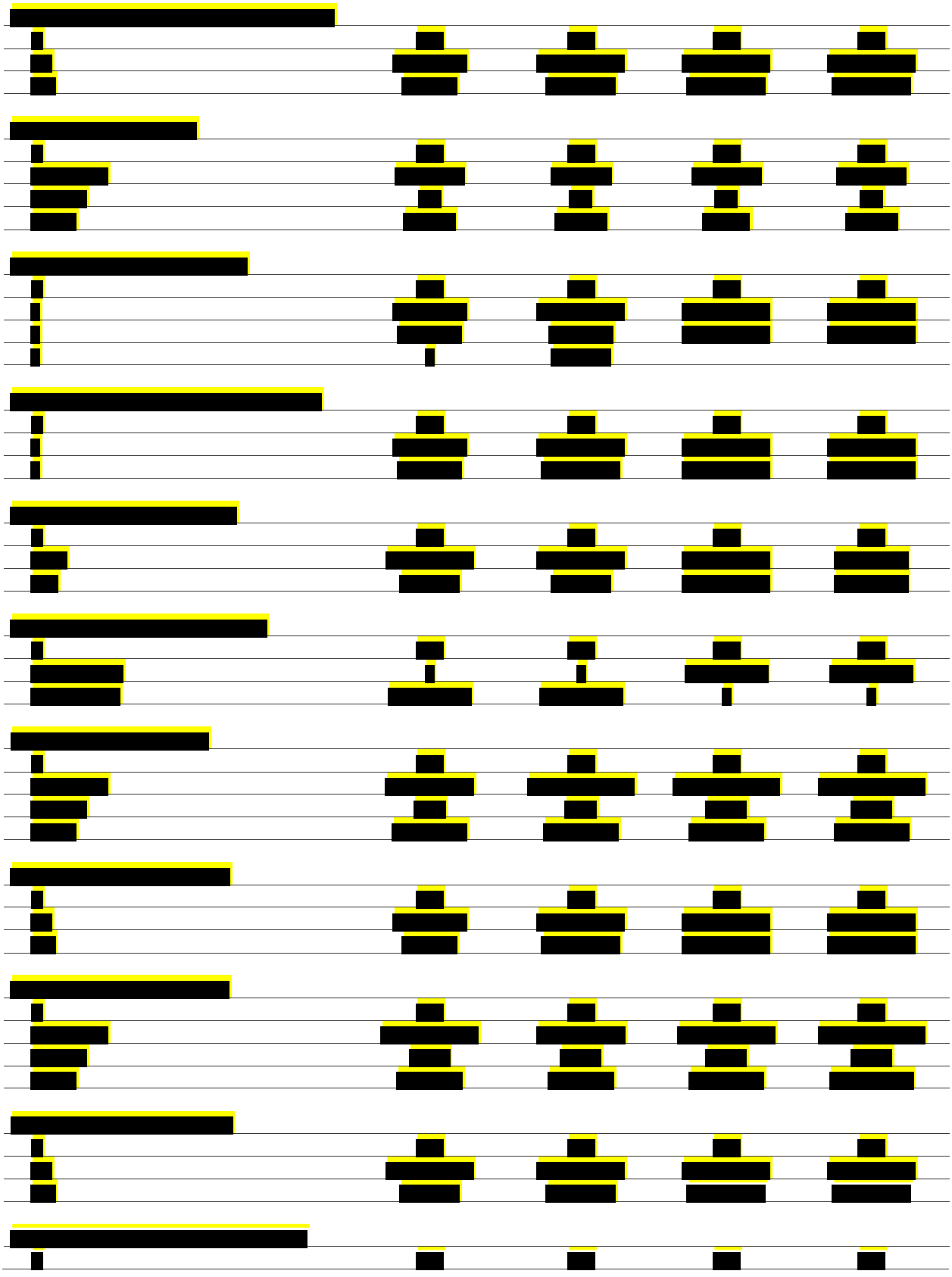
A joint fits approach was used as the base case to model OS using a Lognormal distribution. rPFS was used to define progression, since this was a co-primary endpoint of the TITAN trial. A joint fits approach was used as the base case to model rPFS using a Weibull distribution. Joint fits were chosen since the proportional hazards assumption was not violated in the TITAN trial.

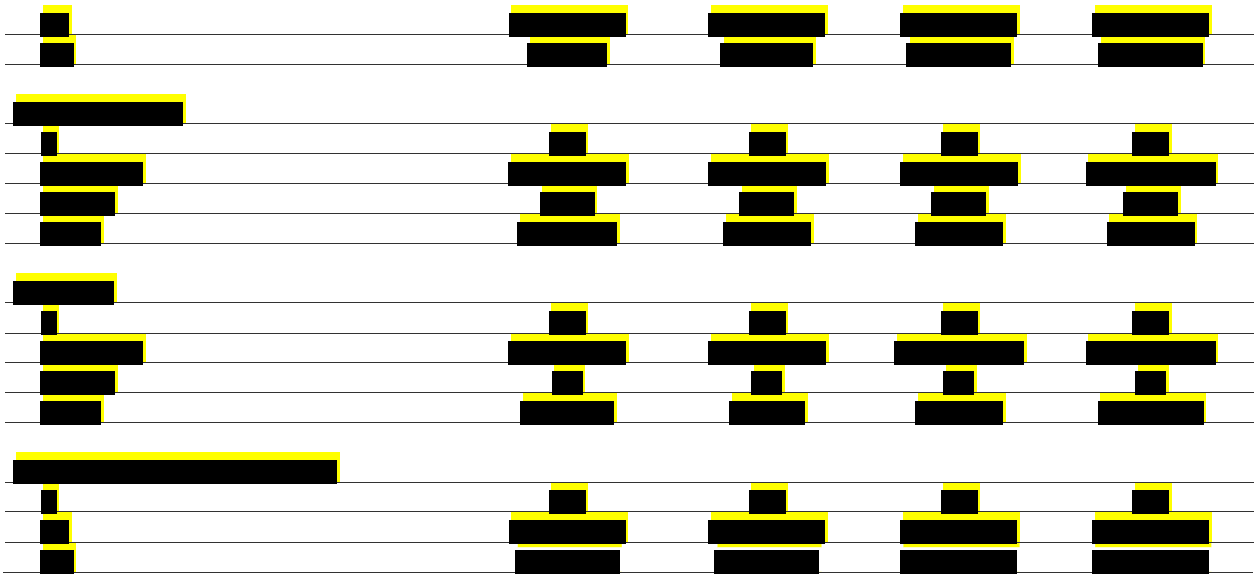
Modelling treatment duration is important in order for drug costs to be estimated in the model. TTTD curves from the TITAN trial were used to model treatment duration for apalutamide + ADT. ADT alone was assumed to be continued until death as determined by clinical experts. An individual fits approach was therefore applied to the apalutamide + ADT arm. Since DOC+ADT is fixed duration therapy; the time on treatment was modelled as such.

Efficacy analyses were performed using either low-volume disease or high-volume disease population. The patient characteristics of the both populations are presented in Table 23.

Table 23: Baseline demographics in the TITAN trial, low- and high-volume disease populations





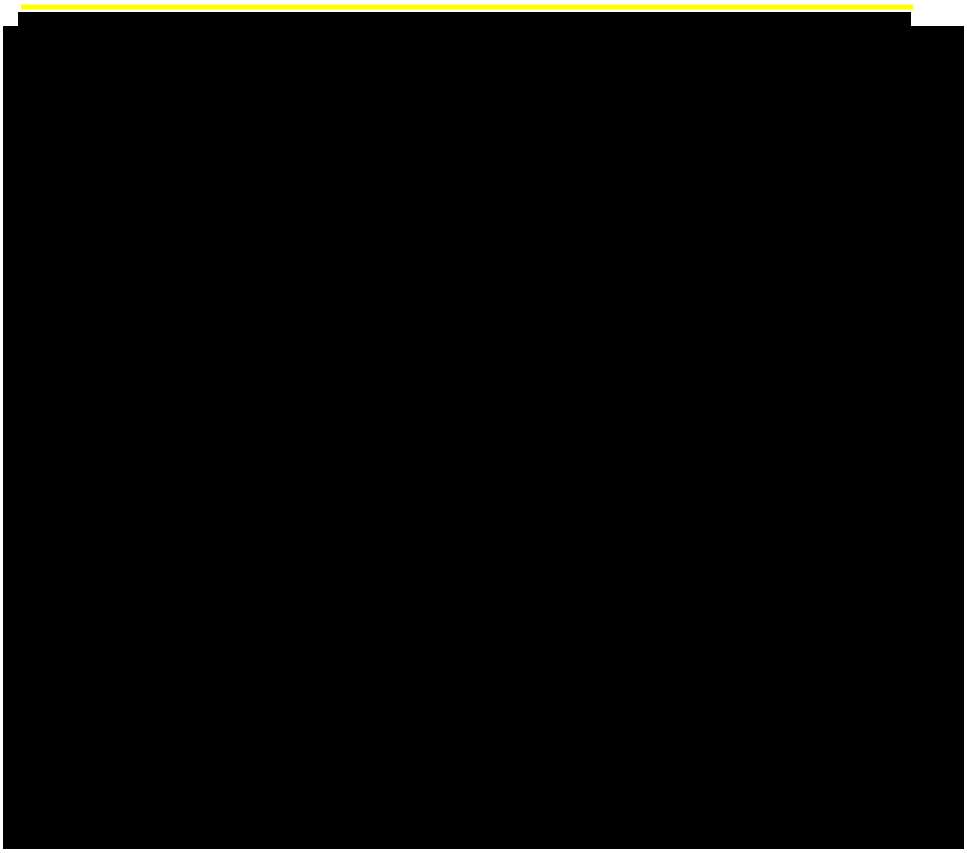


ECOG= Eastern Cooperative Oncology Group; kg= kilograms; mHSPC= metastatic hormone sensitive prostate cancer; N= number; SD= Standard deviation

Radiographic progression free survival (rPFS) – interim analyses (IA1)

Low-volume disease population (LVD)

In the analysis of rPFS, apalutamide + ADT significantly decreased the risk of progression or death compared with ADT alone (HR: 0.359, CI 0.220-0.570). The median rPFS was not reached for the apalutamide + ADT arm, and was 30.49 months for the ADT alone arm (



High-volume disease population (HVD)

In the analysis of rPFS, apalutamide + ADT significantly decreased the risk of progression or death compared with ADT alone (HR: 0.527, CI 0.410-0.670) (44). The median rPFS was not reached for the apalutamide + ADT arm, and was 14.85 months for the ADT alone arm

[redacted]

Overall survival - final analyses (FA)

Low-volume disease population (LVD)

[redacted] presents the Kaplan-Meier data for OS (unadjusted for crossover) from TITAN FA. Median OS was not reached in either the ADT alone or the apalutamide + ADT arms. Results from FA of the TITAN trial (median 44.0 months of follow-up) indicated a decrease in the risk of death (unstratified OS HR: [redacted] stratified OS HR[1]: [redacted] compared to ADT alone. Unadjusted OS at 48 months was 80.4% for apalutamide + ADT and 66.5% for ADT alone.

[1] Based on stratified Analysis (stratified by IWRS Gleason score at diagnosis (=7 versus >7); Region (North America [NA] and European Union [EU] versus Other Countries; and IWRS prior docetaxel use (Yes versus No))

Upon unblinding of the study at IA1, 96/192 or 50% of patients in the control (ADT alone) arm were allowed to cross over to the open-label extension phase and received apalutamide. As such, 50% of patients in the control arm received active treatment as of this time point onwards. Patients switching from ADT alone to apalutamide + ADT 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 analysis will be underestimated. To adjust for this crossover, an RPSFTM approach was undertaken (as mentioned previously in section 7.1.2, section "cross-over adjusted OS") in line with the NICE DSU guidelines. Figure 27 presents the Kaplan-Meier data for OS (adjusted for crossover) from TITAN FA. Median OS was [redacted] months in the ADT alone arm, but was not reached in the apalutamide + ADT arm. Results from FA of the TITAN trial indicated a decrease in the risk of death (RPSFTM OS HR: [redacted] compared to ADT alone. OS at 48 months was [redacted] for apalutamide + ADT and [redacted] for ADT alone.

[redacted]

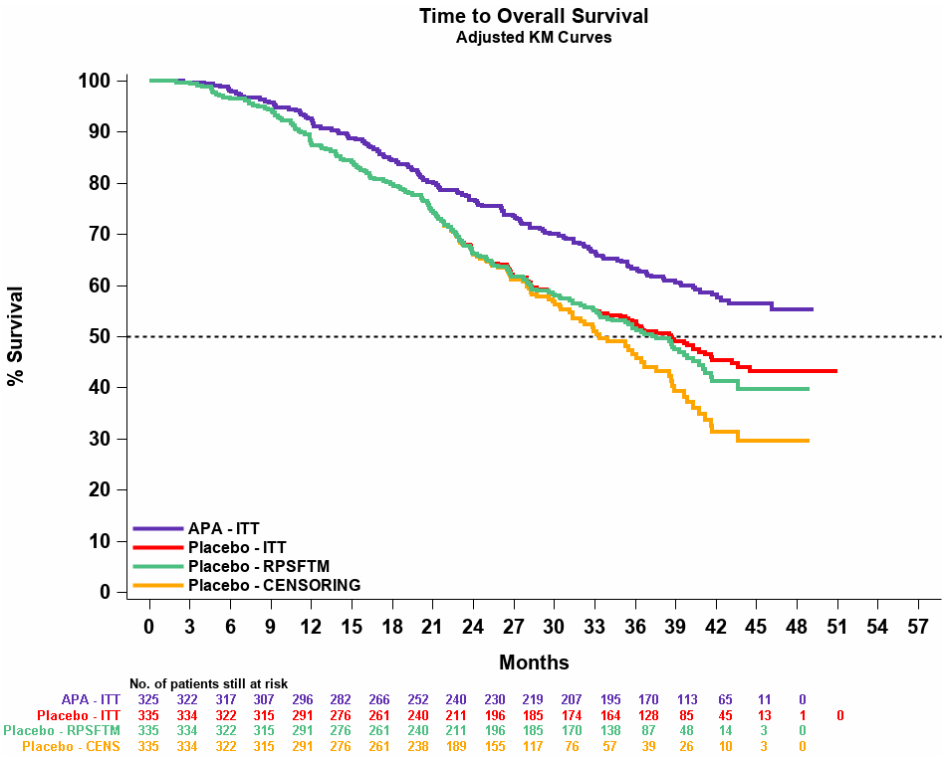
High-volume disease population (HVD)

[redacted] presents the Kaplan-Meier data for OS (unadjusted for crossover) from TITAN FA. Median OS was not reached in the apalutamide + ADT arm, and was 38.67 months in the ADT alone arm. Results from FA of the TITAN trial (median 44.0 months of follow-up) indicated a decrease in the risk of death (unstratified OS HR: 0.699, CI 0.558-0.875, p=0.0018; stratified OS HR[2]: [redacted] compared to ADT alone. Unadjusted OS at 48 months was [redacted] for apalutamide + ADT and [redacted] for ADT alone.

[2] Based on stratified Analysis (stratified by IWRS Gleason score at diagnosis (=7 versus >7); Region (North America [NA] and European Union [EU] versus Other Countries; and IWRS prior docetaxel use (Yes versus No))

Upon unblinding of the study at IA1, 112/335 or 33.4% of patients in the control (ADT alone) arm were allowed to cross over to the open-label extension phase and received apalutamide. As such, 33.4% of patients in the control arm received active treatment as of this time point onwards. Patients switching from ADT alone to apalutamide + ADT 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 analysis will be underestimated. To adjust for this crossover, an RPSFTM approach was undertaken (as mentioned previously in section 7.1.2) in line with the NICE DSU guidelines. Figure 29 presents the Kaplan-Meier data for OS (adjusted for crossover) from TITAN FA. Median OS was 37.28 months in the ADT alone arm, but was not reached in the apalutamide + ADT arm. Results from FA of the TITAN trial indicated a decrease in the risk of death (RPSFTM OS HR: [redacted] compared to ADT alone. OS at 48 months was [redacted] for apalutamide + ADT and [redacted] for ADT alone.

Figure 29: Kaplan-Meier Plot of Overall Survival; High-volume disease Population (Study 56021927PCR3002) – Adjusted for Crossover (RPSFTM); FA

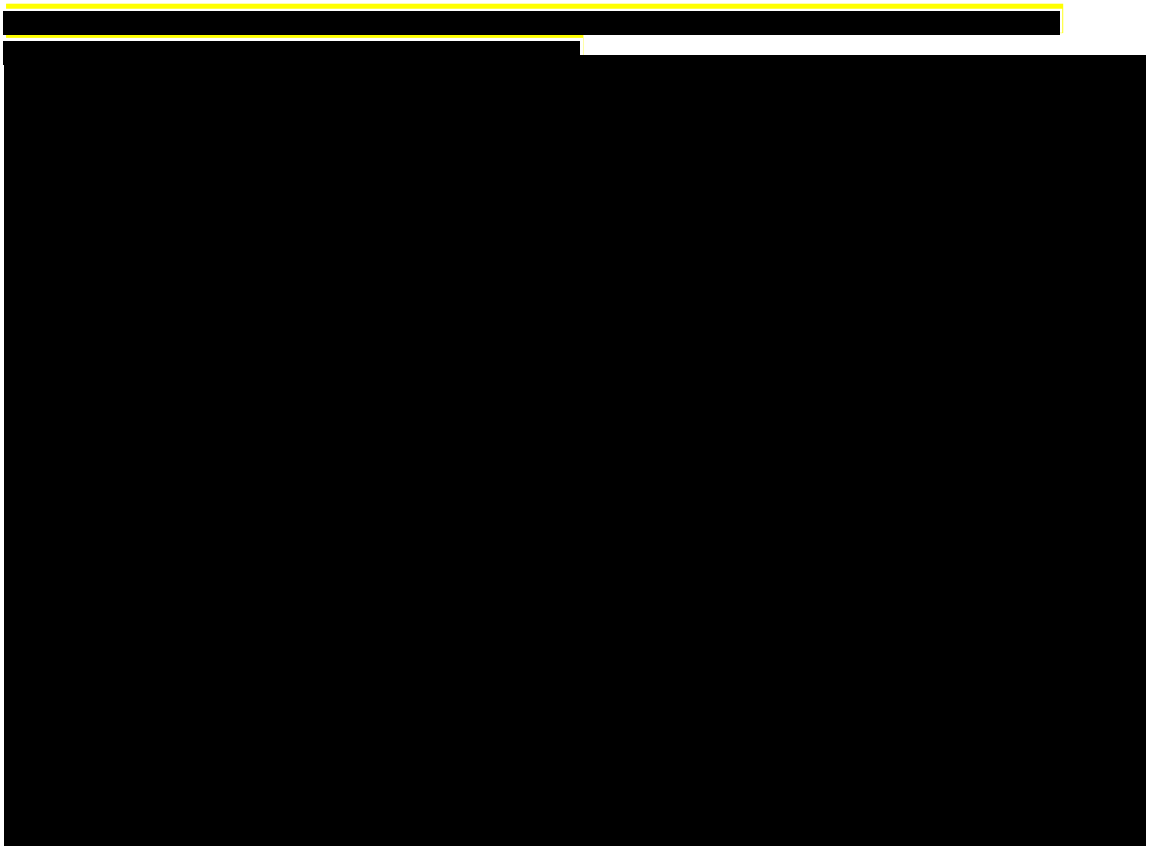


Time to treatment discontinuation (TTTD) final analyses (FA)

Low-volume disease population

Figure 30 presents the TITAN FA Kaplan Meier data for TTTD. Median TTTD was 32.36 months in the ADT alone arm, and not reached in the apalutamide + ADT arm. This results in an unstratified TTTD HR of [redacted]), and a stratified[3] TTTD HR of [redacted] TTTD at 48 months was 66.9% for apalutamide + ADT and [redacted] for ADT alone. Since ADT is modelled until death in the model, adjusting for crossover using the RPSFTM method does not result in any impact to the APA+ADT curve which is being utilised. The adjusted TTTD curves are nevertheless presented in [redacted].

[3] Based on stratified Analysis (stratified by IWRS Gleason score at diagnosis (=7 versus >7); Region (North America [NA] and European Union [EU] versus Other Countries; and IWRS prior docetaxel use (Yes versus No))



High-volume disease population

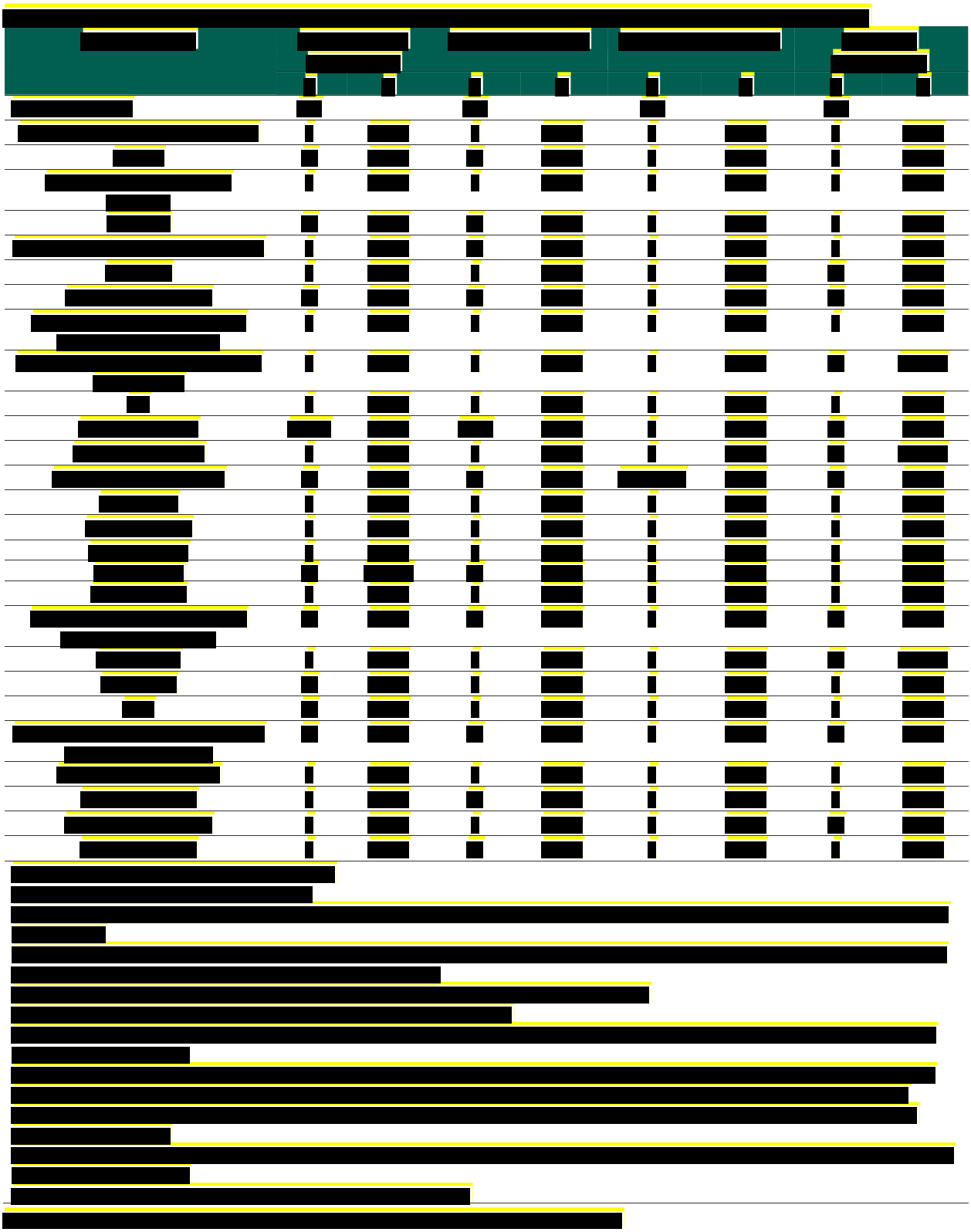
[redacted] presents the TITAN FA Kaplan Meier data for TTTD. Median TTTD was [redacted] months in the ADT alone arm, and [redacted] months in the apalutamide + ADT arm. This results in an unstratified TTTD HR of [redacted]), and a stratified[4] TTTD HR of [redacted] TTTD at 48 months was [redacted] for apalutamide + ADT and [redacted] for ADT alone. The figure also includes a crossover adjusted curve, using Since ADT is modelled until death in the model, adjusting for crossover using the RPSFTM method does not result in any impact to the APA+ADT curve which is being utilised. The adjusted TTTD curves are nevertheless presented in (TTTD HR of [redacted]

[redacted]

8.2.2.7 Adverse reaction outcomes

Treatment emergent adverse events (TEAE) were measured using the safety population of the TITAN trial. During the study period, subjects were assessed for AEs at each clinic visit. 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 (SOC) using MedDRA version 19.1. mHSPC adverse events for outside-trial comparators were sourced from literature. [redacted] presents the number of grade 3 or 4 TEAEs with a frequency of at least 1% in any treatment arm which were included in the model.

[4] Based on stratified Analysis (stratified by IWRS Gleason score at diagnosis (=7 versus >7); Region (North America [NA] and European Union [EU] versus Other Countries; and IWRS prior docetaxel use (Yes versus No))



8.3 Extrapolation of relative efficacy

In order to extrapolate rPFS and OS beyond the TITAN trial, parametric survival models were fitted on the Kaplan-Meier data of the TITAN trial. The following survival extrapolation approaches were used:

- a jointly fitted approach in which ADT was used as a reference curve from the TITAN trial and apalutamide + ADT as a covariate,

In order to use both of these models, the assumption of proportional hazards (PH) needed to be met. The PH assumption was assessed using Schoenfeld residuals plots and log-cumulative hazard plots.

Different parametric models (Weibull, exponential, lognormal, log-logistic, generalized gamma and Gompertz) were fitted on the rPFS and OS data. The selection of the best fitting model was based on clinical, statistical (AIC/BIC) and visual fits. See Appendix G – Extrapolation for results.

8.3.1 Key assumptions for efficacy inputs

- Consistent with a partitioned survival approach, the curves for rPFS, OS, and TTTD are modelled independently (i.e. projections of OS are the only predictor of LYs accrued in the model; rPFS has no impact on this).
- In the development of the statistical projections for rPFS, death events that occurred in the TITAN trial prior to progression were included.

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

A systematic literature review was conducted to identify relevant HRQoL data for adults with mHSPC (original search in 2015 and updated 6 times since). Data presented in economic evaluations, utility elicitation studies, published models, RCTs, validation studies, mapped values studies and technology assessments were eligible for inclusion in the review and the reference lists within reviews were checked for additional references.

No studies from this literature search are included in this submission since no studies were reporting utility scores and hence none were appropriate for cost-effectiveness analysis.

EQ-5D-5L HUI from ITT population of the TITAN trial was the primary source of health state utility values for both the pre-progression and post-progression health states.

HRQoL was assessed in the TITAN trial using the EQ-5D-5L questionnaire. The EQ-5D-5L is a descriptive system comprised of five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and five levels (no problems, slight problems, moderate problems, severe problems and extreme problems). As opposed to the EuroQol five dimensions three levels questionnaire (EQ-5D-3L) which has three levels, the five levels contained within the EQ-5D-5L improves the sensitivity of the analysis as well as reduces the ceiling effect.

8.4.1 Overview of health state utility values (HSUV)

EQ-5D-5L HUI from the intention-to-treat (ITT) population of the TITAN trial was the primary source of health state utility values for both the pre-progression (mCSPC) and post-progression (metastatic castration resistant prostate cancer or mCRPC) health states. As utility values were derived from EQ-5D-5L data gathered directly from patients in the TITAN trial, mapping was not required in this analysis.

Danish-specific preference weights obtained from(68) were used to estimate the EQ-5D-5L value set. The paper presents the Danish EQ-5D-5L value set based on a representative sample of the Danish adult population. A heteroscedastic hybrid model combining composite time trade-off (cTTO) and discrete-choice experiment (DCE) data is demonstrated, and is depicted as an applicable approach to obtain an EQ-5D-5L value set for healthcare prioritization. From this, the mCSPC and mCRPC health state utilities were derived using TITAN data, along with disutilities occurring due to adverse events. A detailed description of the method is available in Appendix K Company-specific appendix: Utility analyses

Table 25 presents the parameter estimates of the final model that was used to obtain the utility values for low-volume disease and high-volume disease populations.

Table 25 Parameter estimates from linear regression models of EQ-5D assessments from the TITAN trial (Low-volume and High-volume disease patients) – Danish Weights

Population	Parameters	Estimate	±SE
Low-volume disease (Model 3)	Intercept	0.890	0.007
	rPFS	-0.058	0.011
	AE	-0.058	0.007
	BQoL	0.023	0.007
	rPFS*AE	-0.054	0.021
High-volume disease (Model 2)	Intercept	0.862	0.006
	rPFS	-0.081	0.006
	AE	-0.070	0.006
	BQoL	0.013	0.006

AE = adverse events, BQoL= baseline quality of life; rPFS= radiographic progression-free survival; SE = standard error

8.4.2 Health state utility values used in the health economic model

Table 26 shown below provides an overview of the estimated health state utilities used in the model for the low-volume disease and high-volume disease population.

Table 26: Estimation of health state utilities (Low-volume and High-volume disease) – Danish Weights

		Mean	Source
Low-volume disease (Model 3)	mHSPC baseline utility	0.911	TITAN RMME analysis (see Appendix K)
	mCRPC utility	0.852	
	Adverse event disutility (pre-progression)	-0.058	
	Adverse event disutility (post-progression)	-0.111	
High-volume disease	mHSPC baseline utility	0.873	

(Model 2)	mCRPC utility	0.793	
	Adverse event disutility (pre-progression)	-0.070	
	Adverse event disutility (post-progression)	-0.070	

mCRPC = metastatic castration-resistant prostate cancer; mHSPC = metastatic hormone-sensitive prostate cancer; RMME = repeated measurement mixed effects

8.5 Resource use and 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
- Medical resource use costs
- End-of-life costs

8.5.1 Treatment acquisition and administration costs

Treatment costs for mHSPC and mCRPC health states were calculated using the following sources:

- Apalutamide costs: Medicinpriser.dk
- ADT costs: Medicinpriser.dk
- mCRPC treatment costs: Medicinpriser.dk
- The dosage of each administration was derived from summaries of product characteristics that is published on EMA website (64). For prednisone, the daily dosage was based on the COU-AA-302 study (69).
- The average weight (78.3 kg) was derived from the TITAN trial(29,31). The average body surface 1.93 m^2 was estimated based on the weight and height from the TITAN trial using the formula by Mosteller (http://www.medcalc.com/body.html). The body surface area (BSA) and weight were applied for determining the average dose applied of docetaxel, cabazitaxel and radium-223.

8.5.2 mHSPC treatments

Treatment costs in mHSPC were derived from the summary of product characteristics of the EMA website (64). Table 27 presents treatment costs of apalutamide, and ADT. Dosing schedules of mHSPC treatments were derived from FASS. The recommended dose of apalutamide is 160 mg (four 40 mg tablets) administered orally once daily. The compliance rate of apalutamide was derived from the TITAN trial (the compliance rate of DOC+ADT is 95% from (70).

- The price of apalutamide in Denmark is 21,810.60 kr for a 112 tablet package (40mg strength). No administration costs are assumed as this is an oral treatment.

- The treatment cost of ADT is based on the treatment costs of different ADT regimens. For subcutaneous ADT regimens an administration cost of 3,235 kr was applied. The subcutaneous treatments that were included are: goserelin, leuprorelin, triptorelin, buserelin, and bicalutamide.
- The price of docetaxel in Denmark is 150 kr for one 80mg vial. The recommended dose of docetaxel is 75 mg/m^2 every 3 weeks for 6 cycles. As docetaxel is administrated subcutaneously, an administration cost of 3,235 kr in the hospital are considered.

The market shares of the different ADT regimens in mCRPC were based on assumptions. The market shares in mHSPC were assumed to be the same as in mCRPC. 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 TITAN trial. The compliance rate of DOC+ADT was sourced from (70).

For all intravenous or subcutaneous treatments, wastage is considered; i.e. no vial-sharing is assumed.

Table 27: Treatment dosing and drug acquisition costs of apalutamide, ADT, and docetaxel

Costs	Name	Dosage	Frequency	Package cost	Package size	Administration cost	Compliance	Annual cost
apalutamide	ERLEADA®	4 tablets of 40 mg	Daily	21,810.60 kr	112 tablets	- kr (oral)	95.43%	Treatment 281,181 kr (APA 271,509 kr + ADT 9,671 kr) Administration: 9,261 kr (ADT)
docetaxel	Accord	75 mg/m2	Every 3 weeks for 6 cycles (95%) [64]	150 kr	per 80 mg vial	3,225 kr	95.0%	Treatment 11,573 kr (DOC 1,945 + ADT 9,628 kr) Administration: 27,659 kr (18440 kr DOC + 9220 ADT)
ADT								Weighted annual cost
Goserelin	Zoladex	1 vial of 10.80 mg	Every 3 months	3174.18 kr	3.60 mg vial	3,225 kr	96.45%	Treatment 9,775 kr

Costs	Name	Dosage	Frequency	Package cost	Package size	Administration cost	Compliance	Annual cost
Leuprorelin	Eligard	1 vial of 22.50 mg	Every 3 months	3,423.85 kr	22.50 mg vial	3,225 kr	96.45%	(25% ADT market shares each) Administration: 9,360 kr
Triptorelin	Pamorelin	1 vial of 11.25 mg	Every 3 months	3,194 kr	11.25 mg vial	3,225 kr	96.45%	
Bicalutamide	Sandoz	3 tablets of 50 mg	Daily	125.01 kr	100 tablets	- kr (oral)	96.45%	

Treatment Duration

The treatment duration of apalutamide was defined by the TTTD curve of apalutamide + ADT in the TITAN trial. ADT was assumed to be continued over the lifetime of a patient. Docetaxel is a fixed duration therapy and was modelled as such.

8.5.3 Subsequent treatments

The method of cost calculations of the subsequent treatments is in line with the ERLEADA nmCRPC model submission.

- The recommended dose of abiraterone is 1000 mg (two 500 mg tablets) administered orally once daily. As abiraterone is an oral treatment no administration costs are considered. Abiraterone is always taken in combination with prednisone (10mg daily).
- The recommended dose of enzalutamide is 160 mg (four 40 mg tablets) administered orally once daily.66 As enzalutamide is an oral treatment no administration costs are considered.
- The recommended dose of docetaxel is 75 mg/m2 every 3 weeks for 10 cycles (19). As docetaxel is administrated subcutaneously, administration costs in the hospital are considered.
- The recommended dose of cabazitaxel is 25 mg/m2 every 3 weeks for 10 cycles (71). As cabazitaxel is administrated subcutaneously, administration costs in the hospital and the travelling costs to and from the hospital are considered. Cabazitaxel is administered alongside a 0.4mg dose of granulocyte colony stimulating factor (G-CSF).
- The recommended dose of radium-223 is 55 kBq/kg every 4 weeks for 6 cycles (72). As radium-223 is administrated intravenously, administration costs in the hospital are considered.
- It was assumed that patients receive ADT beyond any of the subsequent treatments until death. A similar approach was taken to calculate the ADT cost in mCRPC as in the mHSPC state.
- For all intravenous or subcutaneous treatments, wastage is considered; i.e. no vial-sharing is assumed.

Table 28 presents treatment costs of each subsequent treatment:

- The recommended dose of abiraterone is 1000 mg (two 500 mg tablets) administered orally once daily. As abiraterone is an oral treatment no administration costs are considered. Abiraterone is always taken in combination with prednisone (10mg daily).
- The recommended dose of enzalutamide is 160 mg (four 40 mg tablets) administered orally once daily (73). As enzalutamide is an oral treatment no administration costs are considered.
- The recommended dose of docetaxel is 75 mg/m^2 every 3 weeks for 10 cycles(19). As docetaxel is administrated subcutaneously, administration costs in the hospital are considered.
- The recommended dose of cabazitaxel is 25 mg/m^2 every 3 weeks for 10 cycles (71). As cabazitaxel is administrated subcutaneously, administration costs in the hospital and the travelling costs to and from the hospital are considered. Cabazitaxel is administered alongside a 0.4mg dose of granulocyte colony stimulating factor (G-CSF).
- The recommended dose of radium-223 is 55 kBq/kg every 4 weeks for 6 cycles (72). As radium-223 is administrated intravenously, administration costs in the hospital are considered.
- It was assumed that patients receive ADT beyond any of the subsequent treatments until death. A similar approach was taken to calculate the ADT cost in mCRPC as in the mHSPC state.
- For all intravenous or subcutaneous treatments, wastage is considered; i.e. no vial-sharing is assumed.

Table 28: Subsequent treatment acquisition cost

Costs	Name	Dosage	Frequency	Package cost	Package size	Administration cost	Compliance	Week 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	20,548 kr	56 tablets	- kr	100%	Treatment: 5,139 kr (abi 5,137 kr + pred 2 kr)

Costs	Name	Dosage	Frequency	Package cost	Package size	Administration cost	Compliance	Week cost
								Administration: 0 kr
Enzalutamide	Xtandi	4 tablets of 40 mg	Daily	20,997 kr	112 tablets	- kr	100%	Treatment: 5,249 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]	27,602 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								Weighted annual cost
Goserelin	Zoladex	1 vial of 10.80 mg	Every 3 months	3,426 kr	3.60 mg vial	3,225 kr	100%	**10,134 kr** (25% ADT market shares each)
Leuprorelin	Eligard	1 vial of 22.50 mg	Every 3 months	2,765 kr	22.50 mg vial	3,225 kr	100%	
Triptorelin	Pamorelin	1 vial of 11.25 mg	Every 3 months	2,688 kr	11.25 mg vial	3,225 kr	100%	

Costs	Name	Dosage	Frequency	Package cost	Package size	Administration cost	Compliance	Week cost
Bicalutamide		3 tablets of 150 mg	Daily	125,01 kr	100 tablets	- kr (oral)	100%	

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.

The distribution of subsequent treatments in each line, was based on assumed Danish market shares. Also taking in regard that the Cross regional forum for medicine has stated that there should be no sequential use within apalutamide, enzalutamide and abiraterone (74). 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 29.

Table 29: Distribution of subsequent treatments based on assumed Danish market shares

Treatment in mHSPC	Treatment line	Abiraterone	Enzalutamide	Docetaxel	Cabazitaxel	Radium-223
apalutamide + ADT	1st line	0.0%	0.0%	92.0%	7.0%	1.0%
	2nd line	0.0%	0.0%	0.0%	85.0%	15.0%
	3rd line	0.0%	0.0%	0.0%	50.0%	50.0%
ADT alone	1st line	20.0%	60.0%	12.0%	7.0%	1.0%
	2nd line	10.0%	10.0%	68.0%	7.0%	5.0%
	3rd line	0.0%	0.0%	0.0%	50.0%	50.0%
RT + ADT (low-volume disease population)	1st line	20.0%	72.0%	1.0%	7.0%	0.0%
	2nd line	4.0%	4.0%	80.0%	12.0%	0.0%
	3rd line	0.0%	0.0%	50.0%	50.0%	0.0%
DOC + ADT (high-volume disease population)	1st line	20.0%	72.0%	0.0%	7.0%	1.0%
	2nd line	4.0%	4.0%	0.0%	80.0%	12.0%
	3rd line	0.0%	0.0%	0.0%	50.0%	50.0%

8.5.4 Treatment duration of subsequent treatments

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)[5] (Table 30). The duration of each subsequent treatment line is assumed to be the same regardless of the treatment in mHSPC.

Table 30: Treatment duration in each treatment line in mCRPC (Prostate Cancer Registry)

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

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(70,75,76) (see Table 31).
- Other treatments: the treatment cost of ADT is applied continuously.

For the treatments with fixed duration, the average treatment durations are presented in Table 31.

Table 31: 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	1st line: 95.0%* 2nd line:95.0%* 3rd line: 95.0%*	Max of 10 cycles	10	1 every 3 weeks	28.50 weeks	Calculated based on the frequency and the maximum cycle of treatment
cabazitaxel	1st line: 60.0%* 2nd line:60.0%* 3rd line: 60.0%*	Max of 10 cycles	10	1 every 3 weeks	18.00 weeks	
radium-223	1st line: 58.0%* 2nd line:58.0%* 3rd line: 58.0%*	Max of 6 cycles	6	1 every 4 weeks	13.92 weeks	

[5] Data on file (Janssen). Interim analysis of patients with metastatic castrate-resistant prostate cancer (mCRPC) who received abiraterone acetate as the first documented treatment for mCRPC following enrolment into a prospective registry (NCT02236637) 2016.

mCRPC= Metastatic castration resistant prostate cancer

In case the mean time in mCRPC was shorter than the sum of the maximum treatment durations in all lines, the duration of the second- and third-line treatments were limited based on the mean duration of mCRPC. This means that the total duration of the three lines of treatment could not 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 were not overestimated for any of the treatment arms. In the base case analysis, if the total duration of active treatments (e.g. 65.39 months) exceeds the total mCRPC phase, the active treatment duration in 1st, 2nd, and 3rd line is decreased proportionally so patients receive active treatments during the whole mCRPC phase. In a scenario analysis, if the total duration of active treatments does not cover the mCRPC phase, patients receive non-active treatments (ADT) for the rest of their mCRPC phase (see Table 32). In the base case, the treatment duration of subsequent lines (1L: 10.00 months, 2L: 8.30 months, 3L: 6.60 months) is decreased/increased proportionally to match mCRPC duration so patients are treated actively for 100% of the time. In a scenario analysis, the treatment duration of subsequent lines (1L: 16.00 months, 2L: 11.93 months, 3L: 7.85 months) is decreased/increased proportionally to match mCRPC duration so patients are treated actively for 100% of the time.

Table 32: Treatment duration versus the time spend in mCRPC

	Base case (Low-volume disease)			Base case (High-volume disease)			Scenario analysis (Low-volume disease)			Scenario analysis (High-volume disease)		
	APA+ADT	ADT	RT+ADT	APA+ADT	ADT	DOC+ADT	APA+ADT	ADT	RT+ADT	APA+ADT	ADT	DOC+ADT
1st line	26 26 months	16.13 months	24.43 months	19.11 months	16.91 months	19 09 months	29.25 months	17.96 months	27.20 months	21.28 months	18.84 months	21.26 months
2nd line	21 80 months	13.38 months	20.27 months	15.86 months	14.04 months	15 85 months	21.80 months	13.38 months	20.27 months	15.86 months	14.04 months	15.85 months
3rd line	17 33 months	10.64months	16.12 months	12.61 months	11.16 months	12 60 months	14.35 months	8.81 months	13.35 months	10.44 months	9 24 months	10.43 months
Total actively treatment duration	65 39 months	40.15 months	60.82 months	47.58 months	42.12 months	47 54 months	65.39 months	40.15 months	60.82 months	47.58 months	42.12 months	47.54 months
Time spent in mCRPC	65 39 months	40.15 months	60.82 months	47.58 months	42.12 months	47 54 months	65.39 months	40.15 months	60.82 months	47.58 months	42.12 months	47.54 months
% mCRPC duration patients are actively treated	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
No. months non-actively treated	Patients are actively treated till death			Patients are actively treated till death			Patients are actively treated till death			Patients are actively treated till death		

8.5.5 Adverse event cost

The frequencies of grade 3 or 4 AEs associated with apalutamide + ADT and ADT alone in more than 1% of the patients were sourced from the TITAN trial as outlined previously in Table 33. The associated costs of each AE were derived from the DRG tariffs list. Costs were applied once at the start of the treatment in the mHSPC stage. Unit cost of each AE are presented in Table 33. The AE costs were adjusted with the reporting frequencies and applied as a one-off cost to the whole model cohort.

Table 33: Grade 3 or 4 adverse event unit cost per event

Adverse event	Unit cost 2022	Source
Alanine aminotransferase increased	Kr. 2.038	2022 DRG-takst 11MA98
Anemia	Kr. 61.073	2022 DRG-takst Gennemsnit: 16MA05 + 16MP06
Aspartate aminotransferase increased	Kr. 2.038	2022 DRG-takst 11MA98
Back pain	Kr. 2.038	2022 DRG-takst 11MA98
Blood alkaline phosphatase increased	Kr. 2.038	2022 DRG-takst 11MA98
Bone pain	Kr. 2.038	2022 DRG-takst 11MA98
Cardiac disorder (any)	Kr. 2.038	2022 DRG-takst 11MA98
Endocrine disorders (incl. hot flashes & impotence)	Kr. 2.038	2022 DRG-takst 11MA98
Fall	Kr. 2.038	2022 DRG-takst 11MA98
Fatigue / asthenia	Kr. 2.038	2022 DRG-takst 11MA98
Febrile neutropenia	Kr. 18.647	2022 DRG-takst 18MA04
Gastrointestinal disorders	Kr. 2.038	2022 DRG-takst 11MA98
Haematuria	Kr. 2.038	2022 DRG-takst 11MA98
Hyperglycaemia	Kr. 2.038	2022 DRG-takst 11MA98
Hyperkalaemia	Kr. 2.038	2022 DRG-takst 11MA98
Hypertension	Kr. 2.038	2022 DRG-takst 11MA98
Hyponatremia	Kr. 2.038	2022 DRG-takst 11MA98
Nervous system other (including peripheral neuropathy)	Kr. 2.038	2022 DRG-takst 11MA98
Neutropenia	Kr. 2.038	2022 DRG-takst 11MA98
Pneumonia	Kr. 2.038	2022 DRG-takst 11MA98
Rash	Kr. 2.038	2022 DRG-takst 11MA98
Respiratory disorders (incl. thoracic & mediastinal disorders)	Kr. 2.038	2022 DRG-takst 11MA98
Spinal cord compression	Kr. 46.650	2022 DRG-takst 08MP06
Urinary retention	Kr. 2.038	2022 DRG-takst 11MA98
Urinary tract infection	Kr. 27.401	2022 DRG-takst 11MA07
Weight increased	Kr. 2.038	2022 DRG-takst 11MA98

8.5.6 Patient costs

Transportation and patient time costs were considered for the patients when hospital visits were needed both for administration of the treatments and for monitoring. These patient costs were included for patients that received RT or intravenous treatments (ADT or subsequent treatments (docetaxel, cabazitaxel and radium-223)) and therefore had to travel to the hospital. For patients receiving RT we assumed a longer duration per treatment (2 hours instead of 1). The transportation costs and the patient costs per hour were derived from the DMC guideline. It was assumed that a hospital visit would take one hour (excluding the travel time).

8.5.7 Radiotherapy

Transportation and patient time costs were included for the administration of RT. Table 34 presents the annual transportation and patient time costs in mHSPC. The total patient costs for RT in mHSPC were calculated by multiplying the number of visits per year with the transportation and patient time cost per year.

Table 34: Transportation and patient time costs for RT

		Number of visits	Unit costs	Treatment duration	Total costs	Total patient costs per treatment
Radiotherapy (RT)	Transportation cost	20 visits of 2 hours	100 kr per administration	4 weeks	2,000 kr	9,160 kr
	Patient time cost		179 kr per hour		7,160 kr	

8.5.8 Intravenous ADT

Transportation and patient time costs were included for the administration of intravenous ADT. Table 35 presents the annual transportation and patient time costs in mHSPC and mCRPC. The total patient costs for ADT in mHSPC 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 35: 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
mHSPC	Transportation cost of ADT in mHSPC	4 visits of 1 hour	100 kr per administration	75.00%	96.45%	289 kr	807 kr
	Patient time cost of ADT in mCRPC		179 kr per hour			518 kr	
mCRPC	Transportation cost of ADT in mHSPC	4 visits of 1 hour	100 kr per administration		100.00%	300 kr	837 kr

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	Patient time cost of ADT in nmCRPC		179 kr per hour			537 kr	

8.5.9 Intravenous Docetaxel and subsequent treatments

Transportation and patient time costs were included for the administration of Docetaxel and intravenous subsequent treatments. Table 36 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 36 Administration of Docetaxel and intravenous subsequent treatments

		Number of visits	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	

8.5.10 Medical resource use and cost inputs

Based on the advice of Janssens's internal medical team the patients are expected to be subjected to the tests and monitoring listed in Table 37 during their treatment and there are differences in the monitoring required based on the treatment in question. The table also shows the unit costs applied in the health economic models.

Oncologists/urologist/nurse visit

For all health states, oncologists visits are included based on the assumption that the patients require follow-up and monitoring visits both in the mHSPC state and the mCRPC state. The cost applied is derived from the Danish DRG list (11MA98) and covers out patient visit within the disease area.

CT/MRI scan, bone scintigraphy, chest x-ray and ECG

For all health states, CT and MRI scans, bone scintigraphy, chest x-ray and ECG are included based on the assumption that the patients require these examinations at follow-up and monitoring visits both in the mHSPC state and the mCRPC state. The costs are derived from the Danish DRG list for 2022 and are listed in **Table 37.**

FBC, PSA, lipid test, liver function test and kidney function test

These tests are also assumed to be required for all patients regardless of health states at follow-up or monitoring visits. However, these tests are assumed to be included in the DRG tariff (DRG takst) for outpatient visits (oncologists/urologists/nurse visit), and not incur additional costs.

GP visit

All patients are assumed to receive follow-up visits in primary care both in the mHSPC state and in mCRPC. The unit cost is derived from the unit cost document published by the DMC[6]. Since the GP visits can include a wide range of tests and treatments, and these differ significantly from patient to patient, we have only applied the basic consultation cost of 147,85 DKK, which is a very conservative estimate.

Table 37 Medical resource use, unit cost

MRU	Unit Cost	Source/Notes
Oncologist visit	kr 2,038	DRG takster 2022, 11MA98
Nurse visit	kr 2,038	DRG takster 2022, 11MA98
CT scan	kr 2.411	DRG takster 2022, 30PR06
MRI scan	kr 2.057	DRG takster 2022, 30PR03
Bone scintigraphy	kr 3.399	DRG takster 2022, 30PR17
Chest X-ray	kr 1.640	DRG takster 2022, 30PR18
ECG	kr 2.038	DRG takster 2022, 11MA98
Urologist visit	kr 2,038	DRG takster 2022, 11MA98
GP visit	kr 147,85	Værdisætning af omkostninger MC
Kidney function test	kr 89	Rigshospitalets Labportal

Applying the medical resource use cost above Table 38 presents medical resource use for each treatment line. The MRU costs in mCRPC are dependent on the treatments received in the mHSPC health state and the duration of 1st, 2nd and 3rd line treatments (see Table 32). The details of the calculations for each treatment can be found in the medical cost sheet of the health economic models.

Table 38: Disease management costs

	Treatment arm	Annual cost
Planned MRU costs in mHSPC (per year)	apalutamide + ADT	75,043 kr
	RT + ADT	75,228 kr
	DOC + ADT	75,228 kr

Cost inputs for medical resource use in mCSPC and mCRPC are presented in below Table 39 and Table 40. Frequency and percent use estimates are internal Janssen estimates.

[6] https://medicinraadet.dk/media/aunbprvq/v%C3%A6rdis%C3%A6tning-af-enhedsomkostninger-vers-1-6_adlegacy.pdf

Table 39: mCSPC MRU frequencies (per month) and costs

		Oncologist visit	Nurse visit	CT scan	MRI scan	Bone scintigraphy	Chest X-ray	ECG	Urololgist visit	GP visit
APA + ADT	Percent use	100.0%	100.0%	50.0%	100.0%	75.0%	50.0%	100.0%	100.0%	100.0%
	Frequency	1 every 8 weeks	1 every 4 weeks	1 every 18 weeks	1 every 18 weeks	1 every 18 weeks	1 every 18 weeks	1 every 18 weeks	1 every 25 weeks	1 every 10 weeks
	Units per months	0.50	1.00	0.22	0.22	0.22	0.22	0.22	0.16	0.40
ADT	Percent use	100.0%	100.0%	50.0%	100.0%	100.0%	50.0%	50.0%	100.0%	100.0%
	Frequency	1 every 17 weeks	1 every 25 weeks	1 every 52 weeks	1 every 52 weeks	1 every 52 weeks	1 every 52 weeks	1 every 52 weeks	1 every 25 weeks	1 every 10 weeks
	Units per months	0.24	0.16	0.08	0.08	0.08	0.08	0.08	0.16	0.40
DOC+ADT	Percent use	100.0%	0.0%	50.0%	100.0%	75.0%	50.0%	100.0%	100.0%	100.0%
	Frequency	1 every 3 weeks	Included in the admin cost	1 every 18 weeks	1 every 18 weeks	1 every 18 weeks	1 every 18 weeks	1 every 18 weeks	1 every 12 weeks	1 every 10 weeks
	Units per months	1.33	0.00	0.22	0.22	0.22	0.22	0.22	0.33	0.40
Reference for costs		*DRG takster 2022, 11MA98*	*DRG takster 2022, 11MA98*	*DRG takster 2022, 30PR06*	*DRG takster 2022, 30PR03*	*DRG takster 2022, 30PR17*	*DRG takster 2022, 30PR18*	*DRG takster 2022, 11MA98*	*DRG takster 2022, 11MA98*	*DRG takster 2022, 11MA98*

Table 40: mCRPC MRU frequencies (per month) and costs

		Oncologist visit	Nurse visit	CT scan	MRI scan	Bone scintigraphy	Chest X-ray	ECG	Urololgist visit	GP visit
Abiraterone + prednisolone	Percent use	100.0%	100.0%	50.0%	100.0%	75.0%	50.0%	100.0%	100.0%	100.0%

	Frequency	1 every 8 weeks	1 every 4 weeks	1 every 18 weeks	1 every 18 weeks	1 every 18 weeks	1 every 18 weeks	1 every 18 weeks	1 every 25 weeks	1 every 10 weeks
	Units per months	0.50	1.00	0.22	0.22	0.22	0.22	0.22	0.16	0.40
Enzalutamide	Percent use	100.0%	100.0%	50.0%	100.0%	75.0%	50.0%	100.0%	100.0%	100.0%
	Frequency	1 every 8 weeks	1 every 4 weeks	1 every 18 weeks	1 every 18 weeks	1 every 18 weeks	1 every 18 weeks	1 every 18 weeks	1 every 25 weeks	1 every 10 weeks
	Units per months	0.50	1.00	0.22	0.22	0.22	0.22	0.22	0.16	0.40
Docetaxel	Percent use	100.0%	0.0%	50.0%	100.0%	75.0%	50.0%	100.0%	100.0%	100.0%
	Frequency	1 every 3 weeks	Included in the admin cost	1 every 18 weeks	1 every 18 weeks	1 every 18 weeks	1 every 18 weeks	1 every 18 weeks	1 every 12 weeks	1 every 10 weeks
	Units per months	1.33	0.00	0.22	0.22	0.22	0.22	0.22	0.33	0.40
ADT, BSC	Percent use	100.0%	100.0%	50.0%	100.0%	100.0%	50.0%	50.0%	100.0%	100.0%
	Frequency	1 every 17 weeks	1 every 25 weeks	1 every 52 weeks	1 every 52 weeks	1 every 52 weeks	1 every 52 weeks	1 every 52 weeks	1 every 25 weeks	1 every 10 weeks
	Units per months	0.24	0.16	0.08	0.08	0.08	0.08	0.08	0.16	0.40
Cabazitaxel	Percent use	100.0%	0.0%	50.0%	100.0%	75.0%	50.0%	100.0%	100.0%	100.0%
	Frequency	1 every 3 weeks	Included in the admin cost	1 every 18 weeks	1 every 18 weeks	1 every 18 weeks	1 every 18 weeks	1 every 18 weeks	1 every 12 weeks	1 every 10 weeks
	Units per months	1.33	0.00	0.22	0.22	0.22	0.22	0.22	0.33	0.40
Radium-233	Percent use	100.0%	0.0%	50.0%	100.0%	75.0%	50.0%	100.0%	100.0%	100.0%

	Frequency	1 every 3 weeks	Included in the admin cost	1 every 18 weeks	1 every 18 weeks	1 every 18 weeks	1 every 18 weeks	1 every 18 weeks	1 every 12 weeks	1 every 10 weeks
	Units per months	1.33	0.00	0.22	0.22	0.22	0.22	0.22	0.33	0.40
Reference for costs		*DRG takster 2022, 11MA98*	*DRG takster 2022, 11MA98*	*DRG takster 2022, 30PR06*	*DRG takster 2022, 30PR03*	*DRG takster 2022, 30PR17*	*DRG takster 2022, 30PR18*	*DRG takster 2022, 11MA98*	*DRG takster 2022, 11MA98*	*DRG takster 2022, 11MA98*

8.5.11 Administration cost

When calculating the aggregated cost of the different treatments in the model, an administration cost of IV (3,225 DKK) and SC (3,225 DKK) treatments were also applied based on DRG tariffs[7]

8.5.12 End-of-life cost

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. This is the same approach as in the mCRPC submission, approved by DMC. The UK study focused on end-of-life costs and included patients with advanced cancer, including prostate cancer patients (67). 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 81,463,63 kr based on the average exchange rate for 2021 which is the most recent average annual exchange rate available[8]. The exchange rate was lower in 2021 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 0.8% from 2014-2021 [9].. 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 81,463,63 kr accounted to 85,452,93 kr. End-of-life costs of 85,452,93 kr were applied as a one-time cost in the mCRPC stage for each patient that dies.

[7] https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2022 and https://amgros.dk/media/1773/guidelines-for-costanalyses.pdf DRG group: 17MA98 MDC17. Procedures: BWAA31 - Medicingivning ved subkutan injektion (DKK 3235). BWAA62 - Medicingivning ved intravenøs infusion (DKK 3235).

[8] Danmarks nationalbank. Yearly exchange rates by currency, type and methodology; 2020. Available from: URL: https://nationalbanken.statbank.dk/.

[9] Danmarks Statistik. PRIS8: Forbrugerprisindeks, årsgennemsnit (1900=100) efter type; 2020. Available from: URL: https://www.statistikbanken.dk/PRIS8

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8.6 Results

8.6.1 Base case overview

Table 41: Overview of the baseline settings

Category	Parameter	Base case	Justification
Model settings	Patient population	Metastatic hormone sensitive prostate cancer patients	Per TITAN population[4]
	Country	Denmark	Not applicable
	Model perspective	Medical	As recommended by Danish Medicines Council
	Time horizon	30 years	As recommended by Danish Medicines Council
	Cycle length	One week	This cycle length is short enough to capture all relevant events.
	Discount rate	Costs: 3.5% Benefits: 3.5%	As recommended by Danish Medicines Council
	Comparators	Low-volume disease population: • RT + ADT High-volume disease population: • DOC + ADT	Includes all relevant comparators in the mHSPC setting for low-volume disease and high-volume disease population
Clinical inputs	rPFS	Low-volume disease population: • Apalutamide + ADT /ADT alone: Gompertz distribution; Joint fits • RT + ADT: PFS HR applied to APA+ADT from NMA) High-volume disease population: • Apalutamide + ADT /ADT alone: Weibull distribution; Joint fits • DOC + ADT: rPFS HR applied to APA+ADT from NMA)	Low-volume disease population: • A Gompertz distribution was selected because it had the best statistical fit to the data (based on AIC/BIC criteria) and is also clinically plausible since it remains below OS High-volume disease population: • A Weibull distribution was selected because it had a good fit to the data (based on AIC/BIC criteria) and is also clinically plausible since it remains below OS
	OS	Low-volume disease population: • Apalutamide + ADT /ADT alone: Weibull; Joint fits • RT + ADT: OS HR applied to APA+ADT from NMA) High-volume disease population: • Apalutamide + ADT /ADT alone: Lognormal; Joint fits • DOC + ADT: OS HR applied to APA+ADT from NMA)	Low-volume disease population: • A Weibull was selected because it had the best statistical fit to the data (based on AIC/BIC criteria) and was the most clinically plausible High-volume disease population: • A Lognormal was selected because it had the best statistical fit to the data (based on AIC/BIC criteria) and was the most clinically plausible
Treatment duration	TTTD	Low-volume disease population: • Apalutamide + ADT: Gompertz distribution; Individual fits High-volume disease population: • Apalutamide + ADT: Weibull distribution; Individual fits	Low-volume disease population: • A Gompertz distribution was selected to be consistent with the rPFS curve selection. High-volume disease population: • A Weibull distribution was selected to be consistent with the rPFS curve selection.
		Low-volume disease population: RT + ADT	Fixed duration therapy
		High-volume disease population: DOC+ADT	Fixed duration therapy
Cost inputs	Wastage	Considered for intravenous treatments	As recommended by Danish Medicines Council
	Subsequent treatments	Subsequent treatments modelled based on local market shares	Local market shares reflect Danish clinical practice

Utility inputs	mHSPC	Low-volume disease population: • 0.911 High-volume disease population: • 0.873	Individual patient data from the TITAN trial (EQ-5D-5L questionnaire with Danish preference weights applied) - TITAN RMME analysis for low-volume disease and high-volume disease populations (see Appendix I)
	mCRPC	Low-volume disease population: • 0.839 High-volume disease population: • 0.793	
	AE pre-progression	Low-volume disease population: • -0.058 High-volume disease population: • -0.070	
	AE post-progression	Low-volume disease population: • -0.111 High-volume disease population: • -0.070	

Table 42: Overview of the model assumptions

Assumptions	
General	Patient characteristics, efficacy and safety were derived from the TITAN trial and were assumed to be representative of the mHSPC population in Denmark
Model structure	In general, it was assumed that the health states of the model represented the key sequence of events that patients may experience over the course of their treatment for mHSPC and mCRPC. The assumption was made that these events were progressive, mutually exclusive, and irreversible (e.g. a patient who experienced mCRPC and entered the mCRPC state of the model, could not recover from this status, and return to the mHSPC state). This assumption was consistent with the definitions of PFS and OS from clinical trials, and the approaches used in previous economic evaluations in mCRPC.
Survival projections	It was assumed that: • TTTD could not be longer than rPFS • rPFS could not be longer than OS • OS could not be longer than survival in the general population
Utilities	Baseline utility in mHSPC was assumed to be similar for apalutamide + ADT patients, and ADT alone patients
	The disutilities of AEs within each treatment arm were accounted for separately and were therefore treatment-specific
	The applied utility value in mCRPC was assumed to reflect the average utility within mCRPC
	Utilities were age adjusted as recommended by the DMC.
Subsequent treatments	OS data from the TITAN trial was used and external data provided life extending subsequent treatments in the mCRPC setting which were reflective of Danish clinical practice
Costs	ADT was provided over the lifetime of a patient
	It was assumed that the subsequent treatment costs were applied as a one-off cost at the moment of progression.

mCRPC metastatic castration resistant prostate cancer; mHSPC= metastatic hormone-sensitive prostate cancer; OS: overall survival; PFS= progression-free survival; TTTD= time-to-treatment discontinuation

8.6.2 Base case results

Low volume disease

Table 43 shows the results for the base case analysis for low volume patients. Patients on apalutamide+ADT (APA+ADT) had improved survival compared with RT+ADT and spent more time progression-free in mHSPC. Consequently, APA +ADT was associated with the highest LYs and QALYs but also higher costs.

The primary cost driver for APA +ADT was costs acquired during the mHSPC phase and the costs were primarily related to drug acquisition costs of apalutamide. The cost component with the largest savings for APA vs. RT+ADT were mCRPC costs which is explained by the subsequent treatment mix expected in Danish clinical practice, and also because patients on apalutamide treatment take longer to switch to subsequent treatment lines in mCRPC. Hence, patients on the RT+ADT are switched to other therapies following progression, which occurs sooner.

The base case analysis showed that APA+ADT yielded better survival outcomes and was associated with more LYs and QALYs vs. RT+ADT. Incremental QALYs for APA+ADT vs. RT+ADT +0.62 and incremental LYs +0.85. The ICER for APA+ADT vs. RT+ADT was 937,482 DKK/QALY.

Table 43 Base case results, low volume disease

Per patient	Apalutamide+ADT	RT+ADT
Life years gained		
Total life years gained	6.98	6.13
Life years gained (mHSPC)	3.29	2.52
Life years gained (mCRPC)	3.69	3.61
QALY's		
Total QALYs	5,82	5,20
QALYs (mHSPC)	2.92	2.24
QALYs (mCRPC)	3.01	2.97
QALYs (adverse reactions)	-0.11	-0.01
Costs		
Total costs	1,901,474	1,321,742
Drug costs and admin.	903,930	112,219
Planned MRU	246,744	189,484
Adverse reactions costs	3,331	85
Patient time (treatment)	1,595	8,597

Per patient	Apalutamide+ADT	RT+ADT
Patient transport (treatment)	891	2,903
Post progression cost (mCRPC)	680,076	941,037
End of life cost	64,908	67,417
Incremental results		
LYs	Ref	0.85
QALYs	Ref	0.62
Cost	Ref	579,732
ICER (cost per QALY)	Ref	937,482
Cost per LY	Ref	683,536

High volume disease

Table 44 shows the results for the base case analysis for high volume patients. Patients on APA+ADT had improved survival compared with DOC+ADT and spent more time progression-free in mHSPC. Consequently, APA +ADT was associated with the highest LYs and QALYs but also higher costs.

The primary cost driver for APA +ADT was costs acquired during the mHSPC phase and the costs were primarily related to drug acquisition costs of apalutamide. The cost component with the largest savings for APA vs. DOC+ADT were mCRPC costs which is explained by the subsequent treatment mix expected in Danish clinical practice, and also because patients on apalutamide treatment take longer to switch to subsequent treatment lines in mCRPC. Hence, patients on the DOC+ADT are switched to other therapies following progression, which occurs sooner.

The base case analysis showed that APA+ADT yielded better survival outcomes and was associated with more LYs and QALYs vs. DOC+ADT. Incremental QALYs for APA+ADT vs. DOC+ADT +0.18 and incremental LYs +0.20. The ICER for APA+ADT vs. DOC+ADT was 2,170,696 DKK/QALY.

Table 44 Base case results, high volume disease

Per patient	Apalutamide+ADT	DOC+ADT
Life years gained		
Total life years gained	5.24	5.05
Life years gained (mHSPC)	2.64	2.27
Life years gained (mCRPC)	2.60	2.77
QALY's		

Per patient	Apalutamide+ADT	DOC+ADT
Total QALYs	4.11	3.93
QALYs (mHSPC)	2.26	1.94
QALYs (mCRPC)	1,96	2.10
QALYs (adverse reactions)	-0.11	-0.11
Costs		
Total costs	1,621,808	1,251,947
Drug costs and admin.	756,394	63,225
Planned MRU	198,354	170,994
Adverse reactions costs	3,327	5,098
Patient time (treatment)	1,335	2,690
Patient transport (treatment)	746	1,503
Post progression cost (mCRPC)	594,378	940,486
End of life cost	67,275	67,951
Incremental results		
LYs	Ref	0.20
QALYs	Ref	0.18
Cost	Ref	369,861
ICER (cost per QALY)	Ref	2,037,185
Cost per LY	Ref	1,862,974

8.7 Sensitivity analyses

Major model variables were tested in a one-way DSA to identify model drivers and examine key areas of uncertainty. Where possible, CIs were used to define the upper and lower bounds tested for the parameters in the DSA.

Figure 33 and Figure 34 show the results of the one way sensitivity analysis (OWSA) with the top 10 parameters by order of influence on the ICER, for low and high volume disease respectfully.

Figure 33: One-way sensitivity analyses, APA+ADT vs. RT+ADT (low volume disease)

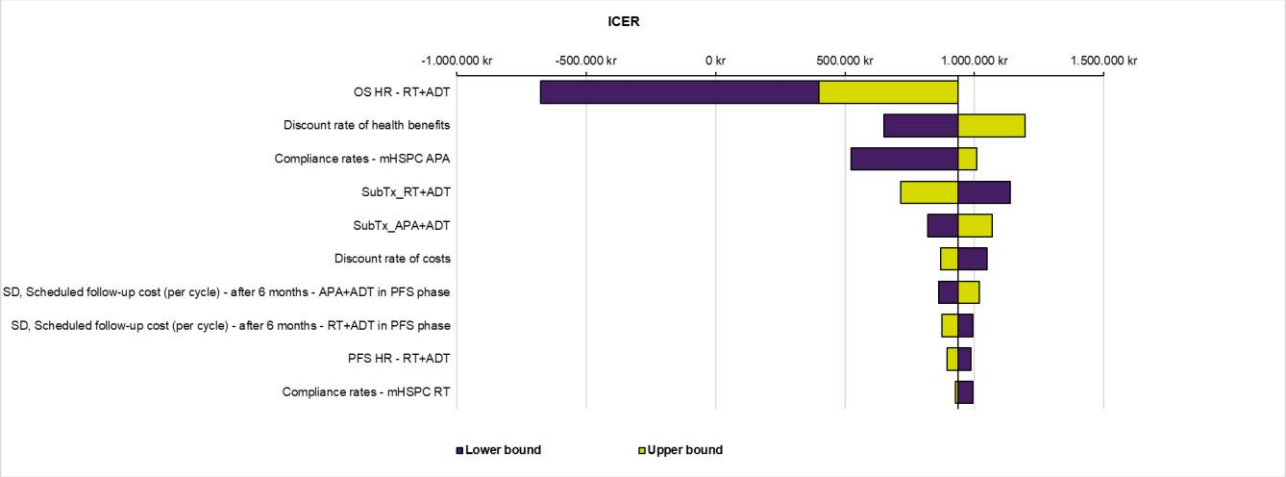
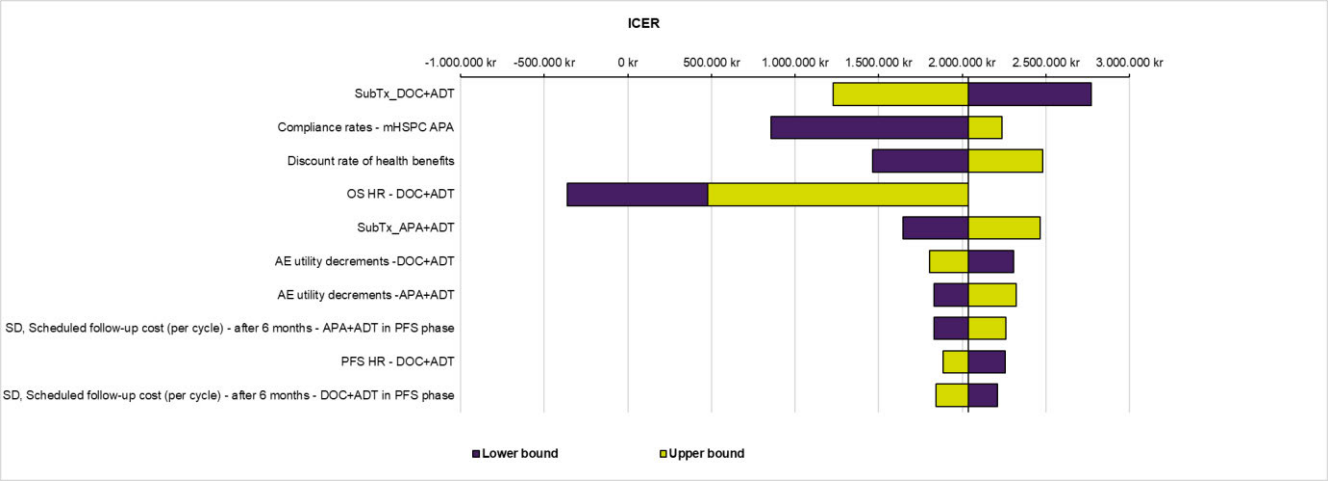


Figure 34: One-way sensitivity analyses, APA+ADT vs. DOC+ADT (high volume disease)



For low volume disease the most influential parameters were the OS HR applied to predict survival, the discount rate of health benefits, the compliance rates in mHSPC of APA+ADT and the subsequent treatment for RT+ADT. For high volume disease the most influential parameters were the subsequent treatment for DOC+ADT, the compliance rates in mHSPC of APA+ADT, the discount rate of health benefits and the OS HR applied to predict survival.

Table 45 and Table 46 shows that the impact on the estimated ICER based on discount in the price of apalutamide.

Table 45: ICERs estimated with different discounts for the drug in low volume disease

	Change	ICER (DKK/QALY) vs. DOC+ADT
Price discount apalutamide **(dominant at 65 % discount)**	0 %	937,482
	25 %	595,868
	50%	254,254
	75%	APA+ADT dominant

Table 46: ICERs estimated with different discounts for the drug in high volume disease

	Change	ICER (DKK/QALY) vs. DOC+ADT
Price discount apalutamide (dominant at 53 % discount)	0 %	2,037,185
	25 %	1,063,531
	50%	89,876
	75%	APA+ADT dominant

8.7.1 Probabilistic sensitivity analyses

To account for the joint uncertainty of the underlying parameter estimates, a second-order stochastic sensitivity analysis (i.e., PSA) was performed. The parameters included in the PSA and how they were varied are shown in the model sheet PSA inputs.

A PSA was performed by varying all model parameters simultaneously and randomly within their probability distributions. A thousand iterations were run in the analysis. The results of the PSA are presented in Table 47 and Table 48 for low and high volume disease respectively.

For low volume the probabilistic ICER is 970,106 kr per QALY gained when comparing APA + ADT to RT+ADT and for high volume the probabilistic ICER is 2,678,926 kr per QALY gained when comparing APA + ADT to DOC+ADT

Table 47: Probabilistic results: APA + ADT versus RT + ADT (low volume disease)

	apalutamide + ADT	RT + ADT	Incremental
Total costs	1,923,525 (SD 150,927)	1,346,700 (SD 238,901)	576,825 (SD 280,557)
Total QALYs	5.85 (SD 0.58)	5.26 (SD 0.70)	0.59 (SD 0.91)
Cost per QALY gained			**970,106 kr**

Table 48: Probabilistic results: APA + ADT versus DOC + ADT (high volume disease)

	apalutamide + ADT	DOC + ADT	Incremental
Total costs	1,623,839 (SD 110,713)	1,278,682 (SD 193,643)	345,157 (SD 222,039)
Total QALYs	4.12 (SD 0.25)	4,00 (SD 0.49)	0.12 (SD 0.53)
Cost per QALY gained			**2,813,443 kr**

The cost-effectiveness (CE)-plane presenting incremental costs and QALYs resulting from each iteration of the PSA is presented in Figure 35 and Figure 36 for low and high volume disease respectively.

Figure 35: PSA Scatter plot APA + ADT versus RT + ADT (low volume disease)

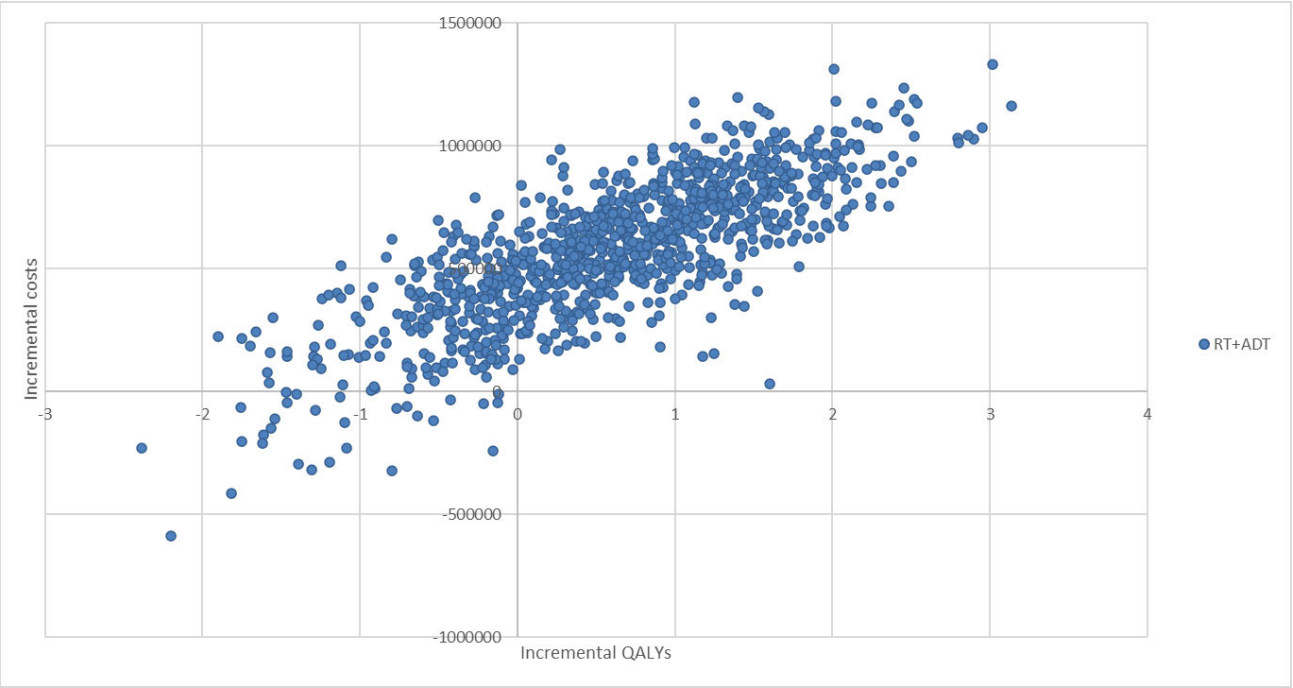
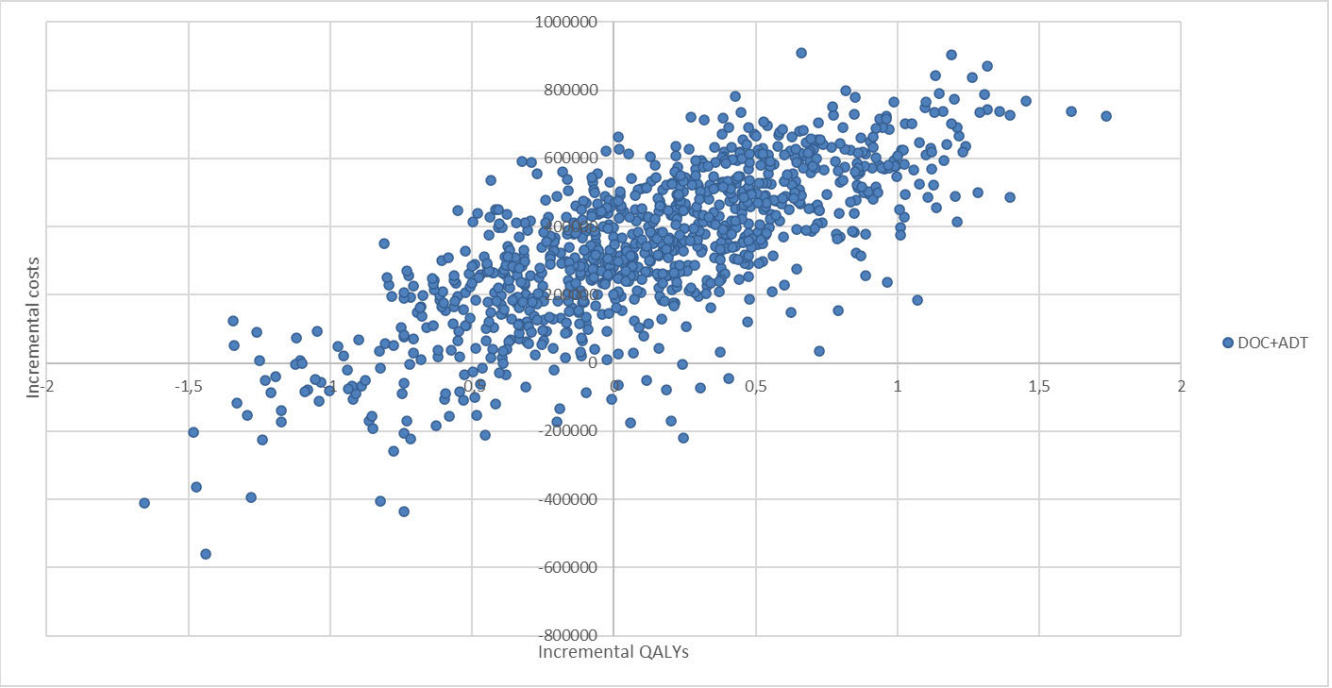


Figure 36 PSA Scatter plot APA + ADT versus DOC + ADT (high volume disease)



It should be noted that it is expected that there will be a difference between the DSA and PSA results. With the DSA, one parameter is varied at a time, keeping all other parameters constant. With the PSA, all parameters are varied at the same time based on probability distributions. Therefore, these results cannot be compared directly.

Cost-effectiveness acceptability curves (CEAC) (Figure 37 and Figure 38) show the probability of each option being cost-effective across a range of possible values of willingness to pay for an additional QALY.

Figure 37 Cost-effectiveness acceptability curve, APA + ADT versus RT + ADT (low volume disease)

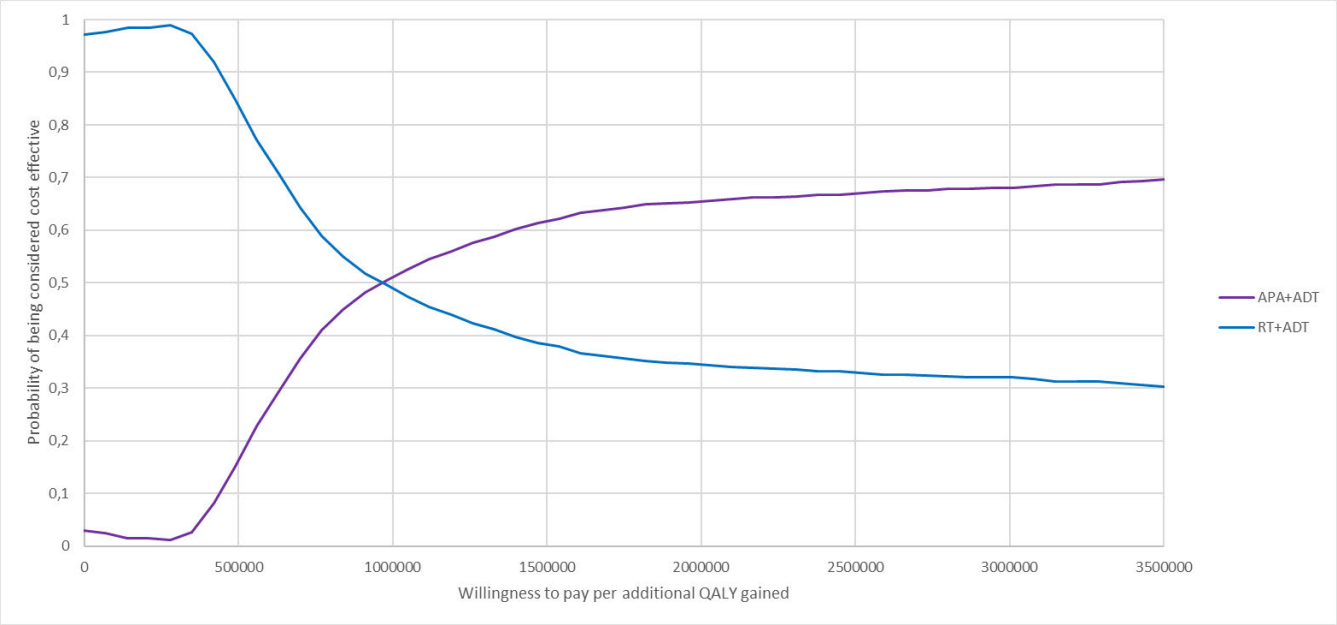
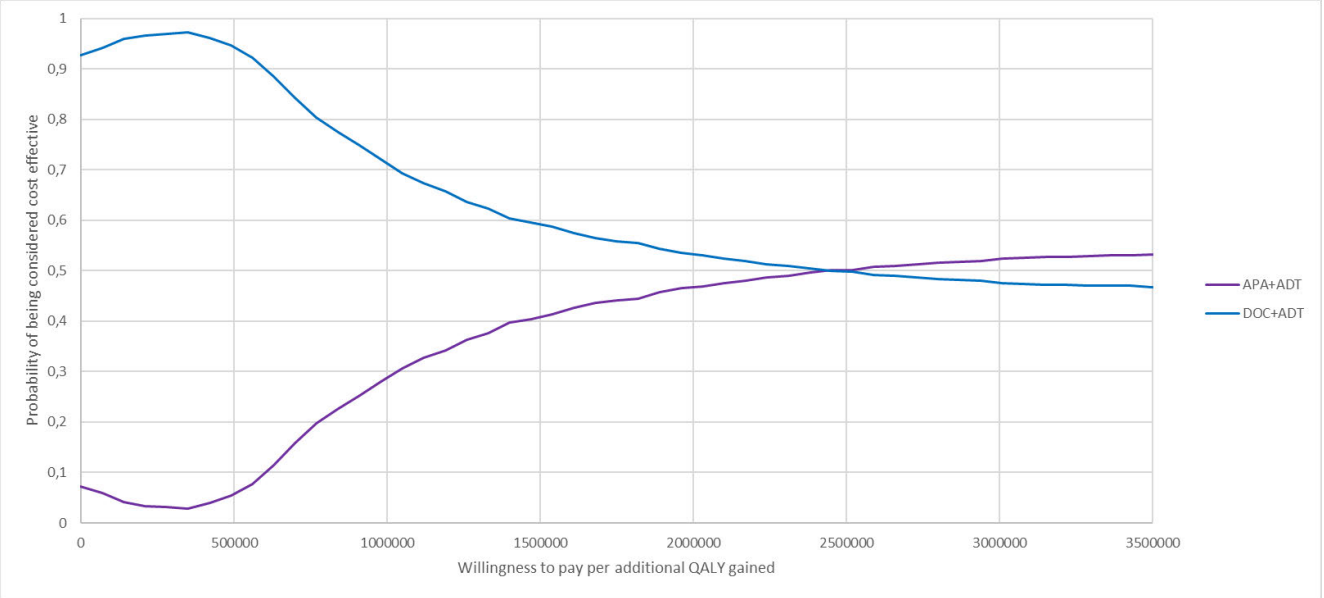


Figure 38 Cost-effectiveness acceptability curve, APA + ADT versus DOC + ADT (high volume disease)



9. Budget impact analysis

The calculations of the budget impact analysis can be found in the cost-effectiveness Excel model. The number of patients per year are assumed to be 500 patients overall in mHSPC, 200 (40%) for low volume disease and 300 (60%) for high volume disease. For the reference scenarios (apalutamide+ADT not recommended), it is assumed that 0% of patients will be administered apalutamide+ADT and 100% docetaxel+ADT or RT+ADT for high and low volume respectively. In the budget impact analysis where apalutamide+ADT is recommended, a gradual uptake for apalutamide+ADT is assumed starting at 50% (225 patients) in year 1, 70% (315 patients) in year 2, and stable market share at 80% in year 3, year 4, and year 5 (see Table 49 and Table 50). The cost included in the analysis are the same as included in the base case analysis but excluding

patient costs and undiscounted according to the Medicines Council guidelines. The budget impact results are presented in Table 55 and Table 58.

The budget impact of recommending apalutamide+ADT for low volume disease range from 4.922.569 DKK in year 1 to 64.609,853 DKK in year 5.

The budget impact of recommending apalutamide+ADT for high volume disease range from 8.910.790DKK in year 1 to 68.429.399DKK in year 5.

Number of patients

Low volume disease

Table 49: Number of patients expected to be treated over the next five-year period - if the pharmaceutical is introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
APA+ADT	100 (50%)	140 (70%)	160 (80%)	160 (80%)	160 (80%)
RT+ADT	100 (50%)	60 (20%)	40 (20%)	40 (20%)	40 (20%)
Total number of patients	200	200	200	200	200

Table 50: Number of patients expected to be treated over the next five-year period - if the pharmaceutical is NOT introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
APA+ADT	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
RT+ADT	200(100%)	200(100%)	200(100%)	200(100%)	200(100%)
Total number of patients	200	200	200	200	200

High volume disease

Table 51: Number of patients expected to be treated over the next five-year period - if the pharmaceutical is introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
APA+ADT	150 (50%)	210 (70%)	240 (80%)	240 (80%)	240 (80%)
DOC+ADT	150 (50%)	90 (20%)	60 (20%)	60 (20%)	60 (20%)
Total number of patients	300	300	300	300	300

Table 52: Number of patients expected to be treated over the next five-year period - if the pharmaceutical is NOT introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
APA+ADT	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
DOC+ADT	300 (100%)	300 (100%)	300 (100%)	300 (100%)	300 (100%)
Total number of patients	300	300	300	300	300

Budget impact

Low volume disease

Table 53: Cost per year - if the pharmaceutical is introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
APA+ADT	16.159.625 kr.	50.953.781 kr.	94.251.036 kr.	140.646.959 kr.	182.487.290 kr.
RT+ADT	11.237.055 kr.	19.598.938 kr.	31.632.033 kr.	44.170.398 kr.	47.353.915 kr.
Total Cost	27.396.680 kr.	70.552.719 kr.	125.883.069 kr.	184.817.357 kr.	229.841.206 kr.

Table 54: Cost per year - if the pharmaceutical is NOT introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
APA+ADT	0	0	0	0	0
RT+ADT	22.474.111 kr.	48.187.520 kr.	87.033.896 kr.	132.791.858 kr.	165.231.353 kr.
Total Cost	22.474.111 kr.	48.187.520 kr.	87.033.896 kr.	132.791.858 kr.	165.231.353 kr.

Table 55: Expected budget impact of recommending the pharmaceutical for the current indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The pharmaceutical under consideration is recommended	27.396.680 kr.	70.552.719 kr.	125.883.069 kr.	184.817.357 kr.	229.841.206 kr.
Minus: The pharmaceutical under consideration is NOT recommended	22.474.111 kr.	48.187.520 kr.	87.033.896 kr.	132.791.858 kr.	165.231.353 kr.
Budget impact of the recommendation	4.922.569 kr.	22.365.198 kr.	38.849.173 kr.	52.025.498 kr.	64.609.853 kr.

High volume disease

Table 56: Cost per year - if the pharmaceutical is introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
APA+ADT	28.133.762 kr.	88.279.920 kr.	152.717.864 kr.	206.310.214 kr.	244.427.628 kr.
DOC+ADT	19.222.972 kr.	46.194.727 kr.	57.917.582 kr.	60.051.174 kr.	59.348.529 kr.
Total Cost	47.356.733 kr.	134.474.647 kr.	210.635.446 kr.	266.361.388 kr.	303.776.157 kr.

Table 57: Cost per year - if the pharmaceutical is NOT introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
APA+ADT	0	0	0	0	0
DOC+ADT	38.445.943 kr.	107.767.832 kr.	166.631.486 kr.	208.308.509 kr.	235.346.758 kr.
Total Cost	38.445.943 kr.	107.767.832 kr.	166.631.486 kr.	208.308.509 kr.	235.346.758 kr.

Table 58: Expected budget impact of recommending the pharmaceutical for the current indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The pharmaceutical under consideration is recommended	47.356.733 kr.	134.474.647 kr.	210.635.446 kr.	266.361.388 kr.	303.776.157 kr.
Minus: The pharmaceutical under consideration is NOT recommended	38.445.943 kr.	107.767.832 kr.	166.631.486 kr.	208.308.509 kr.	235.346.758 kr.
Budget impact of the recommendation	47.356.733 kr.	134.474.647 kr.	210.635.446 kr.	266.361.388 kr.	303.776.157 kr.

10. Discussion on the submitted documentation

Clinical documentation

We were able to run an NMA with relevant comparators in Danish clinical practice, and we were able to run most analyses for HVD and LVD patients separately, showing overall consistent results of benefits of treatment with apalutamide.

All included studies were conducted in patient populations of adult (aged ≥18 years) men with mHSPC. The population definitions based on the enrolment criteria were generally similar across the studies with minor differences in terms of exceptions the trials permitted related to the previous treatment. With the caveats of RCTs, the results are considered generalizable to Danish clinical practice and Danish patient population.

Variations across the studies in terms of how ADT was defined and how PFS was defined, as well as high risk of performance bias in STAMPEDE due to open-label design, may have impacted the results and validity of the analyses, and therefore should be kept in mind when interpreting the results. Specifically for PFS, the STAMPEDE trial reported prostate cancer related deaths while other trials were inclusive of death from all-causes. Variability was observed for definitions of PFS across studies and therefore an analysis of PFS was planned as a sensitivity analysis using the definition applied in the STAMPEDE trial. Use of this definition allowed the network to be expanded to include comparisons to AAP+ADT, DOC+ADT, and radiotherapy+ADT.

The analyses were limited by the low number of eligible trials and limited availability of relevant outcome comparisons. Data was particularly limited for safety analyses, wherein only two trials were available containing one relevant outcome where no analyses was feasible.

Health economic model

A partitioned survival model was developed in line with the recommendations from DMC, containing the two populations: patients with high-volume disease and patients with low-volume disease, as specifically requested by DMC.

The model considered three health states: rPFS (i.e. pre-progression survival), post-progression survival (PPS), and death. Patients who are eligible for treatment enter the model, initiate frontline treatment, and experience an interval of rPFS. Within the rPFS health state, patients were further partitioned according to whether they were on- and off-treatment to more accurately estimate treatment costs.

Strengths of the economic analysis include the NMA and use of TITAN trial (low risk of bias RCT), which was the primary source of clinical parameters and utility values. Furthermore, the model structure is in line with previously accepted models by NICE. Uncertainty in the model inputs was explored in sensitivity and scenario analyses. Also, the model uses Danish inputs for costs and utilities. Like all economic analyses, this analysis has limitations. This includes limited long-term data for the efficacy of APA plus ADT in TITAN. In order to extrapolate rPFS and OS beyond TITAN, a jointly fitted approach in which ADT was used as a reference curve from TITAN and apalutamide + ADT as a covariate, was used.

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Relevance to a Danish context

There have been substantial changes in the management of men with mHSPC over the past years, with upfront combination therapies replacing ADT alone. Based on the analyses presented in this submission, apalutamide is a cost-effective treatment alternative to patients who receive either docetaxel or radiotherapy in the mHSPC setting today.

Apalutamide is the first therapy to enable the broad population of patients with mHSPC to delay disease progression to mCRPC, extend survival, reduce symptom burden and maintain HRQoL. Apalutamide is well tolerated and convenient oral treatment that can be taken at home without food restrictions, and treatment with apalutamide does not require co-administration of steroids or additional monitoring which further reduces time spent in hospitals and thereby minimizes the patient burden.

By introducing apalutamide into the prostate cancer treatment pathway early, patients benefit of an additional treatment option improving their chances of survival.

Just recently at ASGO-GU 202022 post-hoc analysis of TITAN was presented, showing that prior use of docetaxel in patients with mHSPC did not further improve rPFS, OS, time to PSA progression or achievement of deep PSA response following initiative of treatment with apalutamide + ADT (77). Also results from a post-hoc analysis of SPARTAN and TITAN was presented, showing that patients treated with apalutamide in SPARTAN and TITAN had rapid and deep PSA decline that were associated with maintenance of HRQoL, improved patient-reported physical wellbeing, and reduced risk of worsening pain and fatigue intensity (78).

Lastly results from a real-world study of patients with mHSPC was presented, showing that significantly more patients attained an early and deep PSA response when treated with apalutamide relative to enzalutamide. PSA90 response was attained significantly earlier in patients treated with apalutamide. The proportion of patients attaining a PSA90 response by 6 and 12 months following initiation of apalutamide are consistent with those observed in the TITAN study (68% and 71%, respectively) (79).

All pointing to the benefits of treating mHSPC patients with apalutamide, a well-tolerated treatment option that can delay progression, extend survival, and maintain HRQoL by delaying the onset of debilitating symptoms in all patients with mHSPC, regardless of risk stratification or prior treatment.

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

Table 59: Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Embase.com	Not restricted	17.06.2021
Embase in process			
Medline	PubMed		
Medline in process			
CDSR	Cochrane Library		
CENTRAL			
DARE			

Abbreviations: CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Collaboration Central Register of Clinical Trials; DARE = Database of Abstract Reviews

Table 60: Registers included in the search

Database	Platform	Search strategy	Date of search
US NIH registry & results database	https://clinicaltrials.gov		17.06.2021

Table 61: Conference material included in the literature search

Conference	Search strategy	Words/terms searched
ASCO Annual Meeting **ASCO GU** **AUA Annual Meeting** **EAU Annual Congress** **ECCO Congress** **ESMO Congress**	Searches of proceedings from the 2016–17/19/20/21 editions of these conferences were conducted in Embase via Ovid.*	•Prostate cancer •CSPC •HSPC

* Manual searches were also conducted for the 2018 ASCO conference that was not available via embase.com

Search strategy

Indexed-database Searches

Randomised Controlled Trials

The search algorithm below was used to identify RCTs that report on the clinical efficacy and safety of APA combination therapy and relevant comparators for the treatment of men with mHSPC. The results were not limited by language.

Original search

Table 62: Embase and MEDLINE (via EMBASE.com) search strategy

Search Number	Description	Search Algorithm	Search Yield – 18 December 2018
Population			
#1	Metastatic prostate cancer	'prostate cancer'/exp OR (prostat*:ab,ti AND (advanced:ab,ti OR metasta*:ab,ti OR malignan*:ab,ti) AND (cancer:ab,ti OR neoplas*:ab,ti OR carcinoma*:ab,ti OR tum$r*:ab,ti))	210,638
Intervention			
#2	Interventions and comparators	'androgen deprivation therapy'/exp OR 'anti-androgen therapy'/exp OR 'anti androgen':ab,ti OR 'anti-androgen':ab,ti OR 'androgen antagonist':ab,ti OR 'androgen dependent':ab,ti OR 'androgen-dependent':ab,ti OR 'androgen ablation':ab,ti OR 'androgen- ablation':ab,ti OR 'androgen blockade':ab,ti OR 'androgen-blockade':ab,ti OR 'androgen receptor':ab,ti OR 'androgen suppression':ab,ti OR 'luteinizing hormone':ab,ti OR 'luteinising hormone':ab,ti OR 'gonadotropin-releasing hormone':ab,ti OR 'gonadotropin releasing hormone':ab,ti OR lhrh:ab,ti OR gnrh:ab,ti OR abiraterone:ab,ti OR 'abiraterone acetate':ab,ti OR zytiga:ab,ti OR 'androgen deprivation':ab,ti OR adt:ab,ti OR docetaxel:ab,ti OR taxotere:ab,ti OR docecad:ab,ti OR docefrez:ab,ti OR zytax:ab,ti OR enzalutamide:ab,ti OR leuprolide:ab,ti OR leuprorelin:ab,ti OR lupron:ab,ti OR viadur:ab,ti OR eligard:ab,ti OR prostap:ab,ti OR buserelin:ab,ti OR sepref act:ab,ti OR cinnafact:ab,ti OR metrelef:ab,ti OR aminoglutethimide:ab,ti OR cytadren:ab,ti OR xtandi:ab,ti OR goserelin:ab,ti OR zoladex:ab,ti OR triptorelin:ab,ti OR decapeptyl:ab,ti OR diphereline:ab,ti OR gonapeptyl:ab,ti OR trelstar:ab,ti OR variopeptyl:ab,ti OR histrelin:ab,ti OR vantas:ab,ti OR supprelin:ab,ti OR degarelix:ab,ti OR firmagon:ab,ti OR 'antiandrogen':ab,ti OR flutamide:ab,ti OR eulexin:ab,ti OR cytomid:ab,ti OR chimax:ab,ti OR drogenil:ab,ti OR flucinom:ab,ti OR flutamin:ab,ti OR fugerel:ab,ti OR niftolide:ab,ti OR sebatrol:ab,ti OR bicalutamide:ab,ti OR casodex:ab,ti OR cosudex:ab,ti OR calutide:ab,ti OR kalumid:ab,ti OR nilutamide:ab,ti OR nilandron:ab,ti OR anandron:ab,ti OR estrogen:ab,ti OR oestrogen:ab,ti OR ketoconazole:ab,ti OR nizoral:ab,ti OR diethylstilbestrol:ab,ti OR ethinylestradiol:ab,ti OR cyproterone:ab,ti OR 'arn 509':ab,ti OR arn509:ab,ti OR apalutamide:ab,ti OR erleada:ab,ti OR darolutamide:ab,ti OR palbociclib:ab,ti OR ibrance:ab,ti OR ipilimumab:ab,ti OR yervoy:ab,ti	309,128
Study design			
#3	RCTs	'randomized controlled trial'/exp OR 'randomization'/exp OR random*:ab,ti OR 'rct':ab,ti OR 'controlled trial':ab,ti OR 'clinical trial':ab,ti OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'cross over':ab,ti OR 'crossover':ab,ti	2,346,128

		OR 'placebo'/exp OR 'placebo':ab,ti OR (doubl* AND blind*:ab,ti) OR (singl* AND blind*:ab,ti) OR ('open':ab,ti AND label*:ab,ti) OR factorial*:ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti	
#4		#1 AND #2 AND #3	6,934
Limiters			
#5	Narrative reviews	review:it NOT ((systematic OR meta) AND analy* OR ((indirect OR mixed) AND 'treatment comparison'))	2,314,031
#6	Other non-primary studies	'case study'/de OR 'case report'/de OR 'quality control'/de OR 'case control study'/de OR 'theoretical study'/de OR 'retrospective study'/de OR 'methodology'/de OR 'practice guideline'/de	5,722,695
#7	Animal and laboratory studies	'animal cell'/de OR 'animal experiment'/de OR 'animal model'/de OR 'cancer cell culture'/de OR 'human cell'/de OR 'in vitro study'/de OR 'nonhuman'/de OR 'biological model'/de OR 'cell culture'/de OR 'diagnostic test accuracy study'/de	8,175,080
#8	Conference abstracts	'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it	4,001,220
#9		#5 OR #6 OR #7 OR #8	17,553,212
#10		#4 NOT #9	2,514

Table 63: MEDLINE In-Process (via PubMed) search strategy

Search Number	Description	Search Algorithm	Search Yield – 18 December 2018
Population			
#1	Metastatic prostate cancer	"prostate cancer"[Mesh] OR (prostat*[tiab] AND (advanced[tiab] OR metasta*[tiab] OR malignant[tiab]) AND (cancer[tiab] OR neoplas*[tiab] OR carcinoma*[tiab] OR tumor[tiab] OR tumour[tiab]))	42,894
Intervention			
#2	Interventions and comparators	"androgen antagonists"[Mesh] OR "androgen receptor antagonist"[Mesh] OR "anti androgen"[tiab] OR "anti-androgen"[tiab] OR "antiandrogen"[tiab] OR "androgen antagonist"[tiab] OR "androgen dependent"[tiab] OR "androgen-dependent"[tiab] OR "androgen ablation"[tiab] OR "androgen-ablation"[tiab] OR "androgen blockade"[tiab] OR "androgen-blockade"[tiab] OR "androgen receptor"[tiab] OR "androgen suppression"[tiab] OR "luteinizing hormone"[tiab] OR "luteinising hormone"[tiab] OR "gonadotropin-releasing hormone"[tiab] OR "gonadotropin releasing hormone"[tiab] OR lhrh[tiab] OR gnrh[tiab] OR abiraterone[tiab] OR zytiga[tiab] OR "androgen deprivation"[tiab] OR adt[tiab] OR docetaxel[tiab] OR taxotere[tiab] OR docecad[tiab] OR docefrez[tiab] OR zytax[tiab] OR enzalutamide [tiab] OR leuprolide[tiab] OR leuprorelin[tiab] OR lupron[tiab] OR viadur[tiab] OR eligard[tiab] OR prostap[tiab] OR buserelin[tiab] OR seprefact[tiab] OR cinnafact[tiab] OR metrelef[tiab] OR aminoglutethimide[tiab] OR cytadren[tiab] OR xtandi[tiab] OR goserelin[tiab] OR zoladex[tiab] OR triptorelin[tiab] OR decapeptyl[tiab] OR diphereline[tiab] OR gonapeptyl[tiab] OR trelstar[tiab] OR variopeptyl[tiab] OR histrelin[tiab] OR vantas[tiab]	240,158

		OR supprelin[tiab] OR degarelix[tiab] OR firmagon[tiab] OR antiandrogen[tiab] OR flutamide[tiab] OR eulexin[tiab] OR cytomid[tiab] OR chimax[tiab] OR drogenil[tiab] OR flucinom[tiab] OR flutamin[tiab] OR fugerel[tiab] OR niftolide[tiab] OR sebatrol[tiab] OR bicalutamide[tiab] OR casodex[tiab] OR cosudex[tiab] OR calutide[tiab] OR kalumid[tiab] OR nilutamide[tiab] OR nilandron[tiab] OR anandron[tiab] OR estrogen[tiab] OR oestrogen[tiab] OR ketoconazole[tiab] OR nizoral[tiab] OR diethylstilbestrol[tiab] OR ethinylestradiol[tiab] OR cyproterone[tiab] OR arn509 [tiab] OR "arn 509"[tiab] OR apalutamide[tiab] OR erleada[tiab] OR darolutamide[tiab] OR palbociclib[tiab] OR ibrance[tiab] OR ipilimumab[tiab] OR yervoy[tiab]	
Limiters			
#3	Epub ahead of print	publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook OR (pubstatusaheadofprint)	453,490
#4	In-process	inprocess[SB]	660,090
#5		#3 OR #4	1,113,580
#6		#1 AND #2 AND #5	673

Table 64: CDSR, CENTRAL and DARE (via the Cochrane Library) search strategy

Search Number	Description	Search Algorithm	Search Yield – 18 December 2018
	Population		
#1	Metastatic prostate cancer	(prostat*:ab,ti AND (advanced:ab,ti OR metasta*:ab,ti OR malignan*:ab,ti) AND (cancer:ab,ti OR neoplas*:ab,ti OR carcinoma*:ab,ti OR tumor*:ab,ti OR tumour:ab,ti))	3,868
#2		MeSH descriptor: [Prostatic Neoplasms] explode all trees	4,764
	Intervention		
#3	Interventions and comparators	'anti androgen':ab,ti OR 'androgen antagonist':ab,ti OR 'androgen dependent':ab,ti OR 'androgen ablation':ab,ti OR 'androgen blockade':ab,ti OR 'androgen-blockade':ab,ti OR 'androgen receptor':ab,ti OR 'androgen suppression':ab,ti OR 'luteinizing hormone':ab,ti OR 'luteinising hormone':ab,ti OR 'gonadotropin-releasing hormone':ab,ti OR 'gonadotropin releasing hormone':ab,ti OR lhrh:ab,ti OR gnrh:ab,ti OR abiraterone:ab,ti OR 'abiraterone acetate':ab,ti OR zytiga:ab,ti OR 'androgen deprivation':ab,ti OR adt:ab,ti OR docetaxel:ab,ti OR taxotere:ab,ti OR docecad:ab,ti OR docefrez:ab,ti OR zytax:ab,ti OR enzalutamide:ab,ti OR leuprolide:ab,ti OR leuprorelin:ab,ti OR lupron:ab,ti OR viadur:ab,ti OR eligard:ab,ti OR prostap:ab,ti OR buserelin:ab,ti OR seprefact:ab,ti OR cinnafact:ab,ti OR metrelef:ab,ti OR aminoglutethimide:ab,ti OR cytadren:ab,ti OR xtandi:ab,ti OR goserelin:ab,ti OR zoladex:ab,ti OR triptorelin:ab,ti OR decapeptyl:ab,ti OR diphereline:ab,ti OR gonapeptyl:ab,ti OR trelstar:ab,ti OR variopeptyl:ab,ti OR histrelin:ab,ti	22,693

	OR vantas:ab,ti OR supprelin:ab,ti OR degarelix:ab,ti OR firmagon:ab,ti OR 'antiandrogen':ab,ti OR flutamide:ab,ti OR eulexin:ab,ti OR cytomid:ab,ti OR chimax:ab,ti OR drogenil:ab,ti OR flucinom:ab,ti OR flutamin:ab,ti OR fugerel:ab,ti OR niftolide:ab,ti OR sebatrol:ab,ti OR bicalutamide:ab,ti OR casodex:ab,ti OR cosudex:ab,ti OR calutide:ab,ti OR kalumid:ab,ti OR nilutamide:ab,ti OR nilandron:ab,ti OR anandron:ab,ti OR estrogen:ab,ti OR oestrogen:ab,ti OR ketoconazole:ab,ti OR nizoral:ab,ti OR diethylstilbestrol:ab,ti OR ethinylestradiol:ab,ti OR cyproterone:ab,ti OR 'arn 509':ab,ti OR arn509:ab,ti OR apalutamide:ab,ti OR erleada:ab,ti OR darolutamide:ab,ti OR palbociclib:ab,ti OR ibrance:ab,ti OR ipilimumab:ab,ti OR yervoy:ab,ti	
Combined		
#4	(#1 OR #2) AND #3 in Cochrane Reviews and Trials	2,832

*The results in the "Cochrane Reviews" category were retrieved to obtain the results from CDSR and "Trials" category for results from CENTRAL and DARE.

First update

Table 65: Embase and MEDLINE (via EMBASE.com) search strategy

Search Number	Description	Search Algorithm	Search Yield – 2 July 2019
Population			
#1	Metastatic prostate cancer	'prostate cancer'/exp OR (prostat*:ab,ti AND (advanced:ab,ti OR metasta*:ab,ti OR malignan*:ab,ti) AND (cancer:ab,ti OR neoplas*:ab,ti OR carcinoma*:ab,ti OR tum$r*:ab,ti))	240,388
Intervention			
#2	Interventions and comparators	'androgen deprivation therapy'/exp OR 'anti-androgen therapy'/exp OR 'anti androgen':ab,ti OR 'anti-androgen':ab,ti OR 'androgen antagonist':ab,ti OR 'androgen dependent':ab,ti OR 'androgen-dependent':ab,ti OR 'androgen ablation':ab,ti OR 'androgen- ablation':ab,ti OR 'androgen blockade':ab,ti OR 'androgen-blockade':ab,ti OR 'androgen receptor':ab,ti OR 'androgen suppression':ab,ti OR 'luteinizing hormone':ab,ti OR 'luteinising hormone':ab,ti OR 'gonadotropin-releasing hormone':ab,ti OR 'gonadotropin releasing hormone':ab,ti OR lhrh:ab,ti OR gnrh:ab,ti OR abiraterone:ab,ti OR 'abiraterone acetate':ab,ti OR zytiga:ab,ti OR 'androgen deprivation':ab,ti OR adt:ab,ti OR docetaxel:ab,ti OR taxotere:ab,ti OR docecad:ab,ti OR docefrez:ab,ti OR zytax:ab,ti OR enzalutamide:ab,ti OR leuprolide:ab,ti OR leuprorelin:ab,ti OR lupron:ab,ti OR viadur:ab,ti OR eligard:ab,ti OR prostap:ab,ti OR buserelin:ab,ti OR seprefact:ab,ti OR cinnafact:ab,ti OR metrelef:ab,ti OR aminoglutethimide:ab,ti OR cytadren:ab,ti OR xtandi:ab,ti OR goserelin:ab,ti OR zoladex:ab,ti OR triptorelin:ab,ti OR decapeptyl:ab,ti OR diphereline:ab,ti OR gonapeptyl:ab,ti OR trelstar:ab,ti OR variopeptyl:ab,ti OR histrelin:ab,ti OR vantas:ab,ti OR supprelin:ab,ti OR degarelix:ab,ti OR firmagon:ab,ti OR 'antiandrogen':ab,ti OR flutamide:ab,ti OR eulexin:ab,ti OR cytomid:ab,ti OR chimax:ab,ti OR drogenil:ab,ti OR flucinom:ab,ti OR flutamin:ab,ti OR fugerel:ab,ti OR niftolide:ab,ti OR sebatrol:ab,ti OR bicalutamide:ab,ti OR casodex:ab,ti OR cosudex:ab,ti OR calutide:ab,ti OR kalumid:ab,ti OR nilutamide:ab,ti OR nilandron:ab,ti OR anandron:ab,ti OR estrogen:ab,ti OR oestrogen:ab,ti OR ketoconazole:ab,ti OR nizoral:ab,ti OR diethylstilbestrol:ab,ti OR	317,644

		ethinylestradiol:ab,ti OR cyproterone:ab,ti OR 'arn 509':ab,ti OR arn509:ab,ti OR apalutamide:ab,ti OR erleada:ab,ti OR darolutamide:ab,ti OR palbociclib:ab,ti OR ibrance:ab,ti OR ipilimumab:ab,ti OR yervoy:ab,ti	
Study design			
#3	RCTs	'randomized controlled trial'/exp OR 'randomization'/exp OR random*:ab,ti OR 'rct':ab,ti OR 'controlled trial':ab,ti OR 'clinical trial':ab,ti OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'cross over':ab,ti OR 'crossover':ab,ti OR 'placebo'/exp OR 'placebo':ab,ti OR (doubl* AND blind*:ab,ti) OR (singl* AND blind*:ab,ti) OR ('open':ab,ti AND label*:ab,ti) OR factorial*:ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti	2,440,546
#4		#1 AND #2 AND #3	7,412
Limiters			
#5	Narrative reviews	review:it NOT ((systematic OR meta) AND analy* OR ((indirect OR mixed) AND 'treatment comparison'))	2,365,555
#6	Other non-primary studies	'case study'/de OR 'case report'/de OR 'quality control'/de OR 'case control study'/de OR 'theoretical study'/de OR 'retrospective study'/de OR 'methodology'/de OR 'practice guideline'/de	5,886,896
#7	Animal and laboratory studies	'animal cell'/de OR 'animal experiment'/de OR 'animal model'/de OR 'cancer cell culture'/de OR 'human cell'/de OR 'in vitro study'/de OR 'nonhuman'/de OR 'biological model'/de OR 'cell culture'/de OR 'diagnostic test accuracy study'/de	8,430,349
#8	Conference abstracts	'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it	4,181,113
#9		#5 OR #6 OR #7 OR #8	18,061,645
#10		#4 NOT #9	2,717
#11		#10 AND [1-6-2018]/sd	299

Table 66: MEDLINE In-Process (via PubMed) search strategy

Search Number	Description	Search Algorithm	Search Yield – 2 July 2019
Population			
#1	Metastatic prostate cancer	“prostate cancer”[Mesh] OR (prostat*[tiab] AND (advanced[tiab] OR metasta*[tiab] OR malignant[tiab]) AND (cancer[tiab] OR neoplas*[tiab] OR carcinoma*[tiab] OR tumor[tiab] OR tumour[tiab]))	44,539
Intervention			
#2	Interventions and comparators	“androgen antagonists”[Mesh] OR “androgen receptor antagonist”[Mesh] OR “anti androgen”[tiab] OR “anti-androgen”[tiab] OR “antiandrogen”[tiab] OR “androgen antagonist”[tiab] OR “androgen dependent”[tiab] OR “androgen-dependent”[tiab] OR “androgen ablation”[tiab] OR “androgen-ablation”[tiab] OR “androgen blockade”[tiab] OR “androgen-blockade”[tiab] OR “androgen receptor”[tiab] OR “androgen suppression”[tiab] OR “luteinizing hormone”[tiab] OR “luteinising hormone”[tiab] OR “gonadotropin-releasing hormone”[tiab] OR “gonadotropin releasing hormone”[tiab] OR lhrh[tiab] OR gnrh[tiab] OR abiraterone[tiab] OR zytiga[tiab] OR “androgen deprivation”[tiab] OR adt[tiab] OR docetaxel[tiab] OR taxotere[tiab] OR docecad[tiab] OR docefrez[tiab] OR zytax[tiab] OR enzalutamide [tiab] OR leuprolide[tiab] OR leuprorelin[tiab] OR lupron[tiab] OR viadur[tiab] OR eligard[tiab] OR prostap[tiab] OR buserelin[tiab] OR seprefact[tiab] OR cinnafact[tiab] OR	245,383

		metrelef[tiab] OR aminoglutethimide[tiab] OR cytadren[tiab] OR xtandi[tiab] OR goserelin[tiab] OR zoladex[tiab] OR triptorelin[tiab] OR decapeptyl[tiab] OR diphereline[tiab] OR gonapeptyl[tiab] OR trelstar[tiab] OR variopeptyl[tiab] OR histrelin[tiab] OR vantas[tiab] OR supprelin[tiab] OR degarelix[tiab] OR firmagon[tiab] OR antiandrogen[tiab] OR flutamide[tiab] OR eulexin[tiab] OR cytomid[tiab] OR chimax[tiab] OR drogenil[tiab] OR flucinom[tiab] OR flutamin[tiab] OR fugerel[tiab] OR niftolide[tiab] OR sebatrol[tiab] OR bicalutamide[tiab] OR casodex[tiab] OR cosudex[tiab] OR calutide[tiab] OR kalumid[tiab] OR nilutamide[tiab] OR nilandron[tiab] OR anandron[tiab] OR estrogen[tiab] OR oestrogen[tiab] OR ketoconazole[tiab] OR nizoral[tiab] OR diethylstilbestrol[tiab] OR ethinylestradiol[tiab] OR cyproterone[tiab] OR arn509 [tiab] OR "arn 509"[tiab] OR apalutamide[tiab] OR erleada[tiab] OR darolutamide[tiab] OR palbociclib[tiab] OR ibrance[tiab] OR ipilimumab[tiab] OR yervoy[tiab]	
Limiters			
#3	Epub ahead of print	publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook OR (pubstatusaheadofprint)	387,396
#4	In-process	inprocess[SB]	621,664
#5		#3 OR #4	1,009,060
#6		#1 AND #2 AND #5	674

Table 67: CDSR, CENTRAL and DARE (via the Cochrane Library) search strategy

	Search Number	Description	Search Algorithm	Search Yield – 2 July 2019
	Population			
#1	Metastatic prostate cancer		(prostat*:ab,ti AND (advanced:ab,ti OR metasta*:ab,ti OR malignan*:ab,ti) AND (cancer:ab,ti OR neoplas*:ab,ti OR carcinoma*:ab,ti OR tumor*:ab,ti OR tumour:ab,ti))	5,069
#2			MeSH descriptor: [Prostatic Neoplasms] explode all trees	4,968
	Intervention			
	#3	Interventions and comparators	'anti androgen':ab,ti OR 'androgen antagonist':ab,ti OR 'androgen dependent':ab,ti OR 'androgen ablation':ab,ti OR 'androgen blockade':ab,ti OR 'androgen-blockade':ab,ti OR 'androgen receptor':ab,ti OR 'androgen suppression':ab,ti OR 'luteinizing hormone':ab,ti OR 'luteinising hormone':ab,ti OR 'gonadotropin-releasing hormone':ab,ti OR 'gonadotropin releasing hormone':ab,ti OR lhrh:ab,ti OR gnrh:ab,ti OR abiraterone:ab,ti OR 'abiraterone acetate':ab,ti OR zytiga:ab,ti OR 'androgen deprivation':ab,ti OR adt:ab,ti OR docetaxel:ab,ti OR taxotere:ab,ti OR docecad:ab,ti OR docefrez:ab,ti OR zytax:ab,ti OR enzalutamide:ab,ti OR leuprolide:ab,ti OR leuprorelin:ab,ti OR lupron:ab,ti OR viadur:ab,ti OR eligard:ab,ti OR prostap:ab,ti OR buserelin:ab,ti OR seprefact:ab,ti OR cinnafact:ab,ti OR metrelef:ab,ti OR aminoglutethimide:ab,ti OR cytadren:ab,ti OR xtandi:ab,ti OR goserelin:ab,ti OR zoladex:ab,ti OR triptorelin:ab,ti OR decapeptyl:ab,ti OR diphereline:ab,ti OR gonapeptyl:ab,ti OR trelstar:ab,ti OR variopeptyl:ab,ti OR histrelin:ab,ti OR vantas:ab,ti OR supprelin:ab,ti OR degarelix:ab,ti OR firmagon:ab,ti OR 'antiandrogen':ab,ti OR flutamide:ab,ti OR eulexin:ab,ti OR cytomid:ab,ti OR chimax:ab,ti OR drogenil:ab,ti OR flucinom:ab,ti OR flutamin:ab,ti OR fugerel:ab,ti OR niftolide:ab,ti OR sebatrol:ab,ti OR bicalutamide:ab,ti OR casodex:ab,ti OR cosudex:ab,ti OR calutide:ab,ti OR kalumid:ab,ti OR nilutamide:ab,ti OR nilandron:ab,ti OR anandron:ab,ti OR estrogen:ab,ti OR oestrogen:ab,ti OR ketoconazole:ab,ti OR nizoral:ab,ti OR diethylstilbestrol:ab,ti	28,114

		OR ethinylestradiol:ab,ti OR cyproterone:ab,ti OR 'arn 509':ab,ti OR arn509:ab,ti OR apalutamide:ab,ti OR erleada:ab,ti OR darolutamide:ab,ti OR palbociclib:ab,ti OR ibrance:ab,ti OR ipilimumab:ab,ti OR yervoy:ab,ti	
Combined			
#4		(#1 OR #2) AND #3 in Cochrane Reviews and Trials	800

*The results in the "Cochrane Reviews" category were retrieved to obtain the results from CDSR and "Trials" category for results from CENTRAL and DARE.

Second update

Table 68: Embase and MEDLINE (via Ovid) search strategy

ID	Description	Search terms	Search date: 12 Nov 2019
Population			
1	Metastatic prostate cancer	exp prostate cancer/	332,304
2		prostate.ab,ti.	432,754
3		(metasta* or advance* or malignan*).ab,ti.	3,748,250
4		(cancer or neoplas* or carcinoma* or tum$r).ab,ti.	50,60,652
5		2 and 3 and 4	123,819
6		1 or 5	361,554
Intervention			
7	Interventions and comparators	androgen deprivation therapy/ or exp anti-androgen therapy/ or anti androgen.ab,ti. or anti-androgen.ab,ti. or androgen antagonist.ab,ti. or androgen dependent.ab,ti. or androgen-dependent.ab,ti. or androgen ablation.ab,ti. or androgen- ablation.ab,ti. or androgen blockade.ab,ti. or androgen-blockade.ab,ti. or androgen receptor.ab,ti. or androgen suppression.ab,ti. or luteinizing hormone.ab,ti. or luteinising hormone.ab,ti. or gonadotropin-releasing hormone.ab,ti. or gonadotropin releasing hormone.ab,ti. or lhrh.ab,ti. or gnrh.ab,ti. or abiraterone.ab,ti. or abiraterone acetate.ab,ti. or zytiga.ab,ti. or androgen deprivation.ab,ti. or adt.ab,ti. or docetaxel.ab,ti. or taxotere.ab,ti. or docecad.ab,ti. or docefrez.ab,ti. or zytax.ab,ti. or enzalutamide.ab,ti. or leuprolide.ab,ti. or leuprorelin.ab,ti. or lupron.ab,ti. or viadur.ab,ti. or eligard.ab,ti. or prostap.ab,ti. or buserelin.ab,ti. or seprefact.ab,ti. or cinnafact.ab,ti. or metrelef.ab,ti. or aminoglutethimide.ab,ti. or cytadren.ab,ti. or xtandi.ab,ti. or goserelin.ab,ti. or zoladex.ab,ti. or triptorelin.ab,ti. or decapeptyl.ab,ti. or diphereline.ab,ti. or gonapeptyl.ab,ti. or trelstar.ab,ti. or variopeptyl.ab,ti. or histrelin.ab,ti. or vantas.ab,ti. or supprelin.ab,ti. or degarelix.ab,ti. or firmagon.ab,ti. or antiandrogen.ab,ti. or flutamide.ab,ti. or eulexin.ab,ti. or cytomid.ab,ti. or chimax.ab,ti. or drogenil.ab,ti. or flucinom.ab,ti. or flutamin.ab,ti. or fugerel.ab,ti. or niftolide.ab,ti. or sebatrol.ab,ti. or bicalutamide.ab,ti. or casodex.ab,ti. or cosudex.ab,ti. or calutide.ab,ti. or kalumid.ab,ti. or nilutamide.ab,ti. or nilandron.ab,ti. or anandron.ab,ti. or estrogen.ab,ti. or oestrogen.ab,ti. or ketoconazole.ab,ti. or nizoral.ab,ti. or diethylstilbestrol.ab,ti. or ethinylestradiol.ab,ti. or cyproterone.ab,ti. or arn 509.ab,ti. or arn509.ab,ti. or apalutamide.ab,ti. or erleada.ab,ti. or darolutamide.ab,ti. or palbociclib.ab,ti. or ibrance.ab,ti. or ipilimumab.ab,ti. or yervoy.ab,ti.	561,980
Study design			
8	Study design	exp randomized controlled trial/	1,074,458
9		randomized controlled trials as topic/	234,002
10		exp Randomization/	186,072
11		exp clinical trial/	2,285,719
12		double blind.ti,ab.	325,125
13		single blind.ti,ab.	30,862
14		(cross-over or crossover).ti,ab.	183,794

15		randomization/	185,823
16		control group/	112,074
17		(clin$ adj3 trial$).ti,ab.	892,030
18		randomi?ed controlled trial$.mp.	1,487,841
19		RCT.ti,ab.	54,427
20		((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).mp.	531,281
21		placebo$.ti,ab.	509,184
22		(random$ adj2 allocat$).ti,ab.	74,603
23		open label.ti,ab.	115,962
24		(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,ab.	115,412
25		((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).mp.	18,980
26		randomized controlled trial.pt.	494,212
27		or/8-26	3,742,047
28		6 and 7 and 27	15,934
Limiters			
29	Human	limit 28 to human	14,933
30	Time period	limit 29 to yr="2019 -Current"	832
31		remove duplicates from 30	769
32	Other non-primary studies	(systematic or (meta and analy*) or ((indirect or mixed) and treatment comparison)).ti.	432,797
33		(review or letter or editorial or conference abstract or conference paper or conference review).pt.	12,711,401
34		32 or 33	12,912,280
35		31 not 34	278

Table 69: CDSR, CENTRAL and DARE (via Ovid) search strategy

ID	Description	Search terms	Search date: 12 Nov 2019
Population			
1	Metastatic prostate cancer	prostate.ab,ti.	17,405
2		(metasta* or advance* or malignan*).ab,ti.	109,304
3		(cancer or neoplas* or carcinoma* or tum$r).ab,ti.	164,519
4		1 and 2 and 3	5,461
5		exp Prostatic Neoplasms/	5,362
6		4 or 5	8,980
Intervention			
7	Interventions and comparators	(anti androgen or androgen antagonist or androgen dependent or androgen ablation or androgen blockade or androgen-blockade or androgen receptor or androgen suppression or luteinizing hormone or luteinising hormone or gonadotropin-releasing hormone or gonadotropin releasing hormone or lhrh or gnrh or abiraterone or abiraterone acetate or zytiga or androgen deprivation or adt or docetaxel or taxotere or docecad or docefrez or zytax or enzalutamide or leuprolide or leuprorelin or lupron or viadur or eligard or prostap or buserelin or sepretact or cinnafact or metrelef or aminoglutethimide or cytadren or xtandi or goserelin or zoladex or triptorelin or decapeptyl or diphereline or gonapeptyl or trelstar or variopeptyl or histrelin or vantas or supprelin or degarelix or firmagon or antiandrogen or flutamide or eulexin or cytomid or chimax or drogenil or flucinom or flutamin or fugerel or niftolide or sebatrol or bicalutamide or casodex or cosudex or calutide or kalumid or nilutamide or nilandron or	30,323

		anandron or estrogen or oestrogen or ketoconazole or nizoral or diethylstilbestrol or ethinylestradiol or cyproterone or arn 509 or arn509 or apalutamide or erleada or darolutamide or palbociclib or ibrance or ipilimumab or yervoy).ab,ti.	
8		6 and 7	3,887
Limiters			
9	Time period	limit 8 to yr="2019 -Current" [Limit not valid in DARE; records were retained]	222

Third update

Table 70: Embase, MEDLINE and MEDLINE In-Process (via Ovid) search strategy

ID	Description	Search terms	Search date: 02 Jun 2020
Population			
1	Metastatic prostate cancer	exp prostate cancer/	342,803
2		prostate.ab,ti.	447,658
3		(metasta* or advance* or malignan*).ab,ti.	3,917,943
4		(cancer or neoplas* or carcinoma* or tum$r).ab,ti.	5,274,537
5		2 and 3 and 4	129,145
6		1 or 5	373,500
Intervention			
7	Interventions and comparators	androgen deprivation therapy/ or exp anti-androgen therapy/ or anti androgen.ab,ti. or anti-androgen.ab,ti. or androgen antagonist.ab,ti. or androgen dependent.ab,ti. or androgen-dependent.ab,ti. or androgen ablation.ab,ti. or androgen- ablation.ab,ti. or androgen blockade.ab,ti. or androgen-blockade.ab,ti. or androgen receptor.ab,ti. or androgen suppression.ab,ti. or luteinizing hormone.ab,ti. or luteinising hormone.ab,ti. or gonadotropin-releasing hormone.ab,ti. or gonadotropin releasing hormone.ab,ti. or lhrh.ab,ti. or gnrh.ab,ti. or abiraterone.ab,ti. or abiraterone acetate.ab,ti. or zytiga.ab,ti. or androgen deprivation.ab,ti. or adt.ab,ti. or docetaxel.ab,ti. or taxotere.ab,ti. or docecad.ab,ti. or docefrez.ab,ti. or zytax.ab,ti. or enzalutamide.ab,ti. or leuprolide.ab,ti. or leuprorelin.ab,ti. or lupron.ab,ti. or viadur.ab,ti. or eligard.ab,ti. or prostap.ab,ti. or buserelin.ab,ti. or seprefact.ab,ti. or cinnafact.ab,ti. or metrelef.ab,ti. or aminoglutethimide.ab,ti. or cytadren.ab,ti. or xtandi.ab,ti. or goserelin.ab,ti. or zoladex.ab,ti. or triptorelin.ab,ti. or decapeptyl.ab,ti. or diphereline.ab,ti. or gonapeptyl.ab,ti. or trelstar.ab,ti. or variopeptyl.ab,ti. or histrelin.ab,ti. or vantas.ab,ti. or supprelin.ab,ti. or degarelix.ab,ti. or firmagon.ab,ti. or antiandrogen.ab,ti. or flutamide.ab,ti. or eulexin.ab,ti. or cytomid.ab,ti. or chimax.ab,ti. or drogenil.ab,ti. or flucinom.ab,ti. or flutamin.ab,ti. or fugerel.ab,ti. or niftolide.ab,ti. or sebatrol.ab,ti. or bicalutamide.ab,ti. or casodex.ab,ti. or cosudex.ab,ti. or calutide.ab,ti. or kalumid.ab,ti. or nilutamide.ab,ti. or nilandron.ab,ti. or anandron.ab,ti. or estrogen.ab,ti. or oestrogen.ab,ti. or ketoconazole.ab,ti. or nizoral.ab,ti. or diethylstilbestrol.ab,ti. or ethinylestradiol.ab,ti. or cyproterone.ab,ti. or arn 509.ab,ti. or arn509.ab,ti. or apalutamide.ab,ti. or erleada.ab,ti. or darolutamide.ab,ti. or palbociclib.ab,ti. or ibrance.ab,ti. or ipilimumab.ab,ti. or yervoy.ab,ti.	576,773
Study design			
8	Study design	exp randomized controlled trial/	1,114,844
9		randomized controlled trials as topic/	247,807
10		exp Randomization/	190,127
11		exp clinical trial/	2,356,646
12		double blind.ti,ab.	333,109
13		single blind.ti,ab.	32,009
14		(cross-over or crossover).ti,ab.	190,087
15		randomization/	189,875

16		control group/	112,153
17		(clin$ adj3 trial$).ti,ab.	938,532
18		randomi?ed controlled trial$.mp.	1,551,141
19		RCT.ti,ab.	58,563
20		((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).mp.	546,519
21		placebo$.ti,ab.	523,953
22		(random$ adj2 allocat$).ti,ab.	77,822
23		open label.ti,ab.	121,889
24		(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,ab.	121,571
25		((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).mp.	20,451
26		randomized controlled trial.pt.	506,834
27		or/8-26	3,874,493
28		6 and 7 and 27	16,683
Limiters			
29	Human	limit 28 to human	15,625
30	Time period	limit 29 to yr="2019 -Current"	1,542
31	Other non-primary studies	(systematic or (meta and analy*) or ((indirect or mixed) and treatment comparison)).ti.	471,771
32		(review or letter or editorial or conference abstract or conference paper or conference review).pt.	13,156,341
33		31 or 32	13,381,477
34		30 not 33	587
35		remove duplicates from 34	459

Table 71: CDSR, CENTRAL and DARE (via Ovid) search strategy

ID	Description	Search terms	Search date: 02 Jun 2020
Population			
1	Metastatic prostate cancer	prostate.ab,ti.	18,144
2		(metasta* or advance* or malignan*).ab,ti.	115,316
3		(cancer or neoplas* or carcinoma* or tum$r).ab,ti.	171,897
4		1 and 2 and 3	5,771
5		exp Prostatic Neoplasms/	5,484
6		4 or 5	9,353
Intervention			
7	Interventions and comparators	(anti androgen or androgen antagonist or androgen dependent or androgen ablation or androgen blockade or androgen-blockade or androgen receptor or androgen suppression or luteinizing hormone or luteinising hormone or gonadotropin-releasing hormone or gonadotropin releasing hormone or lhrh or gnrh or abiraterone or abiraterone acetate or zytiga or androgen deprivation or adt or docetaxel or taxotere or docecad or docefrez or zytax or enzalutamide or leuprolide or leuprorelin or lupron or viadur or eligard or prostap or buserelin or seprefact or cinnafact or metrelef or aminoglutethimide or cytadren or xtandi or goserelin or zoladex or triptorelin or decapeptyl or diphereline or gonapeptyl or trelstar or variopeptyl or histrelin or vantas or supprelin or degarelix or firmagon or antiandrogen or flutamide or eulexin or cytomid or chimax or drogenil or flucinom or flutamin or fugerel or niftolide or sebatrol or bicalutamide or casodex or cosudex or calutide or kalumid or nilutamide or nilandron or anandron or estrogen or oestrogen or ketoconazole or nizoral or diethylstilbestrol or ethinylestradiol or cyproterone or arn 509 or arn509	30,930

		or apalutamide or erleada or darolutamide or palbociclib or ibrance or ipilimumab or yervoy).ab,ti.	
8		6 and 7	4,099
Limiters			
9	Time period	limit 8 to yr="2019 -Current" [Limit not valid in DARE; records were retained]	419

Fourth update

Table 72: Embase, MEDLINE and MEDLINE In-Process (via Ovid) search strategy

ID	Description	Search terms	Search date: 26 Oct 2020
Population			
1	Metastatic prostate cancer	exp prostate cancer/	352684
2		prostate.ab,ti.	461301
3		(metasta* or advance* or malignan*).ab,ti.	4040559
4		(cancer or neoplas* or carcinoma* or tum$r).ab,ti.	5432967
5		2 and 3 and 4	133322
6		1 or 5	384414
Intervention			
7	Interventions and comparators	androgen deprivation therapy/ or exp anti-androgen therapy/ or anti androgen.ab,ti. or anti-androgen.ab,ti. or androgen antagonist.ab,ti. or androgen dependent.ab,ti. or androgen-dependent.ab,ti. or androgen ablation.ab,ti. or androgen- ablation.ab,ti. or androgen blockade.ab,ti. or androgen-blockade.ab,ti. or androgen receptor.ab,ti. or androgen suppression.ab,ti. or luteinizing hormone.ab,ti. or luteinising hormone.ab,ti. or gonadotropin-releasing hormone.ab,ti. or gonadotropin releasing hormone.ab,ti. or lhrh.ab,ti. or gnrh.ab,ti. or abiraterone.ab,ti. or abiraterone acetate.ab,ti. or zytiga.ab,ti. or androgen deprivation.ab,ti. or adt.ab,ti. or docetaxel.ab,ti. or taxotere.ab,ti. or docecad.ab,ti. or docefrez.ab,ti. or zytax.ab,ti. or enzalutamide.ab,ti. or leuprolide.ab,ti. or leuprorelin.ab,ti. or lupron.ab,ti. or viadur.ab,ti. or eligard.ab,ti. or prostap.ab,ti. or buserelin.ab,ti. or sepretact.ab,ti. or cinnafact.ab,ti. or metrelef.ab,ti. or aminoglutethimide.ab,ti. or cytadren.ab,ti. or xtandi.ab,ti. or goserelin.ab,ti. or zoladex.ab,ti. or triptorelin.ab,ti. or decapeptyl.ab,ti. or diphereline.ab,ti. or gonapeptyl.ab,ti. or trelstar.ab,ti. or variopeptyl.ab,ti. or histrelin.ab,ti. or vantas.ab,ti. or supprelin.ab,ti. or degarelix.ab,ti. or firmagon.ab,ti. or antiandrogen.ab,ti. or flutamide.ab,ti. or eulexin.ab,ti. or cytomid.ab,ti. or chimax.ab,ti. or drogenil.ab,ti. or flucinom.ab,ti. or flutamin.ab,ti. or fugerel.ab,ti. or niftolide.ab,ti. or sebatrol.ab,ti. or bicalutamide.ab,ti. or casodex.ab,ti. or cosudex.ab,ti. or calutide.ab,ti. or kalumid.ab,ti. or nilutamide.ab,ti. or nilandron.ab,ti. or anandron.ab,ti. or estrogen.ab,ti. or oestrogen.ab,ti. or ketoconazole.ab,ti. or nizoral.ab,ti. or diethylstilbestrol.ab,ti. or ethinylestradiol.ab,ti. or cyproterone.ab,ti. or arn 509.ab,ti. or arn509.ab,ti. or apalutamide.ab,ti. or erleada.ab,ti. or darolutamide.ab,ti. or palbociclib.ab,ti. or ibrance.ab,ti. or ipilimumab.ab,ti. or yervoy.ab,ti.	588380
Study design			
8	Study design	exp randomized controlled trial/	1147083
9		randomized controlled trials as topic/	261905
10		exp Randomization/	193011
11		exp clinical trial/	2413350
12		double blind.ti,ab.	338950
13		single blind.ti,ab.	32962
14		(cross-over or crossover).ti,ab.	194345
15		randomization/	192754

16		control group/	112229
17		(clin$ adj3 trial$).ti,ab.	976272
18		randomi?ed controlled trial$.mp.	1603517
19		RCT.ti,ab.	61561
20		((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).mp.	558097
21		placebo$.ti,ab.	535018
22		(random$ adj2 allocat$).ti,ab.	80613
23		open label.ti,ab.	126497
24		(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,ab.	125909
25		((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).mp.	21715
26		randomized controlled trial.pt.	515793
27		or/8-26	3979527
28		6 and 7 and 27	17358
Limiters			
29	Human	limit 28 to human	16281
30	Time period	limit 29 to yr="2020 -Current"	947
31	Other non-primary studies	(systematic or (meta and analy*) or ((indirect or mixed) and treatment comparison)).ti.	505519
32		(review or letter or editorial or conference abstract or conference paper or conference review).pt.	13461748
33		31 or 32	13707926
34		30 not 33	368
35		remove duplicates from 34	327

Table 73: CDSR, CENTRAL and DARE (via Ovid) search strategy

ID	Description	Search terms	Search date: 26 Oct 2020
Population			
1	Metastatic prostate cancer	prostate.ab,ti.	18561
2		(metasta* or advance* or malignan*).ab,ti.	117722
3		(cancer or neoplas* or carcinoma* or tum$r).ab,ti.	175309
4		1 and 2 and 3	5896
5		exp Prostatic Neoplasms/	5573
6		4 or 5	9522
Intervention			
7	Interventions and comparators	(anti androgen or androgen antagonist or androgen dependent or androgen ablation or androgen blockade or androgen-blockade or androgen receptor or androgen suppression or luteinizing hormone or luteinising hormone or gonadotropin-releasing hormone or gonadotropin releasing hormone or lhrh or gnrh or abiraterone or abiraterone acetate or zytiga or androgen deprivation or adt or docetaxel or taxotere or docecad or docefrez or zytax or enzalutamide or leuprolide or leuprorelin or lupron or viadur or eligard or prostap or buserelin or seprefact or cinnafact or metrelef or aminoglutethimide or cytadren or xtandi or goserelin or zoladex or triptorelin or decapeptyl or diphereline or gonapeptyl or trelstar or variopeptyl or histrelin or vantas or supprelin or degarelix or firmagon or antiandrogen or flutamide or eulexin or cytomid or chimax or drogenil or flucinom or flutamin or fugerel or niftolide or sebatrol or bicalutamide or casodex or cosudex or calutide or kalumid or nilutamide or nilandron or anandron or estrogen or oestrogen or ketoconazole or nizoral or diethylstilbestrol or ethinylestradiol or cyproterone or arn 509 or arn509	31403

		or apalutamide or erleada or darolutamide or palbociclib or ibrance or ipilimumab or yervoy).ab,ti.	
8		6 and 7	4194
Limiters			
9	Time period	limit 8 to yr="2020 -Current" [Limit not valid in DARE; records were retained]	158

Fifth update

Table 74: Embase, MEDLINE and MEDLINE In-Process (via Ovid) search strategy

ID	Description	Search terms	Search date: 17 Jun 2021
Population			
1	Metastatic prostate cancer	exp prostate cancer/	364403
2		prostate.ab,ti.	477087
3		(metasta* or advance* or malignan*).ab,ti.	4241690
4		(cancer or neoplas* or carcinoma* or tum$r).ab,ti.	5679029
5		2 and 3 and 4	139387
6		1 or 5	397933
Intervention			
7	Interventions and comparators	androgen deprivation therapy/ or exp anti-androgen therapy/ or anti androgen.ab,ti. or anti-androgen.ab,ti. or androgen antagonist.ab,ti. or androgen dependent.ab,ti. or androgen-dependent.ab,ti. or androgen ablation.ab,ti. or androgen- ablation.ab,ti. or androgen blockade.ab,ti. or androgen-blockade.ab,ti. or androgen receptor.ab,ti. or androgen suppression.ab,ti. or luteinizing hormone.ab,ti. or luteinising hormone.ab,ti. or gonadotropin-releasing hormone.ab,ti. or gonadotropin releasing hormone.ab,ti. or lhrh.ab,ti. or gnrh.ab,ti. or abiraterone.ab,ti. or abiraterone acetate.ab,ti. or zytiga.ab,ti. or androgen deprivation.ab,ti. or adt.ab,ti. or docetaxel.ab,ti. or taxotere.ab,ti. or docecad.ab,ti. or docefrez.ab,ti. or zytax.ab,ti. or enzalutamide.ab,ti. or leuprolide.ab,ti. or leuprorelin.ab,ti. or lupron.ab,ti. or viadur.ab,ti. or eligard.ab,ti. or prostap.ab,ti. or buserelin.ab,ti. or seprefact.ab,ti. or cinnafact.ab,ti. or metrelef.ab,ti. or aminoglutethimide.ab,ti. or cytadren.ab,ti. or xtandi.ab,ti. or goserelin.ab,ti. or zoladex.ab,ti. or triptorelin.ab,ti. or decapeptyl.ab,ti. or diphereline.ab,ti. or gonapeptyl.ab,ti. or trelstar.ab,ti. or variopeptyl.ab,ti. or histrelin.ab,ti. or vantas.ab,ti. or supprelin.ab,ti. or degarelix.ab,ti. or firmagon.ab,ti. or antiandrogen.ab,ti. or flutamide.ab,ti. or eulexin.ab,ti. or cytomid.ab,ti. or chimax.ab,ti. or drogenil.ab,ti. or flucinom.ab,ti. or flutamin.ab,ti. or fugerel.ab,ti. or niftolide.ab,ti. or sebatrol.ab,ti. or bicalutamide.ab,ti. or casodex.ab,ti. or cosudex.ab,ti. or calutide.ab,ti. or kalumid.ab,ti. or nilutamide.ab,ti. or nilandron.ab,ti. or anandron.ab,ti. or estrogen.ab,ti. or oestrogen.ab,ti. or ketoconazole.ab,ti. or nizoral.ab,ti. or diethylstilbestrol.ab,ti. or ethinylestradiol.ab,ti. or cyproterone.ab,ti. or arn 509.ab,ti. or arn509.ab,ti. or apalutamide.ab,ti. or erleada.ab,ti. or darolutamide.ab,ti. or palbociclib.ab,ti. or ibrance.ab,ti. or ipilimumab.ab,ti. or yervoy.ab,ti.	604324
Study design			
8	Study design	exp randomized controlled trial/	1197348
9		randomized controlled trials as topic/	284851
10		exp Randomization/	196729
11		exp clinical trial/	2498383
12		double blind.ti,ab.	348031
13		single blind.ti,ab.	34326
14		(cross-over or crossover).ti,ab.	200784
15		randomization/	196452
16		control group/	111724
17		(clin$ adj3 trial$).ti,ab.	1036560
18		randomi?ed controlled trial$.mp.	1686240
19		RCT.ti,ab.	66767

20		((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).mp.	575938
21		placebo$.ti,ab.	553219
22		(random$ adj2 allocat$).ti,ab.	84658
23		open label.ti,ab.	134483
24		(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,ab.	133443
25		((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).mp.	23591
26		randomized controlled trial.pt.	533470
27		or/8-26	4142799
28		6 and 7 and 27	18105
Limiters			
29	Human	limit 28 to human	16996
30	Time period	limit 29 to yr="2020 -Current"	1700
31	Other non-primary studies	(systematic or (meta and analy*) or ((indirect or mixed) and treatment comparison)).ti.	561810
32		(review or letter or editorial or conference abstract or conference paper or conference review).pt.	13986748
33		31 or 32	14267114
34		30 not 33	709
35		remove duplicates from 34	582

Table 75: CDSR, CENTRAL and DARE (via Ovid) search strategy

ID	Description	Search terms	Search date: 17 Jun 2021
Population			
1	Metastatic prostate cancer	prostate.ab,ti.	19628
2		(metasta* or advance* or malignan*).ab,ti.	125346
3		(cancer or neoplas* or carcinoma* or tum$r).ab,ti.	185351
4		1 and 2 and 3	6347
5		exp Prostatic Neoplasms/	5774
6		4 or 5	10094
Intervention			
7	Interventions and comparators	(anti androgen or androgen antagonist or androgen dependent or androgen ablation or androgen blockade or androgen-blockade or androgen receptor or androgen suppression or luteinizing hormone or luteinising hormone or gonadotropin-releasing hormone or gonadotropin releasing hormone or lhrh or gnrh or abiraterone or abiraterone acetate or zytiga or androgen deprivation or adt or docetaxel or taxotere or docecad or docefrez or zytax or enzalutamide or leuprolide or leuprorelin or lupron or viadur or eligard or prostap or buserelin or sepretact or cinnafact or metrelef or aminoglutethimide or cytadren or xtandi or goserelin or zoladex or triptorelin or decapeptyl or diphereline or gonapeptyl or trelstar or variopeptyl or histrelin or vantas or supprelin or degarelix or firmagon or antiandrogen or flutamide or eulexin or cytomid or chimax or drogenil or flucinom or flutamin or fugerel or niftolide or sebatrol or bicalutamide or casodex or cosudex or calutide or kalumid or nilutamide or nilandron or anandron or estrogen or oestrogen or ketoconazole or nizoral or diethylstilbestrol or ethinylestradiol or cyproterone or arn 509 or arn509 or apalutamide or erleada or darolutamide or palbociclib or ibrance or ipilimumab or yervoy).ab,ti.	32901
8		6 and 7	4512
Limiters			
9	Time period	limit 8 to yr="2020 -Current" [Limit not valid in DARE; records were retained]	464

Search for ongoing studies

As of April 24th, 2022 we have searched for active or unpublished studies that include apalutamide and comparators (docetaxel; radiotherapy/radiation therapy) on the intended patient population (irrespective of HVD or LVD disease) in Clinicaltrials.gov and the EU Clinical Trials Register.

1) *Search results Clinicaltrials.gov (searches run separately for apalutamide and comparators)*

Apalutamide

	Title	Status	Study Results	Conditions	Interventions	Locations
1	Study to Evaluate ctDNA of mCSPC Patients Receiving Apalutamide in Japan	Recruiting	No Results Available	•Metastatic Castration-sensitive Prostate Cancer	•Drug: Apalutamide	•Kindai University Hospital, #saka-sayama, Osaka, Japan
2	Patient Preference of Apalutamide Versus Enzalutamide in Patients With Recurrent or Metastatic Hormone-Sensitive Prostate Cancer	Recruiting	No Results Available	•Prostate Cancer	•Drug: Apalutamide •Drug: Enzalutamide	•Prince of Wales Hospital, Shatin, Hong Kong
3	Study of Relugolix in Men With Metastatic Castration-Sensitive Prostate Cancer or Non-Metastatic or Metastatic Castration-Resistant Prostate Cancer	Recruiting	No Results Available	•Metastatic Castration-Resistant Prostate Cancer •Metastatic Castration-Sensitive Prostate Cancer •Non-Metastatic Castration-Resistant Prostate Cancer	•Drug: Relugolix •Drug: Abiraterone •Drug: Prednisone •Drug: Methylprednisolone •Drug: Apalutamide •Drug: Docetaxel	•Urological Associates of Southern Arizona, P.C., Tucson, Arizona, United States •Chesapeake Urology Research Associates, Baltimore, Maryland, United States •Alliance Urology, Greensboro, North Carolina, United States •Clinical Research Solutions, Middleburg Heights, Ohio, United States •Center for Advanced Urology, LLP d/b/a: MidLantic Urology, Bala-Cynwyd, Pennsylvania, United States •Keystone Urology Specialists, Lancaster, Pennsylvania, United States •Carolina Urologic Research Center, Myrtle Beach, South Carolina, United States •Urology San Antonio, San Antonio, Texas, United States
4	A Study of Adding Apalutamide to Radiotherapy and LHRH Agonist in High-Risk Patients With Prostate-Specific Membrane Antigen-Positron Emission Tomography (PSMA-PET) Positive Hormone-Sensitive Prostate Cancer Participants	Recruiting	No Results Available	•Prostatic Neoplasms	•Radiation: Radiotherapy •Drug: LHRHa •Drug: Apalutamide	•Flinders Medical Centre, Bedford Park, Australia •Bundaberg Hospital, Bundaberg, Australia •Hervey Bay Hospital, Bundaberg, Australia •St Vincent's Hospital - Melbourne, Fitzroy, Australia •Genesis Care Hurstville, Hurstville, Australia •Macquarie University Hospital, North Ryde, Australia •Epworth Healthcare, Richmond, Australia •Calvary Mater Newcastle, Waratah, Australia •GenesisCare Wembley, Wembley, Australia •Medical University Innsbruck, Innsbruck, Austria •and 116 more
5	The Role of Highly Selective Androgen Receptor (AR) Targeted Therapy in Men With Biochemically Relapsed Hormone Sensitive Prostate Cancer	Completed	Has Results	•Prostate Cancer	•Drug: ARN-509 •Drug: LHRH Agonist	•Scottsdale, Arizona, United States •San Francisco, California, United States •Chicago, Illinois, United States •Portland, Oregon, United States •Seattle, Washington, United States

	Title	Status	Study Results	Conditions	Interventions	Locations
6	A Study of Apalutamide (JNJ-56021927, ARN-509) Plus Androgen Deprivation Therapy (ADT) Versus ADT in Participants With mHSPC	Active, not recruiting	Has Results	•Prostate Cancer	•Drug: Apalutamide •Drug: Placebo •Drug: Androgen Deprivation Therapy (ADT)	•Homewood, Alabama, United States •Tucson, Arizona, United States •San Bernardino, California, United States •San Diego, California, United States •Denver, Colorado, United States •Norwalk, Connecticut, United States •Fort Myers, Florida, United States •Chicago, Illinois, United States •Fort Wayne, Indiana, United States •Jeffersonville, Indiana, United States •and 219 more
7	Testing Interruption of Hormonal Medications in Patients Responding Exceptionally to Therapy for Metastatic Prostate Cancer. (A-DREAM)	Not yet recruiting	No Results Available	•Castration-Sensitive Prostate Carcinoma •Metastatic Prostate Carcinoma •Stage IV Prostate Cancer AJCC v8 •Stage IVA Prostate Cancer AJCC v8 •Stage IVB Prostate Cancer AJCC v8	•Other: Pharmacotherapy Discontinuation •Other: Follow-Up •Other: Questionnaire Administration •Other: Quality-of-Life Assessment	

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

Docetaxel

	Title	Status	Study Results	Conditions	Interventions	Locations
1	Toxicity & Pharmacokinetics of 2 & 3-weekly Docetaxel in Metastatic Hormone-Sensitive Prostate Cancer (mHSPC)	Withdrawn	No Results Available	•Metastatic Hormone-Sensitive Prostate Cancer	•Drug: docetaxel 50mg/m2 •Drug: docetaxel 75mg/m2	•University of Kentucky Markey Cancer Center, Lexington, Kentucky, United States
2	ODM-201 in Addition to Standard ADT and Docetaxel in Metastatic Castration Sensitive Prostate Cancer	Active, not recruiting	No Results Available	•Prostatic Neoplasms	•Drug: BAY1841788 / darolutamide (ODM-201) •Drug: Standard ADT (androgen deprivation therapy) •Drug: Docetaxel •Drug: Placebo	•Chandler, Arizona, United States •Tucson, Arizona, United States •Beverly Hills, California, United States •Duarte, California, United States •Los Angeles, California, United States •Stanford, California, United States •Washington, District of Columbia, United States •Boca Raton, Florida, United States •Gainesville, Florida, United States •Tampa, Florida, United States •and 289 more
3	A Trial of Immunotherapy Strategies in Metastatic Hormone-sensitive Prostate Cancer	Active, not recruiting	No Results Available	•Metastatic Hormone-sensitive Prostate Cancer	•Drug: Ipilimumab 5 MG/ML •Drug: Nivolumab 10 MG/ML •Drug: Docetaxel •Drug: ADT (androgen deprivation therapy)	•Hospital Universitario Central de Asturias, Oviedo, Asturias, Spain •Hestia Duran I Reynals, Hospitalet de Llobregat, Barcelona, Spain •Hospital Sant Joan de Deu (Althaia Manresa), Manresa, Barcelona, Spain •Hospital de Sabadell, Sabadell, Barcelona, Spain •Hospital General, Materno E Infantil Reina, Córdoba, Cordoba, Spain •Hospital Son Llatzer, Palma De Mallorca, Islas Baleares, Spain •Hospital Universitario Puerta de Hierro Majadahonda, Majadahonda, Madrid, Spain •Hospital Universitario Infanta Sofía, San Sebastián De Los Reyes, Madrid, Spain •Complejo Hospitalario de Navarra, Pamplona, Navarra, Spain •Hospital Arnau de Vilanova, Valencia, Valenci, Spain •and 20 more
4	Nivolumab + Docetaxel + ADT in mHSPC Patients With DDRD or Inflamed Tumors	Recruiting	No Results Available	•Hormone Sensitive Prostate Cancer •Prostate Adenocarcinoma •Metastasis Prostate Adenocarcinoma	•Drug: Androgen Deprivation Therapy •Drug: Nivolumab •Drug: Docetaxel	•University of California, San Diego, La Jolla, California, United States •H. Lee Moffitt Cancer Center, Tampa, Florida, United States •The Johns Hopkins University School of Medicine, Baltimore, Maryland, United States •Dana Farber Cancer Institute, Boston, Massachusetts, United States •Beth Israel Deaconess Medical Center, Boston, Massachusetts, United States •University of Wisconsin, Madison, Wisconsin, United States

	Title	Status	Study Results	Conditions	Interventions	Locations
5	Androgen Ablation Therapy With or Without Chemotherapy in Treating Patients With Metastatic Prostate Cancer	Active, not recruiting	Has Results	•Metastatic Hormone-sensitive Prostate Cancer	•Drug: androgen-deprivation therapy •Drug: docetaxel	•Providence Cancer Center, Anchorage, Alaska, United States •Fairbanks Cancer Treatment Center at Fairbanks Memorial Hospital, Fairbanks, Alaska, United States •Mayo Clinic Hospital, Phoenix, Arizona, United States •Mayo Clinic Scottsdale, Scottsdale, Arizona, United States •Hembree Mercy Cancer Center at St. Edward Mercy Medical Center, Fort Smith, Arkansas, United States •Arkansas Cancer Research Center at University of Arkansas for Medical Sciences, Little Rock, Arkansas, United States •Alta Bates Summit Comprehensive Cancer Center, Berkeley, California, United States •Peninsula Medical Center, Burlingame, California, United States •California Cancer Care, Incorporated - Greenbrae, Greenbrae, California, United States •USC/Norris Comprehensive Cancer Center and Hospital, Los Angeles, California, United States •and 333 more
6	Study of Relugolix in Men With Metastatic Castration-Sensitive Prostate Cancer or Non-Metastatic or Metastatic Castration-Resistant Prostate Cancer	Recruiting	No Results Available	•Metastatic Castration-Resistant Prostate Cancer •Metastatic Castration-Sensitive Prostate Cancer •Non-Metastatic Castration-Resistant Prostate Cancer	•Drug: Relugolix •Drug: Abiraterone •Drug: Prednisone •Drug: Methylprednisolone •Drug: Apalutamide •Drug: Docetaxel	•Urological Associates of Southern Arizona, P.C., Tucson, Arizona, United States •Chesapeake Urology Research Associates, Baltimore, Maryland, United States •Alliance Urology, Greensboro, North Carolina, United States •Clinical Research Solutions, Middleburg Heights, Ohio, United States •Center for Advanced Urology, LLP d/b/a: MidLantic Urology, Bala-Cynwyd, Pennsylvania, United States •Keystone Urology Specialists, Lancaster, Pennsylvania, United States •Carolina Urologic Research Center, Myrtle Beach, South Carolina, United States •Urology San Antonio, San Antonio, Texas, United States
7	Docetaxel or Abiraterone Acetate With ADT in Treating Patients With Metastatic Hormone Sensitive Prostate Cancer	Terminated	Has Results	•Castration-Sensitive Prostate Carcinoma •Metastatic Prostatic Adenocarcinoma •Stage IV Prostate Cancer •Stage IVA Prostate Cancer •Stage IVB Prostate Cancer	•Drug: Abiraterone Acetate •Drug: Antiandrogen Therapy •Drug: Docetaxel •Drug: Prednisone •Other: Quality-of-Life Assessment •Other: Questionnaire Administration	•Huntsman Cancer Institute/University of Utah, Salt Lake City, Utah, United States
8	Docetaxel and PROSTVAC for Metastatic Castration-Sensitive Prostate Cancer	Active, not recruiting	No Results Available	•Prostate Cancer •Prostate Neoplasms •Neoplasms, Prostatic	•Biological: PROSTVAC-V •Biological: PROSTVAC-F •Drug: Docetaxel	•National Institutes of Health Clinical Center, 9000 Rockville Pike, Bethesda, Maryland, United States
9	REGN2810 Followed by Chemoimmunotherapy for Newly Metastatic Hormone-sensitive Prostate Cancer	Recruiting	No Results Available	•Prostate Cancer Metastatic	•Drug: REGN2810 •Drug: Degarelix •Drug: Leuprolide Acetate •Drug: Docetaxel	•Columbia University Irving Medical Center, New York, New York, United States

	Title	Status	Study Results	Conditions	Interventions	Locations
10	First Strike, Second Strike Therapies for High Risk Metastatic Castration Sensitive Prostate Cancer	Recruiting	No Results Available	•Prostate Cancer •Stage IV Prostate Cancer	•Drug: Luteinizing Hormone Releasing Hormone •Drug: New Hormonal Agent •Drug: Docetaxel •Drug: Tislelizumab	•Moffitt Cancer Center, Tampa, Florida, United States
11	A Trial of Androgen Deprivation, Docetaxel, and Enzalutamide for Metastatic Prostate Cancer	Active, not recruiting	No Results Available	•Prostate Cancer •Prostate Adenocarcinoma	•Drug: ADT+Docetaxel+Enzalutamide	•Levine Cancer Institute, Charlotte, North Carolina, United States
12	Prostate-cancer Treatment Using Stereotactic Radiotherapy for Oligometastases Ablation in Hormone-sensitive Patients	Recruiting	No Results Available	•Oligometastatic Hormone Sensitive Prostate Cancer	•Radiation: Stereotactic Body Radiotherapy (SBRT) •Drug: Standard of care	•ICO Paul Papin, Angers, France •Institut Sainte Catherine, Avignon, France •Institut Bergonié, Bordeaux, France •Centre François Baclesse, Caen, France •Centre Jean Perrin, Clermont-Ferrand, France •Centre Oscar Lambret, Lille, France •Groupe Hospitalier Bretagne Sud, Lorient, France •Institut Paoli Calmettes, Marseille, France •Hôpital de Mercy, Metz, France •ICO René Gaudducheau, Nantes, France •and 11 more
13	Diagnostic and Prognostic Accuracy of FDHT-PET and Liquid Biopsies in Prostate Cancer	Recruiting	No Results Available	•Prostate Cancer	•Diagnostic Test: FDHT-PET Scan •Diagnostic Test: liquid biopsies	•Medical University of Vienna, Vienna, Austria
14	Neoadjuvant Chemo-hormonal Therapy Combined With Radical Prostatectomy for Locally Advanced Prostate Cancer	Not yet recruiting	No Results Available	•Prostate Cancer •Chemotherapy Effect •Hormone Sensitive Prostate Cancer •Locally Advanced Prostate Carcinoma	•Drug: Neoadjuvant chemotherapy combined with hormone therapy •Drug: Neoadjuvant hormone therapy •Procedure: Radical Prostatectomy (RP)+ extended lymph node dissection	

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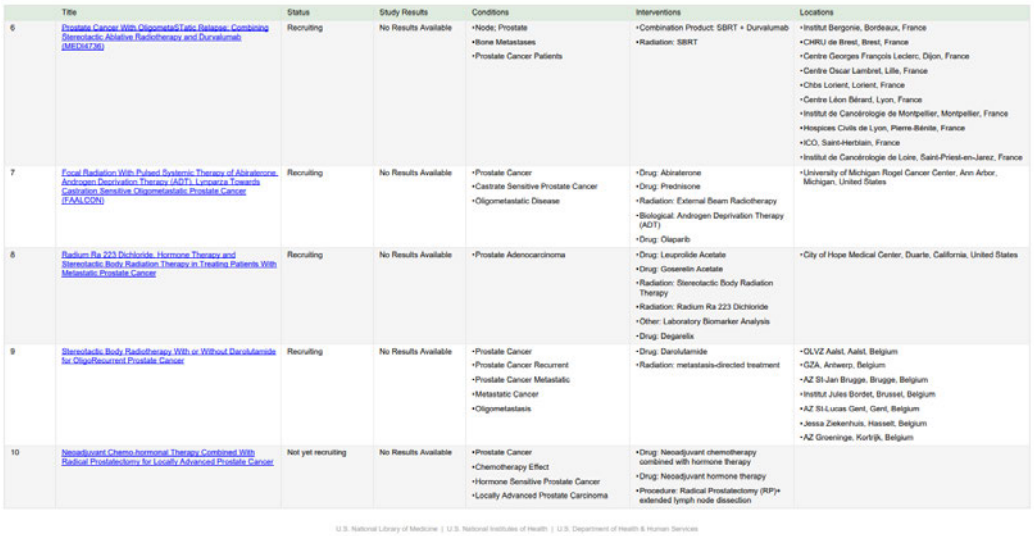
Radiation therapy/Radiotherapy

	Title	Status	Study Results	Conditions	Interventions	Locations
1	Metastasis Directed Stereotactic Body Radiotherapy for Oligo Metastatic Hormone Sensitive Prostate Cancer	Not yet recruiting	No Results Available	•Prostate Cancer Metastatic •Radiation Therapy •Positron-Emission Tomography	•Radiation: stereotactic body radiotherapy •Drug: androgen deprivation therapy •Radiation: Radiotherapy	
2	Prostate-cancer Treatment Using Stereotactic Radiotherapy for Oligometastases Ablation in Hormone-sensitive Patients	Recruiting	No Results Available	•Oligometastatic Hormone Sensitive Prostate Cancer	•Radiation: Stereotactic Body Radiotherapy (SBRT) •Drug: Standard of care	•ICO Paul Papin, Angers, France •Institut Sainte Catherine, Avignon, France •Institut Bergonié, Bordeaux, France •Centre François Baclesse, Caen, France •Centre Jean Perrin, Clermont-Ferrand, France •Centre Oscar Lambret, Lille, France •Groupe Hospitalier Bretagne Sud, Lorient, France •Institut Paoli Calmettes, Marseille, France •Hôpital de Mercy, Metz, France •ICO René Gaudducheau, Nantes, France •and 11 more
3	Different Fractionation Schedules of Radiotherapy to the Primary Tumour in Metastatic Hormone Sensitive Prostate Cancer	Not yet recruiting	No Results Available	•Prostate Cancer •Radiotherapy Side Effect •Metastatic Cancer	•Radiation: Moderate hypo-fractionation •Radiation: Ultra-hypo-fractionation	•Cancercenter University hospital of Umeå, Umeå, Sweden
4	A Study of Adding Apalutamide to Radiotherapy and LHRH Agonist in High-Risk Patients With Prostate-Specific Membrane Antigen-Positron Emission Tomography (PSMA-PET) Positive Hormone-Sensitive Prostate Cancer Participants	Recruiting	No Results Available	•Prostatic Neoplasms	•Radiation: Radiotherapy •Drug: LHRHa •Drug: Apalutamide	•Flinders Medical Centre, Bedford Park, Australia •Bundaberg Hospital, Bundaberg, Australia •Hervey Bay Hospital, Bundaberg, Australia •St Vincent's Hospital - Melbourne, Fitzroy, Australia •Genesis Care Hurstville, Hurstville, Australia •Macquarie University Hospital, North Ryde, Australia •Epworth Healthcare, Richmond, Australia •Calvary Mater Newcastle, Waratah, Australia •GenesisCare Wembley, Wembley, Australia •Medical University Innsbruck, Innsbruck, Austria •and 116 more
5	Study of Abiraterone Acetate, Atezolizumab, GnRH Analog and Radiation Therapy in Men With Newly Diagnosed Hormone-sensitive Prostate Cancer	Recruiting	No Results Available	•Metastatic Prostate Cancer	•Drug: Atezolizumab •Drug: Abiraterone •Drug: Prednisone •Drug: Lupron •Radiation: Stereotactic Body Radiotherapy (SBRT)	•Memorial Sloan Kettering Basking Ridge (Limited Protocol Activities), Basking Ridge, New Jersey, United States •Memorial Sloan Kettering Monmouth (Limited Protocol Activities), Middletown, New Jersey, United States •Memorial Sloan Kettering Bergen (Limited Protocol Activities), Montvale, New Jersey, United States •Memorial Sloan Kettering Cancer Commack (Limited Protocol Activities), Commack, New York, United States •Memorial Sloan Kettering Westchester (Limited Protocol Activities), Harrison, New York, United States •Columbia University, New York, New York, United States •Memorial Sloan Kettering Cancer Center, New York, New York, United States •Memorial Sloan Kettering Nassau (Limited Protocol Activities), Uniondale, New York, United States



	Title	Status	Study Results	Conditions	Interventions	Locations
6	Prostate Cancer With Oligometastatic Relapse: Combining Stereotactic Ablative Radiotherapy and Durvalumab (MEDI4736)	Recruiting	No Results Available	•Node; Prostate •Bone Metastases •Prostate Cancer Patients	•Combination Product: SBRT + Durvalumab •Radiation: SBRT	•Institut Bergonie, Bordeaux, France •CHRU de Brest, Brest, France •Centre Georges François Leclerc, Dijon, France •Centre Oscar Lambret, Lille, France •Chbs Lorient, Lorient, France •Centre Léon Bérard, Lyon, France •Institut de Cancérologie de Montpellier, Montpellier, France •Hospices Civils de Lyon, Pierre-Bénite, France •ICO, Saint-Herblain, France •Institut de Cancérologie de Loire, Saint-Priest-en-Jarez, France
7	Focal Radiation With Pulsed Systemic Therapy of Abiraterone, Androgen Deprivation Therapy (ADT), Lynparza Towards Castration Sensitive Oligometastatic Prostate Cancer (FAALCON)	Recruiting	No Results Available	•Prostate Cancer •Castrate Sensitive Prostate Cancer •Oligometastatic Disease	•Drug: Abiraterone •Drug: Prednisone •Radiation: External Beam Radiotherapy •Biological: Androgen Deprivation Therapy (ADT) •Drug: Olaparib	•University of Michigan Rogel Cancer Center, Ann Arbor, Michigan, United States
8	Radium Ra 223 Dichloride, Hormone Therapy and Stereotactic Body Radiation Therapy in Treating Patients With Metastatic Prostate Cancer	Recruiting	No Results Available	•Prostate Adenocarcinoma	•Drug: Leuprolide Acetate •Drug: Goserelin Acetate •Radiation: Stereotactic Body Radiation Therapy •Radiation: Radium Ra 223 Dichloride •Other: Laboratory Biomarker Analysis •Drug: Degarelix	•City of Hope Medical Center, Duarte, California, United States
9	Stereotactic Body Radiotherapy With or Without Darolutamide for Oligo(Recurrent Prostate Cancer	Recruiting	No Results Available	•Prostate Cancer •Prostate Cancer Recurrent •Prostate Cancer Metastatic •Metastatic Cancer •Oligometastasis	•Drug: Darolutamide •Radiation: metastasis-directed treatment	•OLVZ Aalst, Aalst, Belgium •GZA, Antwerp, Belgium •AZ St-Jan Brugge, Brugge, Belgium •Institut Jules Bordet, Brussel, Belgium •AZ St-Lucas Gent, Gent, Belgium •Jessa Ziekenhuis, Hasselt, Belgium •AZ Groeninge, Kortrijk, Belgium
10	Neoadjuvant Chemo-hormonal Therapy Combined With Radical Prostatectomy for Locally Advanced Prostate Cancer	Not yet recruiting	No Results Available	•Prostate Cancer •Chemotherapy Effect •Hormone Sensitive Prostate Cancer •Locally Advanced Prostate Carcinoma	•Drug: Neoadjuvant chemotherapy combined with hormone therapy •Drug: Neoadjuvant hormone therapy •Procedure: Radical Prostatectomy (RP)+ extended lymph node dissection	

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1) Search results for EU Clinical Trials Register

EudraCT Number: 2015-000735-32
Sponsor Protocol Number: 56021927PCR3002
Sponsor Name: Janssen-Cilag International NV
Full Title: A Phase 3 Randomized, Placebo-controlled, Double-blind Study of Apalutamide Plus Androgen Deprivation Therapy (ADT) Versus ADT in Subjects with Metastatic Hormone-sensitive Prostate Cancer (mHSPC)
Start Date: 2015-09-21
Medical condition: Metastatic Hormone-sensitive Prostate Cancer (mHSPC)
Disease: Version: 21.1, SOC Term: 10029104 - Neoplasms benign, malignant and unspecified (incl cysts and polyps), Classification Code: 10036909, Term: Prostate cancer metastatic, Level: PT
Population Age: Adults, Elderly
Gender: Male
Trial protocol: SE(Completed) GB(GB - no longer in EU/EEA) HU(Completed) DE(Completed) ES(Ongoing) CZ(Completed) PL(Completed) RO(Ongoing) IT(Completed)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-000735-32

EudraCT Number: 2015-003007-38
Sponsor Protocol Number: 56021927PCR3003
Sponsor Name: Janssen-Cilag International NV
Full Title: A Randomized, Double-blind, Placebo-controlled Phase 3 Study of JNJ56021927 in Subjects with High-risk, Localized or Locally Advanced Prostate Cancer Receiving Treatment with Primary Radiation Therapy
Start Date: 2016-01-11
Medical condition: High- or very-high risk, localized or locally advanced prostate cancer
Disease: Version: 20.0, SOC Term: 10029104 - Neoplasms benign, malignant and unspecified (incl cysts and polyps), Classification Code: 10060862, Term: Prostate cancer, Level: PT
Population Age: Adults, Elderly
Gender: Male
Trial protocol: GB(GB - no longer in EU/EEA) SE(Ongoing) CZ(Ongoing) ES(Ongoing) DE(Ongoing) BE(Ongoing) NL(Ongoing) PL(Ongoing) FR(Ongoing) IT(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-003007-38

EudraCT Number: 2022-000082-41

Sponsor Protocol Number: 2021-0486
Sponsor Name: Fundación para la Investigación en Urología
Full Title: Impact of pitavastatin use in prostate cancer patients treated with new generation androgen therapy: multicenter clinical trial
Start Date: 2022-03-31
Medical condition: We propose a multicenter, prospective, randomized, single-blind clinical trial, without conflict of interest, to determine the
clinical benefit of statins (Pitavastatin 2 mg) in prostate cancer pa...
Disease:
Population Age: Adults, Elderly
Gender: Male
Trial protocol: ES(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2022-000082-41

EudraCT Number: 2017-004377-13
Sponsor Protocol Number: CA209-9HX
Sponsor Name: SOGUG (Spanish Genitourinary Oncologic Group)
Full Title: A multi-arm, multi-stage, randomized phase II/III trial of immunotherapy strategies in metastatic hormone-sensitive prostate cancer.
Start Date: 2018-11-21
Medical condition: metastatic hormone-sensitive prostate cancer
Disease: Version: 20.0, SOC Term: 10029104 - Neoplasms benign, malignant and unspecified (incl cysts and polyps), Classification Code: 10036909, Term: Prostate cancer metastatic, Level: PT
Population Age: Adults, Elderly
Gender: Male
Trial protocol: ES(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-004377-13

EudraCT Number: 2020-005611-46
Sponsor Protocol Number: TAVT45C02
Sponsor Name: Tavanta Therapeutics, Inc.
Full Title: Phase 3 study investigating the efficacy and safety of TAVT-45 (abiraterone acetate) Granules for Oral Suspension (a novel abiraterone acetate formulation) relative to a reference abiraterone aceta...
Start Date: 2021-06-21
Medical condition: Metastatic Castrate Sensitive Prostate Cancer (mCSPC) and metastatic Castrate Resistant Prostate Cancer (mCRPC)

Disease: Version: 21.1, SOC Term: 10029104 - Neoplasms benign, malignant and unspecified (incl cysts and polyps), Classification Code: 10036909, Term: Prostate cancer metastatic, Level: PT
Disease: Version: 20.0, SOC Term: 10029104 - Neoplasms benign, malignant and unspecified (incl cysts and polyps), Classification Code: 10060862, Term: Prostate cancer, Level: PT
Disease: Version: 21.1, SOC Term: 10029104 - Neoplasms benign, malignant and unspecified (incl cysts and polyps), Classification Code: 10076506, Term: Castration-resistant prostate cancer, Level: LLT
Population Age: Adults, Elderly
Gender: Male
Trial protocol: FR(Ongoing) SE(Ongoing) HU(Ongoing) ES(Ongoing)

Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-005611-46

EudraCT Number: 2016-001269-10
Sponsor Protocol Number: Doc-Pred
Sponsor Name: Erasmus MC Cancer Institute
Full Title: A pharmacokinetic study of Docetaxel and Prednisone in men with metastatic castration-resistant or hormone-sensitive prostate cancer.
Start Date: 2016-07-14
Medical condition: Metastatic prostate cancer
Disease:
Population Age: Adults, Elderly
Gender: Male
Trial protocol: NL(Completed)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-001269-10

EudraCT Number: 2020-000543-31
Sponsor Protocol Number: ANT-1111-02
Sponsor Name: Antev Ltd.
Full Title: An Adaptive Phase 2, Open-Label, Multicentre Study Investigating the Pharmacokinetics, Pharmacodynamics, Efficacy and Safety of Teverelix Trifluoroacetate, a Gonadotropin-releasing Hormone (GnRH) A...
Start Date: 2021-01-19
Medical condition: Advanced prostate cancer treatment
Disease: Version: 21.1, SOC Term: 10029104 - Neoplasms benign, malignant and unspecified (incl cysts and polyps), Classification Code: 10036909, Term: Prostate cancer metastatic, Level: PT
Disease: Version: 20.0, SOC Term: 10029104 - Neoplasms benign, malignant and unspecified (incl cysts and polyps), Classification Code: 10060862, Term: Prostate cancer, Level: PT
Population Age: Adults, Elderly
Gender: Male
Trial protocol: LT(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-000543-31

EudraCT Number: 2009-018044-18
Sponsor Protocol Number: TaxiumII
Sponsor Name: Meander MC
Full Title: A randomised phase II study of repeated Rhenium-188 HEDP combined with Docetaxel versus Docetaxel alone in castration resistant prostate cancer (CRPC) metastatic to bone'
Start Date: 2012-06-22
Medical condition: Men with castration resistant prostate cancer (CRPC) metastatic to bone
Disease: Version: 16.1, SOC Term: 100000004864, Classification Code: 10036921, Term: Prostate carcinoma, Level: LLT
Disease: Version: 16.1, SOC Term: 100000004864, Classification Code: 10005993, Term: Bone metastases, Level: LLT
Population Age: Adults, Elderly
Gender: Male
Trial protocol: NL(Ongoing)

Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-018044-18

EudraCT Number: 2018-002350-78
Sponsor Protocol Number: ProBio
Sponsor Name: Karolinska Institutet
Full Title: ProBio : an outcome-adaptive and randomised multi-arm biomarker driven study in patients with metastatic prostate cancer
Start Date: 2021-08-30
Medical condition: Patients with metastatic hormone-sensitive and castrate-resistant prostate cancer
Disease: Version: 21.1, SOC Term: 10029104 - Neoplasms benign, malignant and unspecified (incl cysts and polyps), Classification Code: 10076506, Term: Castration-resistant prostate cancer, Level: LLT
Disease: Version: 21.1, SOC Term: 10029104 - Neoplasms benign, malignant and unspecified (incl cysts and polyps), Classification Code: 10071119, Term: Hormone-dependent prostate cancer, Level: PT
Population Age: Adults, Elderly
Gender: Male
Trial protocol: NO(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2018-002350-78

EudraCT Number: 2015-002590-38
Sponsor Protocol Number: 17777
Sponsor Name: Bayer AG
Full Title: A randomized, double-blind, placebo-controlled Phase III study of darolutamide (ODM-201) versus placebo in addition to standard androgen deprivation therapy and docetaxel in patients with metastati...
Start Date: 2016-12-14
Medical condition: Metastatic hormone-sensitive prostate cancer (mHSPC)
Disease: Version: 21.1, SOC Term: 10029104 - Neoplasms benign, malignant and unspecified (incl cysts and polyps), Classification Code: 10036909, Term: Prostate cancer metastatic, Level: PT
Population Age: Adults, Elderly
Gender: Male
Trial protocol: GB(GB - no longer in EU/EEA) SE(Completed) BE(Ongoing) ES(Ongoing) FI(Ongoing) DE(Ongoing) CZ(Ongoing) NL(Ongoing) PL(Ongoing) FR(Ongoing) BG(Ongoing) IT(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-002590-38

EudraCT Number: 2018-004853-26
Sponsor Protocol Number: T315/2018
Sponsor Name: Turku University Hospital
Full Title: The effect of androgen deprivation therapy on the expression of prostate specific membrane antigen (PSMA) in treatment naive metastatic prostate cancer
Start Date: 2019-03-25
Medical condition: Metastatic prostate cancer
Disease: Version: 20.0, SOC Term: 10029104 - Neoplasms benign, malignant and unspecified (incl cysts and polyps), Classification Code: 10036909, Term: Prostate cancer metastatic, Level: PT

Disease: Version: 20.0, SOC Term: 10029104 - Neoplasms benign, malignant and unspecified (incl cysts and polyps), Classification Code: 10071119, Term: Hormone-dependent prostate cancer, Level: PT
Population Age: Adults, Elderly
Gender: Male
Trial protocol: FI(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2018-004853-26

EudraCT Number: 2020-000209-10
Sponsor Protocol Number: D8731C00002
Sponsor Name: AstraZeneca AB
Full Title: A Phase II, Open-label Study to Assess the Efficacy, Safety, and Tolerability of AZD4635 in Combination with Durvalumab and in Combination with Cabazitaxel and Durvalumab in Patients Who Have Progr...
Start Date: 2020-11-20
Medical condition: Progressive Metastatic Castrate-Resistant Prostate Cancer
Disease: Version: 21.1, SOC Term: 10029104 - Neoplasms benign, malignant and unspecified (incl cysts and polyps), Classification Code: 10036909, Term: Prostate cancer metastatic, Level: PT
Population Age: Adults, Elderly
Gender: Male
Trial protocol: DE(Ongoing) FR(Completed) DK(Completed) NL(Completed) IT(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-000209-10

EudraCT Number: 2018-004321-86
Sponsor Protocol Number: RN5609C00
Sponsor Name: BioNTech SE
Full Title: First-in-human, dose titration and expansion trial to evaluate safety, immunogenicity and preliminary efficacy of W_pro1 (BNT112) monotherapy and in combination with cemiplimab in patients with pr...
Start Date: 2019-07-24
Medical condition: Male adults with prostate cancer, both mCRPC (Arms 1A & 1B) and LPC (ARms 2&3) patients, will be treated with W_pro1 alone or in combination with cemiplimab. LPC patients will also receive neo-adju...
Disease: Version: 20.0, SOC Term: 10029104 - Neoplasms benign, malignant and unspecified (incl cysts and polyps), Classification Code: 10007113, Term: Cancer of prostate, Level: LLT
Disease: Version: 21.1, SOC Term: 10029104 - Neoplasms benign, malignant and unspecified (incl cysts and polyps), Classification Code: 10036909, Term: Prostate cancer metastatic, Level: PT
Population Age: Adults, Elderly
Gender: Male
Trial protocol: GB(GB - no longer in EU/EEA) HU(Ongoing) DE(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2018-004321-86

EudraCT Number: 2018-003461-34
Sponsor Protocol Number: UR1840
Sponsor Name: Department of Oncology, Herlev & Gentofte Hospital
Full Title: Randomised phase 2 trial of stereotactic body radiation therapy, SBRT, in combination with checkpoint inhibitors in metastatic castration-resistant prostate cancer
Start Date: 2019-07-09

Medical condition: metastatic castration-resistant prostate cancer
Disease: Version: 21.1, SOC Term: 10029104 - Neoplasms benign, malignant and unspecified (incl cysts and polyps), Classification Code: 10036909, Term: Prostate cancer metastatic, Level: PT
Disease: Version: 21.0, SOC Term: 10029104 - Neoplasms benign, malignant and unspecified (incl cysts and polyps), Classification Code: 10036920, Term: Prostate cancer stage IV, Level: PT
Disease: Version: 21.1, SOC Term: 10029104 - Neoplasms benign, malignant and unspecified (incl cysts and polyps), Classification Code: 10076506, Term: Castration-resistant prostate cancer, Level: LLT
Population Age: Adults, Elderly
Gender: Male
Trial protocol: DK(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2018-003461-34

EudraCT Number: 2015-004937-29
Sponsor Protocol Number: NL55621.029.15
Sponsor Name: VU University Medical Center
Full Title: Towards early identification of response to CABAZItaxel in patients with metastatic castration-resistant prostate cancer: potential of 18F-Choline PET-CT (CABAZIPET).
Start Date: 2016-06-14
Medical condition: Metastatic castration-resistant prostate cancer.
Disease: Version: 19.1, SOC Term: 10029104 - Neoplasms benign, malignant and unspecified (incl cysts and polyps), Classification Code: 10036909, Term: Prostate cancer metastatic, Level: PT
Disease: Version: 19.1, SOC Term: 10029104 - Neoplasms benign, malignant and unspecified (incl cysts and polyps), Classification Code: 10076506, Term: Castration-resistant prostate cancer, Level: LLT
Population Age: Adults, Elderly
Gender: Male
Trial protocol: NL(Completed)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-004937-29

EudraCT Number: 2020-000348-77
Sponsor Protocol Number: XL184-315
Sponsor Name: Exelixis, Inc.
Full Title: A Phase 3, Randomized, Open-Label, Controlled Study of Cabozantinib (XL184) in Combination with Atezolizumab vs Second Novel Hormonal Therapy (NHT) in Subjects with Metastatic Castration-Resistant ...
Start Date: 2020-07-22
Medical condition: Metastatic Castration-Resistant Prostate Cancer
Disease: Version: 21.1, SOC Term: 100000004864, Classification Code: 10076506, Term: Castration-resistant prostate cancer, Level: LLT
Population Age: Adults, Elderly
Gender: Male
Trial protocol: HU(Ongoing) GB(GB - no longer in EU/EEA) PT(Ongoing) DE(Ongoing) FR(Ongoing) PL(Ongoing) AT(Ongoing) GR(Ongoing) CZ(Ongoing) IT(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-000348-77

EudraCT Number: 2015-003869-28
Sponsor Protocol Number: 9785-CL-0335

Sponsor Name: Astellas Pharma Global Development, Inc (APGD)
Full Title: ARCHES: A Multinational, Phase 3, Randomized, Double-blind, Placebo-controlled Efficacy and Safety Study of Enzalutamide Plus Androgen Deprivation Therapy (ADT) Versus Placebo Plus ADT in Patients ...
Start Date: 2016-08-04
Medical condition: Metastatic Hormone Sensitive Prostate Cancer (mHSPC)
Disease: Version: 21.1, SOC Term: 10029104 - Neoplasms benign, malignant and unspecified (incl cysts and polyps), Classification Code: 10036909, Term: Prostate cancer metastatic, Level: PT
Population Age: Adults, Elderly
Gender: Male
Trial protocol: NL(Ongoing) BE(Ongoing) ES(Restarted) DK(Restarted) FI(Restarted) SE(Ongoing) DE(Ongoing) SK(Ongoing) GB(GB - no longer in EU/EEA) FR(Ongoing) IT(Restarted)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-003869-28

EudraCT Number: 2019-002957-46
Sponsor Protocol Number: 56021927PCR3015
Sponsor Name: Janssen-Cilag International NV
Full Title: A Randomized, Controlled, Multicenter, Open-label Study to Investigate the Efficacy and Safety of Adding Apalutamide to Radiotherapy and LHRH Agonist in High-Risk Patients with PSMA-PET-Positive Ho...
Start Date: 2020-05-13
Medical condition: High risk recurrent prostate cancer previously treated with radical prostatectomy
Disease: Version: 21.0, SOC Term: 10029104 - Neoplasms benign, malignant and unspecified (incl cysts and polyps), Classification Code: 10036911, Term: Prostate cancer recurrent, Level: PT
Population Age: Adults, Elderly
Gender: Male
Trial protocol: SE(Ongoing) CZ(Ongoing) DK(Ongoing) PL(Ongoing) ES(Ongoing) AT(Ongoing) PT(Ongoing) BE(Ongoing) SK(Ongoing) IT(Ongoing) HU(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2019-002957-46

EudraCT Number: 2014-001787-36
Sponsor Protocol Number: 1333-GUCG
Sponsor Name: European Organisation for Research and Treatment of Cancer (EORTC)
Full Title: A Randomized multicenter phase III trial comparing enzalutamide vs. a combination of Ra223 and enzalutamide in asymptomatic or mildly symptomatic castration resistant prostate cancer patients metas...
Start Date: 2015-09-14
Medical condition: Castration resistant prostate cancer patients metastatic to bone.
Disease: Version: 21.1, SOC Term: 10029104 - Neoplasms benign, malignant and unspecified (incl cysts and polyps), Classification Code: 10036909, Term: Prostate cancer metastatic, Level: PT
Population Age: Adults, Elderly
Gender: Male
Trial protocol: BE(Ongoing) ES(Ongoing) DK(Ongoing) PL(Ongoing) IE(Restarted) FR(Ongoing) NO(Ongoing) IT(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-001787-36

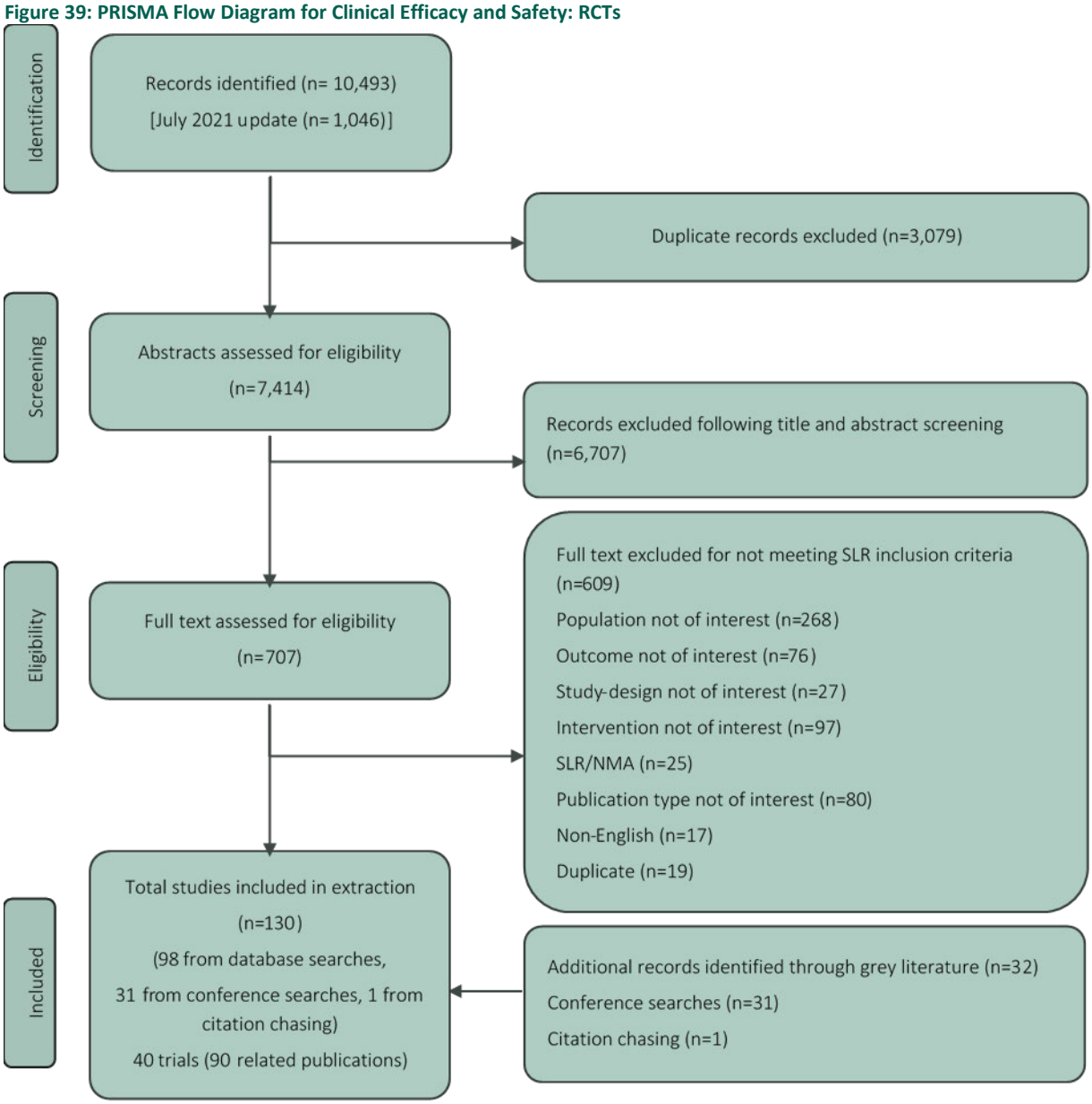
EudraCT Number: 2017-003549-72

Sponsor Protocol Number: SMR-3165
Sponsor Name: Oncology Venture Aps
Full Title: Phase II study of Irofulven in AR-targeted and Docetaxel-Pretreated Metastatic Castration-Resistant Prostate Cancer Patients, who have a Drug Response Predictor (DRP™) indicating a high likelihood ...
Start Date: 2017-12-22
Medical condition: AR-targeted and Docetaxel-Pretreated Metastatic Castration-Resistant Prostate Cancer
Disease: Version: 20.0, SOC Term: 10029104 - Neoplasms benign, malignant and unspecified (incl cysts and polyps), Classification Code: 10036909, Term: Prostate cancer metastatic, Level: PT
Population Age: Adults, Elderly
Gender: Male
Trial protocol: DK(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-003549-72

Systematic selection of studies

As per PRISMA methodology we end up with 10,493 records identified. The original search had some discrepancies which impacted the updated version that followed (7792 vs. 7584 as of 1st update), but we do not find any reason that it has impacted on the final identified records. The searches were supplemented by grey literature search, manual bibliography review, and clinicialtrials.gov, hence we would have identified any missing relevant records.

Figure 39: PRISMA Flow Diagram for Clinical Efficacy and Safety: RCTs



Abbreviations: CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Collaboration Central Register of Clinical Trials; DARE = Database of Abstract Reviews; NMA = network meta-analysis; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT = randomised controlled trial; SLR = systematic literature review

Table xx: List and characteristics of included studies (40 trials from 5th SLR update)

Sr. No.	Author & Year (Primary Study)	Trial Name/ID	Geographical location	Sample size	Intervention/comparison
1	Armstrong, AJ., et al., 2019	ARCHES (NCT02677896)	North and Latin America, Europe, and Asia	1150	Enzalutamide + ADT vs. Placebo + ADT
2	Smith, MR., et., 2014	CALGB 90202 (Alliance)	NR	645	Zoledronic acid vs. Placebo
3	Sweeney, CJ., et al., 2015	CHAARTED (NCT00309985)	USA	790	Docetaxel+ADT vs. ADT alone

4	Davis, ID., et al., 2019	ENZAMET (NCT02446405)	USA, Australia, Canada, Ireland, New Zealand, and UK	1125	Enzalutamide + ADT vs. NSAA + ADT
5	Pavone-Macaluso, M., et al., 1986	EORTC 30761	Europe	118	DES vs. Cyproterone acetate vs. Medroxyprogesterone acetate
6	Smith, PH., et al., 1986	EORTC 30762	UK, France, Belgium	96	Estramustine phosphate vs. DES
7	Robinson, 1995	EORTC 30805	Europe	262	Bilateral ORCH vs. Bilateral ORCH + Cyproterone acetate vs. Stilboestrol
8	Gravis G, 2013	GETUG-AFU 15 (NCT00104715)	France, Belgium	385	Docetaxel+ADT vs. ADT alone
9	Boeve, LM., et al., 2019	HORRAD (ISRCTN06890529)	The Netherlands	432	ADT with EBRT vs. ADT
10	Fizazi K, 2017	LATITUDE (NCT01715285)	International (235 sites in 34 countries)	1199	ADT + Abiraterone acetate + Prednisone vs. ADT + Placebo
11	Garnick, MB., et al., 1984	Leuprolide Study Group	North America	199	DES vs. Leuprolide
12	Huben, RP., et al., 1988	National Prostatic Cancer Treatment Group Protocol 1700	NR	265	DES/ORCH vs. Buserelin vs. Methotrexate + DES/ORCH
13	Dearnaley, DP., et al., 2009	PR05 (ISRCTN38477744)	UK	418	Sodium clodronate vs. Placebo
14	Pummer, K., et al., 1997	Pummer Austrian study	NR	79	TAB vs. E-TAB
15	Hedlund, PO., et al., 2008	SPCG 5	Denmark, Norway, Sweden, Finland, Iceland	910	High-dose polyestradiol phosphate vs. CAD: Flutamide; Triptorelin/Optional basis bilateral ORCH
16	Yu, EY., et al., 2015	SWOG S0925 (NCT01120236)	USA and Canada	210	ADT + Cixutumumab vs. ADT
17	Murphy, GP., et al., 1986	The National Prostatic Cancer Project (Protocol 1300)	USA	312	DES or bilateral ORCH vs. Cyclophosphamide + 5-fluorouracil + DES vs. Estramustine phosphate
18	Chi, KN., et al., 2019	TITAN (NCT02489318)	International (260 sites in 23 countries)	1052	ADT + Apalutamide vs. ADT + Placebo
19	Ueno, S., et al., 2013	ZABTON-PC (UMIN000001137)	Japan	60	CAB bicalutamide + LHRH vs. CAB + Zoledronic acid
20	Kamba, T., et al., 2017	ZAPCA (NCT00685646)	Japan	219	ADT + Zoledronic acid vs. ADT
21	Vaishampayan UN, 2021	NA	NR	71	ADT + Enzalutamide vs. ADT + Bicalutamide
22	Millikan, RE., et al., 2008	NA	NR	306	Hormone therapy vs. Hormone therapy + Vinblastine and Estramustine

23	Fontana, D., et al., 1998	NA	Italy	55	Goserelin vs. Goserelin + Mitomycin C
24	Hedlund, PO., et al., 1997	NA	Scandinavia	194	Estramustine phosphate vs. DES
25	Chang A., et al., 1996	NA	9 ECOG institutions	92	DES vs. Flutamide
26	Lukkarinen, O., et al., 1994	NA	Finland	236	Goserelin acetate vs. Polyestradiol phosphate
27	Citrin, DL., et al., 1991	NA	USA	67	DES vs. Goserelin acetate
28	Johansson, JE., et al., 1991	NA	Sweden	150	Polyestradiol phosphate + Ethinyl estradiol vs. Bilateral total ORCH
29	Venner, PM., et al., 1988	NA	NR	81	Megestrol acetate + minidose DES vs. DES
30	Johansson, JE., et al., 1987	NA	Sweden	30	Estramustine phosphate vs. Flutamide
31	Winfield, H., et al., 1984	NA	NR	23	DES vs. ADT
32	Palmbos PL, 2021	NCT02059213	USA	60	ADT + Palbociclib vs. ADT
33	Bruun, E., et al., 1996	NA	Denmark	140	Buserelin vs. Estrogen vs. Subcapsular bilateral ORCH
34	Fujimura, T., et al., 2015	UMIN000006400	Japan	15	ADT vs. Toremifene + ADT vs. Raloxifene + ADT
35	No author listed	NCT00081159	USA	80	HAT/bilateral ORCH + Doxorubicin + Zoledronate + Strontium chloride vs. HAT/bilateral ORCH + Doxorubicin + Zoledronate
36	Andren, O., et al., 2017	NCT01978873	Sweden	400	Cabazitaxel + Prednisone/Prednisolone + ADT vs. ADT
37	Sharifi, R., et al., 1985	NA	USA	21	Leuprolide vs. DES
38	Sydes, MR., et al., 2018	STAMPEDE (NCT00268476)	UK and Switzerland	342	SoC + Docetaxel + Prednisolone vs. SoC + Abiraterone acetate + Prednisolone
	Mason, MD., et al., 2017		UK and Switzerland	755	SoC vs. SoC + Celecoxib vs. SoC + Celecoxib + Zoledronic acid
	James, ND., et al., 2016		UK and Switzerland	1817	SoC vs. SoC + Zoledronic acid vs. SoC + Docetaxel + Prednisolone vs. SoC + Zoledronic acid + Docetaxel + Prednisolone
	Parker, CC., et al., 2018		UK and Switzerland	2061	SoC vs. SoC + Radiotherapy
	James, N., et al., 2017		UK and Switzerland	1002	SoC vs. SoC + Abiraterone acetate + Prednisolone

	Clarke, NW., et al., 2019		UK and Switzerland	2172	SoC vs. SoC + Docetaxel
39	Dai, B., et al., 2020	NCT02742675	China	200	ADT + Radical local therapy vs ADT only
40	Fizazi, K., et al., 2021	PEACE-1 (NCT01957436)	Belgium, Switzerland, Spain, France, Romania, Italy, Ireland,	1173	SoC ± RT vs. SoC + AAP ± RT

Table 76: List of Studies Excluded at Full-text Review with Reasons for Exclusion

Sr. No.	Author	Title	Year	Exclusion reason
1	Østergren, P. B., et al.	Metabolic consequences of gonadotropin-releasing hormone agonists vs orchiectomy: a randomized clinical study.	2018	Population not of interest
2	Zhang, T., et al.	Clinical evaluation of tamsulosin in the relief of lower urinary tract symptoms in advanced prostate cancer patients.	2017	Population not of interest
3	Østergren, P. B., et al.	Luteinizing Hormone-Releasing Hormone Agonists are Superior to Subcapsular Orchiectomy in Lowering Testosterone Levels of Men with Prostate Cancer: Results from a Randomized Clinical Trial.	2017	Population not of interest
4	Gilbert, D. C., et al.	Quality-of-life outcomes from the Prostate Adenocarcinoma: TransCutaneous Hormones (PATCH) trial evaluating luteinising hormone-releasing hormone agonists versus transdermal oestradiol for androgen suppression in advanced prostate cancer.	2017	Population not of interest
5	Patel, S. A., et al.	The impact of comorbidity and PSA doubling time on the risk of death in men experiencing PSA failure following radiation therapy with or with androgen deprivation therapy for unfavorable-risk prostate cancer.	2017	Population not of interest
6	Wu, J., et al.	Network meta-analysis of the efficacy and adverse effects of several treatments for advanced/metastatic prostate cancer.	2017	Population not of interest
7	Jin, C., et al.	A meta-analysis of cardiovascular events in intermittent androgen-deprivation therapy versus continuous androgen-deprivation therapy for prostate cancer patients.	2016	Population not of interest
8	McKay, R. R., et al.	A randomized Phase II trial of short-course androgen deprivation therapy with or without bevacizumab for patients with recurrent prostate cancer after definitive local therapy.	2016	Population not of interest
9	Duchesne, G. M., et al.	Timing of androgen-deprivation therapy in patients with prostate cancer with a rising PSA (TROG 03.06 and VCOG PR 01-03 [TOAD]): a randomized, multicentre, non-blinded, Phase 3 trial.	2016	Population not of interest

10	Iversen, P., et al.	Degarelix monotherapy compared with luteinizing hormone-releasing hormone (LHRH) agonists plus anti-androgen flare protection in advanced prostate cancer: An analysis of two randomized controlled trials.	2016	Population not of interest
11	Chandra, R. A., et al.	Age, Comorbidity, and the Risk of Prostate Cancer-Specific Mortality in Men with Biopsy Gleason Score 4+3: Implications on Patient Selection for Multiparametric MRI.	2015	Population not of interest
12	Qiao, L., et al.	Endothelin-A receptor antagonists in prostate cancer treatment-a meta-analysis.	2015	Population not of interest
13	Klotz, L., et al.	Nadir testosterone within first year of androgen-deprivation therapy (ADT) predicts for time to castration-resistant progression: A secondary analysis of the PR-7 trial of intermittent versus continuous ADT.	2015	Population not of interest
14	Yu, E. Y., et al.	Selective estrogen receptor alpha agonist GTx-758 decreases testosterone with reduced side effects of androgen deprivation therapy in men with advanced prostate cancer.	2015	Population not of interest
15	Rajan, P., et al.	Feasibility study of a randomized controlled trial comparing docetaxel chemotherapy and androgen deprivation therapy with sequential prostatic biopsies from patients with advanced non-castration-resistant prostate cancer.	2015	Population not of interest
16	Lebret, T., et al.	Efficacy of triptorelin pamoate 11.25 mg administered subcutaneously for achieving medical castration levels of testosterone in patients with locally advanced or metastatic prostate cancer.	2015	Population not of interest
17	Studer, U. E., et al.	Differences in time to disease progression do not predict for cancer-specific survival in patients receiving immediate or deferred androgen-deprivation therapy for prostate cancer: Final results of EORTC randomized trial 30891 with 12 years of follow-up.	2014	Population not of interest
18	Phillips, J. G., et al.	Percent positive biopsy cores and the risk of death from prostate cancer in men with unfavorable-risk prostate cancer.	2014	Population not of interest
19	Keane, F. K., et al.	The likelihood of death from prostate cancer in men with favorable or unfavorable intermediate-risk disease.	2014	Population not of interest
20	Martin, N. E., et al.	Natural history of untreated prostate specific antigen radiorecurrent prostate cancer in men with favorable prognostic indicators.	2014	Population not of interest
21	Kanetake, H., et al.	Efficacy of flutamide-combined androgen blockade therapy in advanced prostate cancer patients: A Phase III randomized, comparative trial.	2014	Population not of interest

22	Igawa, T., et al.	Oncological outcomes of hormonal therapy with a gonadotropin-releasing hormone agonist combined with a steroidal or non-steroidal antiandrogen in patients with prostate cancer.	2014	Population not of interest
23	Braunstein, L. Z., et al.	Obesity and the odds of weight gain following androgen deprivation therapy for prostate cancer.	2014	Population not of interest
24	Crawford, E. D., et al.	Long-term tolerability and efficacy of degarelix: 5-year results from a phase III extension trial with a 1-arm crossover from leuprolide to degarelix.	2014	Population not of interest
25	Lang, J. M., et al.	A randomized phase ii trial evaluating different schedules of zoledronic acid on bone mineral density in patients with prostate cancer beginning androgen deprivation therapy.	2013	Population not of interest
26	Schweizer, M. T., et al.	Adjuvant leuprolide with or without docetaxel in patients with high-risk prostate cancer after radical prostatectomy (TAX-3501): Important lessons for future trials.	2013	Population not of interest
27	Beer, T. M., et al.	Quality of life after sipuleucel-t therapy: Results from a randomized, double-blind study in patients with androgen-dependent prostate cancer.	2013	Population not of interest
28	Langenhuijsen, J. F., et al.	Continuous vs intermittent androgen deprivation therapy for metastatic prostate cancer.	2013	Population not of interest
29	Ishizuka, O., et al.	Comparison of efficacy and safety of 1- and 3-month luteinizing hormone-releasing hormone agonist depots as initial therapies for prostate cancer.	2013	Population not of interest
30	Langley, R. E., et al.	Cardiovascular outcomes in patients with locally advanced and metastatic prostate cancer treated with luteinising-hormone-releasing-hormone agonists or transdermal oestrogen: The randomized, Phase 2 MRC PATCH trial (PR09).	2013	Population not of interest
31	Kunath, F., et al.	Early versus deferred androgen suppression therapy for patients with lymph node-positive prostate cancer after local therapy with curative intent: A systematic review.	2013	Population not of interest
32	Geiges, G., et al.	Clinical development of two innovative pharmaceutical forms of leuprorelin acetate.	2013	Population not of interest
33	Saggar, V., et al.	Alopecia with endocrine therapies in patients with cancer.	2013	Population not of interest
34	Salonen, A. J., et al.	Advanced prostate cancer treated with intermittent or continuous androgen deprivation in the randomized FinnProstate study VII: Quality of life and adverse effects.	2013	Population not of interest

35	Anderson, J., et al.	Degarelix versus goserelin (+ antiandrogen flare protection) in the relief of lower urinary tract symptoms secondary to prostate cancer: Results from a Phase IIIb study (NCT00831233).	2013	Population not of interest
36	Kellokumpu-Lehtinen, P. L., et al.	Toxicity in patients receiving adjuvant docetaxel hormonal treatment after radical radiotherapy for intermediate or high-risk prostate cancer: A pre-planned safety report of the SPCG-13 trial.	2012	Population not of interest
37	Tunn, U. W., et al.	Testosterone recovery in the off-treatment time in prostate cancer patients undergoing intermittent androgen deprivation therapy.	2012	Population not of interest
38	Silva, E. D., et al.	Goserelin versus leuprolide in the chemical castration of patients with prostate cancer.	2012	Population not of interest
39	Kishan, A. U., et al.	Low rate of clinician-scored gynecomastia induced by 6 months of combined androgen blockade in a randomized trial: Implications for prophylactic breast irradiation.	2012	Population not of interest
40	Damber, J. E., et al.	The effect of baseline testosterone on the efficacy of degarelix and leuprolide: Further insights from a 12-month, comparative, Phase III study in prostate cancer patients.	2012	Population not of interest
41	Ozono, S., et al.	The efficacy and safety of degarelix, a GnRH antagonist: A 12-month, multicentre, randomized, maintenance dose-finding phase II study in Japanese patients with prostate cancer.	2012	Population not of interest
42	Salonen, A. J., et al.	The FinnProstate study VII: Intermittent versus continuous androgen deprivation in patients with advanced prostate cancer.	2012	Population not of interest
43	James, N. D., et al.	Celecoxib plus hormone therapy versus hormone therapy alone for hormone-sensitive prostate cancer: First results from the STAMPEDE multiarm, multistage, randomized controlled trial.	2012	Population not of interest
44	Dutkiewicz, S. A., et al.	Comparison of maximal and more maximal intermittent androgen blockade during 5-year treatment of advanced prostate cancer T3NxMx-1.	2012	Population not of interest
45	Ward, J. E., et al.	A randomized, phase II study of pazopanib in castrate-sensitive prostate cancer: A University of Chicago Phase II Consortium/Department of Defense Prostate Cancer Clinical Trials Consortium study.	2012	Population not of interest
46	Axcrona, K., et al.	Androgen deprivation therapy for volume reduction, lower urinary tract symptom relief and quality of life improvement in patients with prostate cancer: Degarelix vs goserelin plus bicalutamide.	2012	Population not of interest

47	D'Amico, A. V., et al.	Duration of short-course androgen suppression therapy and the risk of death as a result of prostate cancer.	2011	Population not of interest
48	Kapoor, A., et al.	Effect of zoledronic acid on bone mineral density in men with prostate cancer receiving gonadotropin-releasing hormone analog.	2011	Population not of interest
49	Smith, M. R., et al.	Gonadotropin-releasing hormone blockers and cardiovascular disease risk: Analysis of prospective clinical trials of degarelix.	2011	Population not of interest
50	Crawford, E. D., et al.	A phase III extension trial with a 1-arm crossover from leuprolide to degarelix: Comparison of gonadotropin-releasing hormone agonist and antagonist effect on prostate cancer.	2011	Population not of interest
51	Johansson, E., et al.	Long-term quality-of-life outcomes after radical prostatectomy or watchful waiting: The Scandinavian Prostate Cancer Group-4 randomized trial.	2011	Population not of interest
52	Beer, T. M., et al.	Randomized trial of autologous cellular immunotherapy with sipuleucel-T in androgen-dependent prostate cancer.	2011	Population not of interest
53	Iversen, P., et al.	Hot flushes in prostatic cancer patients during androgen-deprivation therapy with monthly dose of degarelix or leuprolide.	2011	Population not of interest
54	Dorff, T. B., et al.	Adjuvant androgen deprivation for high-risk prostate cancer after radical prostatectomy: SWOG S9921 study.	2011	Population not of interest
55	De La Rosette, J., et al.	Efficacy and safety of androgen deprivation therapy after switching from monthly leuprolide to monthly degarelix in patients with prostate cancer.	2011	Population not of interest
56	Watkins Bruner, D., et al.	Randomized, Double-Blinded, Placebo-Controlled Crossover Trial of Treating Erectile Dysfunction with Sildenafil After Radiotherapy and Short-Term Androgen Deprivation Therapy: Results of RTOG 0215.	2011	Population not of interest
57	Lamb, D. S., et al.	A comparison of the prognostic value of early PSA test-based variables following external beam radiotherapy, with or without preceding androgen deprivation: Analysis of data from the TROG 96.01 randomized trial.	2011	Population not of interest
58	Smith, M. R., et al.	Cardiovascular safety of degarelix: Results from a 12-month, comparative, randomized, open label, parallel group Phase III trial in patients with prostate cancer.	2010	Population not of interest
59	Ploussard, G., et al.	Pilot trial of adjuvant paclitaxel plus androgen deprivation for patients with high-risk prostate cancer after radical prostatectomy: Results on toxicity, side effects and quality-of-life.	2010	Population not of interest

60	Kearns, A. E., et al.	Osteoporosis prevention in prostate cancer patients receiving androgen ablation therapy: Placebo-controlled double-blind study of estradiol and risedronate: N01C8.	2010	Population not of interest
61	Matousek, R. H., et al.	A randomized controlled trial of add-back estrogen or placebo on cognition in men with prostate cancer receiving an antiandrogen and a gonadotropin-releasing hormone analog.	2010	Population not of interest
62	Irani, J., et al.	Efficacy of venlafaxine, medroxyprogesterone acetate, and cyproterone acetate for the treatment of vasomotor hot flushes in men taking gonadotropin-releasing hormone analogues for prostate cancer: a double-blind, randomized trial.	2010	Population not of interest
63	Smith, M. R., et al.	Effects of Denosumab on Bone Mineral Density in Men Receiving Androgen Deprivation Therapy for Prostate Cancer.	2009	Population not of interest
64	Denham, J. W., et al.	Why are pretreatment prostate-specific antigen levels and biochemical recurrence poor predictors of prostate cancer survival?.	2009	Population not of interest
65	Sommerauer, M., et al.	The efficacy and safety of degarelix: A 12-month, comparative, randomized, open-label, parallel-group Phase III study in patients with prostate cancer.	2009	Population not of interest
66	Tunn, U. W., et al.	Safety and clinical efficacy of a new 6-month depot formulation of leuprorelin acetate in patients with prostate cancer in Europe.	2009	Population not of interest
67	Sakai, H., et al.	Hot Flashes During Androgen Deprivation Therapy With Luteinizing Hormone-Releasing Hormone Agonist Combined With Steroidal or Nonsteroidal Antiandrogen for Prostate Cancer.	2009	Population not of interest
68	Figg, W. D., et al.	A Double-Blind Randomized Crossover Study of Oral Thalidomide Versus Placebo for Androgen Dependent Prostate Cancer Treated With Intermittent Androgen Ablation.	2009	Population not of interest
69	Schröder, F. H., et al.	Early Versus Delayed Endocrine Treatment of T2–T3 pN1-3 M0 Prostate Cancer Without Local Treatment of the Primary Tumour: Final Results of European Organisation for the Research and Treatment of Cancer Protocol 30846 After 13 Years of Follow-up (A Randomized Controlled Trial).	2009	Population not of interest
70	D'Amico, A. V., et al.	Causes of death in men undergoing androgen suppression therapy for newly diagnosed localized or recurrent prostate cancer.	2008	Population not of interest

71	Arai, Y., et al.	Evaluation of quality of life in patients with previously untreated advanced prostate cancer receiving maximum androgen blockade therapy or LHRHa monotherapy: A multicenter, randomized, double-blind, comparative study.	2008	Population not of interest
72	Klotz, L., et al.	The efficacy and safety of degarelix: A 12-month, comparative, randomized, open-label, parallel-group Phase III study in patients with prostate cancer.	2008	Population not of interest
73	Pasquier, D., et al.	Adjuvant and Salvage Radiotherapy After Prostatectomy for Prostate Cancer: A Literature Review.	2008	Population not of interest
74	Gittelman, M., et al.	A 1-Year, Open Label, Randomized Phase II Dose Finding Study of Degarelix for the Treatment of Prostate Cancer in North America.	2008	Population not of interest
75	Mathew, P., et al.	Dynamic change in phosphorylated platelet-derived growth factor receptor in peripheral blood leukocytes following docetaxel therapy predicts progression-free and overall survival in prostate cancer.	2008	Population not of interest
76	Smith, M. R., et al.	Toremifene improves lipid profiles in men receiving androgen-deprivation therapy for prostate cancer: Interim Analysis of a multicenter phase III study.	2008	Population not of interest
77	Van Poppel, H., et al.	Degarelix: A Novel Gonadotropin-Releasing Hormone (GnRH) Receptor Blocker-Results from a 1-yr, Multicentre, Randomized, Phase 2 Dosage-Finding Study in the Treatment of Prostate Cancer.	2008	Population not of interest
78	Salonen, A. J., et al.	Finnish Multicenter Study Comparing Intermittent to Continuous Androgen Deprivation for Advanced Prostate Cancer: Interim Analysis of Prognostic Markers Affecting Initial Response to Androgen Deprivation.	2008	Population not of interest
79	Irani, J., et al.	Continuous versus Six Months a Year Maximal Androgen Blockade in the Management of Prostate Cancer: A Randomized Study.	2008	Population not of interest
80	Taxel, P., et al.	The effect of short-term estradiol therapy on clotting and inflammatory markers in older men receiving hormonal suppression therapy for prostate cancer.	2008	Population not of interest
81	Di Silverio, F., et al.	Etoricoxib and Intermittent Androgen Deprivation Therapy in Patients with Biochemical Progression After Radical Prostatectomy.	2008	Population not of interest
82	Strasser, F., et al.	Prevention of docetaxel- or paclitaxel-associated taste alterations in cancer patients with oral glutamine: A randomized, placebo-controlled, double-blind study.	2008	Population not of interest

83	Dockery, F., et al.	Anti-androgens increase N-terminal pro-BNP levels in men with prostate cancer.	2008	Population not of interest
84	Mao, S., et al.	Employing the treatment-free interval of intermittent androgen ablation to screen candidate prostate cancer therapies.	2007	Population not of interest
85	Bostancic, C., et al.	Isotope and Patient Age Predict for PSA Spikes After Permanent Prostate Brachytherapy.	2007	Population not of interest
86	Black, P. C., et al.	A randomized prospective trial evaluating testosterone, haemoglobin kinetics and quality of life, during and after 12 months of androgen deprivation after prostatectomy: Results from the Postoperative Adjuvant Androgen Deprivation trial.	2007	Population not of interest
87	Ryan, C. W., et al.	Suppression of bone density loss and bone turnover in patients with hormone-sensitive prostate cancer and receiving zoledronic acid.	2007	Population not of interest
88	Fradet, Y., et al.	Tamoxifen as Prophylaxis for Prevention of Gynaecomastia and Breast Pain Associated with Bicalutamide 150 mg Monotherapy in Patients with Prostate Cancer: A Randomized, Placebo-Controlled, Dose-Response Study.	2007	Population not of interest
89	Usami, M., et al.	Bicalutamide 80 mg combined with a luteinizing hormone-releasing hormone agonist (LHRH-A) versus LHRH-A monotherapy in advanced prostate cancer: Findings from a phase III randomized, double-blind, multicenter trial in Japanese patients.	2007	Population not of interest
90	Rodrigues, P., et al.	Comparative study of the protective effect of different intravenous bisphosphonates on the decrease in bone mineral density in patients submitted to radical prostatectomy undergoing androgen deprivation therapy.	2007	Population not of interest
91	Tanaka, N., et al.	Endocrine response to a single injection of goserelin 3.6 mg or leuprolide 3.75 mg in men with prostate cancer.	2007	Population not of interest
92	Ryan, C. W., et al.	Zoledronic Acid Initiated During the First Year of Androgen Deprivation Therapy Increases Bone Mineral Density in Patients With Prostate Cancer.	2006	Population not of interest
93	Scattoni, V., et al.	Pathological changes of high-grade prostatic intraepithelial neoplasia and prostate cancer after monotherapy with bicalutamide 150 mg.	2006	Population not of interest
94	Berry, D. L., et al.	Quality of life and pain in advanced stage prostate cancer: Results of a Southwest Oncology Group randomized trial comparing docetaxel and estramustine to mitoxantrone and prednisone.	2006	Population not of interest

95	Messing, E. M., et al.	Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy.	2006	Population not of interest
96	Abdel-Wahab, M., et al.	Influence of number of CAG repeats on local control in the RTOG 86-10 protocol.	2006	Population not of interest
97	Roach, M., et al.	Radiotherapy plus adjuvant goserelin improves survival in men with poor prognosis prostate cancer.	2005	Population not of interest
98	Boccardo, F., et al.	Exploratory study of drug plasma levels during bicalutamide 150 mg therapy co-administered with tamoxifen or anastrozole for prophylaxis of gynecomastia and breast pain in men with prostate cancer.	2005	Population not of interest
99	Magno, C., et al.	Preventing bone loss during androgen deprivation therapy for prostate cancer: Early experience with neridronate.	2005	Population not of interest
100	Montero, A., et al.	Docetaxel for treatment of solid tumours: A systematic review of clinical data.	2005	Population not of interest
101	Hoenjet, K. M. J. L. F., et al.	Effect of a nutritional supplement containing vitamin E, selenium, vitamin C and coenzyme Q10 on serum PSA in patients with hormonally untreated carcinoma of the prostate: A randomized placebo-controlled study.	2005	Population not of interest
102	Sugiono, M., et al.	Bicalutamide vs cyproterone acetate in preventing flare with LHRH analogue therapy for prostate cancer – A pilot study.	2005	Population not of interest
103	Teillac, P., et al.	Pharmacodynamic equivalence of a decapeptyl 3-month SR formulation with the 28-day SR formulation in patients with advanced prostate cancer.	2004	Population not of interest
104	Zinner, N. R., et al.	Similar frequency of testosterone surge after repeat injections of goserelin (Zoladex) 3.6 mg and 10.8 mg: Results of a randomized open-label trial.	2004	Population not of interest
105	Smith, M. R., et al.	Bicalutamide monotherapy versus leuprolide monotherapy for prostate cancer: Effects on bone mineral density and body composition.	2004	Population not of interest
106	Murphy, J. C., et al.	Flutamide administration at 500 mg daily has similar effects on serum testosterone to 750 mg daily.	2004	Population not of interest
107	Schröder, F. H., et al.	Metastatic prostate cancer treated by Flutamide versus Cyproterone acetate: Final analysis of the "European Organization for Research and Treatment of Cancer" (EORTC) protocol 30892.	2004	Population not of interest

108	Noguchi, M., et al.	Chemohormonal therapy as primary treatment for metastatic prostate cancer: A randomized study of estramustine phosphate plus luteinizing hormone-releasing hormone agonist versus flutamide plus luteinizing hormone-releasing hormone agonist.	2004	Population not of interest
109	Akaza, H., et al.	Superior anti-tumor efficacy of bicalutamide 80 mg in combination with a luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist monotherapy as first-line treatment for advanced prostate cancer: Interim results of a randomized study in Japanese patients.	2004	Population not of interest
110	Heyns, C. F., et al.	Comparative efficacy of triptorelin pamoate and leuprolide acetate in men with advanced prostate cancer.	2003	Population not of interest
111	Van Andel, G., et al.	The impact of androgen deprivation therapy on health related quality of life in asymptomatic men with lymph node positive prostate cancer.	2003	Population not of interest
112	Williams, G., et al.	Randomized crossover trial to assess the tolerability of LHRH analogue administration.	2003	Population not of interest
113	Oefelein, M. G., et al.	Health related quality of life using serum testosterone as the trigger to re-dose long acting depot luteinizing hormone-releasing hormone agonists in patients with prostate cancer.	2003	Population not of interest
114	Green, H. J., et al.	Altered cognitive function in men treated for prostate cancer with luteinizing hormone-releasing hormone analogues and cyproterone acetate: A randomized controlled trial.	2002	Population not of interest
115	De Leval, J., et al.	Intermittent versus continuous total androgen blockade in the treatment of patients with advanced hormone-naive prostate cancer: Results of a prospective randomized multicenter trial.	2002	Population not of interest
116	Boccardo, F., et al.	Bicalutamide monotherapy versus flutamide plus goserelin in prostate cancer: Updated results of a multicentric trial.	2002	Population not of interest
117	Sharifi, R., et al.	Serum testosterone suppression and potential for agonistic stimulation during chronic treatment with monthly and 3-month depot formulations of leuprolide acetate for advanced prostate cancer.	2002	Population not of interest
118	Trachtenberg, J., et al.	A Phase 3, multicenter, open label, randomized study of abarelix versus leuprolide plus daily antiandrogen in men with prostate cancer.	2002	Population not of interest

119	Ferrari, A. C., et al.	13-cis retinoic acid and complete androgen blockade in advanced hormone-naive prostate cancer patients: Report of a phase II randomized study.	2002	Population not of interest
120	Tsushima, T., et al.	Optimal starting time for flutamide to prevent disease flare in prostate cancer patients treated with a gonadotropin-releasing hormone agonist.	2001	Population not of interest
121	Kuriyama, M., et al.	Prospective and randomized comparison of combined androgen blockade versus combination with oral UFT as an initial treatment for prostate cancer.	2001	Population not of interest
122	Noguchi, K., et al.	Inhibition of PSA flare in prostate cancer patients by administration of flutamide for 2 weeks before initiation of treatment with slow-releasing LH-RH agonist.	2001	Population not of interest
123	Ozono, S., et al.	A prospective randomized multicenter study of chlormadinone acetate versus flutamide in total androgen blockade for prostate cancer.	2000	Population not of interest
124	Fowler Jr, J. E., et al.	Safety and efficacy of an implantable leuprolide delivery system in patients with advanced prostate cancer.	2000	Population not of interest
125	Yamamoto, A., et al.	Prevention of the initial testosterone surge induced by a luteinizing hormone-releasing hormone analogue in prostate cancer patients: The endocrinological effects of pretreatment with chlormadinone acetate.	1999	Population not of interest
126	Kaisary, A. V., et al.	Pharmacodynamics of a long acting depot preparation of avorelin in patients with prostate cancer.	1999	Population not of interest
127	Kotake, T., et al.	Goserelin acetate with or without antiandrogen or estrogen in the treatment of patients with advanced prostate cancer: a multicenter, randomized, controlled trial in Japan. Zoladex Study Group.	1999	Population not of interest
128	Henriksson, P., et al.	Time for revival of estrogens in the treatment of advanced prostatic carcinoma? Pharmacokinetics, and endocrine and clinical effects, of a parenteral estrogen regimen.	1999	Population not of interest
129	Boccardo, F., et al.	Bicalutamide monotherapy versus flutamide plus goserelin in prostate cancer patients: Results of an Italian prostate cancer project study.	1999	Population not of interest
130	Seidenfeld, J., et al.	Relative effectiveness and cost-effectiveness of methods of androgen suppression in the treatment of advanced prostate cancer. Evidence report/technology assessment (Summary).	1999	Population not of interest
131	Sarosdy, M. F., et al.	Comparison of goserelin and leuprolide in combined androgen blockade therapy.	1998	Population not of interest

132	De Voogt, H. J., et al.	Maximum androgen blockade using LHRH agonist buserelin in combination with short-term (2 weeks) or long-term (continuous) cyproterone acetate is not superior to standard androgen deprivation in the treatment of advanced prostate cancer. Final analysis of EORTC GU group trial 30843.	1998	Population not of interest
133	Kuhn, J. M., et al.	A randomized comparison of the clinical and hormonal effects of two GnRH agonists in patients with prostate cancer.	1997	Population not of interest
134	Pilepich, M. V., et al.	Phase III trial of androgen suppression using goserelin in unfavorable- prognosis carcinoma of the prostate treated with definitive radiotherapy: Report of Radiation Therapy Oncology Group protocol 85-31.	1997	Population not of interest
135	Miyake, H., et al.	Comparison of hormonal therapy and chemohormonal therapy in patients with newly diagnosed clinical stage D prostatic cancer.	1996	Population not of interest
136	Fernandez Del Moral, P., et al.	Three-month depot of goserelin acetate: Clinical efficacy and endocrine profile.	1996	Population not of interest
137	Asbell, S. O., et al.	Development of anemia and recovery in prostate cancer patients treated with combined androgen blockade and radiotherapy.	1996	Population not of interest
138	Ferrari, P., et al.	Combination treatment versus LHRH alone in advanced prostatic cancer.	1996	Population not of interest
139	Debruyne, F. M., et al.	A new long acting formulation of the luteinizing hormone-releasing hormone analogue, goserelin: Results of studies in prostate cancer.	1996	Population not of interest
140	Rana, A., et al.	A case for synchronous reduction of testicular androgen, adrenal androgen and prolactin for the treatment of advanced carcinoma of the prostate.	1995	Population not of interest
141	Aro, J., et al.	Polyestradiol phosphate (160 mg/month) or LHRH analog (buserelin depot) in the treatment of locally advanced or metastasized prostatic cancer.	1993	Population not of interest
142	Boccardo, F., et al.	Goserelin acetate with or without flutamide in the treatment of patients with locally advanced or metastatic prostate cancer.	1993	Population not of interest
143	Akaza, H., et al.	A randomized phase II trial of flutamide vs chlormadinone acetate in previously untreated advanced prostatic cancer. The Japan Flutamide Study Group.	1993	Population not of interest
144	Waymont, B., et al.	Phase III randomized study of Zoladex versus Stilboestrol in the treatment of advanced prostate cancer.	1992	Population not of interest

145	Henriksson, P., et al.	Hormonal regulation of serum Lp (a) levels. Opposite effects after estrogen treatment and orchidectomy in males with prostatic carcinoma.	1992	Population not of interest
146	Pummer, K., et al.	Epirubicin plus flutamide and orchidectomy in previously untreated advanced prostatic cancer.	1991	Population not of interest
147	Johansson, J. E., et al.	Prognostic factors in progression-free survival and corrected survival in patients with advanced prostatic cancer: Results from a randomized study comprising 150 patients treated with orchiectomy or estrogens.	1991	Population not of interest
148	Aro, J., et al.	Cardiovascular and all-cause mortality in prostatic cancer patients treated with estrogens or orchiectomy as compared to the standard population.	1991	Population not of interest
149	Osborne, C. K., et al.	Combined versus sequential chemo-endocrine therapy in advanced prostate cancer: Final results of a randomized Southwest Oncology Group Study.	1990	Population not of interest
150	Williams, G., et al.	Pituitary adrenal and gonadal endocrine suppression for the primary treatment of prostate cancer.	1990	Population not of interest
151	Henriksson, P., et al.	Effects of oestrogen therapy and orchidectomy on coagulation and prostanoid synthesis in patients with prostatic cancer.	1989	Population not of interest
152	Lunglmayr, G., et al.	'Zoladex' versus 'Zoladex' plus flutamide in the treatment of advanced prostate cancer. First interim analysis of an international trial. International Prostate Cancer Study Group.	1989	Population not of interest
153	Emtage, L. A., et al.	A phase III open randomized study of Zoladex 3.6 mg depot vs DES 3 mg per day in untreated advanced prostate cancer: a West Midlands Urological Research Group Study.	1989	Population not of interest
154	Botto, H., et al.	Decapeptyl in the treatment of advanced prostatic cancer: comparative study with pulpectomy.	1989	Population not of interest
155	Kotake, T., et al.	LH-RH agonist, Zoladex (goserelin), depot formulation in the treatment of prostatic cancer: Randomized dose-finding trial in Japan.	1988	Population not of interest
156	Emtage, L. A., et al.	Interim report of a randomized trial comparing Zoladex 3.6 mg depot with diethylstilbestrol 3 mg/day in advanced prostate cancer: The West Midlands Urology Research Group.	1988	Population not of interest
157	Schulze, H., et al.	Evaluation of total versus partial androgen blockade in the treatment of advanced prostatic cancer.	1988	Population not of interest
158	Lund, F., et al.	Flutamide versus Stilboestrol in the management of advanced prostatic cancer. A controlled prospective study.	1988	Population not of interest

159	Stege, R., et al.	Serum prolactin assays have no prognostic value in treatment of prostatic cancer by orchidectomy or estrogens.	1987	Population not of interest
160	Cikes, M., et al.	Randomized trial of buserelin (HOE 766) alone versus buserelin and antiandrogens in advanced prostatic cancer. Preliminary results.	1986	Population not of interest
161	Benson Jr, R. C., et al.	Estramustine phosphate compared with diethylstilbestrol. A randomized, double-blind, crossover trial for stage D prostate cancer.	1986	Population not of interest
162	Henriksson, P., et al.	Orchidectomy versus oestrogen for prostatic cancer: Cardiovascular effects.	1986	Population not of interest
163	Parmar, H., et al.	Randomized controlled study of orchidectomy vs long-acting D-Trp-6-LHRH microcapsules in advanced prostatic carcinoma.	1985	Population not of interest
164	Benson Jr, R. C., et al.	A randomized double blind crossover trial of diethylstilbestrol (DES) and estramustine phosphate (Emcyt®) for stage D prostatic carcinoma.	1983	Population not of interest
165	Gibbons, R. P., et al.	The addition of chemotherapy to hormonal therapy for treatment of patients with metastatic carcinoma of the prostate.	1983	Population not of interest
166	Alfthan, O., et al.	Cisobitan® in treatment of prostatic cancer. A prospective controlled multicentre study.	1983	Population not of interest
167	Sander, S., et al.	Orchiectomy combined with cyproterone acetate or prednisone in the treatment of advanced prostatic carcinoma. A randomized clinical and endocrine study.	1982	Population not of interest
168	Airhart, R. A., et al.	Flutamide therapy for carcinoma of the prostate.	1978	Population not of interest
169	Jordan Jr, W. P., et al.	Reconsideration of orchiectomy in the treatment of advanced prostatic carcinoma.	1977	Population not of interest
170	Jacobo, E., et al.	Comparison of flutamide (SCH 13521) and diethylstilbestrol in untreated advanced prostatic cancer.	1976	Population not of interest
171	Tejada, F., et al.	Initial chemotherapeutic trials in patients with inoperable or recurrent cancer of the prostate.	1975	Population not of interest
172	Alloul, K., et al.	Meta-analysis and economic evaluation of LH-RH agonists' depot formulations in advanced prostatic carcinoma.	1998	Population not of interest
173	Jocham, D., et al.	Leuprorelin three-month depot in the treatment of advanced and metastatic prostate cancer: long-term follow-up results.	1998	Population not of interest

174	Tolis, G., et al.	Advanced prostatic adenocarcinoma: biological aspects and effects of androgen deprivation achieved by castration or agonistic analogues of LHRH.	1984	Population not of interest
175	Ferrari, P., et al.	Combination treatment in M1 prostate cancer.	1993	Population not of interest
176	Debruyne, F. J., et al.	Liarozole--a novel treatment approach for advanced prostate cancer: results of a large randomized trial versus cyproterone acetate. Liarozole Study Group.	1998	Population not of interest
177	Boccardo, F., et al.	Zoladex with or without flutamide in the treatment of locally advanced or metastatic prostate cancer: interim analysis of an ongoing PONCAP study. Italian Prostatic Cancer Project (PONCAP).	1990	Population not of interest
178	Wechsel, H. W., et al.	Randomized open labelled comparative study of the efficacy, safety and tolerability of leuprorelin acetate 1M and 3M depot in patients with advanced prostatic cancer.	1996	Population not of interest
179	Tunn, U. W., et al.	Comparison of LH-RH analogue 1-month depot and 3-month depot by their hormone levels and pharmacokinetic profile in patients with advanced prostate cancer.	1998	Population not of interest
180	Aro, J., et al.	Polyestradiol phosphate (160 mg/month) or LHRH analog (buserelin depot) in the treatment of locally advanced or metastasized prostatic cancer. The FinnProstate Group.	1993	Population not of interest
181	Iversen, P., et al.	Zoladex plus flutamide vs orchidectomy for advanced prostatic cancer. Danish Prostatic Cancer Group (DAPROCA).	1990	Population not of interest
182	Bono, A. V., et al.	Complete androgen blockade versus chemical castration in advanced prostatic cancer: analysis of an Italian multicentre study. Italian Leuprorelin Group.	1998	Population not of interest
183	Moffat, L. E., et al.	Comparison of Zoladex, diethylstilbestrol and cyproterone acetate treatment in advanced prostate cancer.	1990	Population not of interest
184	Ruff, P., et al.	Sequential hormonal therapy and sequential hormonal and chemotherapy for advanced prostatic cancer.	1989	Population not of interest
185	Klijn, J. G., et al.	Short-term versus long-term addition of cyproterone acetate to buserelin therapy in comparison with orchidectomy in the treatment of metastatic prostate cancer. European Organization for Research and Treatment of Cancer--Genitourinary Group.	1993	Population not of interest

186	Fourcade, R. O., et al.	Total androgen blockade with Zoladex plus flutamide vs Zoladex alone in advanced prostatic carcinoma: interim report of a multicenter, double-blind, placebo-controlled study.	1990	Population not of interest
187	Lunglmayr, G., et al.	A multicenter trial comparing the luteinizing hormone releasing hormone analog Zoladex, with Zoladex plus flutamide in the treatment of advanced prostate cancer. The International Prostate Cancer Study Group.	1990	Population not of interest
188	Iversen, P., et al.	Long-term results of Danish Prostatic Cancer Group trial 86. Goserelin acetate plus flutamide versus orchiectomy in advanced prostate cancer.	1993	Population not of interest
189	Johansson, J. E., et al.	Primary orchiectomy versus estrogen therapy in advanced prostatic cancer – a randomized study: results after 7 to 10 years of follow-up.	1991	Population not of interest
190	De Sy, W. A., et al.	A comparative study of a long acting luteinizing hormone releasing hormone agonist (Decapeptyl) and orchiectomy in the treatment of advanced prostatic cancer. Preliminary report.	1986	Population not of interest
191	de Voogt, H. J., et al.	Orchidectomy versus Buserelin in combination with cyproterone acetate, for 2 weeks or continuously, in the treatment of metastatic prostatic cancer. Preliminary results of EORTC-trial 30843.	1990	Population not of interest
192	Thrasher, J. B., et al.	Comparative study of the clinical efficacy of two dosing regimens of flutamide.	2000	Population not of interest
193	Dijkman, G. A., et al.	A randomized trial comparing the safety and efficacy of the Zoladex 10.8 mg depot, administered every 12 weeks, to that of the Zoladex 3.6 mg depot, administered every 4 weeks, in patients with advanced prostate cancer. The Dutch South East Cooperative Urological Group.	1995	Population not of interest
194	Soloway, M. S., et al.	A controlled trial of Casodex (bicalutamide) vs flutamide, each in combination with luteinising hormone-releasing hormone analogue therapy in patients with advanced prostate cancer. Casodex Combination Study Group.	1996	Population not of interest
195	Dijkman, G. A., et al.	A Phase III randomized trial comparing the efficacy and safety of the 3-monthly 10.8 mg depot of Zoladex with the monthly 3.6 mg depot in patients with advanced prostate cancer. Dutch South East Cooperative Urological Group.	1994	Population not of interest
196	Kühn, M. W., et al.	Primary therapy of metastatic prostate carcinoma with depot gonadotropin-releasing hormone analogue goserelin versus estramustine phosphate. The Prostate Cancer Study Group.	1994	Population not of interest

197	Beer, T. M., et al.	C-reactive protein as a prognostic marker for men with androgen-independent prostate cancer: results from the ASCENT trial.	2008	Population not of interest
198	Jacobi, G. H., et al.	Treatment of advanced prostatic cancer with parenteral cyproterone acetate: a Phase III randomized trial.	1980	Population not of interest
199	Salonen, A. J., et al.	FinnProstate study VII: intermittent versus continuous androgen deprivation in patients with advanced prostate cancer.	2012	Population not of interest
200	Da Silva Jr, F. C., et al.	Evaluation of 1045 patients with locally advanced and metastatic prostate cancer treated with IAT or MAB - South European urooncological group.	2014	Population not of interest
201	Mason, M., et al.	Degarelix as neoadjuvant hormone therapy in patients with prostate cancer: results from a Phase IIIb randomized, comparative trial versus goserelin plus bicalutamide.	2012	Population not of interest
202	Boccardo, F., et al.	Zoladex with or without flutamide in the treatment of locally advanced or metastatic prostate cancer: interim analysis of an ongoing PONCAP study.	1990	Population not of interest
203	Hassani, A., et al.	An update on clinical outcome data for a phase II randomized study comparing androgen deprivation therapy plus docetaxel versus androgen deprivation therapy alone in men with locally advanced/metastatic hormone sensitive prostate cancer.	2017	Population not of interest
204	Bono, A. V., et al.	Complete androgen blockade versus chemical castration in advanced prostatic cancer: analysis of an Italian multicentre study.	1998	Population not of interest
205	Pavone-Macaluso, M., et al.	Cyproterone acetate versus medroxyprogesterone acetate versus diethylstilbestrol in the treatment of prostate cancer: results from EORTC Study 30761.	1987	Population not of interest
206	Sugiono, M., et al.	Bicalutamide vs cyproterone acetate in preventing flare with LHRH analogue therapy for prostate cancer--a pilot study.	2005	Population not of interest
207	Klotz, L. H., et al.	Long-term follow-up of a randomized trial of 0 versus 3 months of neoadjuvant androgen ablation before radical prostatectomy.	2003	Population not of interest
208	Hauchecorne, J., et al.	French multicenter study on the use of estramustine phosphate versus diethylstilbestrol.	1987	Population not of interest
209	Benson, R. C., et al.	Estramustine phosphate vs diethylstilbestrol in the treatment of stage D prostate cancer.	1989	Population not of interest
210	Benson, R. C., et al.	A randomized double blind crossover trial of diethylstilbestrol (DES) and estramustine phosphate (Emcyt) for stage D prostatic carcinoma.	1983	Population not of interest

211	Aro, J. L., et al.	High dose polyoestradiol phosphate with and without acetosalicylic acid versus orchiectomy in the treatment of prostatic cancer. FinnProstate Group.	1989	Population not of interest
212	Brisset, J. M., et al.	Anandron (RU 23908) associated to surgical castration in previously untreated stage D prostate cancer: a multicenter comparative study of two doses of the drug and of a placebo.	1987	Population not of interest
213	De la Grange, A. B., et al.	Randomized, double-blind study of estramustine phosphate and leuprolide acetate.	1987	Population not of interest
214	Mercader, M., et al.	Early effects of pharmacological androgen deprivation in human prostate cancer.	2007	Population not of interest
215	Crook, J. M., et al.	Twenty-four-month post-radiation prostate biopsies are strongly predictive of 7-year disease-free survival: results from a Canadian randomized trial.	2009	Population not of interest
216	Green, H. J., et al.	Coping and health-related quality of life in men with prostate cancer randomly assigned to hormonal medication or close monitoring.	2002	Population not of interest
217	Casey, R., et al.	Long term zoledronic acid during androgen blockade for prostate cancer.	2010	Population not of interest
218	McLeod, D., et al.	A Phase 3, multicenter, open-label, randomized study of abarelix versus leuprolide acetate in men with prostate cancer.	2001	Population not of interest
219	Duchesne, G. M., et al.	Health-related quality of life for immediate versus delayed androgen-deprivation therapy in patients with asymptomatic, non-curable prostate cancer (TROG 03.06 and VCOG PR 01-03): a randomized, multicentre, non-blinded, Phase 3 trial.	2017	Population not of interest
220	Calais Da Silva Junior, F., et al.	Phase III study of intermittent monotherapy versus continuous combined androgen deprivation.	2017	Population not of interest
221	Da Silva, F. C., et al.	Phase III study of intermittent monotherapy versus continuous combined androgen deprivation.	2017	Population not of interest
222	Bertetto, O., et al.	Goserelin versus goserelin plus mitomycin C in advanced prostatic cancer: a randomized study.	1992	Population not of interest
223	Margel, D., et al.	Early cardiovascular morbidity in a pilot prospective randomized trial comparing LHRH agonist and antagonist among patients with advanced prostate cancer.	2017	Population not of interest
224	Lunglmayr, G., et al.	A multicenter trial comparing the luteinizing hormone releasing hormone analog Zoladex, with Zoladex plus flutamide in the treatment of advanced prostate cancer.	1990	Population not of interest

225	Pinthus, J. H., et al.	Early cardiovascular morbidity in a pilot prospective randomized trial comparing luteinizing hormone-releasing hormone agonist and antagonist among patients with advanced prostate cancer.	2017	Population not of interest
226	James, N. D., et al.	Docetaxel and/or zoledronic acid for hormone-naive prostate cancer: first overall survival results from STAMPEDE (NCT00268476).	2015	Population not of interest
227	Sydes, M. R., et al.	PR Adding abiraterone acetate plus prednisolone (AAP) or docetaxel for patients (pts) with high-risk prostate cancer (PCa) starting long-term androgen deprivation therapy (ADT): directly randomized data from STAMPEDE (NCT00268476).	2017	Population not of interest
228	James, N. D., et al.	Docetaxel (Doc) +/- zoledronic acid (ZA) for hormone-naive prostate cancer: first overall survival results from STAMPEDE & treatment effects within subgroups (NCT00268476).	2015	Population not of interest
229	Scailteux, L. M., et al.	Cardiovascular risk and androgen deprivation therapy for prostate cancer: systematic review and meta-analysis of randomized controlled trials and observational studies (METADTCR).	2015	Population not of interest
230	Shore, N., et al.	TAK-385, an oral GnRH antagonist: efficacy and safety results from a randomized Phase 2 trial in prostate cancer patients (PTS).	2015	Population not of interest
231	Sagaster, P., et al.	Complete androgen blockade with or without Methotrexate for the treatment of metastatic prostate cancer: a randomized study.	1991	Population not of interest
232	Chatelain, C., et al.	French multicentre trial comparing Casodex (ICI 176,334) monotherapy with gastration plus nilutamide in metastatic prostate cancer: a preliminary report.	1994	Population not of interest
233	Malone, S., et al.	Preliminary results of a randomized trial of optimal timing of dose escalated (76 GY) radiation and 6 months ADT in prostate cancer.	2012	Population not of interest
234	Gonzalez-san Segundo, C., et al.	Testoterone kinetics after androgen-deprivation therapy in intermediate and high risk prostate cancer: results from a randomized trial (DART01/05).	2013	Population not of interest
235	Antonarakis, E. S., et al.	Randomized Phase II trial evaluating the optimal sequencing of sipuleucel-T and androgen-deprivation therapy (ADT) in patients (pts) with biochemically recurrent prostate cancer (BRPC).	2013	Population not of interest
236	Thrasher, J. B., et al.	Comparative study of the clinical efficacy of 500 mg QD vs 250 mg TID dosing of flutamide in metastatic prostate cancer.	2000	Population not of interest

237	Dias, E., et al.	No equivalence and sufficiency of leuprolide and goserelin acetates to suppress serum total testosterone and PSA levels.	2013	Population not of interest
238	Morris, M. J., et al.	A randomized, open label, multicenter, Phase 3, 2-arm study of androgen deprivation with leuprolide (L), +/- docetaxel (D) for clinically asymptomatic prostate cancer (PC) subjects with a rising PSA following definitive local therapy: safety results.	2014	Population not of interest
239	Pedley, I. D., et al.	Tolerability and efficacy of anti-androgen manipulation versus Taxotere and anti-androgen manipulation in patients with hormone-naive, high-risk/metastatic prostate cancer: a Phase II, open-label, randomized study.	2011	Population not of interest
240	Boeve, L., et al.	A prospective, randomized controlled trial evaluating overall survival in patients with primary bone metastatic prostate cancer (MPCA) receiving either androgen deprivation therapy (ADT) or adt combined with concurrent radiation therapy to the prostate, final data from the HORRAD trial.	2018	Population not of interest
241	Shore, N., et al.	PSA-PFS in metastatic or high risk prostate cancer patients treated with GnRH antagonist (degarelix) versus LHRH agonists-A pooled analysis of data from the Americas, Europe and Asia.	2016	Population not of interest
242	Akaza, H., et al.	Leuprorelin acetate depot: results of a multicentre Japanese trial. TAP-144-SR Study Group.	1990	Population not of interest
243	Shipley, W. U., et al.	Initial report of RTOG 9601, a Phase III trial in prostate cancer: effect of anti-androgen therapy (AAT) with bicalutamide during and after radiation therapy (RT) on freedom from progression and incidence of metastatic disease in patients following radical prostatectomy (RP) with pT2-3,N0 disease and elevated PSA levels.	2011	Population not of interest
244	Da Silva Jr, F. C., et al.	Effects of prior use of statins in a Phase 3 study of intermittent versus continuous combined androgen deprivation.	2014	Population not of interest
245	Da Silva, F. C., et al.	Phase 3 study of intermittent monotherapy versus continuous combined androgen deprivation.	2018	Population not of interest
246	Da Silva Jr, F. C., et al.	Phase 3 study of intermittent monotherapy versus continuous combined androgen deprivation.	2018	Population not of interest
247	Charalambous, A., et al.	Parallel and serial mediation analysis between pain, anxiety, depression, fatigue and nausea, vomiting and retching within a randomized controlled trial in patients with breast and prostate cancer.	2019	Population not of interest

248	Keyes, M., et al.	American Brachytherapy Society Task Group Report: Use of androgen deprivation therapy with prostate brachytherapy – A systematic literature review.	2017	Population not of interest
249	Zurita, AJ., et al.	Randomized phase II trial of presurgical androgen deprivation therapy (ADT) with or without axitinib in prostate cancer (PCa) presenting with lymph node (LN) metastasis.	2019	Population not of interest
250	Hearn, JWD., et al.	HSD3B1 and overall survival (OS) in men with low-volume (LV) metastatic prostate cancer (PCa) treated with androgen deprivation therapy (ADT) or chemohormonal therapy in the CHAARTED Randomized trial.	2019	Population not of interest
251	Spratt, DE., et al.	Two Years of Anti-Androgen Treatment Increases Other-Cause Mortality in Men Receiving Early Salvage Radiotherapy: a Secondary Analysis of the NRG Oncology/RTOG 9601 Randomized Phase III Trial.	2019	Population not of interest
252	Margel, D., et al.	Cardiovascular morbidity in a randomized trial comparing GnRH-agonist and antagonist among patients with advanced prostate cancer.	2019	Population not of interest
253	Kellokumpu-Lehtinen, P-L., et al.	Docetaxel Versus Surveillance After Radical Radiotherapy for Intermediate- or High-risk Prostate Cancer. Results from the Prospective, Randomized, Open-label Phase III SPCG-13 Trial.	2019	Population not of interest
254	Kapoor R., et al.	A phase II randomized placebo-controlled double-blind study of salvage radiation therapy plus placebo versus SRT plus enzalutamide with high-risk PSA-recurrent prostate cancer after radical prostatectomy (SALV-ENZA).	2019	Population not of interest
255	Margel, D., et al.	Cardiovascular Morbidity in a Randomized Trial Comparing GnRH Agonist and GnRH Antagonist among Patients with Advanced Prostate Cancer and Pre-existing Cardiovascular Disease.	2019	Population not of interest
256	Jena R.	Relugolix - The novel oral androgen deprivation therapy for prostate cancer	2020	Population not of interest
257	Sun Y.	Efficacy and safety of degarelix in patients with prostate cancer: Results from a phase III study in China	2020	Population not of interest
258	Shore N	Hero phase 3 trial: results comparing relugolix, an oral GNRH receptor antagonist, vs leuprolide acetate for advanced prostate cancer	2020	Population not of interest
259	Shore N.	Oral relugolix for androgen-deprivation therapy in advanced prostate cancer	2020	Population not of interest

260	Hershman, D. L., et al.	Adverse Health Events Following Intermittent and Continuous Androgen Deprivation in Patients with Metastatic Prostate Cancer.	2016	Intervention not of interest
261	Silva, F. C. D., et al.	Locally advanced and metastatic prostate cancer treated with intermittent androgen monotherapy or maximal androgen blockade: Results from a randomized Phase 3 study by the South European Uroncological Group.	2014	Intervention not of interest
262	Salonen, A. J., et al.	Comparison of intermittent and continuous androgen deprivation and quality of life between patients with locally advanced and patients with metastatic prostate cancer: A post hoc analysis of the randomized FinnProstate Study VII.	2014	Intervention not of interest
263	Hussain, M., et al.	Intermittent versus continuous androgen deprivation in prostate cancer.	2013	Intervention not of interest
264	Mottet, N., et al.	Intermittent hormonal therapy in the treatment of metastatic prostate cancer: A randomized trial.	2012	Intervention not of interest
265	Schröder, F. H., et al.	Changes in alkaline phosphatase levels in patients with prostate cancer receiving degarelix or leuprolide: Results from a 12-month, comparative, Phase III study.	2010	Intervention not of interest
266	Tombal, B., et al.	Additional Analysis of the Secondary End Point of Biochemical Recurrence Rate in a Phase 3 Trial (CS21) Comparing Degarelix 80 mg Versus Leuprolide in Prostate Cancer Patients Segmented by Baseline Characteristics.	2010	Intervention not of interest
267	Akaza, H., et al.	Combined androgen blockade with bicalutamide for advanced prostate cancer: Long-term follow-up of a Phase 3, double-blind, randomized study for survival.	2009	Intervention not of interest
268	Calais da Silva, F. E. C., et al.	Intermittent Androgen Deprivation for Locally Advanced and Metastatic Prostate Cancer: Results from a Randomized Phase 3 Study of the South European Uroncological Group.	2009	Intervention not of interest
269	Beduk, Y., et al.	The comparison of the efficacy of cyproterone acetate and castration monotherapies in metastatic prostate cancer: A multicenter study of a Turkish uro-oncology group.	2007	Intervention not of interest
270	Tyrrell, C. J., et al.	Tolerability, efficacy and pharmacokinetics of bicalutamide 300 mg, 450 mg or 600 mg as monotherapy for patients with locally advanced or metastatic prostate cancer, compared with castration.	2006	Intervention not of interest
271	Ansari, M. S., et al.	Combined androgen blockade in the management of advanced prostate cancer: A sensible or ostensible approach.	2004	Intervention not of interest

272	Kulkarni, J. N., et al.	Early report of randomized double blind clinical trial of hormonal therapy of carcinoma of prostate (CaP) stage D2.	2003	Intervention not of interest
273	Soloway, M. S., et al.	Bicalutamide and flutamide, each in combination with luteinizing hormone-releasing hormone analogs, in advanced prostate cancer: Exploratory analysis of impact of extent of disease by bone scan on outcome.	2000	Intervention not of interest
274	Tyrrell, C. J., et al.	Comparison of an LH-RH analogue (goserelin acetate, 'Zoladex') with combined androgen blockade in advanced prostate cancer: Final survival results of an international multicentre randomized-trial.	2000	Intervention not of interest
275	Moinpour, C. M., et al.	Quality of life in advanced prostate cancer: Results of a randomized therapeutic trial.	1998	Intervention not of interest
276	Eisenberger, M. A., et al.	Bilateral orchiectomy with or without flutamide for metastatic prostate cancer.	1998	Intervention not of interest
277	Denis, L. J., et al.	Maximal androgen blockade: Final analysis of EORTC Phase III trial 30853.	1998	Intervention not of interest
278	Boccon-Gibod, L., et al.	Flutamide versus orchidectomy in the treatment of metastatic prostate carcinoma.	1997	Intervention not of interest
279	Schellhammer, P. F., et al.	Clinical benefits of bicalutamide compared with flutamide in combined androgen blockade for patients with advanced prostatic carcinoma: Final report of a double-blind, randomized, multicenter trial.	1997	Intervention not of interest
280	Zalcberg, J. R., et al.	Bilateral orchidectomy and flutamide versus orchidectomy alone in newly diagnosed patients with metastatic carcinoma of the prostate an Australian multicentre trial.	1996	Intervention not of interest
281	Akaza, H., et al.	Recommended dose of flutamide with LH-RH agonist therapy in patients with advanced prostate cancer.	1996	Intervention not of interest
282	Zerbib, M., et al.	A controlled trial of bicalutamide versus flutamide, each in combination with luteinizing hormone-releasing hormone analogue therapy, in patients with advanced prostate cancer [1].	1996	Intervention not of interest
283	Iversen, P., et al.	Randomized study of Casodex 50 MG monotherapy vs orchidectomy in the treatment of metastatic prostate cancer.	1996	Intervention not of interest
284	Sagaster, P., et al.	Maximal androgen blockade in combination with methotrexate for treatment of metastatic prostate cancer.	1996	Intervention not of interest
285	Chodak, G., et al.	Single-agent therapy with bicalutamide: A comparison with medical or surgical castration in the treatment of advanced prostate carcinoma.	1995	Intervention not of interest

286	Schellhammer, P., et al.	A controlled trial of bicalutamide versus flutamide, each in combination with luteinizing hormone-releasing hormone analogue therapy, in patients with advanced prostate cancer.	1995	Intervention not of interest
287	Vogelzang, N. J., et al.	Goserelin versus orchiectomy in the treatment of advanced prostate cancer: Final results of a randomized trial.	1995	Intervention not of interest
288	Jorgensen, T., et al.	Extent of disease based on initial bone scan: Important prognostic predictor for patients with metastatic prostatic cancer: Experience from the Scandinavian Prostatic Cancer Group Study No. 2 (SPCG-2).	1995	Intervention not of interest
289	Jorgensen, T., et al.	Total androgen suppression: Experience from the Scandinavian prostatic cancer group study No. 2.	1993	Intervention not of interest
290	Denis, L. J., et al.	Goserelin acetate and flutamide versus bilateral orchiectomy: A Phase III EORTC trial (30853).	1993	Intervention not of interest
291	Janknegt, R. A., et al.	Orchiectomy and nilutamide or placebo as treatment of metastatic prostatic cancer in a multinational double-blind randomized trial.	1993	Intervention not of interest
292	Benson Jr, R. C., et al.	National Cancer Institute study of luteinizing hormone-releasing hormone plus flutamide versus luteinizing hormone-releasing hormone plus placebo.	1991	Intervention not of interest
293	Jurincic, C. D., et al.	Combined treatment (goserelin plus flutamide) versus monotherapy (goserelin alone) in advanced prostate cancer: A randomized study.	1991	Intervention not of interest
294	Tyrrell, C. J., et al.	A multicenter randomized trial comparing the luteinizing hormone-releasing hormone analogue goserelin acetate alone and with flutamide in the treatment of advanced prostate cancer.	1991	Intervention not of interest
295	Kaisary, A. V., et al.	Comparison of LHRH analogue (Zoladex) with orchiectomy in patients with metastasis prostatic carcinoma.	1991	Intervention not of interest
296	Ostri, P., et al.	Treatment of symptomatic metastatic prostatic cancer with cyproterone acetate versus orchiectomy: A prospective randomized trial.	1991	Intervention not of interest
297	Soloway, M. S., et al.	Zoladex versus orchiectomy in treatment of advanced prostate cancer: A randomized trial.	1991	Intervention not of interest
298	Crawford, E. D., et al.	Combined androgen blockade: Leuprolide and flutamide versus leuprolide and placebo.	1990	Intervention not of interest
299	Peeling, W. B., et al.	A comparison between surgical orchidectomy and the LHRH agonist 'Zoladex' (ICI 188630) in the treatment of metastatic cancer of the prostate.	1989	Intervention not of interest
300	Crawford, E. D., et al.	A controlled trial of leuprolide with and without flutamide in prostatic carcinoma.	1989	Intervention not of interest

301	Peeling, W. B., et al.	Phase III studies to compare goserelin (Zoladex) with orchiectomy and with diethylstilbestrol in treatment of prostatic carcinoma.	1989	Intervention not of interest
302	Ryan, P. G., et al.	U.K. trials of treatment for M1 prostatic cancer: The LH-RH analogue Zoladex vs orchidectomy.	1988	Intervention not of interest
303	Beland, G., et al.	Total androgen blockade for metastatic cancer of the prostate.	1988	Intervention not of interest
304	Namer, M., et al.	Anandron (RU 23908) associated with orchiectomy in stage D prostate cancer: Preliminary results of a randomized, double-blind study.	1988	Intervention not of interest
305	Béland, G., et al.	Total androgen blockade for metastatic cancer of the prostate.	1988	Intervention not of interest
306	Kaisary, A. V., et al.	A comparison between surgical orchidectomy and LH-RH analogue ('Zoladex', ICI 118,630) in the treatment of advanced prostatic carcinoma--a multi-centre clinical study.	1988	Intervention not of interest
307	Turkes, A. O., et al.	Treatment of patients with advanced cancer of the prostate: Phase III trial, Zoladex against castration; A study of the British Prostate Group.	1987	Intervention not of interest
308	Parmar, H., et al.	Orchiectomy versus long-acting D-Trp-6-LHRH in advanced prostatic cancer.	1987	Intervention not of interest
309	Murphy, G. P., et al.	Zoladex (ICI 118,630): Clinical trial of new luteinizing hormone-releasing hormone analog in metastatic prostatic carcinoma.	1987	Intervention not of interest
310	Crawford, E. D., et al.	Leuprolide with and without flutamide in advanced prostate cancer.	1990	Intervention not of interest
311	Bales, G. T., et al.	A controlled trial of bicalutamide versus castration in patients with advanced prostate cancer.	1996	Intervention not of interest
312	Rizzo, M., et al.	Leuprorelin acetate depot in advanced prostatic cancer: a phase II multicentre trial.	1990	Intervention not of interest
313	No authors listed	Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council Trial. The Medical Research Council Prostate Cancer Working Party Investigators Group.	1997	Intervention not of interest
314	Tyrrell, C. J., et al.	A randomized comparison of 'Casodex' (bicalutamide) 150 mg monotherapy versus castration in the treatment of metastatic and locally advanced prostate cancer.	1998	Intervention not of interest
315	Parmar, H., et al.	How would you like to have an orchidectomy for advanced prostatic cancer?.	1988	Intervention not of interest

316	Di Silverio, F., et al.	Zoladex vs Zoladex plus cyproterone acetate in the treatment of advanced prostatic cancer: a multicenter Italian study.	1990	Intervention not of interest
317	Kaisary, A. V., et al.	A randomized comparison of monotherapy with Casodex 50 mg daily and castration in the treatment of metastatic prostate carcinoma. Casodex Study Group.	1995	Intervention not of interest
318	Iversen, P., et al.	A Phase III trial of Zoladex and flutamide versus orchiectomy in the treatment of patients with advanced carcinoma of the prostate.	1990	Intervention not of interest
319	McLeod, D. G., et al.	Controversies in the treatment of metastatic prostate cancer.	1992	Intervention not of interest
320	Tyrrell, C. J., et al.	Multicenter randomized trial comparing Zoladex with Zoladex plus flutamide in the treatment of advanced prostate cancer. Survival update.	1993	Intervention not of interest
321	Dijkman, G. A., et al.	Long-term efficacy and safety of nilutamide plus castration in advanced prostate cancer, and the significance of early prostate specific antigen normalization. International Anandron Study Group.	1997	Intervention not of interest
322	Crawford, E. D., et al.	Treatment of newly diagnosed state D2 prostate cancer with leuprolide and flutamide or leuprolide alone, Phase III, intergroup study 0036.	1990	Intervention not of interest
323	McLeod, D. G., et al.	Exploratory analysis on the effect of race on clinical outcome in patients with advanced prostate cancer receiving bicalutamide or flutamide, each in combination with LHRH analogues. The Casodex Combination Study Group.	1999	Intervention not of interest
324	Schellhammer, P. F., et al.	A controlled trial of bicalutamide versus flutamide, each in combination with luteinizing hormone-releasing hormone analogue therapy, in patients with advanced prostate carcinoma. Analysis of time to progression. CASODEX Combination Study Group.	1996	Intervention not of interest
325	Crawford, E. D., et al.	Combination studies with leuprolide.	1990	Intervention not of interest
326	Béland, G., et al.	A controlled trial of castration with and without nilutamide in metastatic prostatic carcinoma.	1990	Intervention not of interest
327	Schröder, F. H., et al.	Metastatic prostate cancer treated by flutamide versus cyproterone acetate. Final analysis of the "European Organization for Research and Treatment of Cancer" (EORTC) Protocol 30892.	2004	Intervention not of interest
328	Keuppens, F., et al.	Orchidectomy versus goserelin plus flutamide in patients with metastatic prostate cancer (EORTC 30853).	1993	Intervention not of interest

329	No authors listed	Total androgen ablation in the treatment of metastatic prostatic cancer. The Canadian Anandron Study Group.	1990	Intervention not of interest
330	Denis, L., et al.	Orchidectomy versus Zoladex plus Eulexin in patients with metastatic prostate cancer (EORTC 30853).	1990	Intervention not of interest
331	Denis, L., et al.	Orchidectomy vs Zoladex plus flutamide in patients with metastatic prostate cancer. The EORTC GU Group.	1990	Intervention not of interest
332	McLeod, D. G., et al.	The use of flutamide in hormone-refractory metastatic prostate cancer.	1993	Intervention not of interest
333	Beland, G., et al.	Combination of Anandron with orchiectomy in treatment of metastatic prostate cancer. Results of a double-blind study.	1991	Intervention not of interest
334	Janknegt, R. A., et al.	Total androgen blockade with the use of orchiectomy and nilutamide (Anandron) or placebo as treatment of metastatic prostate cancer.	1993	Intervention not of interest
335	Keuppens, F., et al.	Zoladex and flutamide versus bilateral orchiectomy. A randomized phase III EORTC 30853 study. The EORTC GU Group.	1990	Intervention not of interest
336	Thorpe, S. C., et al.	A prospective, randomized study to compare goserelin acetate (Zoladex®) versus cyproterone acetate (Cyprostat®) versus a combination of the two in the treatment of metastatic prostatic carcinoma.	1996	Intervention not of interest
337	Navratil, H., et al.	Double-blind study of Anandron versus placebo in stage D2 prostate cancer patients receiving buserelin. Results on 49 cases from a multicentre study.	1987	Intervention not of interest
338	Namer, M., et al.	A randomized double-blind study evaluating Anandron associated with orchiectomy in stage D prostate cancer.	1990	Intervention not of interest
339	Béland, G., et al.	Total androgen ablation: Canadian experience.	1991	Intervention not of interest
340	Béland, G., et al.	Total androgen blockade vs orchiectomy in stage D2 prostate cancer.	1987	Intervention not of interest
341	Carvalho, A. P., et al.	Zoladex and flutamide vs orchidectomy: a phase III EORTC 30853 trial. EORTC Urological Group.	1989	Intervention not of interest
342	Denis, L., et al.	Complete androgen blockade: data from an EORTC 30853 trial.	1990	Intervention not of interest
343	Kirby, R., et al.	Finasteride in association with either flutamide or goserelin as combination hormonal therapy in patients with stage M1 carcinoma of the prostate gland. International Prostate Health Council (IPHC) Trial Study Group.	1999	Intervention not of interest

344	Benson, R. C., et al.	Total androgen blockade: the United States experience.	1993	Intervention not of interest
345	Soloway, M. S., et al.	A controlled trial of Casodex® (bicalutamide) vs flutamide, each in combination with luteinising hormone-releasing hormone analogue therapy in patients with advanced prostate cancer.	1996	Intervention not of interest
346	Mottet, N., et al.	Intermittent versus continuous hormone deprivation in metastatic prostate cancer: preliminary data from an ongoing European study.	1999	Intervention not of interest
347	Moinpour, C., et al.	Preliminary quality-of-life outcomes for SWOG-9346: intermittent androgen deprivation in patients with hormone-sensitive metastatic prostate cancer (HSM1PC)-Phase III.	2012	Intervention not of interest
348	Schellhammer, P., et al.	Maximal androgen blockade for patients with metastatic prostate cancer: outcome of a controlled trial of bicalutamide versus flutamide, each in combination with luteinizing hormone-releasing hormone analogue therapy.	1995	Intervention not of interest
349	Choi, Y. H., et al.	A randomized, double-blind, placebo-controlled trial to evaluate the role of curcumin in prostate cancer patients with intermittent androgen deprivation.	2019	Intervention not of interest
350	Boeve L.M.S., et al.	Effect on Survival of Androgen Deprivation Therapy Alone Compared to Androgen Deprivation Therapy Combined with Concurrent Radiation Therapy to the Prostate in Patients with Primary Bone Metastatic Prostate Cancer in a Prospective Randomized Clinical Trial: Data from the HORRAD Trial.	2019	Intervention not of interest
351	Ali SA., et al.	Benefit of prostate radiotherapy for patients with lymph node only or < 4 bone metastasis and no visceral metastases: exploratory analyses of metastatic site and number in the STAMPEDE 'M1jRT comparison'	2019	Intervention not of interest
352	Ebbinge, M., et al.	Clinical and prognostic significance of changes in haemoglobin concentration during 1 year of androgen-deprivation therapy for hormone-naïve bone-metastatic prostate cancer.	2018	Outcomes not of interest
353	Romo, M. L., et al.	Pharmacologic androgen deprivation and cardiovascular disease risk factors: A systematic review.	2015	Outcomes not of interest
354	Fazeli, F., et al.	Comparison of the efficacy of two brands of triptorelin (Microrelin and Diphereline) in reducing prostate-specific antigen and serum testosterone in prostate cancer: A double-blinded randomized clinical trial.	2015	Outcomes not of interest

355	Verhagen, P. C., et al.	Intermittent versus continuous cyproterone acetate in bone metastatic prostate cancer: results of a randomized trial.	2014	Outcomes not of interest
356	Shore, N. D., et al.	Comparison of tolerability and adverse events following treatment with two GnRH agonists in patients with advanced prostate cancer.	2013	Outcomes not of interest
357	Khera, M., et al.	Testosterone replacement in men with treated and untreated prostate cancer.	2013	Outcomes not of interest
358	Morgans, A. K., et al.	Racial differences in bone mineral density and fractures in men receiving androgen deprivation therapy for prostate cancer.	2012	Outcomes not of interest
359	Hedlund, P. O., et al.	Significance of pre-treatment cardiovascular morbidity as a risk factor during treatment with parenteral oestrogen or combined androgen deprivation of 915 patients with metastasized prostate cancer: Evaluation of cardiovascular events in a randomized trial.	2011	Outcomes not of interest
360	Satoh, T., et al.	Single infusion of zoledronic acid to prevent androgen deprivation therapy-induced bone loss in men with hormone-naive prostate carcinoma.	2009	Outcomes not of interest
361	Loprinzi, C. L., et al.	A phase III randomized, double-blind, placebo-controlled trial of gabapentin in the management of hot flashes in men (N00CB).	2009	Outcomes not of interest
362	Smith, M. R., et al.	Toremifene Increases Bone Mineral Density in Men Receiving Androgen Deprivation Therapy for Prostate Cancer: Interim Analysis of a Multicenter Phase 3 Clinical Study.	2008	Outcomes not of interest
363	Ryan, C. W., et al.	Lifestyle Factors and Duration of Androgen Deprivation Affect Bone Mineral Density of Patients with Prostate Cancer During First Year of Therapy.	2007	Outcomes not of interest
364	Diamond, T. H., et al.	The antiosteoporotic efficacy of intravenous pamidronate in men with prostate carcinoma receiving combined androgen blockade: A double blind, randomized, placebo-controlled crossover study.	2001	Outcomes not of interest
365	Sarosdy, M. F., et al.	Does prolonged combined androgen blockade have survival benefits over short-term combined androgen blockade therapy?.	2000	Outcomes not of interest
366	Schröder, F. H., et al.	Prostate cancer treated by anti-androgens: Is sexual function preserved?	2000	Outcomes not of interest
367	Eriksson, A., et al.	Prognostic value of serum hormone concentrations in prostatic cancer.	1988	Outcomes not of interest

368	De Voogt, H. J., et al.	Cardiovascular side effects of diethylstilbestrol, cyproterone acetate, medroxyprogesterone acetate and estramustine phosphate used for the treatment of advanced prostatic cancer: Results from European Organization for Research on Treatment of Cancer trials 30761 and 30762.	1986	Outcomes not of interest
369	Walker, K. J., et al.	Treatment of patients with advanced cancer of the prostate using a slow-release (depot) formation of the LHRH agonist ICI 118630 (ZOLADEX®).	1984	Outcomes not of interest
370	Paulson, D. F., et al.	Extended field radiation therapy versus delayed hormonal therapy in node positive prostatic adenocarcinoma.	1982	Outcomes not of interest
371	Morales, A., et al.	Clinical relevance of plasma testosterone and prolactin changes in advanced cancer of prostate treated with diethylstilbestrol or estramustine phosphate.	1985	Outcomes not of interest
372	Shevrin, D. H., et al.	Effect of dutasteride on tumor proliferation during the regrowth phase of intermittent androgen ablation therapy in men with advanced prostate cancer.	2013	Outcomes not of interest
373	Schröder, F. H., et al.	Prostate cancer treated by anti-androgens: is sexual function preserved? EORTC Genitourinary Group. European Organization for Research and Treatment of Cancer.	2000	Outcomes not of interest
374	James, N. D., et al.	Survival with Newly Diagnosed Metastatic Prostate Cancer in the "Docetaxel Era": data from 917 Patients in the Control Arm of the STAMPEDE Trial (MRC PR08, CRUK/06/019).	2015	Outcomes not of interest
375	Robinson, M. R., et al.	EORTC protocol 30805: a phase III trial comparing orchidectomy versus orchidectomy and cyproterone acetate and low dose Stilboestrol in the management of metastatic carcinoma of the prostate.	1988	Outcomes not of interest
376	Tunn, U. W., et al.	Clinical experience with cyproterone acetate in a randomized and in an open trial.	1987	Outcomes not of interest
377	Green, H. J., et al.	Quality of life compared during pharmacological treatments and clinical monitoring for non-localized prostate cancer: a randomized controlled trial.	2004	Outcomes not of interest
378	No authors listed	The Efficacy and Safety of Degarelix One Month Dosing Regimens in Prostate Cancer.	2006	Outcomes not of interest
379	Walker, K. J., et al.	Treatment of patients with advanced cancer of the prostate using a slow-release (depot) formation of the LHRH agonist ICI 118630 (ZOLADEX®).	1984	Outcomes not of interest

380	Getzenberg, R., et al.	Confirmation of the free hormone hypothesis: decreases in PSA correlate with free testosterone rather than total testosterone in men with advanced prostate cancer treated with GTX-758.	2013	Outcomes not of interest
381	Langley, R. E., et al.	Bone density in men receiving androgen deprivation therapy for prostate cancer: a randomized comparison between transdermal estrogen and luteinising hormone-releasing hormone agonists.	2014	Outcomes not of interest
382	Verhagen, P., et al.	Intermittent versus continuous cyproterone acetate in bone metastatic prostate cancer: results of a randomized trial.	2013	Outcomes not of interest
383	Oestergren, P. B., et al.	Luteinizing hormone releasing hormone agonists lower testosterone levels more than subcapsular orchiectomy: results from a randomized trial.	2016	Outcomes not of interest
384	de Voogt, H. J., et al.	Orchidectomy versus buserelin in combination with CPA for 2 weeks or continuously in the treatment in the treatment of metastatic prostate cancer (EORTC 30843).	1990	Outcomes not of interest
385	Rosendahl, K. I., et al.	A quality-adjusted survival (Q-TWiST) analysis of EORTC trial 30853 comparing maximal androgen blockade with orchiectomy in patients with metastatic prostate cancer.	1997	Outcomes not of interest
386	Hussain, M., et al.	Absolute PSA value after androgen deprivation (AD) is a strong independent predictor of survival in new metastatic (D2) prostate cancer (PCa): data from Southwest Oncology Group Trial 9346 (INT-0162).	2006	Outcomes not of interest
387	Feyerabend, S., et al.	LATITUDE, a Phase 3 double-blind, randomized trial of androgen deprivation therapy (ADT) with abiraterone acetate (AA) plus prednisone (P) or placebos (PBOs) in patients (pts) with newly diagnosed high-risk metastatic hormone-naive prostate cancer (mHNPC).	2017	Outcomes not of interest
388	Hoyle, A. P., et al.	Influence of high and low disease volume on docetaxel response in M1 Ca prostate in the STAMPEDE trial.	2018	Outcomes not of interest
389	Langley R., et al.	PATCH-Prostate adenocarcinoma: transcutaneous hormones. A randomized comparison evaluating cardiovascular morbidity and mortality of transdermal oestradiol versus luteinising hormone-releasing hormone agonists in advanced prostate cancer.	2018	Outcomes not of interest
390	Schuurhuizen CSEW, et al.	Impact of patient- And clinician-reported cumulative toxicity on quality of life in patients with metastatic castration-naive prostate cancer.	2018	Outcomes not of interest

391	James, N., et al.	Addition of docetaxel to first-line long-term hormone therapy in prostate cancer (STAMPEDE): long-term survival, quality-adjusted survival, and cost-effectiveness analysis. Addition of docetaxel to first-line long-term hormone therapy in prostate cancer (STAMPEDE): long-term survival, quality-adjusted survival, and cost-effectiveness analysis.	2018	Outcomes not of interest
392	Supiot, S., et al.	Prostate cancer with oligometastatic relapse: combining stereotactic ablative radiotherapy and durvalumab, a randomized phase II trial (POSTCARD - GETUG-P13).	2019	Outcomes not of interest
393	Marvaso, G., et al.	Radioablation +/- hormonotherapy for prostate cancer oligorecurrences (Radiosa trial): potential of imaging and biology (AIRC IG-22159).	2019	Outcomes not of interest
394	No authors listed	Goserelin 10.8mg Injection in Treatment of Advanced Prostate Cancer.	2019	Outcomes not of interest
395	No authors listed	Radioablation with or without androgen deprivation therapy in metachronous prostate cancer oligometastasis.	2019	Outcomes not of interest
396	Belderbos, B.P.S., et al.	Effects of prednisone on docetaxel pharmacokinetics in men with metastatic prostate cancer: a randomized drug-drug interaction study.	2019	Outcomes not of interest
397	No authors listed	A Trial of Immunotherapy Strategies in Metastatic Hormone-sensitive Prostate Cancer.	2019	Outcomes not of interest
398	No authors listed	An Efficacy and Safety Study of Enzalutamide Plus Androgen Deprivation Therapy (ADT) Versus Placebo Plus ADT in Chinese Patients With Metastatic Hormone Sensitive Prostate Cancer (mHSPC).	2019	Outcomes not of interest
399	No authors listed	Androgen-deprivation therapy plus abiraterone and prednisolone vs combined androgen blockade for high-risk, metastatic, castration-sensitive prostate cancer : a randomized controlled trial.	2019	Outcomes not of interest
400	No authors listed	The impact of prostatectomy combined with systemic therapy in men with metastatic prostate cancer.	2019	Outcomes not of interest
401	No authors listed	Long-time survival of radical prostatectomy in combination with PSMA-SPECT/CT guided radiotherapy of metastatic sites and androgen deprivation therapy compared with androgen deprivation therapy alone in oligo-metastatic prostate cancer: an open-label, Phase II, randomized controlled trial.	2019	Outcomes not of interest

402	No authors listed	A prospective randomized controlled trial comparing systemic therapy combined with prostate cryoablation with systemic therapy alone in the treatment of metastatic prostate cancer.	2019	Outcomes not of interest
403	No authors listed	Randomized controlled study of GnRH antagonist monotherapy and CAB with GnRH agonist plus bicalutamide for patients with metastatic prostate cancer.(KYUCOG-1401).	2019	Outcomes not of interest
404	No authors listed	Docetaxel or Abiraterone Acetate With ADT in Treating Patients With Metastatic Hormone Sensitive Prostate Cancer.	2019	Outcomes not of interest
405	Margel, D., et al.	Cardiovascular morbidity in a randomized trial comparing GnRH-agonist and GnRH-antagonist among patients with advanced prostate-cancer and pre-existing cardiovascular disease.	2019	Outcomes not of interest
406	Dallos, M., et al.	A randomized Phase Ib/II study of nivolumab with or without BMS-986253 in combination with a short course of ADT in men with castration-sensitive prostate cancer (MAGIC-8).	2019	Outcomes not of interest
407	Dizdar, O., et al.	Gleason score and docetaxel response in advanced hormone-sensitive prostate cancer: The lower the better.	2019	Outcomes not of interest
408	Stenzl A., et al.	Effect of Enzalutamide plus Androgen Deprivation Therapy on Health-related Quality of Life in Patients with Metastatic Hormone-sensitive Prostate Cancer: An Analysis of the ARCHES Randomized, Placebo-controlled, Phase 3 Study.	2020	Outcomes not of interest
409	Dess RT., et al.	Association of Pre-salvage Radiotherapy PSA Levels after Prostatectomy with Outcomes of Long-term Antiandrogen Therapy in Men with Prostate Cancer.	2020	Outcomes not of interest
410	Emmett L, et al.	Rapid Modulation of PSMA Expression by Androgen Deprivation: Serial 68Ga-PSMA-11 PET in Men with Hormone-Sensitive and Castrate-Resistant Prostate Cancer Commencing Androgen Blockade.	2019	Outcomes not of interest
411	Melloni C., et al.	Cardiovascular Safety of Degarelix Versus Leuprolide for Advanced Prostate Cancer: the PRONOUNCE Trial Study Design	2020	Outcomes not of interest
412	Rush HL., et al.	Comparative quality of life in patients randomized contemporaneously to docetaxel or abiraterone in the STAMPEDE trial	2020	Outcomes not of interest
413	No authors listed	Bioequivalence study of Luphere Depot Injection 30 mg in adult male subjects with metastatic prostate cancer. (CTRI/2019/07/020258)	2019	Outcomes not of interest

414	No authors listed	Leuprorelin Acetate Injectable Suspension 11.25 mg in male subjects with metastatic prostate cancer.(CTRI/2019/08/020820)	2019	Outcomes not of interest
415	No authors listed	Leuprolide acetate in the treatment of advanced prostate cancer. (CTRI/2019/11/021843)	2019	Outcomes not of interest
416	No authors listed	A clinical study on SHR3680 combined with androgen deprived therapy (ADT) versus Bicalutamide combined with ADT in treatment of prostate cancer.(EUCTR2018-003190-96-BG)	2019	Outcomes not of interest
417	Stockler MR., et al.	Health-related quality of life (HRQL) in a randomized phase III trial of enzalutamide with standard first-line therapy for metastatic, hormone-sensitive prostate cancer (mHSPC): ENZAMET (ANZUP 1304), an ANZUP-led, international, co-operative group trial	2019	Outcomes not of interest
418	Ostergren PB., et al.	Metabolic consequences of gonadotropin-releasing hormone agonists vs orchiectomy: a randomized clinical study	2019	Outcomes not of interest
419	No authors listed	Parallel Group Single Blind Study to Compare the Pharmacokinetic Profiles and Pharmacodynamic Response of a New Depot Formulation of Goserelin Acetate Capsule/Implant for Subcutaneous Injection, Pepti 10.8 mg, to Zoladex 10.8 mg Capsule/Implant in Ambulatory Patients With Advanced Carcinoma of the Prostate.(PER-006-19)	2019	Outcomes not of interest
420	Brown JE., et al.	Baseline fracture risk in men with prostate cancer starting the STAMPEDE trial	2019	Outcomes not of interest
421	Mintz HP., et al.	Retrospective evaluation of neutropenic admission events in metastatic or high-risk hormone-sensitive prostate cancer (HSPC) patients having docetaxel chemotherapy upfront or for castrate resistant prostate cancer (CRPC) in STAMPEDE	2019	Outcomes not of interest
422	Nct	Androgen Deprivation Therapy for Oligo-recurrent Prostate Cancer in Addition to radioTherapy	2020	Outcomes not of interest
423	Klaff, R., et al.	Clinical characteristics and quality-of-life in patients surviving a decade of prostate cancer with bone metastases.	2016	Study design not of interest
424	Varenhorst, E., et al.	Predictors of early androgen deprivation treatment failure in prostate cancer with bone metastases.	2016	Study design not of interest
425	Ost, P., et al.	Metastasis-directed therapy of regional and distant recurrences after curative treatment of prostate cancer: A systematic review of the literature.	2015	Study design not of interest

426	Okegawa, T., et al.	Zoledronic acid improves clinical outcomes in patients with bone metastatic hormone-naïve prostate cancer in a multicenter clinical trial.	2014	Study design not of interest
427	Berruti, A., et al.	Osteoblastic flare assessed by serum alkaline phosphatase activity is an index of short duration of response in prostate cancer patients with bone metastases submitted to systemic therapy.	1997	Study design not of interest
428	Sharifi, R., et al.	Leuprolide acetate 22.5 mg 12-week depot formulation in the treatment of patients with advanced prostate cancer.	1996	Study design not of interest
429	Hoogendijk, E., et al.	Treatment of advanced prostatic cancer with anti-androgens alone and a combination of anti-androgen with anti-prolactin – a pilot study.	1986	Study design not of interest
430	Tombal, B. F., et al.	Long-term efficacy and safety of enzalutamide (ENZ) monotherapy in hormone-naive prostate cancer (HNPC): 3-year, open-label, follow-up results.	2017	Study design not of interest
431	Tunn, U., et al.	Intermittent androgen deprivation in patients with PSA relapse after radical prostatectomy.	2013	Study design not of interest
432	Kamiya, N., et al.	Additive effect of zoledronic acid on serum prostate-specific antigen changes for hormone-sensitive prostate cancer patients with bone metastasis treated by combined androgen blockade.	2012	Study design not of interest
433	Alibhai, S. M. H., et al.	Bone Health and Bone-targeted Therapies for Prostate Cancer: a Programme in Evidence-based Care – Cancer Care Ontario Clinical Practice Guideline.	2017	Study design not of interest
434	Hoyle A.P., et al.	Abiraterone in "High-" and "Low-risk" Metastatic Hormone-sensitive Prostate Cancer.	2019	Study design not of interest
435	Patel, A., et al.	Baseline serum testosterone - does it influence androgen deprivation therapy outcomes in hormone naive advanced prostate cancer patients?	2019	Study design not of interest
436	Hoyle, AP., et al.	The role of abiraterone acetate plus prednisone/prednisolone in high- and low-risk metastatic hormone sensitive prostate cancer.	2019	Study design not of interest
437	Damodaran, S., et al.	Targeting Metastatic Hormone Sensitive Prostate Cancer: chemo-hormonal Therapy and New Combinatorial Approaches.	2019	Study design not of interest
438	Kunath, F., et al.	Early versus deferred standard androgen suppression therapy for advanced hormone-sensitive prostate cancer.	2019	Study design not of interest
439	Anonymous	Enzalutamide Bests Older NSAAs in mHSPC.	2019	Study design not of interest

440	Patel A.	Does baseline serum testosterone influence androgen deprivation therapy outcomes in hormone naïve advanced prostate cancer patients?	2019	Study design not of interest
441	Graff J. N	Phase II Study of Ipilimumab in Men With Metastatic Prostate Cancer With an Incomplete Response to Androgen Deprivation Therapy	2020	Study design not of interest
442	Zhuang J	Short-term outcomes of neoadjuvant chemohormonal therapy followed by radical prostatectomy for Chinese patients with regional lymph node metastatic prostate cancer	2020	Study design not of interest
443	Gravis, G., et al.	Chemotherapy in hormone-sensitive metastatic prostate cancer: Evidences and uncertainties from the literature.	2017	Publication type not of interest
444	Scott, E., et al.	Chemo-hormonal therapy in metastatic hormone-sensitive prostate cancer.	2017	Publication type not of interest
445	Abdel-Rahman, O., et al.	Combined Chemo-hormonal Strategy in Hormone-Sensitive Prostate Cancer: A Pooled Analysis of Randomized Studies.	2016	Publication type not of interest
446	Kimura, T., et al.	Re: Randomized controlled trial of early zoledronic acid in men with castration-sensitive prostate cancer and bone metastases: Results of CALGB 90202 (Alliance).	2016	Publication type not of interest
447	Kunath, F., et al.	Non-steroidal antiandrogen monotherapy compared with luteinizing hormone-releasing hormone agonists or surgical castration monotherapy for advanced prostate cancer: A Cochrane systematic review.	2015	Publication type not of interest
448	Klotz, L., et al.	Disease control outcomes from analysis of pooled individual patient data from five comparative randomized clinical trials of degarelix versus luteinising hormone-releasing hormone agonists.	2014	Publication type not of interest
449	Kunath, F., et al.	Non-steroidal antiandrogen monotherapy compared with luteinising hormone-releasing hormone agonists or surgical castration monotherapy for advanced prostate cancer.	2014	Publication type not of interest
450	Botrel, T. E. A., et al.	Intermittent versus continuous androgen deprivation for locally advanced, recurrent or metastatic prostate cancer: A systematic review and meta-analysis.	2014	Publication type not of interest
451	Cui, Y., et al.	Degarelix versus goserelin plus bicalutamide therapy for lower urinary tract symptom relief, prostate volume reduction and quality of life improvement in men with prostate cancer: A systematic review and meta-analysis.	2014	Publication type not of interest

452	Kratiras, Z., et al.	A review of continuous vs intermittent androgen deprivation therapy: Redefining the gold standard in the treatment of advanced prostate cancer. Myths, facts and new data on a "perpetual dispute".	2014	Publication type not of interest
453	Rocha, P., et al.	Prognostic impact of C-reactive protein in metastatic prostate cancer: A systematic review and meta-analysis.	2014	Publication type not of interest
454	Brungs, D., et al.	Intermittent androgen deprivation is a rational standard-of-care treatment for all stages of progressive prostate cancer: Results from a systematic review and meta-analysis.	2014	Publication type not of interest
455	Gravis, G., et al.	Re: Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): A randomized, open-label, Phase 3 trial.	2013	Publication type not of interest
456	Trump, D. L., et al.	Commentary on "Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): A randomized, open-label, Phase 3 trial."	2013	Publication type not of interest
457	Trump, D. L., et al.	Commentary on "Intermittent versus continuous androgen deprivation in prostate cancer."	2013	Publication type not of interest
458	Sciarra, A., et al.	Intermittent androgen-deprivation therapy in prostate cancer: A critical review focused on Phase 3 trials.	2013	Publication type not of interest
459	Tsai, H. T., et al.	Efficacy of intermittent androgen deprivation therapy vs conventional continuous androgen deprivation therapy for advanced prostate cancer: A meta-analysis.	2013	Publication type not of interest
460	Niraula, S., et al.	Treatment of prostate cancer with intermittent versus continuous androgen deprivation: A systematic review of randomized trials.	2013	Publication type not of interest
461	Zhu, J., et al.	Intermittent androgen blockade or continuous androgen blockade in advanced prostate cancer: A meta-analysis of efficacy, quality of life and side effects.	2012	Publication type not of interest
462	Serpa Neto, A., et al.	Bisphosphonate therapy in patients under androgen deprivation therapy for prostate cancer: A systematic review and meta-analysis.	2012	Publication type not of interest
463	Almasi, C. E., et al.	Prognostic and predictive value of intact and cleaved forms of the urokinase plasminogen activator receptor in metastatic prostate cancer.	2011	Publication type not of interest
464	No authors listed	Degarelix: More rapid medical castration, nothing more.	2010	Publication type not of interest

465	Trump, D. L., et al.	Commentary on A double-blind randomized crossover study of oral thalidomide versus placebo for androgen dependent prostate cancer treated with intermittent androgen ablation.	2009	Publication type not of interest
466	Flaig, T. W., et al.	Randomization reveals unexpected acute leukemias in Southwest Oncology Group prostate cancer trial.	2008	Publication type not of interest
467	Langley, R. E., et al.	Early hormonal data from a multicentre phase II trial using transdermal oestrogen patches as first-line hormonal therapy in patients with locally advanced or metastatic prostate cancer.	2008	Publication type not of interest
468	Norman, G., et al.	Parenteral oestrogen in the treatment of prostate cancer: A systematic review.	2008	Publication type not of interest
469	Gravina, G. L., et al.	Surgical and Biologic Outcomes After Neoadjuvant Bicalutamide Treatment in Prostate Cancer.	2007	Publication type not of interest
470	Parker, C., et al.	RADICALS (Radiotherapy and Androgen Deprivation in Combination after Local Surgery).	2007	Publication type not of interest
471	Lukka, H., et al.	Maximal androgen blockade for the treatment of metastatic prostate cancer - A systematic review.	2006	Publication type not of interest
472	Swanson, G., et al.	Metastatic Prostate Cancer-Does Treatment of the Primary Tumor Matter?.	2006	Publication type not of interest
473	No authors listed	Bisphosphonates effective in preventing bone complications associated with androgen deprivation therapy.	2006	Publication type not of interest
474	Efficace, F., et al.	Health related quality of life in prostate carcinoma patients: A systematic review of randomized controlled trials.	2003	Publication type not of interest
475	Samson, D. J., et al.	Systematic review and meta-analysis of monotherapy compared with combined androgen blockade for patients with advanced prostate carcinoma.	2002	Publication type not of interest
476	Nair, B., et al.	Early versus deferred androgen suppression in the treatment of advanced prostatic cancer.	2002	Publication type not of interest
477	Schmitt, B., et al.	Combined androgen blockade with nonsteroidal antiandrogens for advanced prostate cancer: a systematic review.	2001	Publication type not of interest
478	Dalesio, O., et al.	Maximum androgen blockade in advanced prostate cancer: An overview of the randomized trials.	2000	Publication type not of interest
479	Seidenfeld, J., et al.	Single-therapy androgen suppression in men with advanced prostate cancer: A systematic review and meta-analysis.	2000	Publication type not of interest
480	Mahoney, J., et al.	Flutamide did not prolong survival and increased toxic effects after orchiectomy in metastatic prostate cancer.	1999	Publication type not of interest

481	Bennett, C. L., et al.	Maximum androgen-blockade with medical or surgical castration in advanced prostate cancer: A meta-analysis of nine published randomized controlled trials and 4128 patients using flutamide.	1999	Publication type not of interest
482	Schellhammer, P. F., et al.	Erattum: Clinical benefits of bicalutamide compared with flutamide in combined androgen blockade for patients with advanced prostatic carcinoma: Final report of a double-blind, randomized, multicenter trial (Urology (September 1997) 50 (330–336)).	1998	Publication type not of interest
483	Caubet, J. F., et al.	Maximum androgen blockade in advanced prostate cancer: A meta-analysis of published randomized controlled trials using nonsteroidal antiandrogens.	1997	Publication type not of interest
484	Crawford, E. D., et al.	A controlled trial of bicalutamide versus flutamide, each in combination with luteinizing hormone-releasing hormone analogue therapy, in patients with advanced prostate cancer.	1995	Publication type not of interest
485	Dalesio, O., et al.	Maximum androgen blockade in advanced prostate cancer: An overview of 22 randomized trials with 3283 deaths in 5710 patients.	1995	Publication type not of interest
486	Bertagna, C., et al.	Efficacy of the combination of nilutamide plus orchidectomy in patients with metastatic prostatic cancer. A meta-analysis of seven randomized double-blind trials (1056 patients).	1994	Publication type not of interest
487	Waxman, J., et al.	The clinical and endocrine assessment of three different antiandrogen regimens combined with a very long-acting gonadotrophin-releasing hormone analogue.	1988	Publication type not of interest
488	Perren, T. J., et al.	Pharmacokinetic and endocrinological parameters of a slow-release depot preparation of the GnRH analogue ICI 118630 (Zoladex) compared with a subcutaneous bolus and continuous subcutaneous infusion of the same drug in patients with prostatic cancer.	1986	Publication type not of interest
489	Wallis, C. J. D., et al.	Adding abiraterone to androgen deprivation therapy in men with metastatic hormone-sensitive prostate cancer: A systematic review and meta-analysis.	2018	Publication type not of interest
490	Vale, C., et al.	Re: Christopher J.D. Wallis, Zachary Klaassen, Bimal Bhindi, et al. Comparison of Abiraterone Acetate and Docetaxel with Androgen Deprivation Therapy in High-risk and Metastatic Hormone-naive Prostate Cancer: A Systematic Review and Network Meta-analysis.	2017	Publication type not of interest

491	Scott, E., et al.	Chemo-hormonal therapy in metastatic hormone-sensitive prostate cancer.	2017	Publication type not of interest
492	Smith, J. A., et al.	Effect of androgen deprivation therapy on local symptoms and tumour progression in men with metastatic carcinoma of the prostate.	1997	Publication type not of interest
493	Waxman, J., et al.	The clinical and endocrine assessment of three different antiandrogen regimens combined with a very long-acting gonadotrophin-releasing hormone analogue.	1988	Publication type not of interest
494	Bilen, M. A., et al.	A randomized phase II study of bone-targeted therapy in advanced androgen-dependent prostate cancer.	2011	Publication type not of interest
495	Yu, E. Y., et al.	SWOG S0925: a randomized Phase 2 study of androgen deprivation combined with cixutumumab versus androgen deprivation alone in patients with new metastatic hormone-sensitive prostate cancer.	2014	Publication type not of interest
496	Bailar, J. C., et al.	Estrogen treatment for cancer of the prostate. Early results with 3 doses of diethylstilbestrol and placebo.	1970	Publication type not of interest
497	Byar, D. P., et al.	VACURG studies of post-prostatectomy survival.	1980	Publication type not of interest
498	Blackard, C. E., et al.	Serum corticosteroid-binding globulin, cortisol, and nonprotein-bound cortisol levels in patients receiving estrogen for carcinoma of the prostate.	1973	Publication type not of interest
499	Iversen, P., et al.	Update of monotherapy trials with the new anti-androgen, Casodex (ICI 176,334).	1994	Publication type not of interest
500	Tyrrell, C. J., et al.	Tolerability and quality of life aspects with the anti-androgen Casodex (ICI 176,334) as monotherapy for prostate cancer. International Casodex Investigators.	1994	Publication type not of interest
501	Sweeney, C. J., et al.	ECOG: cHAARTED – chemo hormonal therapy versus androgen ablation randomized trial for extensive disease in prostate cancer.	2006	Publication type not of interest
502	Denis, L., et al.	Combined castration and androgen blockade therapy in prostate cancer.	1990	Publication type not of interest
503	Clarke, N. W., et al.	Survival with newly diagnosed metastatic prostate cancer in the "docetaxel era": data from > 600 patients in the control arm of the STAMPEDE trial (NCT00268476).	2013	Publication type not of interest
504	Eggener, S., et al.	Commentary on "Intermittent versus continuous androgen deprivation in prostate cancer."	2014	Publication type not of interest

505	Vogelzang, N. J., et al.	A randomized double-blind trial in 813 previously untreated metastatic prostate cancer (CAP) patients (PTS) comparing a new antiandrogen casodex (Bicalutamide) with eulexin (Flutamide) in combination with luteinizing hormone releasing hormone analogue (LHRH-A) therapy.	1995	Publication type not of interest
506	Hussain, M., et al.	Intermittent (IAD) versus continuous androgen deprivation (CAD) in hormone sensitive metastatic prostate cancer (HSM1PC) patients (pts): results of S9346 (INT-0162), an international Phase III trial.	2012	Publication type not of interest
507	James, N. D., et al.	Celecoxib plus hormone therapy vs hormone therapy alone for hormone-sensitive prostate cancer: first results from the STAMPEDE randomized controlled trial (MRC PR08).	2011	Publication type not of interest
508	James, N. D., et al.	Celecoxib plus hormone therapy versus hormone therapy alone for hormone-sensitive prostate cancer: first results from STAMPEDE (MRC PR08, CRUK/06/019), a randomized controlled trial.	2012	Publication type not of interest
509	Smith, M. R., et al.	Efficacy and safety of zoledronic acid in men with castration-sensitive prostate cancer and bone metastases: results of CALGB 90202 (Alliance).	2013	Publication type not of interest
510	Gravis, G., et al.	Identification of prognostic groups in patients with hormone-sensitive metastatic prostate cancer at the present time: an analysis of the GETUG 15 phase III trial.	2013	Publication type not of interest
511	Sweeney, C., et al.	Impact on overall survival (OS) with chemo-hormonal therapy versus hormonal therapy for hormone-sensitive newly metastatic prostate cancer (MPRCA): an ECOG-led phase iii randomized trial.	2014	Publication type not of interest
512	Vogelzang, N. J., et al.	A randomized double-blind trial in 813 previously untreated metastatic prostate cancer (CaP) patients (pts) comparing a new antiandrogen Casodex (bicalutamide) with Eulexin (flutamide) in combination with luteinizing hormone releasing hormone analog (LHRH-a) therapy.	1995	Publication type not of interest
513	Kamba, T., et al.	A Pphase III, multicenter, randomized, controlled study of maximum androgen blockade with versus without zoledronic acid in treatment-naive prostate cancer patients with bone metastases: results of ZAPCA study.	2015	Publication type not of interest

514	Schellhammer, P. F., et al.	Updated results of a randomized, double-blind trial in 813 previously untreated metastatic prostate cancer (CaP) patients (pts) comparing the antiandrogens CASODEX (bicalutamide) and EULEXIN (flutamide) in combination with luteinizing hormone releasing hormone analogue (LHRH-A) therapy.	1996	Publication type not of interest
515	De Conti, P., et al.	Intermittent versus continuous androgen suppression for prostatic cancer.	2007	Publication type not of interest
516	Kunath F, et al.	Early versus deferred standard androgen suppression therapy for advanced hormone-sensitive prostate cancer.	2019	Publication type not of interest
517	Boegemann M.	Enzalutamide-new option in metastatic castration-sensitive prostate cancer? preliminary results of a randomized phase III trial (ENZAMET)	2020	Publication type not of interest
518	Kumar G.	TITAN trial; Shifting focus from hormone-refractory to hormone-sensitive prostate cancer	2020	Publication type not of interest
519	Mori K.	Re: Cabazitaxel Versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer	2020	Publication type not of interest
520	Roviello G.	Treating De Novo Metastatic Castration-Sensitive Prostate Cancer With Visceral Metastases: An Evolving Issue	2020	Publication type not of interest
521	Feyerabend, S., et al.	Survival benefit, disease progression and quality-of-life outcomes of abiraterone acetate plus prednisone versus docetaxel in metastatic hormone-sensitive prostate cancer: A network meta-analysis.	2018	SLR/NMA
522	Gravis, G., et al.	Burden of Metastatic Castrate Naive Prostate Cancer Patients, to Identify Men More Likely to Benefit from Early Docetaxel: Further Analyses of CHAARTED and GETUG-AFU15 Studies.	2018	SLR/NMA
523	Vale, C. L., et al.	What is the optimal systemic treatment of men with metastatic, hormone-naive prostate cancer? A STOPCAP systematic review and network meta-analysis.	2018	SLR/NMA
524	Rydzewska, L. H. M., et al.	Adding abiraterone to androgen deprivation therapy in men with metastatic hormone-sensitive prostate cancer: A systematic review and meta-analysis.	2017	SLR/NMA
525	Ramos-Esquivel, A., et al.	Androgen-deprivation therapy plus chemotherapy in metastatic hormone-sensitive prostate cancer. A systematic review and meta-analysis of randomized clinical trials.	2016	SLR/NMA
526	Tassinari, D., et al.	Early docetaxel and androgen deprivation in the treatment of metastatic, hormone-sensitive prostate cancer.	2016	SLR/NMA

527	Sciarra, A., et al.	A meta-analysis and systematic review of randomized controlled trials with degarelix versus gonadotropin-releasing hormone agonists for advanced prostate cancer.	2016	SLR/NMA
528	Scailteux, L. M., et al.	Mortality, cardiovascular risk, and androgen deprivation therapy for prostate cancer: A systematic review with direct and network meta-analyses of randomized controlled trials and observational studies.	2016	SLR/NMA
529	Botrel, T. E. A., et al.	Efficacy and safety of combined androgen deprivation therapy (ADT) and docetaxel compared with ADT alone for metastatic hormone-naive prostate cancer: A systematic review and meta-analysis.	2016	SLR/NMA
530	Tucci, M., et al.	Addition of docetaxel to androgen deprivation therapy for patients with hormone-sensitive metastatic prostate cancer: A systematic review and meta-analysis.	2016	SLR/NMA
531	Vale, C. L., et al.	Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: A systematic review and meta-analyses of aggregate data.	2016	SLR/NMA
532	Lei, J. H., et al.	Androgen-deprivation therapy alone versus combined with radiation therapy or chemotherapy for nonlocalized prostate cancer: A systematic review and meta-analysis.	2016	SLR/NMA
533	Sathianathen, N. J., et al.	Taxane-based chemo-hormonal therapy for metastatic hormone-sensitive prostate cancer.	2018	SLR/NMA
534	Sun, G., et al.	What kind of patients with castration-naive prostate cancer can benefit from upfront docetaxel and abiraterone: A systematic review and a network meta-analysis.	2018	SLR/NMA
535	Tan, P. S., et al.	Addition of abiraterone, docetaxel, bisphosphonate, celecoxib or combinations to androgen-deprivation therapy (ADT) for metastatic hormone-sensitive prostate cancer (mHSPC): a network meta-analysis.	2018	SLR/NMA
536	Kassem, L., et al.	Abiraterone acetate/androgen deprivation therapy combination versus docetaxel/androgen deprivation therapy combination in advanced hormone-sensitive prostate cancer: a network meta-analysis on safety and efficacy.	2018	SLR/NMA

537	Wallis, C. J. D., et al.	Comparison of Abiraterone Acetate and Docetaxel with Androgen Deprivation Therapy in High-risk and Metastatic Hormone-naive Prostate Cancer: A Systematic Review and Network Meta-analysis.	2018	SLR/NMA
538	Burdett, S., et al.	Prostate Radiotherapy for Metastatic Hormone-sensitive Prostate Cancer: A STOPCAP Systematic Review and Meta-analysis.	2019	SLR/NMA
539	Zhang, Q., et al.	Different therapeutic regimens in the treatment of metastatic prostate cancer by performing a Bayesian network meta-analysis.	2019	SLR/NMA
540	Sun, G., et al.	Androgen deprivation therapy with chemotherapy or abiraterone for patients with metastatic hormone-naive prostate cancer: A systematic review and meta-analysis.	2019	SLR/NMA
541	Yang, Y., et al.	Efficacy and safety of combined androgen blockade with antiandrogen for advanced prostate cancer.	2019	SLR/NMA
542	Dizdar, O., et al.	Gleason score and docetaxel response in advanced hormone-sensitive prostate cancer: The lower the better.	2019	SLR/NMA
543	Landre, T., et al.	Is There a Benefit of Addition Docetaxel, Abiraterone, Celecoxib, or Zoledronic Acid in Initial Treatments for Patients Older Than 70 Years With Hormone-sensitive Advanced Prostate Cancer? A Meta-analysis.	2019	SLR/NMA
544	Chen, J., et al.	The effect of additional chemotherapy on high-risk prostate cancer: A systematic review and meta-analysis.	2018	SLR/NMA
545	Rashid, M., et al.	Efficacy and safety of Nilutamide in patients with metastatic prostate cancer who underwent orchiectomy: A systematic review and meta-analysis.	2019	SLR/NMA
546	Anderson, D., et al.	Cost effectiveness of GnRH antagonists in patients with prostate cancer and cardiovascular risk: Comparative analysis against Leuprorelin by the Number Needed to Treat.	2017	Non-English
547	Namiki, S., et al.	Quality of life following endocrine therapy for advanced prostate cancer: A comparative study between LH-RH agonist 1-month depot and 3-month depot.	2008	Non-English
548	Botto, H., et al.	Multicentre randomized trial comparing triptorelin medical castration versus surgical castration in the treatment of locally advanced or metastatic prostate cancer.	2007	Non-English
549	Zerbib, M., et al.	Effectiveness and tolerance of three month sustained release leuprorelin in the treatment of metastatic prostatic cancer (comparative, randomized, multicentric study.)	1997	Non-English

550	Fujii, A., et al.	Treatment for newly diagnosed stage D2 prostatic carcinoma with hormonal therapy alone, or chemotherapy agents in combination with hormones.	1991	Non-English
551	Knonagel, H., et al.	Therapy of metastatic prostate carcinoma: Orchiectomy and Anandron versus orchiectomy and placebo. Preliminary results of a randomized multicenter study.	1989	Non-English
552	Pavone-Macaluso, M., et al.	Medroxyprogesterone acetate, diethylstilboestrol and cyproterone acetate in the treatment of prostatic cancer. Interim report of a protective randomized study of the EORTC genito-urinary tract cooperative group.	1982	Non-English
553	Kondo, I., et al.	Combination therapy with estrogen and UFT in newly diagnosed prostatic cancer (poorly differentiated, stage D2). Hinyokika kiyo.	1996	Non-English
554	Haefliger, J. M., et al.	Randomized study comparing Zoladex versus Zoladex plus flutamide in treatment of advanced cancer of the prostate.	1992	Non-English
555	Knönagel, H., et al.	Therapy of metastatic prostatic cancer by orchiectomy plus Anandron versus orchiectomy plus placebo. Initial results of a randomized multicenter study.	1989	Non-English
556	Selvaggi, F. P., et al.	Goserelin depot versus Goserelin depot plus flutamide in the treatment of advanced prostate carcinoma. Results of a randomized international multicentric study.	1992	Non-English
557	Kondo, I., et al.	Combination therapy with estrogen and UFT® in newly diagnosed prostatic cancer (poorly differentiated, stage D2).	1996	Non-English
558	Sakai, H., et al.	Randomized trial of chemo-endocrine therapy versus endocrine therapy alone in newly diagnosed patients with advanced prostate cancer.	1999	Non-English
559	Leitenberger, A., et al.	Goserelin acetate (Zoladex) versus goserelin acetate plus flutamide (Fugerel) in advanced prostatic carcinoma: a phase III-trial.	1990	Non-English
560	Kotake, T., et al.	Clinical early phase II study of bicalutamide (Casodex®) in patients with prostatic cancer.	1996	Non-English
561	Knonagel, H., et al.	Therapy of metastatic prostate carcinoma: orchiectomy and Anandron versus orchiectomy and placebo. Preliminary results of a randomized multicenter study.	1989	Non-English
562	Crook, J. M., et al.	Twenty-four-month post-radiation prostate biopsies are strongly predictive of 7-year disease-free survival.	2009	Duplicate

563	Dijkman, G. A., et al.	A randomized trial comparing the safety and efficacy of the Zoladex 10.8 mg depot, administered every 12 weeks, to that of the Zoladex 3.6 mg depot, administered every 4 weeks, in patients with advanced prostate cancer.	1995	Duplicate
564	Aro, J. L. V., et al.	High dose polyoestradiol phosphate with and without acetosalicylic acid versus orchiectomy in the treatment of prostatic cancer.	1989	Duplicate
565	Emtage, L. A., et al.	Interim report of a randomized trial comparing Zoladex 3.6 mg depot with diethylstilbestrol 3 mg/day in advanced prostate cancer. The West Midlands Urology Research Group.	1988	Duplicate
566	Boccardo, F., et al.	Goserelin acetate with or without flutamide in the treatment of patients with locally advanced or metastatic prostate cancer. The Italian Prostatic Cancer Project (PONCAP) Study Group.	1993	Duplicate
567	Duchesne, G. M., et al.	Timing of androgen-deprivation therapy in patients with prostate cancer with a rising PSA (TROG 03.06 and VCOG PR 01-03): a randomized, multicentre, non-blinded, phase 3 trial.	2016	Duplicate
568	Kotake, T., et al.	LH-RH agonist, Zoladex (Goserelin), depot formulation in the treatment of prostatic cancer. Randomized dose-finding trial in Japan.	1988	Duplicate
569	Fernandez del Moral, P., et al.	Three-month depot of goserelin acetate: clinical efficacy and endocrine profile. Dutch South East Cooperative Urological Group.	1996	Duplicate
570	Berruti, A., et al.	Osteoblastic flare assessed by serum alkaline phosphatase activity is an index of short duration of response in prostate cancer patients with bone metastases submitted to systemic therapy. Gruppo Onco Urologico Piemontese (G.O.U.P).	1997	Duplicate
571	Denis, L., et al.	Orchidectomy versus Zoladex® plus Eulexin® in patients with metastatic prostate cancer (EORTC 30853).	1990	Duplicate
572	Okegawa, T., et al.	Zoledronic acid improves clinical outcomes in patients with bone metastatic hormone-naive prostate cancer in a multicenter clinical trial.	2014	Duplicate
573	Kunath, F., et al.	Non-steroidal antiandrogen monotherapy compared with luteinising hormone–releasing hormone agonists or surgical castration monotherapy for advanced prostate cancer.	2014	Duplicate
574	Vaishampayan U., et al.	Randomized trial of enzalutamide versus bicalutamide in combination with androgen deprivation in metastatic hormone sensitive prostate cancer: a Prostate Cancer Clinical Trials Consortium trial.	2018	Duplicate

575	Fizazi K., et al.	Abiraterone acetate (AA) plus prednisone (P) 5 mg QD in metastatic castration-naive prostate cancer (mCNPC): detailed safety analyses from the LATITUDE phase 3 trial.	2018	Duplicate
576	Palmbos P., et al.	Cotargeting AR signaling and cell cycle: a randomized phase II study of androgen deprivation therapy with or without palbociclib in RB-positive metastatic hormone sensitive prostate cancer (mHSPC).	2018	Duplicate
577	Matsubara N.	Correlation of Prostate-specific Antigen Kinetics with Overall Survival and Radiological Progression-free Survival in Metastatic Castration-sensitive Prostate Cancer Treated with Abiraterone Acetate plus Prednisone or Placebos Added to Androgen Deprivation Therapy: Post Hoc Analysis of Phase 3 LATITUDE Study	2020	Duplicate
578	A.S. Bjartell	Apalutamide APA for metastatic castration-sensitive prostate cancer mCSPC in TITAN: outcomes in patients pts with de novo D1 mCSPC vs progression to mCSPC after localized disease D0 at diagnosis	2020	Duplicate
579	Ozguroglu M	Apalutamide APA for metastatic castration-sensitive prostate cancer mCSPC in TITAN: outcomes in patients pts with low- and high-risk disease	2020	Duplicate
580	Stenzl A	ARCHES: efficacy of androgen deprivation therapy ADT with enzalutamide ENZA or placebo PBO in metastatic hormone-sensitive prostate cancer mHSPC by prior local and systemic treatment	2020	Duplicate
581	Saad F	A drug safety evaluation of enzalutamide to treat advanced prostate cancer.	2021	Publication type not of interest
582	Smith K.R.	Clinical Outcomes and Racial Disparities in Metastatic Hormone-Sensitive Prostate Cancer in the Era of Novel Treatment Options.	2021	Study design not of interest
583	Cone E.B.	Cardiovascular toxicities associated with abiraterone compared to enzalutamide-A pharmacovigilance study.	2021	Study design not of interest

584	Okamoto T.	Impact of pretreatment anemia on upfront abiraterone acetate therapy for metastatic hormone-sensitive prostate cancer: a multicenter retrospective study.	2021	Study design not of interest
585	Li E.V.	Efficacy and Adverse Events of Docetaxel for Metastatic, Hormone-sensitive Prostate Cancer Among Elderly Men: A Post Hoc Analysis of the CHAARTED Trial.	2021	Outcomes not of interest
586	Alsubait S.	Oral Relugolix Yields Superior Testosterone Suppression and Decreased Cardiovascular Events Compared with GnRH Agonist.	2020	Population not of interest
587	Coelingh Bennink H.J.T.	Estetrol Cotreatment of Androgen Deprivation Therapy in Infiltrating or Metastatic, Castration-sensitive Prostate Cancer: A Randomized, Double-blind, Phase II Trial (PCombi).	2021	Population not of interest
588	Ali A.	Association of Bone Metastatic Burden with Survival Benefit from Prostate Radiotherapy in Patients with Newly Diagnosed Metastatic Prostate Cancer: A Secondary Analysis of a Randomized Clinical Trial.	2021	Intervention not of interest
589	Langley R.E.	Transdermal oestradiol for androgen suppression in prostate cancer: long-term cardiovascular outcomes from the randomised Prostate Adenocarcinoma Transcutaneous Hormone (PATCH) trial programme.	2021	Population not of interest
590	Galvao D.A.	Psychological distress in men with prostate cancer undertaking androgen deprivation therapy: modifying effects of exercise from a year-long randomized controlled trial.	2021	Intervention not of interest
591	Cirne F.	THE CARDIOVASCULAR EFFECTS OF GNRH ANTAGONISTS IN MEN WITH PROSTATE CANCER.	2021	Study design not of interest
592	Ali A.	The Automated Bone Scan Index as a Predictor of Response to Prostate Radiotherapy in Men with Newly Diagnosed Metastatic Prostate Cancer: An Exploratory Analysis of STAMPEDE's "M1, RT Comparison".	2020	Intervention not of interest

593	Shore N.	A phase 3, open-label, multicenter study of a 6-month pre-mixed depot formulation of leuprolide mesylate in advanced prostate cancer patients.	2020	Study design not of interest
594	Sathianathen NJ	Abiraterone acetate in combination with androgen deprivation therapy compared to androgen deprivation therapy only for metastatic hormone-sensitive prostate cancer.	2020	Study design not of interest
595	Shore N	Major adverse cardiovascular events: number needed to treat analysis for the phase 3 randomized controlled trial (HERO) of relugolix versus current standard of care (leuprolide) in men with advanced prostate cancer	2020	Population not of interest
596	George D	Impact of concomitant prostate cancer therapy on efficacy and safety of relugolix versus leuprolide in men with advanced prostate cancer: subgroup analysis from the phase III HERO study	2021	Population not of interest
597	Soares A	Health-related quality-of-life (HRQoL) analysis from a randomized phase II trial of androgen signaling inhibitors with or without androgen deprivation therapy (ADT) for castrationsensitive prostate cancer: LACOG 0415	2021	Population not of interest
598	Brausi M	Intermittent androgen blockade can be a therapeutic option in patients with locally advanced and metastatic prostate cancer: long-term results from a pooled analysis of 2 prospective randomised trials (9401-9901) from SEUG (South European Uro-Onco Group)	2020	Population not of interest
599	Lage D	Outcomes of older men receiving docetaxel for metastatic hormonesensitive prostate cancer	2021	Outcomes not of interest
600	Chi K	Androgen receptor (AR) and non-AR aberrations associated with outcomes in metastatic castration-sensitive prostate cancer (mCSPC) treated with apalutamide (APA) plus androgen deprivation therapy (ADT) in TITAN	2020	Outcomes not of interest
601	Park H	Combined androgen blockade (CAB) versus luteinizing hormone-releasing hormone (LHRH) agonist monotherapy for androgen deprivation therapy	2020	Population not of interest

602	Merseburger A	TITAN study: evaluation of apalutamide in patients with metastatic hormone-sensitive prostate cancer - Treatment of metastatic hormone-sensitive prostate cancer (mHSPC)	2020	Non-English
603	Zahirovic D	Hormonal therapy of prostate cancer	2020	Publication type not of interest
604	Lara P	Bone metabolism biomarkers (BMB) and progression-free survival (PFS) in men with metastatic hormone-sensitive prostate cancer (HSPC): SWOG S1216, a phase III trial of androgen deprivation therapy (ADT) with or without orteronel	2020	Outcomes not of interest
605	Maluf F	Phase II randomized study of abiraterone acetate plus prednisone (AAP) added to ADT versus apalutamide alone (APA) versus AAP+APA in patients with advanced prostate cancer with noncastrate testosterone levels: (LACOG 0415)	2020	Population not of interest
606	Barata P	Early PSA decline as a predictor of progression in patients with metastatic castration-naive prostate cancer (mCNPC) treated with abiraterone acetate and prednisone (AA/P)	2020	Study design not of interest
607	Kyriakopoulos C	Multicenter Phase 1 Trial of a DNA Vaccine Encoding the Androgen Receptor Ligand Binding Domain (pTVG-AR, MVI-118) in Patients with Metastatic Prostate Cancer	2020	Intervention not of interest
608	Boeve L	The effect on quality of life of androgen deprivation therapy (ADT) combined with local external prostate radiotherapy in patients with primary metastatic prostate cancer, results from the HORRAD trial	2020	Outcomes not of interest
609	Heidenreich A	Oncological and functional outcomes of cytoreductive radical prostatectomy (cRP) in men with metastatic hormone-naive prostate cancer (mhnPCA)	2020	Intervention not of interest

Appendix B Main characteristics of included studies

Trial name: CHAARTED	NCT number: NCT00309985
Objective	*Evaluate the ability of early chemotherapy to improve overall survival of patients commencing androgen deprivation for metastatic prostate cancer.*
Publications – title, author, journal, year	*Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, Wong YN, Hahn N, Kohli M, Cooney MM, Dreicer R, Vogelzang NJ, Picus J, Shevrin D, Hussain M, Garcia JA, DiPaola RS. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. N Engl J Med. 2015 Aug 20;373(8):737-46. doi: 10.1056/NEJMoa1503747. Epub 2015 Aug 5.* *Martini A, Pfail J, Montorsi F, Galsky MD, Oh WK. Surrogate endpoints for overall survival for patients with metastatic hormone-sensitive prostate cancer in the CHAARTED trial. Prostate Cancer Prostatic Dis. 2020 Dec;23(4):638-645. doi: 10.1038/s41391-020-0231-5. Epub 2020 Apr 20.* *Morgans AK, Chen YH, Sweeney CJ, Jarrard DF, Plimack ER, Gartrell BA, Carducci MA, Hussain M, Garcia JA, Cella D, DiPaola RS, Patrick-Miller LJ. Quality of Life During Treatment With Chemohormonal Therapy: Analysis of E3805 Chemohormonal Androgen Ablation Randomized Trial in Prostate Cancer. J Clin Oncol. 2018 Apr 10;36(11):1088-1095. doi: 10.1200/JCO.2017.75.3335. Epub 2018 Mar 9.* *Kyriakopoulos CE, Chen YH, Carducci MA, Liu G, Jarrard DF, Hahn NM, Shevrin DH, Dreicer R, Hussain M, Eisenberger M, Kohli M, Plimack ER, Vogelzang NJ, Picus J, Cooney MM, Garcia JA, DiPaola RS, Sweeney CJ. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer: Long-Term Survival Analysis of the Randomized Phase III E3805 CHAARTED Trial. J Clin Oncol. 2018 Apr 10;36(11):1080-1087. doi: 10.1200/JCO.2017.75.3657. Epub 2018 Jan 31.* *Harshman LC, Chen YH, Liu G, Carducci MA, Jarrard D, Dreicer R, Hahn N, Garcia JA, Hussain M, Shevrin D, Eisenberger M, Kohli M, Plimack ER, Cooney M, Vogelzang NJ, Picus J, Dipaola R, Sweeney CJ; ECOG-ACRIN 3805 Investigators. Seven-Month Prostate-Specific Antigen Is Prognostic in Metastatic Hormone-Sensitive Prostate Cancer Treated With Androgen Deprivation With or Without Docetaxel. J Clin Oncol. 2018 Feb 1;36(4):376-382. doi: 10.1200/JCO.2017.75.3921. Epub 2017 Dec 20.* *Scott E. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, Wong YN, Hahn N, Kohli M, Cooney MM, Dreicer R, Vogelzang NJ, Picus J, Shevrin D, Hussain M, Garcia JA, DiPaola RS. Department of Medicine; Department of Biostatistics and Computational Biology; Dana-Farber Cancer Institute, Boston; Harvard Medical School, Boston; Johns Hopkins University, Baltimore; University of Wisconsin Carbone Cancer Center; School of Medicine and Public Health; Madison; Fox Chase Cancer Center, Temple University Health System, Philadelphia; Indiana University Melvin and Bren Simon Cancer Center, Indianapolis; Mayo Clinic, Rochester, MN; University Hospitals Case Medical Center, Seidman Cancer Center; Cleveland Clinic Taussig Cancer Institute; Both in Cleveland; University of Virginia Cancer Center, Charlottesville; Comprehensive Cancer Centers of Nevada, Las Vegas; Siteman Cancer Center, Washington University School of Medicine, St. Louis; NorthShore University Health System, Evanston, IL; University of Michigan Comprehensive Cancer Center, Ann Arbor; Rutgers Cancer Institute of New Jersey, New Brunswick.N Engl J Med. 2015 Aug 20;373(8):737-46. [Epub 2015 Aug 5]. doi: 10.1056/NEJMoa1503747. Urol Oncol. 2017 Mar;35(3):123. doi: 10.1016/j.urolonc.2016.12.021. Epub 2017 Feb 1.*

Trial name: CHAARTED		NCT number: NCT00309985
Study type and design	*Interventional* *Phase 3* *Allocation: Randomized* *Intervention Model: Parallel Assignment* *Masking: None (Open Label)* *Status: Ongoing*	
Sample size (n)	*790*	

Main inclusion and exclusion criteria	*Inclusion Criteria:*
	Histologically or cytologically confirmed prostate cancer
	Metastatic disease
	On androgen-deprivation therapy for < 120 days
	Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2
	PS 2 eligible only if decline in PS is due to metastatic prostate cancer
	Absolute neutrophil count ≥ 1,500/mm^3
	Platelet count ≥ 100,000/mm^3
	Bilirubin ≤ upper limit of normal (ULN)
	Alanine aminotransferase (ALT) ≤ 2.5 times ULN
	Creatinine clearance ≥ 30 mL/min
	Prothrombin time (PT) and international normalized ratio (INR) ≤ 1.5 times ULN (unless on therapeutic anticoagulation)
	Partial thromboplastin time (PTT) ≤ 1.5 times ULN (unless on therapeutic anticoagulation)
	Fertile patients must use effective contraception
	At least 4 weeks since prior major surgery and recovered from all toxicity prior to randomization
	Prior adjuvant or neoadjuvant hormonal therapy allowed provided the following are true:
	Therapy was discontinued ≥ 12 months ago AND there is no evidence of disease, as defined by 1 of the following:
	PSA < 0.1 ng/dL after prostatectomy plus hormonal therapy
	PSA < 0.5 ng/dL and has not doubled above nadir after radiotherapy plus hormonal therapy
	Therapy lasted no more than 24 months
	Last depot injection must have expired by the 24-month mark
	Prior palliative radiotherapy allowed if commenced within 30 days before starting androgen deprivation
	Anti-androgen therapy allowed as single-agent therapy ≤ 7 days before medial castration to prevent flare
	More than 30 days (or 6 half-lives) (whichever is longer) since prior participation in another clinical trial
	Concurrent participation in nontherapeutic trials allowed
	Concurrent antiandrogen therapy (e.g., bicalutamide or flutamide) allowed, but not as sole hormonal therapy
	Exclusion Criteria:

Trial name: CHAARTED	NCT number: NCT00309985
	Prostate-specific antigen (PSA) level has risen and met criteria for progression from its lowest point between the start of androgen-deprivation therapy and randomization *Prior malignancy in the past 5 years except for basal cell or squamous cell carcinoma of the skin* *Other malignancies that are considered to have low potential to progress (e.g., grade 2, T1a transitional cell carcinoma) may be allowed if approved by study chair* *Peripheral neuropathy > grade 1* *History of severe hypersensitivity reaction to docetaxel or other drugs formulated with polysorbate 80* *Active cardiac disease, including the following:* *Active angina* *Symptomatic congestive heart failure* *Myocardial infarction within the past 6 months* *Prior chemotherapy in adjuvant or neoadjuvant setting* *Prior hormone therapy in the metastatic setting* *Concurrent 5-alpha reductase inhibitors* *Simultaneous enrollment on Cancer and Leukemia Group B (CALGB) 90202*
Intervention	*Experimental: Androgen-Deprivation Therapy and Docetaxel* *Patients receive androgen-deprivation therapy (including luteinizing hormone-releasing hormone [LHRH] agonist therapy, LHRH antagonist therapy, or surgical castration). Patients also receive docetaxel IV over 1 hour on day 1. Treatment with docetaxel repeats every 21 days for up to 6 courses in the absence of disease progression or unacceptable toxicity.* *Interventions:* *Drug: androgen-deprivation therapy* *Drug: docetaxel* *(N=397)*
Comparator(s)	*Active Comparator: Androgen-Deprivation Therapy alone* *Patients receive androgen-deprivation therapy (including luteinizing hormone-releasing hormone [LHRH] agonist therapy, LHRH antagonist therapy, or surgical castration) alone.* *Intervention: Drug: androgen-deprivation therapy* *(N=393)*
Follow-up time	*Median follow-up: 53.7 months*
Is the study used in the health economic model?	*Yes*

Primary, secondary and exploratory endpoints	***Primary endpoint:*** *Overall Survival [Time Frame: Assessed every 3 months if patient is < 2 years from study entry; every 6 months if patient is 2 - 5 years from study entry; then annually if patient is 5 - 10 years from study entry]* *Overall survival is defined as the time from randomization to death or date last known alive.* ***Secondary endpoints:*** *Time to Clinical Progression [Time Frame: Assessed every 3 months if patient is < 2 years from study entry; every 6 months if patient is 2 - 5 years from study entry; then annually if patient is 5 - 10 years from study entry]* *Time to clinical progression is defined as the time from randomization to clinical progression. Clinical progression is defined as increasing symptomatic bone metastases, progression per Response Evaluation Criteria In Solid Tumors (RECIST) criteria or clinical deterioration due to cancer per investigator's opinion. Patients without documented clinical progression were censored at the date of last disease assessment. Secondary endpoint data reflect the database as of December 23, 2014.* *Time to Castration Resistant Prostate Cancer (Hormone Refractory Disease) [Time Frame: Assessed every 3 months if patient is < 2 years from study entry; every 6 months if patient is 2 - 5 years from study entry; then annually if patient is 5 - 10 years from study entry]* *Time to castration resistant prostate cancer is defined as the time from randomization to PSA progression or clinical progression, whichever occurred first. Patients without documented progression were censored at the date of last disease assessment. Secondary endpoint data reflect the database as of December 23, 2014.* *Proportion of Patients With PSA Complete Response (CR) at 6 Months [Time Frame: Assessed at 6 months]* *PSA CR is defined as a PSA level less than 0.2 ng/ml measured for 2 consecutive measurements at least 4 weeks apart. Patients who met the criterion of PSA CR and had PSA level less than 0.2 ng/ml before and after the 6-month time point are considered as having a PSA CR at 6 months.* *Proportion of Patients With PSA Complete Response (CR) at 12 Months [Time Frame: Assessed at 12 months]* *PSA CR is defined as a PSA level less than 0.2 ng/ml measured for 2 consecutive measurements at least 4 weeks apart. Patients who met the criterion of PSA CR and had PSA level less than 0.2 ng/ml before and after the 12-month time point are considered as having a PSA CR at 12 months.* *QOL Change From Baseline to 3 Months [Time Frame: Assessed at baseline and 3 months]* *The primary QOL change was evaluated by the Functional Assessment of Cancer Therapy - Prostate (FACT-P) instrument. FACT-P is a self-report measure of both general and disease-specific QOL. Higher scores represent better QOL. The FACT-P (version 4) contains 39 likert items distributed over 5 subscales: physical (7 items), social/family (7 items), emotional (6 items), and functional (7 items) well-being, and the additional concerns related to prostate cancer scale (12 items). The FACT-P total score is calculated by summing all these 5 subscales and ranges from 0 to 156.* **Endpoints included in this application:** *Overall Survival.*

Trial name: CHAARTED	NCT number: NCT00309985
Method of analysis	*Kaplan–Meier estimates were used for event-time distributions. Cox proportional-hazard model were used to estimate hazard ratios for time-to-event end points. Stratified log-rank tests were used to compare event-time distributions between the two groups. Response rates were compared with the use of Fisher's exact test. An intention-to-treat analysis was conducted that included all randomly assigned patients regardless of eligibility and treatment status.*
Subgroup analyses	*None relevant to this submission.*
Other relevant information	

Trial name: GETUG-AFU15	NCT number: NCT00104715
Objective	*This randomized phase III trial is studying hormone therapy and docetaxel to see how well they work compared to hormone therapy alone in treating patients with metastatic prostate cancer.*

Trial name: GETUG-AFU15	NCT number: NCT00104715

Publications – title, author, journal, year	*Gravis G, Fizazi K, Joly F, et al.: Safety results from a phase III trial comparing androgen-deprivation therapy (ADT) plus docetaxel versus ADT alone in hormone-naïve metastatic prostate cancer (GETUG-AFU 15/0403). [Abstract] 2010 Genitourinary Cancers Symposium, March 5-7, 2010, San Francisco, California. A-43, 2010.* *Gravis G, Fizazi K, Joly F, et al.: Randomized phase III study comparing docetaxel and androgen deprivation therapy (ADT) versus ADT alone in androgen dependent metastatic prostate cancer (GETUG-15/0403): a French national muticentric study sponsored by the French Federation des Centres. [Abstract] American Society of Clinical Oncology 2007 Prostate Cancer Symposium, 22-24 February 2007, Orlando, FL. A-161, 2007.* *Campillo-Gimenez B, Buscail C, Zekri O, Laguerre B, Le Prisé E, De Crevoisier R, Cuggia M. Improving the pre-screening of eligible patients in order to increase enrollment in cancer clinical trials. Trials. 2015 Jan 16;16:15. doi: 10.1186/s13063-014-0535-7.* *Trump DL. Commentary on "Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial." Gravis G, Fizazi K, Joly F, Oudard S, Priou F, Esterni B, Latorzeff I, Delva R, Krakowski I, Laguerre B, Rolland F, Théodore C, Deplanque G, Ferrero JM, Pouessel D, Mourey L, Beuzeboc P, Zanetta S, Habibian M, Berdah JF, Dauba J, Baciuchka M, Platini C, Linassier C, Labourey JL, Machiels JP, El Kouri C, Ravaud A, Suc E, Eymard JC, Hasbini A, Bousquet G, Soulie M, Medical Oncology and Biostatistics, Institut Paoli-Calmettes, Marseille, France. Lancet Oncol 2013;14(2):149-58 [Epub 2013 Jan 8]. Urol Oncol. 2013 Nov;31(8):1845. doi: 10.1016/j.urolonc.2013.08.011.* *Gravis G, Fizazi K, Joly F, Oudard S, Priou F, Esterni B, Latorzeff I, Delva R, Krakowski I, Laguerre B, Rolland F, Théodore C, Deplanque G, Ferrero JM, Pouessel D, Mourey L, Beuzeboc P, Zanetta S, Habibian M, Berdah JF, Dauba J, Baciuchka M, Platini C, Linassier C, Labourey JL, Machiels JP, El Kouri C, Ravaud A, Suc E, Eymard JC, Hasbini A, Bousquet G, Soulie M. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013 Feb;14(2):149-58. doi: 10.1016/S1470-2045(12)70560-0. Epub 2013 Jan 8.* *Huang X, Chau CH, Figg WD. Challenges to improved therapeutics for metastatic castrate resistant prostate cancer: from recent successes and failures. J Hematol Oncol. 2012 Jul 2;5:35. doi: 10.1186/1756-8722-5-35. Review.*
Study type and design	*Interventional* *Phase 3* *Allocation: Randomized* *Intervention Model: Parallel Assignment* *Masking: None (Open Label)*
Sample size (n)	*385*

Main inclusion and exclusion criteria	*Ages Eligible for Study:*	*18 Years to 120 Years (Adult, Older Adult)*
	Sexes Eligible for Study:	*Male*
	Accepts Healthy Volunteers:	*No*

Criteria

DISEASE CHARACTERISTICS:

Histologically confirmed prostate adenocarcinoma

Metastatic disease

Measurable or evaluable disease

No brain metastases

PATIENT CHARACTERISTICS:

Age

18 and over

Performance status

ECOG 0-2

Life expectancy

At least 3 months

Hematopoietic

WBC ≥ 2,000/mm^3

Absolute neutrophil count ≥ 1,000/mm^3

Platelet count ≥ 100,000/mm^3

Hepatic

Bilirubin ≤ 1.5 times upper limit of normal (ULN) (2.5 times normal if hepatic metastases are present)

AST and ALT ≤ 1.5 times ULN (2.5 times normal if hepatic metastases are present)

Renal

Creatinine ≤ 150 µmol/L

Cardiovascular

No symptomatic coronary disease

No congenital cardiac insufficiency

No New York Heart Association class III or IV cardiovascular disease

	No other severe cardiovascular disease *Other* *No severe peripheral neuropathy* *No active infection* *No other malignancy within the past 5 years except basal cell skin cancer* *No familial, social, geographical, or psychological situation that would preclude study compliance and follow-up* *No other serious disease that would preclude study participation* *PRIOR CONCURRENT THERAPY:* *Biologic therapy* *Not specified* *Chemotherapy* *No prior chemotherapy for metastatic prostate cancer* *Prior chemotherapy allowed provided all of the following are true:* *Chemotherapy was completed > 1 year ago* *Prostate-specific antigen level has remained stable* *No development of metastases within 1 year after completion of chemotherapy* *Endocrine therapy* *Prior hormonal therapy within the past 2 months allowed for metastatic prostate cancer* *Radiotherapy* *More than 4 weeks since prior radiotherapy to metastatic sites* *Surgery* *No prior surgical castration* *Other* *No other concurrent investigational drugs*
Intervention	*Docetaxel (75 mg/m(2) intravenously on the first day of each 21-day cycle; up to nine cycles) + ADT (orchiectomy or luteinising hormone-releasing hormone agonists, alone or combined with non-steroidal antiandrogens)* *(N=192)*

Trial name: GETUG-AFU15		NCT number: NCT00104715
Comparator(s)	*ADT (orchiectomy or luteinising hormone-releasing hormone agonists, alone or combined with non-steroidal antiandrogens)* *(N=193)*	
Follow-up time	*Median follow-up of 83.9 months*	
Is the study used in the health economic model?	*Yes*	
Primary, secondary and exploratory endpoints	***Primary (all stated as primary at clinicaltrials.gov):*** *Overall survival at 36 months* *Progression-free survival (biological progression and/or clinical progression) at 24 months* *Quality of life* *Treatment costs* *Toxicity and tolerance* *Tumor profiles of gene expression as measured by biochips with DNA and tissue microarrays* **Endpoints included in this application:** *OS, rPFS, PFS and SAE* **Other endpoints:**	
Method of analysis	*Efficacy analyses were done by intention to treat.*	
Subgroup analyses	*None relevant to this submission.*	
Other relevant information		

Trial name: HORRAD		NCT number: ISRCTN06890529
Objective	*To study the efficacy of external beam radiation therapy to the prostate in addition to standard ADT in patients with metastatic PC.*	
Publications – title, author, journal, year	*Boéve LMS et al Effect on Survival of Androgen Deprivation Therapy Alone Compared to Androgen Deprivation Therapy Combined with Concurrent Radiation Therapy to the Prostate in Patients with Primary Bone Metastatic Prostate Cancer in a Prospective Randomised Clinical Trial: Data from the HORRAD Trial. Eur Urol 2019 Mar;75(3):410-418. doi: 10.1016/j.eururo.2018.09.008. Epub 2018 Sep 25.*	

Trial name: HORRAD	NCT number: ISRCTN06890529
Study type and design	*Multicenter RCT* *Randomisation was done centrally by an independent trial office (CuraTrial). Patients were assigned in a 1:1 ratio by using a restricted blockwise randomisation (block size 6 = 2 treatments x 3 patients per treatment).* *All patients and investigators were aware of study group assignments (unblinded).*
Sample size (n)	*432*
Main inclusion and exclusion criteria	***Inclusion criteria:*** *Patients were eligible if they had a previously untreated, histologically confirmed diagnosis of* *adenocarcinoma of the prostate with any number of bone metastases on bone scintigraphy. Tumours could be of any grade (Gleason score 6–10) and T stage (cT1-cT4; cN0-cN1; M1) [11].* ***Exclusion criteria:*** *Age >80 yr; PSA <20 ng/ml; previous treatment for prostate cancer; insufficient cognitive ability to understand the study or questionnaires; and concurrent malignancies, except for basal cell carcinoma of the skin.*
Intervention	***External beam radiation therapy (EBRT) + ADT*** *ADT as described below. Within 3 mo of starting ADT, patients in the EBRT group commenced EBRT. The initial prescribed dose was 70 Gy in 35 fractions of 2 Gy, during an overall treatment time of 7 wk. During the study period, an optional schedule was added that was considered biologically equivalent and consisted of a dose schedule of 57.76 Gy in 19 fractions of 3.04 Gy, three times a week for 6 wk.*
Comparator(s)	***ADT alone:*** *An androgen receptor inhibitor (eg, bicalutamide, 50 mg once daily) for 4 wk as flare reduction and concurrent treatment with a luteinising hormone-releasing-hormone (LHRH) agonist. All patients started with an LHRH agonist 1–2 wk after randomisation*
Follow-up time	*Median follow-up of 47 months*
Is the study used in the health economic model?	*No. The HORRAD study was included to investigate the clinical efficacy and safety of EBRT+ADT compared to APA+ADT. EBRT+ADT is included in the clinical guidelines for some patients, and can be considered a relevant comparator.*
Primary, secondary and exploratory endpoints	*The **primary** outcome of the HORRAD trial was overall survival, defined as time between date of diagnosis at prostatic biopsy and date of death.* ***Secondary** oncological endpoint was time to PSA progression, defined as time between diagnosis and a PSA increase after initiation of ADT of more than 50% of the lowest PSA value after start of treatment (PSA-nadir), with a minimum of 1 ng/ml. As serum testosterone levels were not assessed accordingly, PSA progression was only an indication for castration-resistant disease.*

Trial name: HORRAD	NCT number: ISRCTN06890529
Method of analysis	*Intention-to-treat analysis was performed for all eligible randomized patients, including patients with a protocol violation. We calculated Kaplan-Meier curves with time to mortality and time to PSA progression as outcomes and used log rank tests to compare curves between treatment arms. For mortality and PSA progression, Cox proportional hazard regression analyses were applied to evaluate the treatment effect, both crude and adjusted, for several covariates: age at diagnosis, performance status, initial pain score, initial PSA, number of bone metastases (<5 lesions, 5–15 lesions, >15 lesions), Gleason sum score (7, 8, 9), and T stage (cT1-cT3).*
Subgroup analyses	*None relevant to this submission.*
Other relevant information	

Trial name: STAMPEDE	NCT number: NCT00268476
Objective	*To compare the safety and efficacy of novel therapeutic strategies against the current standard-of-care for men with high-risk locally advanced or metastatic prostate cancer starting long-term ADT for the first time*

Publications – title, author, journal, year	*Sydes MR, Parmar MK, James ND, Clarke NW, Dearnaley DP, Mason MD, Morgan RC, Sanders K, Royston P. Issues in applying multi-arm multi-stage methodology to a clinical trial in prostate cancer: the MRC STAMPEDE trial. Trials. 2009 Jun 11;10:39. doi: 10.1186/1745-6215-10-39.* *Sydes MR, Parmar MK, Mason MD, Clarke NW, Amos C, Anderson J, de Bono J, Dearnaley DP, Dwyer J, Green C, Jovic G, Ritchie AW, Russell JM, Sanders K, Thalmann G, James ND. Flexible trial design in practice - stopping arms for lack-of-benefit and adding research arms mid-trial in STAMPEDE: a multi-arm multi-stage randomized controlled trial. Trials. 2012 Sep 15;13:168. doi: 10.1186/1745-6215-13-168.* *Parker CC, Sydes MR, Mason MD, Clarke NW, Aebersold D, de Bono JS, Dearnaley DP, Ritchie AW, Russell JM, Thalmann G, Parmar MK, James ND. Prostate radiotherapy for men with metastatic disease: a new comparison in the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial. BJU Int. 2013 May;111(5):697-9. doi: 10.1111/bju.12087. Review.* *Attard G, Sydes MR, Mason MD, Clarke NW, Aebersold D, de Bono JS, Dearnaley DP, Parker CC, Ritchie AW, Russell JM, Thalmann G, Cassoly E, Millman R, Matheson D, Schiavone F, Spears MR, Parmar MK, James ND. Combining enzalutamide with abiraterone, prednisone, and androgen deprivation therapy in the STAMPEDE trial. Eur Urol. 2014 Nov;66(5):799-802. doi: 10.1016/j.eururo.2014.05.038. Epub 2014 Jun 27.* *James ND, Spears MR, Clarke NW, Dearnaley DP, De Bono JS, Gale J, Hetherington J, Hoskin PJ, Jones RJ, Laing R, Lester JF, McLaren D, Parker CC, Parmar MKB, Ritchie AWS, Russell JM, Strebel RT, Thalmann GN, Mason MD, Sydes MR. Survival with Newly Diagnosed Metastatic Prostate Cancer in the "Docetaxel Era": Data from 917 Patients in the Control Arm of the STAMPEDE Trial (MRC PR08, CRUK/06/019). Eur Urol. 2015 Jun;67(6):1028-1038. doi: 10.1016/j.eururo.2014.09.032. Epub 2014 Oct 6.* *James ND, Spears MR, Clarke NW, Dearnaley DP, Mason MD, Parker CC, Ritchie AW, Russell JM, Schiavone F, Attard G, de Bono JS, Birtle A, Engeler DS, Elliott T, Matheson D, O'Sullivan J, Pudney D, Srihari N, Wallace J, Barber J, Syndikus I, Parmar MK, Sydes MR; STAMPEDE Investigators. Failure-Free Survival and Radiotherapy in Patients With Newly Diagnosed Nonmetastatic Prostate Cancer: Data From Patients in the Control Arm of the STAMPEDE Trial. JAMA Oncol. 2016 Mar;2(3):348-57. doi: 10.1001/jamaoncol.2015.4350. Erratum in: JAMA Oncol. 2016 Feb;2(2):279.* *Gillessen S, Gilson C, James N, Adler A, Sydes MR, Clarke N; STAMPEDE Trial Management Group. Repurposing Metformin as Therapy for Prostate Cancer within the STAMPEDE Trial Platform. Eur Urol. 2016 Dec;70(6):906-908. doi: 10.1016/j.eururo.2016.07.015. Epub 2016 Jul 19.* *Gilbert DC, Duong T, Sydes M, Bara A, Clarke N, Abel P, James N, Langley R, Parmar M; STAMPEDE and PATCH Trial Management Groups. Transdermal oestradiol as a method of androgen suppression for prostate cancer within the STAMPEDE trial platform. BJU Int. 2018 May;121(5):680-683. doi: 10.1111/bju.14153. Epub 2018 Feb 28.* *Parmar MK, Barthel FM, Sydes M, Langley R, Kaplan R, Eisenhauer E, Brady M, James N, Bookman MA, Swart AM, Qian W, Royston P. Speeding up the evaluation of new agents in cancer. J Natl Cancer Inst. 2008 Sep 3;100(17):1204-14. doi: 10.1093/jnci/djn267. Epub 2008 Aug 26.* *James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Anderson J, Popert RJ, Sanders K, Morgan RC, Stansfeld J, Dwyer J, Masters J, Parmar MK. Systemic therapy for advancing or metastatic prostate cancer (STAMPEDE): a multi-arm,*

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Trial name: STAMPEDE		NCT number: NCT00268476
Study type and design	*Phase 3* *Allocation: Randomized* *Intervention Model: Parallel Assignment* *Intervention Model Description:* *Multi-arm Multi-Stage* *Masking: None (Open Label)*	
Sample size (n)	*1817 (Number of patients in the subgroup with metastatic prostate cancer at randomization)*	

Trial name: STAMPEDE	NCT number: NCT00268476

Main inclusion and exclusion criteria

Inclusion Criteria Participants must fulfil all the criteria in one of the following three categories. Additionally, all patients must fulfil the criteria in Section 4.

1. *High-Risk Newly-Diagnosed Non-Metastatic Node-Negative (N0/Nx) Disease*

   Both:

   • At least two of: T category T3/4, PSA≥40ng/ml or Gleason sum score 8-10

   • Intention to treat with radical radiotherapy (unless there is a contra-indication)

   OR

2. *Newly-Diagnosed Metastatic Or Node-Positive Disease*

   At least one of:

   - *Stage Tany N+ M0*
   - *Stage Tany Nany M+*

   OR

3. *Previously Radically Treated, Now Relapsing (Prior Radical Surgery And/or Radiotherapy)*

   At least one of:

   • PSA ≥4ng/ml and rising with doubling time less than 6 months

   • PSA ≥20ng/ml

   • N+

   • M+

   AND

4. *General Inclusion Criteria Required For All Participants*

1. *Histologically confirmed prostate adenocarcinoma*
2. *Intention to treat with long-term androgen deprivation therapy*
3. *Fit for all protocol treatment and follow up, WHO performance status 0-2*
4. *Have completed the appropriate investigations prior to randomisation*
5. *Adequate haematological function: neutrophil count ≥1.5x109/l and platelets ≥100x109/l*
6. *Adequate renal function, defined as GFR ≥30ml/min/1.73m2*
7. *Written informed consent*
8. *Willing and expected to comply with follow up schedule*
9. *Using effective contraceptive method if applicable*

Trial name: STAMPEDE	NCT number: NCT00268476
Intervention	*The STAMPEDE trial is a multi-arm study that investigates several interventions, only the interventions relevant to this application is listed.* ***Study arm C*** *Docetaxel (75 mg/m2) was given for six 3-weekly cycles with prednisolone (10 mg) daily, and standard premedication before each injection (N=362)* ***Study arm H*** *External-beam radiotherapy to the prostate was given as one of two schedules nominated before randomisation: either 36 Gy in six consecutive weekly fractions of 6 Gy,or 55 Gy in 20 daily fractions of 2·75 Gy over 4 weeks (N=1032)*
Comparator(s)	***Study arm A (Standard of Care)*** *Androgen Deprivation Therapy [ADT] as either gonadotrophin-releasing hormone agonists or antagonists or orchidectomy.*
Follow-up time	*Median follow-up 40 months – 73.5 months (Median follow-up reported for all randomised patients (standard of care [SoC], DOC + SoC, zoledronic acid [ZA] + SoC, DOC + ZA + SoC). For RT comparison (arm H), median follow-up was 37 months.*
Is the study used in the health economic model?	*Yes*

Primary, secondary and exploratory endpoints	***Primary endpoint:***
	• *Overall survival*
	Secondary endpoints
	• *Failure-free survival*
	  ○ *Report of time from initiation of treatment to the first progression event of each patient*
	• *Cost effectiveness by EuroQol*
	  ○ *Reporting the comparison of costs associated with the additional treatments provided and the survival gain attributed to the additional treatments, to SOC alone.*
	• *Quality of life (QOL) by EORTC QOL Questionnaire C30 and prostate specific 25-item*
	  ○ *Determination of changes in quality of life with interventions*
	• *Number of participants with treatment-related side effects as assessed by CTCAE v4.0*
	  ○ *Reporting the incidence, type and severity of side effects within the trial populaiton. CTCAE v4.0 will be used to classify the events names and severity.*
	• *Skeletal related events*
	  ○ *Reporting the incidence and types of skeletal related events*
	• *Biochemical failure*
	  ○ *For the purposes of the STAMPEDE trial, a unique threshold PSA value for biochemical failure is calculated for each patient, referred to as the PSA progression value. A. If PSA nadir in the 24 weeks following randomisation is more than 4ng/ml and more than 50% of the pre-treatment PSA level - immediate treatment failure. B. If PSA nadir in the 24 weeks following randomisation is less than or equal to 50% of the pre-treatment PSA level but remains above 4ng/ml - treatment failure will be defined as a rise of 50% above the nadir level. C. If PSA nadir in the 24 weeks following randomisation is less than or equal to 4ng/ml - treatment failure will be defined as at least 50% rise above the nadir value and also above 4ng/ml.*
	• *Progression-free survival*
	  ○ *Reporting the incidence of mortality without a progression event*
	• *Lymph node progression*
	  ○ *Reporting the incidence and severity of lymph node events*
	• *Distant metastases*
	  ○ *Reporting the incidence and severity of distant metastatic events*
	• *Treatment for progression*
	  ○ *Identifying and reporting the treatments used in second line treatment. Incidence and types of treatments.*
	• *Disease-specific survival*

Trial name: STAMPEDE	NCT number: NCT00268476

- *Reporting the mortality attributed to Prostate Cancer*

- *Non-prostate cancer death*
  - *Reporting the mortality not attributed to Prostate Cancer*
- *Metabolic effects*
  - *Reporting the incidence and severity of effects on metabolic systems*

Endpoints included in this application:

- *Overall survival*
- *Progression free survival (only for study arm H vs A)*

Method of analysis	***Study arm C vs A*** *All patients are included in the efficacy analyses according to allocated treatment on an intention-to-treat basis.* *Standard survival analysis methods were used to analyse time-to-event data. Cox proportional hazards regression models were used to estimate most relative treatment effects. This model was adjusted for stratification factors (except hospital and planned hormone therapy), and stratified by time periods defined by addition of a new research group or end in recruitment to an ongoing research group. An HR below 1·00 favoured the research group.* ***Study arm H vs A*** *Standard survival analysis methods were used to analyse time-to-event data. A nonparametric stratified log-rank test was used to detect a difference in survival between treatment groups; this analysis was stratified across the minimisation factors used at randomisation (except hospital and planned androgen deprivation therapy) plus protocol-specific periods defined by other arms recruiting to STAMPEDE or changes to standard of care that could affect the population being randomised. Cox proportional hazards regression models adjusting for the same stratification factors and stratified by time were used to estimate relative treatment effects.*
Subgroup analyses	*None relevant to this submission.*
Other relevant information	

Trial name: TITAN	NCT number: NCT02489318
Objective	*The purpose of this study is to determine if the addition of apalutamide to ADT provides superior efficacy in improving radiographic progression-free survival (rPFS) or overall survival (OS) for participants with mHSPC.*

Trial name: TITAN	NCT number: NCT02489318
Publications – title, author, journal, year	*Agarwal N, McQuarrie K, Bjartell A, Chowdhury S, Pereira de Santana Gomes AJ, Chung BH, Özgüroğlu M, Juárez Soto Á, Merseburger AS, Uemura H, Ye D, Given R, Basch E, Miladinovic B, Lopez-Gitlitz A, Chi KN. Apalutamide plus Androgen Deprivation Therapy for Metastatic Castration-Sensitive Prostate Cancer: Analysis of Pain and Fatigue in the Phase 3 TITAN Study. J Urol. 2021 Oct;206(4):914-923. doi: 10.1097/JU.0000000000001841. Epub 2021 May 27.* *Chi KN, Chowdhury S, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, Juárez A, Merseburger AS, Özgüroğlu M, Uemura H, Ye D, Brookman-May S, Mundle SD, McCarthy SA, Larsen JS, Sun W, Bevans KB, Zhang K, Bandyopadhyay N, Agarwal N. Apalutamide in Patients With Metastatic Castration-Sensitive Prostate Cancer: Final Survival Analysis of the Randomized, Double-Blind, Phase III TITAN Study. J Clin Oncol. 2021 Jul 10;39(20):2294-2303. doi: 10.1200/JCO.20.03488. Epub 2021 Apr 29.* *Uemura H, Koroki Y, Iwaki Y, Imanaka K, Kambara T, Lopez-Gitlitz A, Smith A, Uemura H. Skin rash following Administration of Apalutamide in Japanese patients with Advanced Prostate Cancer: an integrated analysis of the phase 3 SPARTAN and TITAN studies and a phase 1 open-label study. BMC Urol. 2020 Sep 2;20(1):139. doi: 10.1186/s12894-020-00689-0. Erratum in: BMC Urol. 2020 Oct 22;20(1):166.* *Agarwal N, McQuarrie K, Bjartell A, Chowdhury S, Pereira de Santana Gomes AJ, Chung BH, Özgüroğlu M, Juárez Soto Á, Merseburger AS, Uemura H, Ye D, Given R, Cella D, Basch E, Miladinovic B, Dearden L, Deprince K, Naini V, Lopez-Gitlitz A, Chi KN; TITAN investigators. Health-related quality of life after apalutamide treatment in patients with metastatic castration-sensitive prostate cancer (TITAN): a randomised, placebo-controlled, phase 3 study. Lancet Oncol. 2019 Nov;20(11):1518-1530. doi: 10.1016/S1470-2045(19)30620-5. Epub 2019 Sep 29.* *Chi KN, Agarwal N, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, Juárez Soto Á, Merseburger AS, Özgüroğlu M, Uemura H, Ye D, Deprince K, Naini V, Li J, Cheng S, Yu MK, Zhang K, Larsen JS, McCarthy S, Chowdhury S; TITAN Investigators. Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med. 2019 Jul 4;381(1):13-24. doi: 10.1056/NEJMoa1903307. Epub 2019 May 31.*
Study type and design	*Phase 3* *Allocation: Randomized* *Intervention Model: Parallel Assignment* *Masking: Triple (Participant, Care Provider, Investigator)*
Sample size (n)	*1,052*

Trial name: TITAN	NCT number: NCT02489318

Main inclusion and exclusion criteria	***Inclusion Criteria:***

- *Diagnosis of prostate adenocarcinoma as confirmed by the investigator*
- *Metastatic disease documented by greater than or equal to (>=) 1 bone lesions on 99mTc bone scan. Participants with a single bone lesion must have confirmation of bone metastasis by computed tomography (CT) or magnetic resonance imaging (MRI)*
- *Eastern Cooperative Oncology Group Performance Status (ECOG PS) grade of 0 or 1*
- *Participants who received docetaxel treatment must meet the following criteria: a) Received a maximum of 6 cycles of docetaxel therapy for mHSPC; b) Received the last dose of docetaxel <=2 months prior to randomization; c) Maintained a response to docetaxel of stable disease or better, by investigator assessment of imaging and PSA, prior to randomization*
- *Other allowed prior treatment for mHSPC: a) Maximum of 1 course of radiation or surgical intervention; radiation therapy for metastatic lesions must be completed prior to randomization; b) Less than or equal to (<=) 6 months of ADT prior to randomization*
- *Allowed prior treatments for localized prostate cancer (all treatments must have been completed >= 1 year prior to randomization) a) <= 3 years total of ADT; b) All other forms of prior therapies including radiation therapy, prostatectomy,lymph node dissection, and systemic therapies*

Exclusion Criteria:

- *Pathological finding consistent with small cell, ductal or neuroendocrine carcinoma of the prostate*
- *Known brain metastases*
- *Lymph nodes as only sites of metastases*
- *Visceral (ie, liver or lung) metastases as only sites of metastases*
- *Other prior malignancy less than or equal to 5 years prior to randomization with the exception of squamous or basal cell skin carcinoma or non-invasive superficial bladder cancer*
- *Prior treatment with other next generation anti-androgens or other CYP17 inhibitors, immunotherapy or radiopharmaceutical agents for prostate cancer*
- *History of seizures or medications known to lower seizure threshold*

Intervention	***Apalutamide*** *Participants will receive apalutamide 240 mg (4 x 60 mg) tablets orally once daily in each 28 day treatment cycles.*

Trial name: TITAN	NCT number: NCT02489318
Comparator(s)	***Androgen Deprivation Therapy (ADT) + Placebo*** *All participants will receive and remain on a stable regimen of ADT (gonadotropin releasing hormone analog [GnRHa] or surgical castration). The choice of the GnRHa (agonist or antagonist) will be at discretion of the Investigator. Dosing (dose and frequency of administration) will be consistent with the prescribing information.*
Follow-up time	*Median follow-up 22.7/44 months (median follow up at IA1 was 22.7 months (used for rPFS and PFS analyses); at FA it was 44 months (used for OS, TTNSRE, TTPSA and safety analyses).*
Is the study used in the health economic model?	*Yes*

Trial name: TITAN	NCT number: NCT02489318

Primary, secondary and exploratory endpoints	***Primary endpoints:***
	• *Radiographic Progression-Free Survival (rPFS)*
	  ○ *The rPFS is defined as the duration from the date of randomization to the date of first documentation of radiographic progressive disease or death due to any cause, whichever occurs first.*
	• *Overall Survival (OS)*
	  ○ *The OS is defined as the time from date of randomization to date of death from any cause.*
	Secondary endpoints
	• *Time to Pain Progression*
	  ○ *Time to pain progression is defined as the time from the date of randomization to the date of the first observation of pain progression.*
	• *Time to Skeletal-Related Event (SRE)*
	  ○ *Time to SRE is defined as the time from the date of randomization to the date of the first occurrence of a fracture or treatment for the fracture. The SRE is defined as the occurrence of symptomatic pathological fracture, spinal cord compression, radiation to new bone lesions, or surgery to bone.*
	• *Time to Chronic Opioid Use*
	  ○ *Time to chronic opioid use is defined as the time from date of randomization to the first date of opioid use or first date of an increase in the total daily dose.*
	• *Time to Initiation of Cytotoxic Chemotherapy*
	  ○ *Time to initiation of cytotoxic chemotherapy is defined as the time from date of randomization to the date of initiation of cytotoxic chemotherapy.*
	Endpoints included in this application:
	• *OS*
	• *rPFS*
	• *PFS*
	Other end points
	• *Exploratory: Time to prostate-specific antigen (PSA) progression*

Method of analysis	*The primary statistical method of comparison for time-to-event end points was a stratified log-rank test, with stratification according to prespecified factors. The Kaplan–Meier product-limit method and Cox proportional-hazards model were used to estimate time-to-event variables and determine hazard ratios and associated confidence intervals.*
Subgroup analyses	*HVD and LVD*
Other relevant information	

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

Table 77: Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	CHAARTED	GETUG-AFU 15	HORRAD	STAMPEDE	TITAN
NCT number	NCT00309985	NCT00104715	ISRCTN06890529	NCT00268476	NCT02489318
Therapy	•DOC + ADT (75mg/m2 every 3 weeks for six cycles) •ADT alone	•DOC + ADT (75mg/m2 every 3 weeks for up to nine cycles) •ADT alone	•EBRT + ADT •ADT alone	•DOC + SOC (75mg/m2 every 3 weeks for six cycles) + P (10mg daily) •SoC (ADT ± RT)	•APA + ADT (240 mg oral, once daily) •Placebo + ADT
Patient population	Patients with mHSPC	Patients with metastatic non-castrate PC	Primary bone metastatic prostate cancer	Patients with PC that was newly diagnosed as metastatic, node positive, or high risk locally advanced (with at least two of T3/4, Gleason score of 8–10, and PSA ≥40ng/ml); or previously treated with radical surgery, RT, or both and relapsing with high risk features	Patients with mCSPC
Patients with newly diagnosed mHSPC	75%	71%	NR	100%	81%
Patients with high volume disease[a]	65% (514/790)	52% (202/385)[b]	NR	NR[c]	62.7%
Median age, years (range)	64 (36–91)	64 (57–70)	NR	65 (42–84)	68 (43–94)
Gleason score of 8–10	61%	56%	66% (286/432)	70%	67.4%
Performance status of 0–1	98%	NR	96% (416/432)	99%	NR
Prior adjuvant hormonal therapy	Permitted if ADT was ≤24 months in duration and	Permitted if ADT discontinued 12	No prior treatment permitted	Permitted if ADT discontinued 12 months	<= 6 months of ADT prior to randomisation; Allowed prior

	progression had occurred >12 months after completion of therapy	months before study entry		before study entry and ≤12 months in duration	treatments for localised PC (all treatments must have been completed >= 1 year prior to randomisation) a) <= 3 years total of ADT; b) All other forms of prior therapies including RT, prostatectomy, lymph node dissection, and systemic therapies
Median follow-up	53.7 months	83.9 months	47 months	40 months[d] – 73.5 months	22.7/44 months[e]

Abbreviations: ADT = androgen deprivation therapy; APA = apalutamide; DOC = docetaxel; EBRT = external beam radiation treatment; mCSPC = metastatic castration-sensitive prostate cancer; mHSPC = metastatic hormone-sensitive prostate cancer; NCT = National Clinical Trial; NMA = network meta-analyses; NR = not reported; OS = overall survival; PC = prostate cancer; PSA = prostate-specific antigen; rPFS = radiographic progression-free survival; RT = radiotherapy; SOC = standard of care.

[a]High volume disease defined as visceral metastases and/or ≥4 bone metastases with at least one metastasis beyond the pelvis or vertebral column

[b]High volume disease was retrospectively defined in the GETUG-AFU 15 trial following the CHAARTED definition (visceral metastases and/or ≥4 bone metastases with at least one metastasis beyond the pelvis or vertebral column)

[c]An analysis of patients with high volume mHSPC in the STAMPEDE trial is not currently available

[d]Median follow-up reported for all randomised patients (standard of care [SoC], DOC + SoC, zoledronic acid [ZA] + SoC, DOC + ZA + SoC). For RT comparison (arm H) median follow-up was 37 months..

[e]Median follow up at IA1 was 22.7 months (used for rPFS and PFS analyses); at FA it was 44 months (used for OS, TTNSRE, TTPSA and safety analyses).

Comparability of patients across studies

All studies were conducted in patient populations of adult (aged ≥18 years) men with mHSPC. The population definitions based on the enrolment criteria were generally similar across the studies with minor differences in terms of exceptions the trials permitted related to the previous treatment.

Comparability of the study populations with Danish patients eligible for treatment

There is no published epidemiological data on the proportion of different patient populations in the mHSPC setting and therefore we can't know for sure if this represents real life population. However, the selection of study participants resemble the selection in the nmCRPC studies, previously assessed by DMC expert committee to be comparable to Danish patients.

Appendix D Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

Table 78: Summary of Efficacy Outcome Definitions from included Studies

Trial	INV/IRC	OS	rPFS	PFS	Time to PSA Progression	Time to Next Subsequent Treatment for PC
CHAARTED	INV*	Time from randomisation to death from any cause	*Outcome NR*	*Outcome NR*	*Outcome NR*	*Outcome NR*
GETUG-AFU 15	INV*	Time from randomisation to death from any cause	Time from randomisation to the occurrence of radiographic progression or death from any cause	*Outcome NR*	*Outcome NR*	Median time to subsequent treatment
HORRAD	INV*	Time between date of diagnosis at prostatic biopsy and date of death	*Outcome NR*	*Outcome NR*	*Time between diagnosis and a PSA increase after initiation of ADT of more than 50% of the lowest PSA value after start of treatment (PSA-nadir), with a minimum of 1 ng/ml.*	*Outcome NR*
STAMPEDE	INV	Time from randomisation to death from any cause	*Outcome NR*	Progression-free survival including death from prostate cancer	*Outcome NR*	*Outcome NR*
TITAN	INV	Time from randomisation to death from any cause	Time from randomisation to the occurrence of radiographic progression or death from any cause	*Outcome NR*	Time to PSA progression as date of random assignment to date of PSA progression, based on PCWG2 criteria	Time to initiation of cytotoxic chemotherapy

Abbreviations: ADT = androgen deprivation therapy; INV = investigator assessed; IRC = independent review committee; NR = not reported; OS = overall survival; PC = prostate cancer; PCWG2 = Prostate Cancer Clinical Trials Working Group 2; PFS = progression-free survival; PSA = prostate-specific antigen; rPFS = radiographic progression-free survival.
*Assumed to be INV

Results per study

Table A3a Results of TITAN (NCT02489318)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
OS (follow up, 44 months)	APA+ADT	525	Not reached	median OS not reached	NR	NR	HR: 0.651	0.534-0.793	<0.0001	*OS based on Kaplan-Meier estimator. The HR is based on a stratified Cox proportional-hazards model. Stratification factors used: Gleason score at diagnosis (≤7 vs. >7), geographic regions (NA/EU vs. Other Countries) and prior docetaxel use (yes vs. no).*	(35)
	Placebo+ADT	527	52.2 months				**HVD HR: 0.700**	**[0.560; 0.880]**			
							LVD HR: 0.520	**[0.350; 0.790]**			
	APA+ADT	525	Not reached	NR	NR	NR	HR: 0.604	0.479-0.763			(35)

Table A3a Results of TITAN (NCT02489318)											
OS cross over adjusted (follow up, 44 months)	Placebo+ADT	527	52.2 months				**HVD HR: 0.651** **LVD HR: 0.478**	**[0.501; 0.870]** **[0.220; 0.570]**		*A Rank Preserving Structural Failure Time Model (RPSFTM) with no recensoring was used in order to reconstruct the survival duration of ADT patients that crossed over to apalutamide, as if they had never received apalutamide. Adjustment was performed in line with NICE DSU guidelines*	
rPFS/PFS (follow up, 22.7 months)	APA+ADT	525	Not reached	NR	NR	NR	HR: 0.484	0.391–0.600	<0.0001	*As for OS*	(31)
	Placebo+ADT	527	22.1 (18.5-32.9) months				**HVD HR: 0.530** **LVD HR: 0.360**	**[0.410; 0.670]** **[0.220; 0.570]**			
TTPSA (follow up, 44 months)	APA+ADT	525	Not reached	NR	NR	NR	HR: 0.266	0.218-0.325		*As for OS*	(35)
	Placebo+ADT	527	12.9 months								

Abbreviations: ADT = androgen deprivation therapy; APA = apalutamide; CI = confidence interval; DOC = docetaxel; HR = hazard ratio; HVD = high volume disease; LVD = low volume disease; NR= not reported; OS = overall survival; PSA = prostate-specific antigen; rPFS = radiographic progression-free survival; RT = radiotherapy; TTNSRE = time to next skeletal-related event; TTPSA = time to PSA progression.

Table A3b Results of CHAARTED (NCT00309985)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
OS (follow up, 28.9 months)	DOC+ADT	397	57.6 months **HVD: 49.2 months, LVD: not reached**	13.6 months **HVD: 17 months**	NR	NR	HR: 0.610 **HVD HR: 0.600** **LVD HR: 0.600**	0.470-0.800 **[0.450; 0.810]** **[0.320; 1.130]**	<0.001	*Kaplan–Meier estimates were used for event-time distributions. Cox proportional-hazard models were used to estimate hazard ratios for time-to-event end points, and stratified according to age (<70 years vs. ≥70 years), ECOG performance-status score (0 or 1 vs. 2), and planned use of combined androgen blockade for more than 30 days (yes vs. no) or agents approved for prevention of skeletal-related events in castration-resistant disease (zoledronic acid or denosumab) (yes vs. no). Patients were also stratified according to the duration of prior adjuvant ADT (<12 months vs. ≥12 months) and the extent of metastases (high volume [defined as the presence of visceral metastases or ≥4 bone lesions with*	(36)
	Placebo+ADT	393	44.0 months **HVD: 32.2 months, LVD: not reached**								

Table A3b Results of CHAARTED (NCT00309985)

										≥1beyond the vertebral bodies and pelvis] vs. low volume).	

Abbreviations: ADT = androgen deprivation therapy; CI = confidence interval; DOC = docetaxel; HR = hazard ratio; HVD = high volume disease; LVD = low volume disease; NR = not reported; OS = overall survival.

Table A3c Results of GETUG-AFU15 (NCT00104715)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
OS (follow up, 50 months)	DOC+ADT	**192**	58.9 (50.8-69.1) months	4,7 months	NR	NR	HR: 1.010	0.750-1.360	<0.955	*Cox proportional hazards regression model with terms for the randomized treatment arm.*	(30)
	Placebo+ADT	193	54.2 (42.2-not reached) months				**HVD HR (83.9M): 0.780**	**[0.560; 1.090]**			
							LVD HR (83.9M): 1.020	**[0.670; 1.550]**			
rPFS/PFS (follow up, 83.9 months)	APA+ADT	525	22.9 (20.5-31.4) months	7,6 months	NR	NR	HR: 0.690	0.550-0.870		*As above.*	(23)
	Placebo+ADT	527	15.3 (12.4-19.8) months				**HVD HR (83.9M): 0.610**	**[0.440; 0.830]**			
							LVD HR (83.9M): 0.810	**[0.570; 1.140]**			

Table A3c Results of GETUG-AFU15 (NCT00104715)

Abbreviations: ADT = androgen deprivation therapy; CI = confidence interval; DOC = docetaxel; HR = hazard ratio; HVD = high volume disease; LVD = low volume disease; NR = not reported; OS = overall survival; PSA = prostate-specific antigen; rPFS = radiographic progression-free survival.

Table A3d Results of STAMPEDE (NCT00268476)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
OS (follow up, 43 months; 78,2 months for HVD+LVD)	DOC+ADT	592	60 (IQR 27-103) months **HVD: 39.9 months** **LVD: 93.2 months**	15 months **HVD: 4.7 months** **LVD: 16,5 months**	NR	NR	HR: 0.760 **HVD HR (78.2M): 0.810** **LVD HR (78.2M): 0.760**	0.620-0.920 **[0.640; 1.020]** **[0.540; 1.070]**	0.005	*Cox proportional hazards regression models, adjusted for stratification factors.*	(26) (42)
	Placebo+ADT	1184	45 (IQR 23-91) months **HVD: 35.2 months** **LVD: 76.7 months**								

Table A3d Results of STAMPEDE (NCT00268476)												
OS (follow up, 37 months)	RT+ADT	1032	42.5 (NR) months **HVD: 37.6 months** **LVD: 49.1 months**	1.0 months **HVD: -1.2 months** **LVD: 3.6 months**	-0.6 to 2.5 **HVD: -3.5 to 1.1** **LVD: 1.0 to 6.2**	NR	HR: 0.920 **HVD HR: 1.070** **LVD HR: 0.680**	0.800-1.060 **[0.900; 1.280]** **[0.520; 0.900]**	0.266	*A nonparametric stratified log-rank test was used to detect a difference in survival between treatment groups; this analysis was stratified across the minimisation factors used at randomisation (except hospital and planned androgen deprivation therapy) plus protocol-specific periods defined by other arms recruiting to STAMPEDE or changes to standard of care that could affect the population being randomised. Cox proportional hazards regression models adjusting for the same stratification factors and stratified by time were used to estimate relative treatment effects.*	(28)
	Placebo+ADT	1029	41.6 (NR) months **HVD: 38.8 months** **LVD: 45.4 months**								
PFS (follow up, 78,2 months)	DOC+ADT	362		RMST: 12.8 months **RMST: HVD: 12.6 months**	RMST:7.2-18.3 RMST:5.3-19.8	NR	HR: 0.690 **HVD HR: 0.680**	0.590-0.810 **[0.540; 0.850]**	0<001	*Cox proportional hazards regression models, adjusted for stratification factors. Competing risks model used.*	(32)
	Placebo + ADT	724									

Table A3d Results of STAMPEDE (NCT00268476)											
				RMST: LVD: 17.5 months	RMST:7.4-27.6		**LVD HR: 0.620**	**[0.450; 0.850]**			
PFS (follow up, 37 months)	RT+ADT	1032	33.1 (NR) months **HVD: 26.2 months** **LVD: 42.9 months**	0.7 months **HVD: -1.8 months** **LVD: 3.5 months**	-0.9 to 2.3 **HVD: -4.3 to 0.8** **LVD: 0.4 to 6.7**	NR	HR: 0.960 **HVD HR: 1.090** **LVD HR: 0.780**	0.850–1.080 **[0.940; 1.260]** **[0.630; 0.980]**	NR	*As above*	(28)
	Placebo+ADT	1029	32.4 (NR) months **HVD: 28.0 months** **LVD: 39.4 months**								

Abbreviations: ADT = androgen deprivation therapy; CI = confidence interval; DOC = docetaxel; HR = hazard ratio; **HVD = high volume disease; LVD = low volume disease**; NR = not reported; OS = overall survival; rPFS = radiographic progression-free survival; RT = radiotherapy. RMST: restricted mean survival times

Table A3e Results of HORRAD (ISRCTN06890529)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
OS (follow up, 47 months)	RT+ADT	216	45 (40.4-49.6) months	2 months	NR	NR	HR: 0.900	0.700-1.140	0.400	*Cox proportional hazard regression analyses were applied to evaluate the treatment effect, both crude and adjusted, for several covariates: age at diagnosis, performance status, initial pain score, initial PSA, number of bone metastases (<5 lesions, 5–15 lesions, >15 lesions), Gleason sum score (7, 8, 9), and T stage (cT1-cT3)*	(24)
	Placebo+ADT	216	43 (32.6-53.4) months								
TTPSA (follow up, 47 months)	RT+ADT	216	15 (11.8-18.2) months	3 months	NR	NR	HR: 0.780	0.630–0.970	0.02	*As above*	(24)
	Placebo+ADT	216	12 (10.6-13.4) months								

Abbreviations: ADT = androgen deprivation therapy; CI = confidence interval; DOC = docetaxel; HR = hazard ratio; HVD = high volume disease; LVD = low volume disease; NR = not reported; OS = overall survival; PSA = prostate-specific antigen; RT = radiotherapy; TTNSRE = time to next skeletal-related event; TTPSA = time to PSA progression.

Appendix E Safety data for intervention and comparator(s)

Study	Trial Name, Population Description	Arm	AEs (overall)		Discontinuations			Death		
			Any	**Severe**	**All cause**	**AEs**	**Loss of Efficacy**	**All cause**	**Treatment-related**	**Metastases-related**
Chi et al 2019 (31) related to Chi et al 2021(35)	TITAN	APA+ADT	507/524 (96.8%)	153/524 (29.2%)	NR	42/524 (8%)	NR	18/524 (3.4%)	10/524 (1.9%)	8/524 (1.5%)
		Placebo+ADT	509/527 (96.6%)	115/527 (21.8%)	NR	28/527 (5.3%)	NR	23/527 (4.4%)	16/527 (3%)	7/527 (1.3%)
Sweeney et al, 2015 (36)	CHAARTED[1]	DOC+ADT	NR	NR	NR	NR	NR	188/397 (47.4%)	NR	85/397 (21.4%)
		ADT	NR	NR	NR	NR	NR	211/393 (53.7%)	NR	114/393 (29%)
Gravis et al (2013) (30); related to Gravis et al (2016) (23); Gravis et al (2017) (80); Marino et al (2017) (44)	GETUG-AFU 15	DOC+ADT	NR	NR	NR	NR	NR	88/188 (46%)	2/189 (2%)	68/189 (77%)
		ADT	NR	NR	NR	NR	NR	88/186 (47%)	0/186 (0%)	75/186 (85%)
James et al (2016) (26)	STAMPEDE[2]	SOC (hormone therapy with gonadotropin-releasing hormone agonists or antagonists or oral anti-androgens)	NR	NR	NR	NR	NR	350/724 (48.3%)	NR	NR
		SOC+DOC+prednisolone	NR	NR	NR	NR	NR	144/362 (39.8%)	NR	NR

Parker et al (2018) (28)	STAMPEDE[3]	SOC (ADT as either gonadotrophin-releasing hormone agonists or antagonists or orchidectomy)	NR	NR	NR	NR	NR	327/1029 (32%)	NR	NR
		SOC+ radiotherapy	NR	NR	NR	NR	NR	313/1032 (30%)	NR	NR
Boeve et al (2019) (24)	HORRAD[4]	EBRT+ADT	NR	NR	NR	NR	NR	131/216 (60.6%)	NR	NR
		ADT	NR	NR	NR	NR	NR	139/216 (64.4%)	NR	NR
Clarke et al (2019) (81)	STAMPEDE[2]	SOC	NR	NR	NR	NR	NR	494/724	NR	NR
		SOC+DOC	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviations: ADT = androgen-deprivation therapy; APA = apalutamide; DOC = docetaxel; EBRT = external beam radiation therapy; mHSPC = metastatic hormone-sensitive prostate cancer; MMC = mitomycin; NR = not reported; PC = prostate cancer; SOC = standard of care.

[1] All grade 3 or higher toxic effects in the combination group were captured, and an attribution of relatedness to study therapy was made by the local investigators. Adverse events among patients assigned to ADT alone were not routinely documented, although major adverse events were to be reported. In the group receiving ADT plus docetaxel the rate of grade 3 or 4 febrile neutropenia was 6.2%, the rate of grade 3 or 4 infection with neutropenia was 2.3%, and the rate of grade 3 sensory neuropathy and of grade 3 motor neuropathy was 0.5%.

[2] Toxic effects and symptoms were reported at regular follow-up visits. Serious adverse events, including serious adverse reactions, were reported accordingly. The proportion of patients reporting worst adverse event ever as grade 3 or higher was highest with SOC + Doc (288 patients [52%]). There were eight deaths probably or possibly related to the research treatment: one on SOC + Doc (neutropenic sepsis).
In Clarke et al. (2019) results are reported up to one year and after one year. G3-5 toxicity was reported for 28% SOC and 27% docetaxel (in patients still on followup at 1 year without prior progression).

[3] Toxic effects and symptoms were reported at regular follow up visits or when an adverse event was categorized as serious. Adverse effects on the bowel and bladder during radiotherapy, and possible long-term effects of radiotherapy, were recorded separately in patients assigned standard of care and radiotherapy using the Radiation Therapy Oncology Group (RTOG) scale. 48 (5%) adverse events (Radiation Therapy Oncology Group grade 3–4) were reported during radiotherapy and 37 (4%) after radiotherapy. The proportion reporting at least one severe adverse event was similar by treatment group in the safety population (398 [38%] with control and 380 [39%] with radiotherapy).43 (5%) patients reported their worst acute bladder toxic effect as grade 3 or 4, and eight (1%) reported their worst acute bowel toxic effect as grade 3 or 4. No deaths were reported as related to the research treatment.

[4]No safety data reported.

Below tabel presents the number of grade 3 or 4 TEAEs with a frequency of at least 1% in any treatment arm which were included in the HE model.

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Preferred term	apalutamide + ADT (TITAN)		ADT alone (TITAN)		RT+ADT (STAMPEDE-HA)		DOC+ADT (STAMPEDE-CA)	
	N	**%**	N	%	N	%	N	%
Safety population	**524**		**527**		**988**		**550**	
Alanine aminotransferase increased	3	0.57%	6	1.14%	0	0.00%	0	0.00%
Anemia	12	2.29%	19	3.61%	0	0.00%	0	0.00%
Aspartate aminotransferase increased	2	0.38%	6	1.14%	0	0.00%	0	0.00%
Back pain	13	2.48%	15	2.85%	0	0.00%	0	0.00%
Blood alkaline phosphatase increased	2	0.38%	13	2.47%	0	0.00%	0	0.00%
Bone pain	6	1.15%	9	1.71%	0	0.00%	32	5.82%
Cardiac disorder (any)	27	5.15%	10	1.90%	0	0.00%	16	2.91%
Cystitis*(only included in the low-volume disease analysis)*	1	0.19%	0	0.00%	7	0.71%	0	0.00%
Endocrine disorders (incl. hot flashes & impotence)	0	0.00%	1	0.19%	0	0.00%	57	10.36%
Fall	7	1.34%	5	0.95%	0	0.00%	0	0.00%
Fatigue / asthenia	(8+11)	3.63%	(3+7)	1.90%	0	0.00%	34	6.18%
Febrile neutropenia	1	0.19%	0	0.00%	0	0.00%	84	15.27%
Gastrointestinal disorders	16	3.05%	10	1.90%	(12+11+1)	2.43%	45	8.18%
Haematuria	9	1.72%	3	0.57%	6	0.61%	0	0.00%
Hyperglycaemia	6	1.15%	3	0.57%	0	0.00%	0	0.00%
Hyperkalaemia	6	1.15%	5	0.95%	0	0.00%	0	0.00%
Hypertension	54	10.31%	47	8.92%	0	0.00%	0	0.00%
Hyponatremia	4	0.76%	8	1.52%	0	0.00%	0	0.00%
Nervous system other (including peripheral neuropathy)	39	7.44%	21	3.98%	0	0.00%	19	3.45%
Neutropenia	4	0.76%	1	0.19%	0	0.00%	66	12.00%
Pneumonia	12	2.29%	4	0.76%	0	0.00%	0	0.00%
Rash	35	6.68%	4	0.76%	0	0.00%	0	0.00%
Respiratory disorders (incl. thoracic & mediastinal disorders)	22	4.20%	12	2.28%	0	0.00%	29	5.27%
Spinal cord compression	3	0.57%	9	1.71%	0	0.00%	0	0.00%
Urinary retention	5	0.95%	11	2.09%	4	0.40%	0	0.00%

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Urinary tract infection	9	1.72%	3	0.57%	0	0.00%	23	4.18%
Weight increased	6	1.15%	10	1.90%	0	0.00%	0	0.00%

Note: Percent is based on the Safety population.
Note: Table does not include Grade 5 events.
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+30 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 the worst toxicity grade is used.
Note: Adverse events are coded using Medical Dictionary for Regulatory Activities Version 20.0.
Note: Toxicity grade is based on NCI common toxicity criteria, version 4.03.
***Gastrointestinal disorders is a grouped term, but excludes diarrhoea (since it is already listed). A full list of terms used is available in table TSFAE04 of the TITAN CSR.**
****Rash is a grouped term including rash, butterfly rash, erythematous rash, exfoliative rash, follicular rash, generalized rash, macular rash, maculopapular rash, papules, papular rash, pruritic rash, pustular rash, genital rash, blister, skin exfoliation, exfoliative dermatitis, skin reaction, systemic lupus erythematosus rash, toxic skin eruption, mouth ulceration, drug eruption, conjunctivitis, erythema multiforme, stomatitis, and urticaria**
*****Respiratory disorder is a grouped term which also includes thoracic and mediastinal disorders. A full list of terms used is available in table TSFAE04 of the TITAN CSR.**
†Part of general disorder (includes lethargy and fever); ††Fatigue only.

ADT= androgen deprivation therapy; DOC= docetaxel; N= number; RT= radiotherapy

Appendix F Comparative analysis of efficacy and safety

Refer to section 7.1.3.

Narrative report of safety for comparators

Below is a narrative report of safety for docetaxel and radiation therapy, based on available data.

Adverse events for Docetaxel

According to the summary of product characteristics for Taxotere (82), the adverse effects most commonly reported with docetaxel 75 mg/ m 2 when used for prostate cancer are neutropenia (32%), anaemia (4.9%), fatigue (3.9%) and infection (3.3%).

Four deaths in GETUG-AFU 15, 1 death in CHAARTED and 8 deaths in STAMPEDE (1 with docetaxel plus ADT and 7 with docetaxel, zoledronic acid and ADT) were considered possibly or probably related to docetaxel treatment. In men taking docetaxel plus ADT, severe, life-threatening or disabling adverse events or death (grade 3–5 adverse events) were reported in 38.1% of men in GETUGAFU 15, 29.5% of men in CHAARTED and 52.4% of men in STAMPEDE. 32.5% of men taking ADT alone in STAMPEDE reported grade 3–5 adverse events. In GETUG-AFU 15, CHAARTED and STAMPEDE, toxicity associated with docetaxel was mainly hematologic: 12% to 15% of patients had grade 3 to 4 neutropenia, 6% to 15% of patients had grade 3 to 4 febrile neutropenia

The list of adverse reactions/events in the product Information of Docetaxel (from STAMPEDE and GETUG AFU15 studies) (82) is:

Very common adverse reactions reported are Neutropenia (G3-4: 12%), Anaemia, Febrile neutropenia (G3-4: 15%), Insomnia (G3:1%), Peropheral sensory neuropathy (≥3:2%), Headache, Dyspnea (G3: 1%), Coughing (G3:0%), Upper respiratory tract infection (G3:1%), Diarrhea (G3: 3%), Stomatitis (G3: 0%), Constipation (G3: 0%), Nausea (G3: 1%), Dyspepsia Abdominal pain (G3: 0%), Flatulence, Alopecia (G3: 3%), Nail changes (G3: 1%), Myalgia, Lethargy (G3-4: 2%), Flu-like symptoms (G3: 0%), Asthenia (G3: 0%), Fluid retention

Common adverse events reported are Hypersensitvity (G3-4: 1%), Diabetes (G3-4: 1%), Anorexia, Diziness, Blurred vision, Hypotension (G3:0%), Pharyngitis (G3:0%), Vomiting (G3:1%), Rash, Fever (G3: 1%) Oral candidiasis Hypocalcaemia (G3: 0%) Hypophosphataemia (G3-4: 1%) Hypokalaemia (G3: 0%)

Adverse events for Radiation therapy

In the systematic review and meta-analysis by Burdett et al. 2019 (83) they reported based on the results collected from STAMPEDE that 4% of men who received prostate radiotherapy had severe acute bladder toxicity, and 1% had severe acute bowel toxicity (RTOG scale). Reported STAMPEDE results showed that 4% of men had severe late effects.
For HORRAD a poster was presented at EAU 2020 reporting that patients in the radiotherapy group reported significantly more diarrhoea, bowel symptoms and urinary symptoms than patients in the control group. The urinary complaints disappeared after 6 months. After 2 years,

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the only significant between-arm difference that remained were the bowel syndrome scores. (Boevé et al. EAU 2020 Poster and abstract #578: HORRAD).

Urinary problems are usually caused by irritation to the urethra and bladder lining due to RT. Patients report needing to urinate frequently, night time incontinence and leaking, difficulty urinating or a sudden urge to urinate, a burning feeling while urinating and blood in the urine. RT may also result in a narrowing of the urethra which may cause additional problems with urination. Common bowel problems include flatulence, diarrhoea, abdominal pain, a feeling of being unable to empty the bowel fully, bleeding and faecal incontinence. Patients who wish to have a family are generally advised to store semen samples before commencing RT as the cells that produce semen may be damaged during the treatment.

Results from Random-Effects (RE) models

Below we present matrix data when using random-effects models, as requested by DMC. As stated in section 7.1.3, compared to the fixed-effects model, wider confidence intervals were observed for all treatment comparisons. Within the random effect models, wider credible intervals resulted in no observed advantages between any combination treatment vs. placebo for the outcomes of OS, rPFS, and PFS. In the fixed-effect models, all combination treatments were found to have an advantage over placebo + ADT, so the conclusions of the fixed effects vs. random effects analyses are substantially different.

The fixed-effects models are chosen due to limitations of most of the outcome networks (i.e., the presence of only one or few studies per treatment comparison) and based on the Deviance Information Criterion (DIC) as a measure of model fit (preferring smaller values), in line with NICE TSD recommendations for choice between FE and RE models.

OS

Figure 40: OS Matrix total population: HR [95% Confidence intervals], p(HR<1), random effects

OS	APA+ADT	DOC+ADT	Radioth+ADT	PL+ADT
APA+ADT		0.85 [0.376; 1.86] 75%	0.71 [0.308; 1.66] 87%	0.65 [0.326; 1.30] 94%
DOC+ADT	1.18 [0.537; 2.66] 25%		0.84 [0.453; 1.61] 80%	0.77 [0.516; 1.17] 93%
Radioth+ADT	1.40 [0.602; 3.25] 13%	1.19 [0.622; 2.21] 20%		0.91 [0.559; 1.48] 74%
PL+ADT	1.54 [0.771; 3.07] 6%	1.30 [0.857; 1.94] 7%	1.10 [0.677; 1.79] 26%	

Comparators are ordered according to the SUCRA. Cells contain HR with [95% Confidence intervals], and P(HR<1) (row vs column). Abbreviations: ADT = androgen deprivation therapy; APA = apalutamide; DOC = docetaxel; HR = hazard ratio; OS = overall survival; P = probability; PL = placebo; Radioth = Radiation therapy.

Figure 41: OS Matrix HVD patients: HR [95% Confidence intervals], p(HR<1), random effects

OS	APA+ADT	DOC+ADT	PL+ADT	Radioth+ADT
APA+ADT		0.96 [0.372; 2.50] 56%	0.70 [0.308; 1.60] 89%	0.65 [0.207; 2.07] 87%
DOC+ADT	1.04 [0.399; 2.69] 44%		0.73 [0.448; 1.18] 94%	0.68 [0.262; 1.75] 88%
PL+ADT	1.43 [0.626; 3.24] 11%	1.37 [0.849; 2.23] 6%		0.93 [0.416; 2.11] 63%
Radioth+ADT	1.53 [0.484; 4.84] 13%	1.47 [0.572; 3.82] 12%	1.07 [0.474; 2.41] 37%	

Comparators are ordered according to the SUCRA. Cells contain HR with [95% Confidence intervals], and P(HR<1) (row vs column). Abbreviations: ADT = androgen deprivation therapy; APA = apalutamide; DOC = docetaxel; HR = hazard ratio; HVD = high volume disease; OS = overall survival; P = probability; PL = placebo; Radioth = Radiation therapy.

Figure 42: OS Matrix LVD patients: HR [95% Confidence intervals], p(HR<1), random effects

OS	APA+ADT	Radioth+ADT	DOC+ADT	PL+ADT
APA+ADT		0.76 [0.190; 3.06] 72%	0.65 [0.211; 2.10] 84%	0.52 [0.194; 1.41] 93%
Radioth+ADT	1.31 [0.328; 5.27] 28%		0.85 [0.284; 2.68] 68%	0.68 [0.263; 1.78] 87%
DOC+ADT	1.54 [0.475; 4.74] 16%	1.18 [0.373; 3.53] 32%		0.80 [0.438; 1.41] 85%
PL+ADT	1.92 [0.708; 5.16] 7%	1.47 [0.563; 3.80] 13%	1.25 [0.709; 2.28] 15%	

Comparators are ordered according to the SUCRA. Cells contain HR with [95% Confidence intervals], and P(HR<1) (row vs column). Abbreviations: ADT = androgen deprivation therapy; APA = apalutamide; DOC = docetaxel; HR = hazard ratio; LVD=low volume disease; OS = overall survival; P = probability; PL = placebo; Radioth = Radiation therapy.

rPFS

Figure 43: rPFS Matrix total population: HR [95% Confidence intervals], p(HR<1), random effects

rPFS	APA+ADT	DOC+ADT	PL+ADT
APA+ADT		0.70 [0.117; 4.22] 73%	0.48 [0.136; 1.73] 91%
DOC+ADT	1.43 [0.237; 8.55] 27%		0.69 [0.195; 2.46] 80%
PL+ADT	2.07 [0.578; 7.34] 9%	1.45 [0.407; 5.13] 20%	

Comparators are ordered according to the SUCRA. Cells contain HR with [95% Confidence intervals], and P(HR<1) (row vs column). Abbreviations: ADT = androgen deprivation therapy; APA = apalutamide; DOC = docetaxel; HR = hazard ratio; P = probability; PL = placebo; rPFS = radiographic progression-free survival.

Figure 44: rPFS Matrix HVD population: HR [95% Confidence intervals], p(HR<1), random effects

rPFS	APA+ADT	DOC+ADT	PL+ADT
APA+ADT		0.87 [0.144; 5.31] 60%	0.53 [0.150; 1.90] 89%
DOC+ADT	1.15 [0.188; 6.97] 40%		0.61 [0.168; 2.19] 84%
PL+ADT	1.89 [0.527; 6.69] 11%	1.64 [0.457; 5.94] 16%	

Comparators are ordered according to the SUCRA. Cells contain HR with [95% Confidence intervals], and P(HR<1) (row vs column). Abbreviations: ADT = androgen deprivation therapy; APA = apalutamide; DOC = docetaxel; HR = hazard ratio; HVD= high volume disease; P = probability; PL = placebo; rPFS = radiographic progression-free survival.

Figure 45: rPFS Matrix LVD population: HR [95% Confidence intervals], p(HR<1), random effects

rPFS	APA+ADT	DOC+ADT	PL+ADT
APA+ADT		0.45 [0.072; 2.79] 86%	0.36 [0.097; 1.35] 95%
DOC+ADT	2.25 [0.359; 13.96] 14%		0.81 [0.225; 2.92] 69%
PL+ADT	2.78 [0.741; 10.34] 5%	1.23 [0.343; 4.44] 31%	

Comparators are ordered according to the SUCRA. Cells contain HR with [95% Confidence intervals], and P(HR<1) (row vs column). Abbreviations: ADT = androgen deprivation therapy; APA = apalutamide; DOC = docetaxel; HR = hazard ratio; LVD= low volume disease; P = probability; PL = placebo; rPFS = radiographic progression-free survival.

PFS

Figure 46: PFS Matrix total population: HR [95% Confidence intervals], p(HR<1), random effects

PFS	APA+ADT	DOC+ADT	Radioth+ADT	PL+ADT
APA+ADT		0.70 [0.225; 2.20] 85%	0.50 [0.137; 1.88] 92%	0.48 [0.191; 1.24] 96%
DOC+ADT	1.42 [0.454; 4.45] 15%		0.72 [0.232; 2.27] 85%	0.69 [0.356; 1.33] 93%
Radioth+ADT	1.98 [0.533; 7.32] 8%	1.39 [0.441; 4.30] 15%		0.96 [0.379; 2.40] 60%
PL+ADT	2.06 [0.806; 5.24] 4%	1.45 [0.754; 2.81] 7%	1.04 [0.416; 2.64] 40%	

Comparators are ordered according to the SUCRA. Cells contain HR with [95% Confidence intervals], and P(HR<1) (row vs column). Abbreviations: ADT = androgen deprivation therapy; APA = apalutamide; DOC = docetaxel; HR = hazard ratio; P = probability; PL = placebo; PFS = progression-free survival; Radioth = radiation therapy.

Figure 47: PFS Matrix HVD population: HR [95% Confidence intervals], p(HR<1), random effects

PFS	APA+ADT	DOC+ADT	PL+ADT	Radioth+ADT
APA+ADT		0.81 [0.243; 2.80] 73%	0.53 [0.197; 1.44] 94%	0.49 [0.121; 1.98] 91%
DOC+ADT	1.23 [0.357; 4.11] 27%		0.65 [0.318; 1.31] 93%	0.60 [0.175; 1.98] 89%
PL+ADT	1.89 [0.693; 5.09] 6%	1.54 [0.765; 3.15] 7%		0.92 [0.341; 2.45] 66%
Radioth+ADT	2.05 [0.506; 8.27] 9%	1.67 [0.506; 5.73] 11%	1.09 [0.407; 2.93] 34%	

Comparators are ordered according to the SUCRA. Cells contain HR with [95% Confidence intervals], and P(HR<1) (row vs column). Abbreviations: ADT = androgen deprivation therapy; APA = apalutamide; DOC = docetaxel; HR = hazard ratio; HVD = high volume disease; P = probability; PL = placebo; PFS = progression-free survival; Radioth = radiation therapy

Figure 48: PFS Matrix LVD population: HR [95% Confidence intervals], p(HR<1), random effects

PFS	APA+ADT	DOC+ADT	Radioth+ADT	PL+ADT
APA+ADT		0.51 [0.129; 1.98] 89%	0.46 [0.097; 2.19] 90%	0.36 [0.115; 1.11] 97%
DOC+ADT	1.96 [0.506; 7.75] 11%		0.90 [0.240; 3.38] 61%	0.70 [0.328; 1.54] 88%
Radioth+ADT	2.17 [0.456; 10.28] 10%	1.11 [0.296; 4.17] 39%		0.78 [0.266; 2.28] 78%
PL+ADT	2.78 [0.898; 8.68] 3%	1.42 [0.649; 3.05] 12%	1.28 [0.439; 3.75] 22%	

Comparators are ordered according to the SUCRA. Cells contain HR with [95% Confidence intervals], and P(HR<1) (row vs column). Abbreviations: ADT = androgen deprivation therapy; APA = apalutamide; DOC = docetaxel; HR = hazard ratio; LVD = low volume disease; P = probability; PL = placebo; PFS = progression-free survival; Radioth = radiation therapy

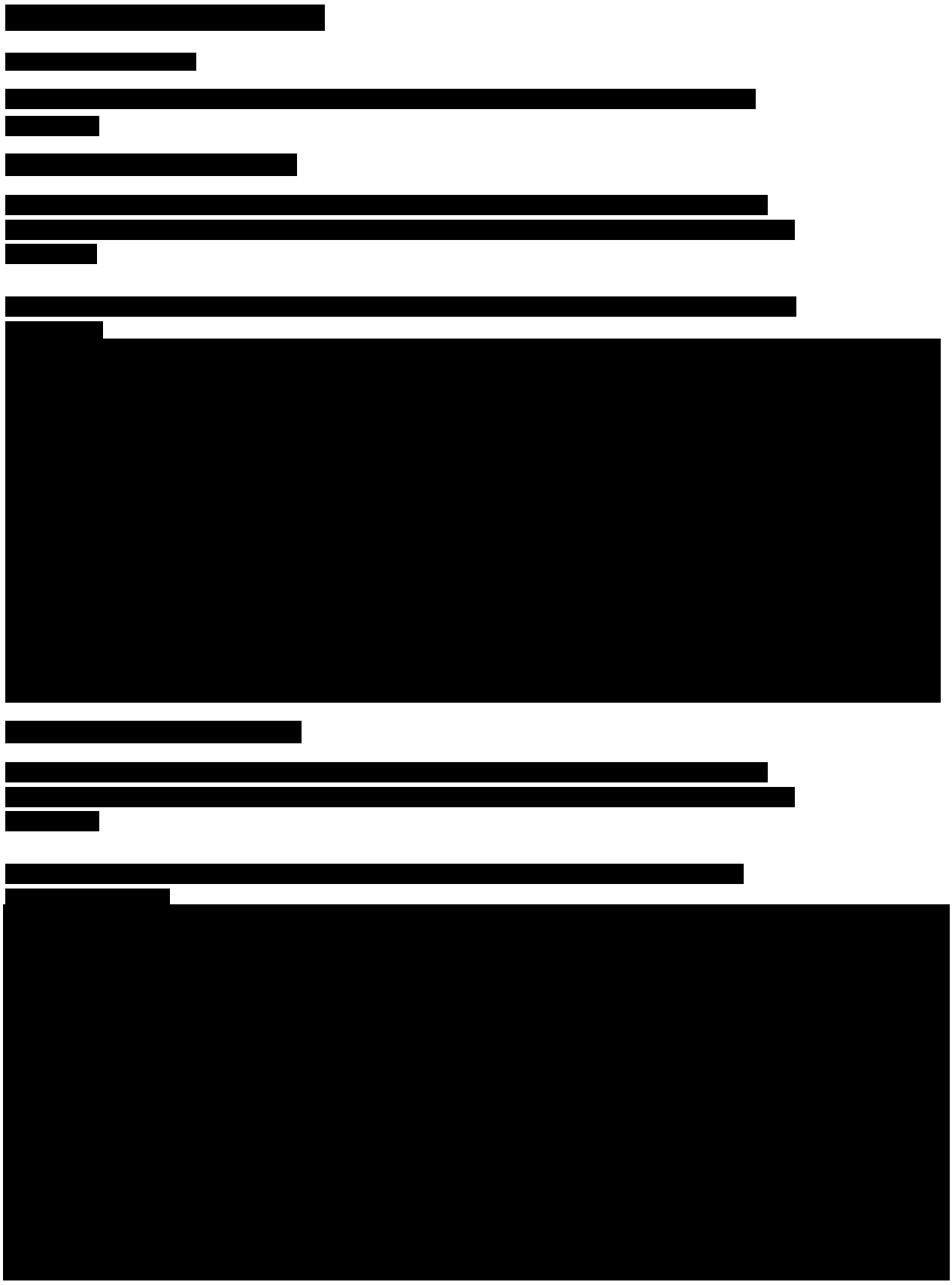
Time to PSA progression

Figure 49: Time PSA Progression Matrix total population: HR [95% Confidence intervals], p(HR<1), random effects

TTPSA	APA+ADT	Radioth+ADT	PL+ADT
APA+ADT		0.34 [0.056; 2.08] 91%	0.27 [0.075; 0.95] 98%
Radioth+ADT	2.94 [0.481; 17.71] 9%		0.78 [0.217; 2.75] 73%
PL+ADT	3.76 [1.049; 13.37] 2%	1.28 [0.363; 4.60] 27%	

Comparators are ordered according to the SUCRA. Cells contain HR with [95% Confidence intervals], and P(HR<1) (row vs column). Abbreviations: ADT = androgen deprivation therapy; APA = apalutamide; HR = hazard ratio; P = probability; PL = placebo; PSA = prostate-specific antigen; Radioth = radiation therapy; TTPSA: time to PSA progression.

The scenarios for HVD and LVD have not been run because of no data available.



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Appendix H – Literature search for HRQoL data

A systematic literature review was conducted to identify relevant HRQoL data for adults with mHSPC (original search in 2015 and updated 6 times since). Data presented in economic evaluations, utility elicitation studies, published models, RCTs, validation studies, mapped values studies and technology assessments were eligible for inclusion in the review and the reference lists within reviews were checked for additional references.

The following electronic databases were searched

Topic	Electronic Literature Database
HRQL/utilities	• EMBASE® • MEDLINE®, MEDLINE In Process® • National Health Service Economic Evaluations Database (NHS EED)Health technology assessment (HTA) Database
Economic evaluations, and cost and resource use	• EMBASE® • MEDLINE®, MEDLINE In Process® • National Health Service Economic Evaluations Database (NHS EED) • Health technology assessment (HTA) Database • EconLit

The followed list of conference searched, by topic

Topic	Conferences
HRQL/utilities	• American Society of Clinical Oncology (ASCO) Annual Meeting • American Society of Clinical Oncology Genitourinary Cancers Symposium (ASCO GU) • American Urological Association (AUA) Annual Meeting • European Association of Urology (EAU) Annual Congress • European Cancer Organisation (ECCO) Congress (except for 2018 as abstracts were not publicly available) • European Society for Medical Oncology (ESMO) Congress • International Society for Quality of Life Research (ISOQOL)
Economic evaluations, and cost and resource use	• American Society of Clinical Oncology (ASCO) Annual Meeting • American Society of Clinical Oncology Genitourinary Cancers Symposium (ASCO GU) • American Urological Association (AUA) Annual Meeting • European Association of Urology (EAU) Annual Congress • European Cancer Organisation (ECCO) Congress (except for 2018 as abstracts were not made publicly available) • European Society for Medical Oncology (ESMO) Congress • International Society for Pharmacoeconomics and Outcomes Research (ISPOR) all meetings

No studies from this literature search are included in this submission since no studies were reporting utility scores and hence none were appropriate for cost-effectiveness analysis.

EQ-5D-5L HUI from ITT population of the TITAN trial was the primary source of health state utility values for both the pre-progression and post-progression health states.

Therefore we have not included the full literature search with its updates, in line with guidance from DMC.

Appendix I Mapping of HRQoL data

As utility values were derived from EQ-5D-5L data gathered directly from patients in the TITAN trial, mapping was not required.

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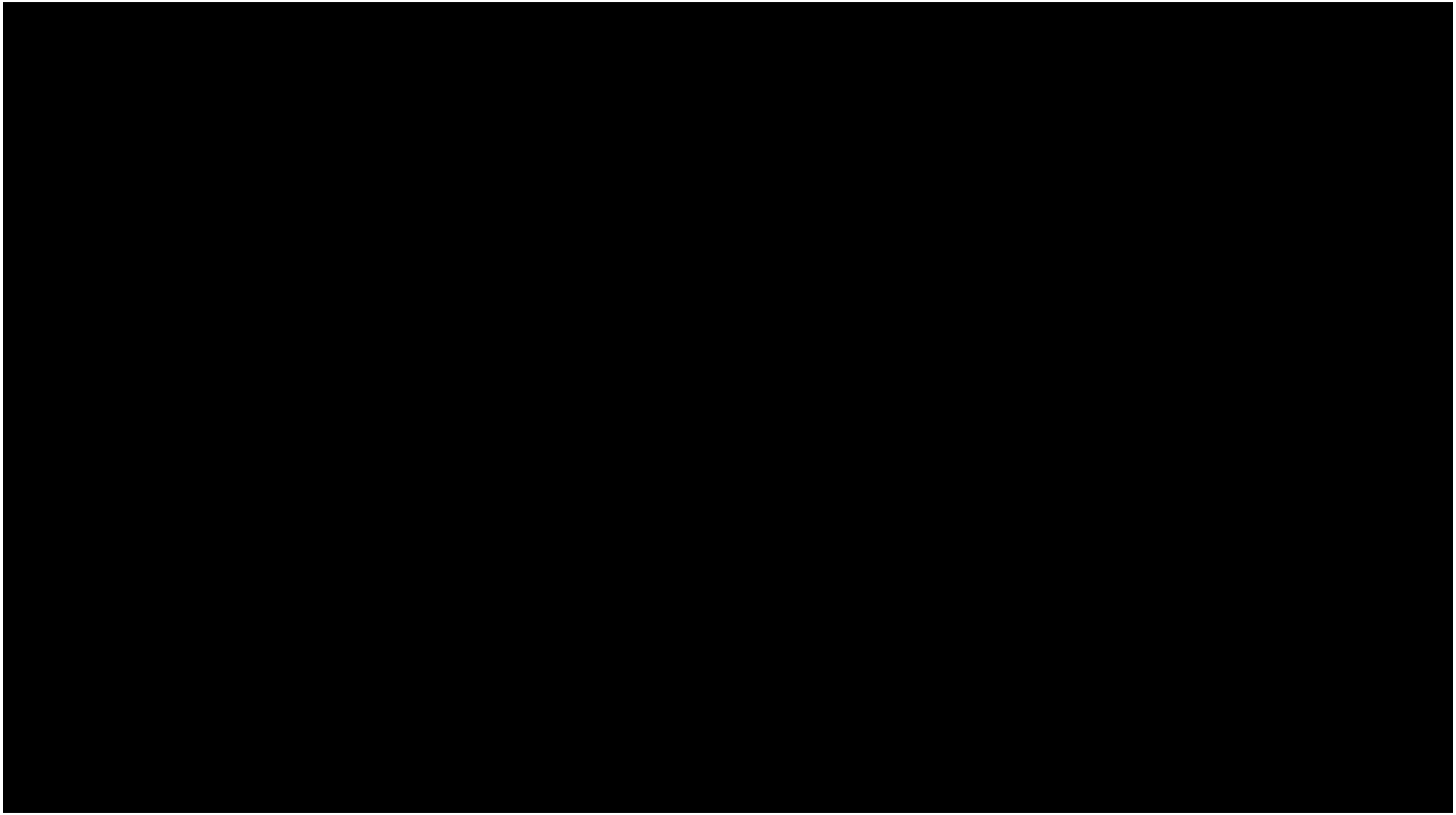

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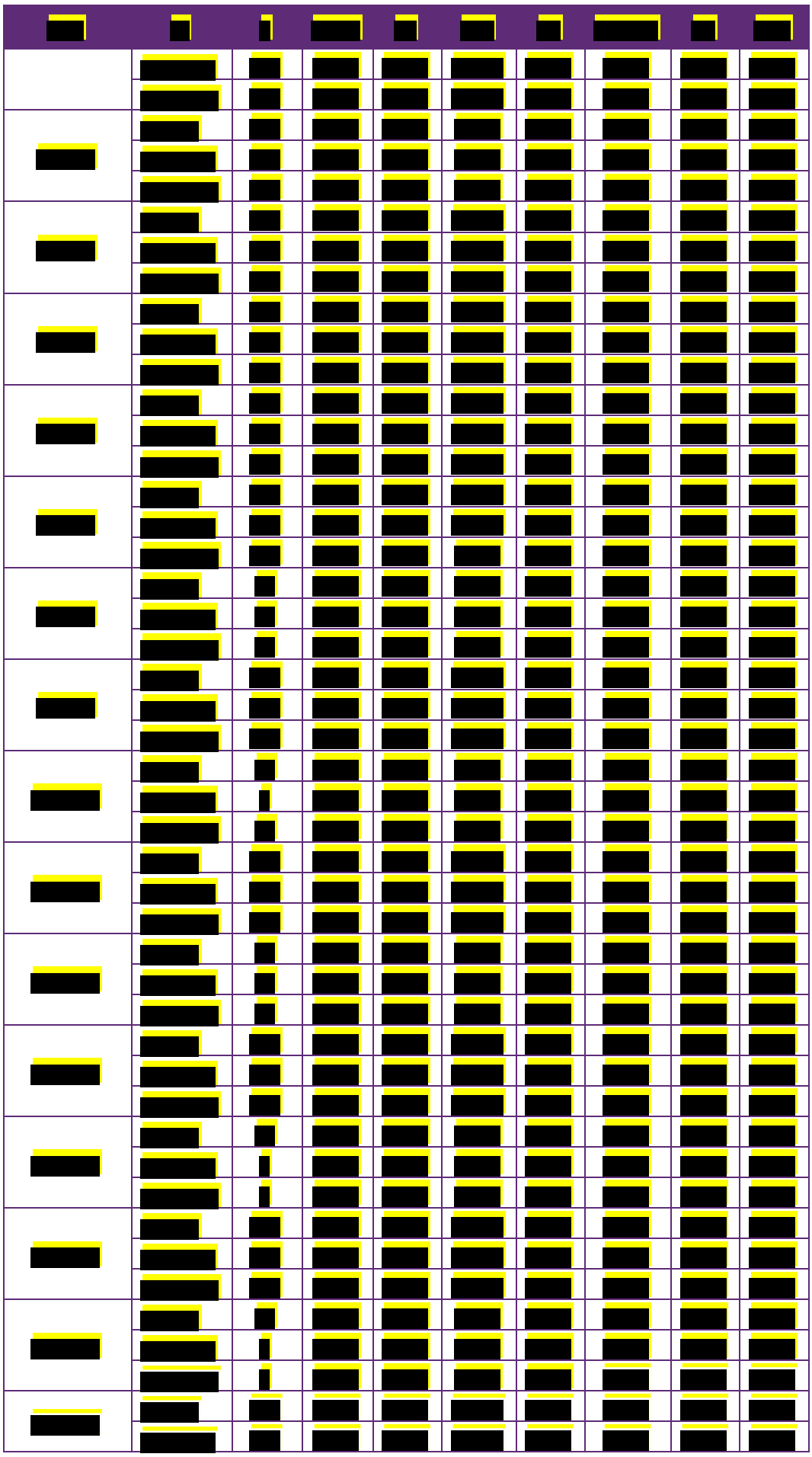

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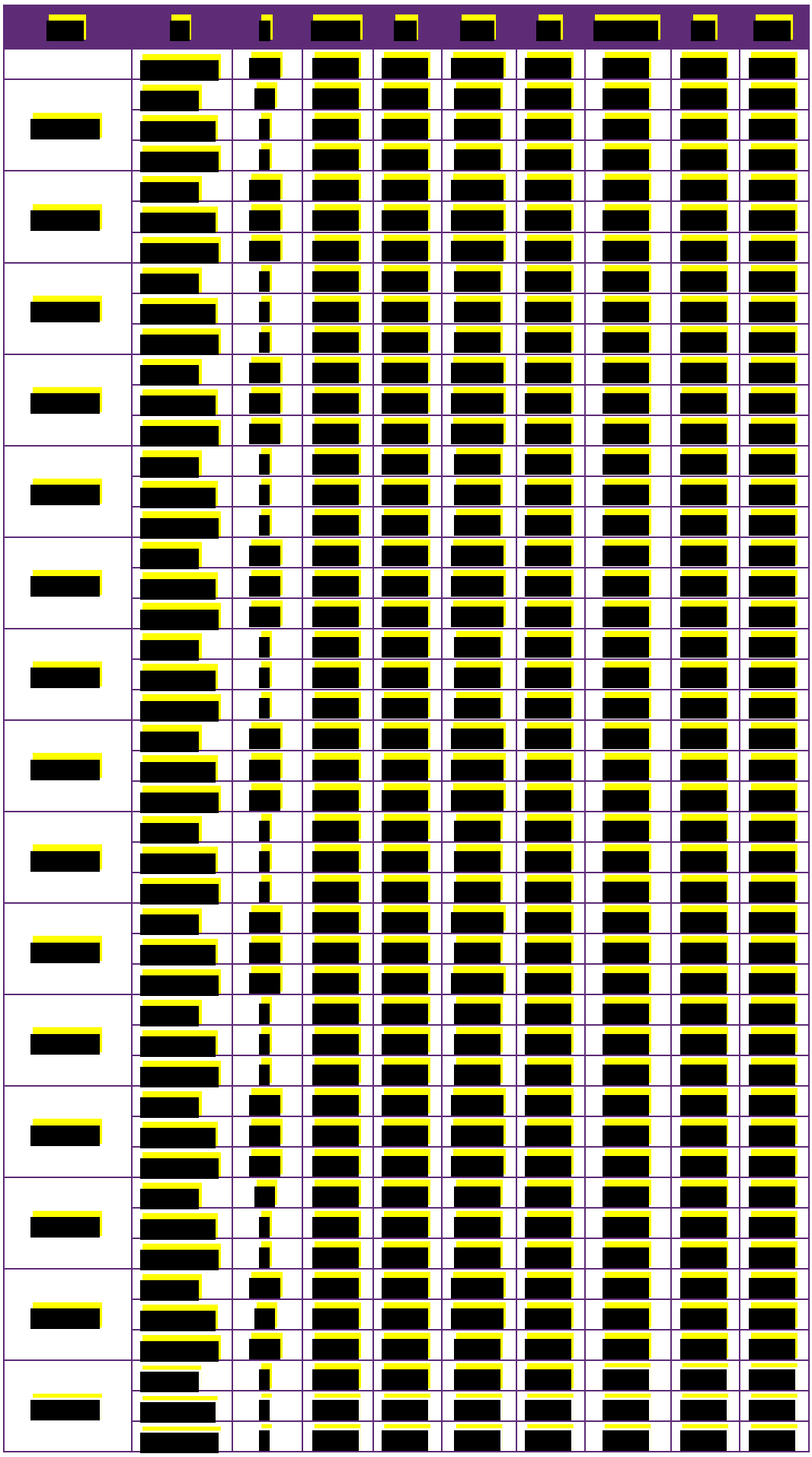

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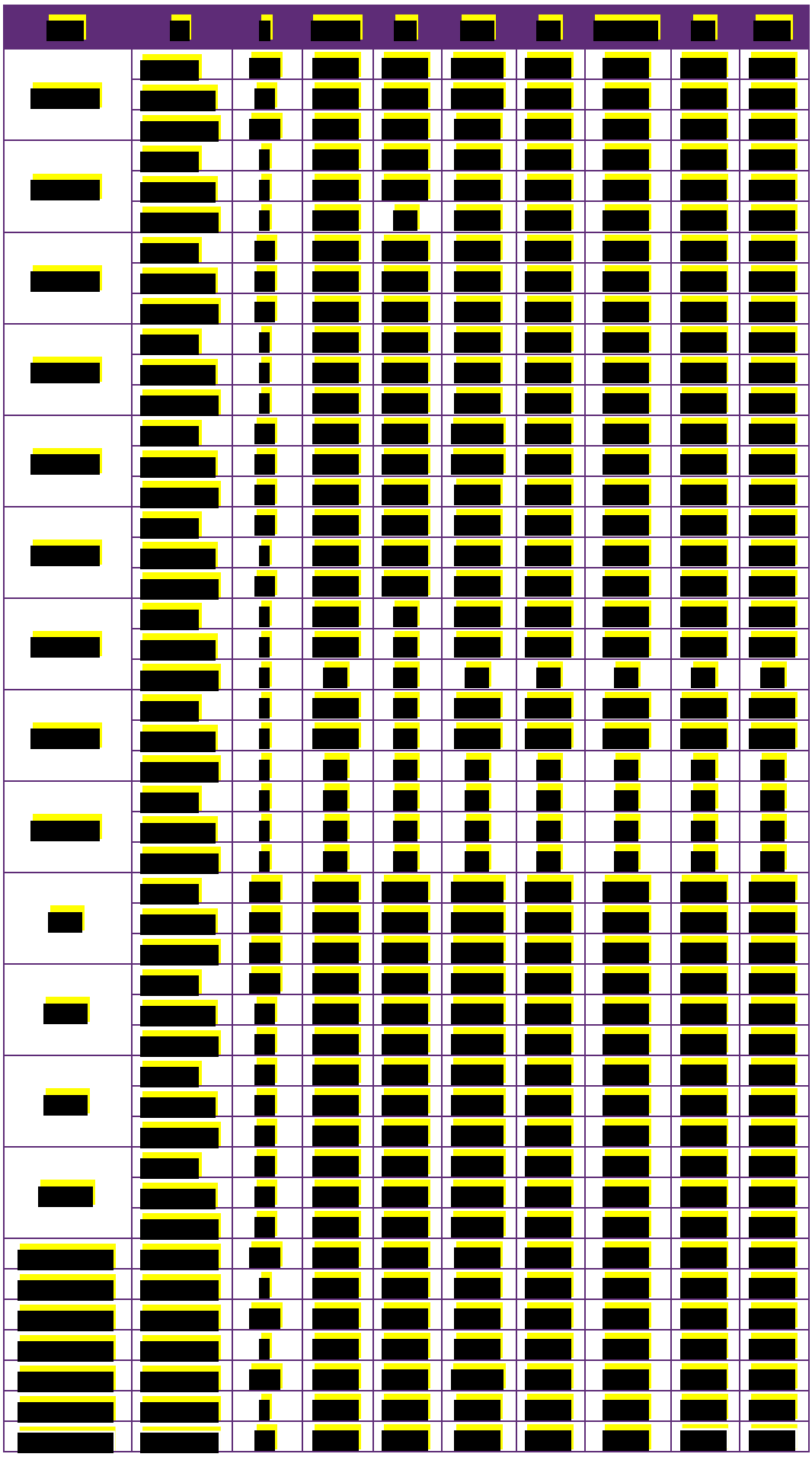

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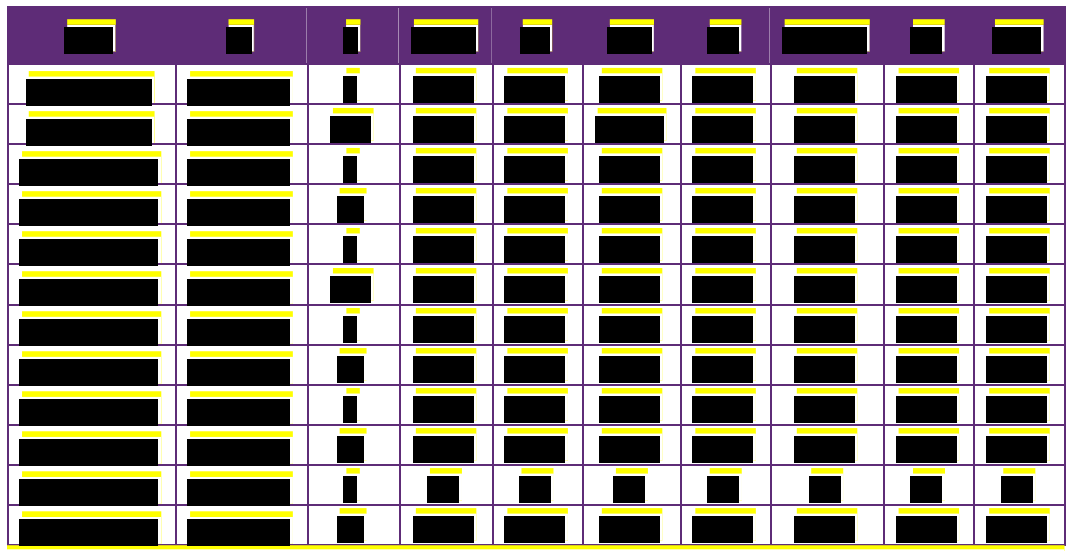

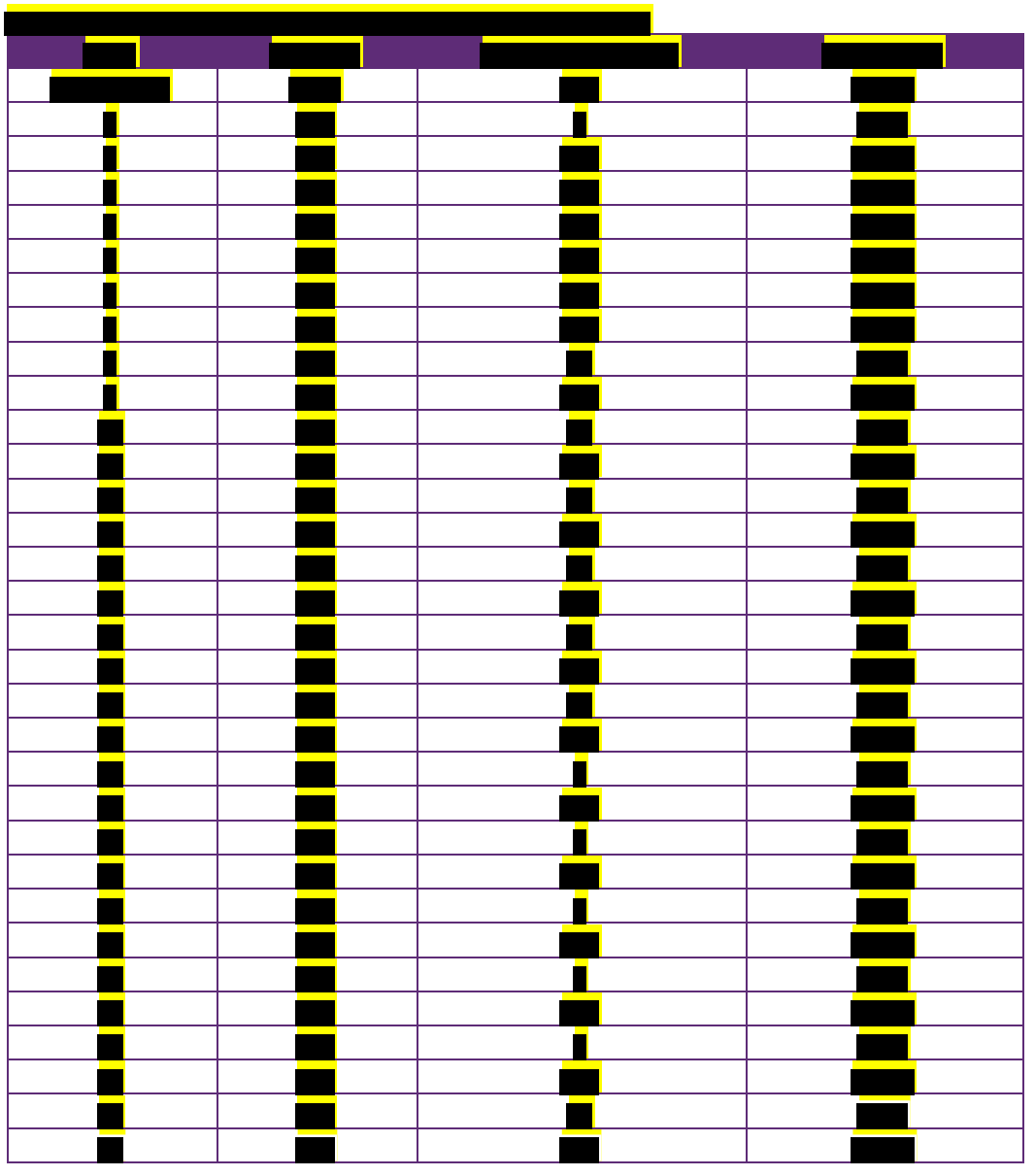

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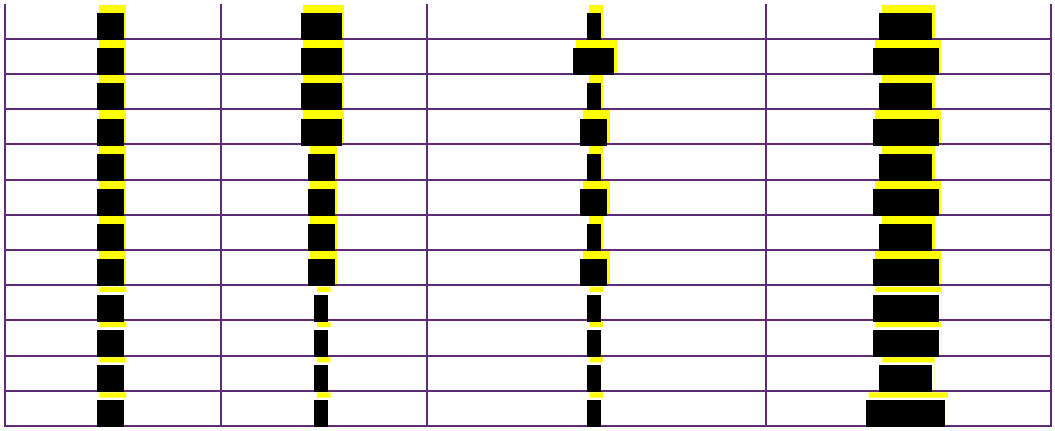

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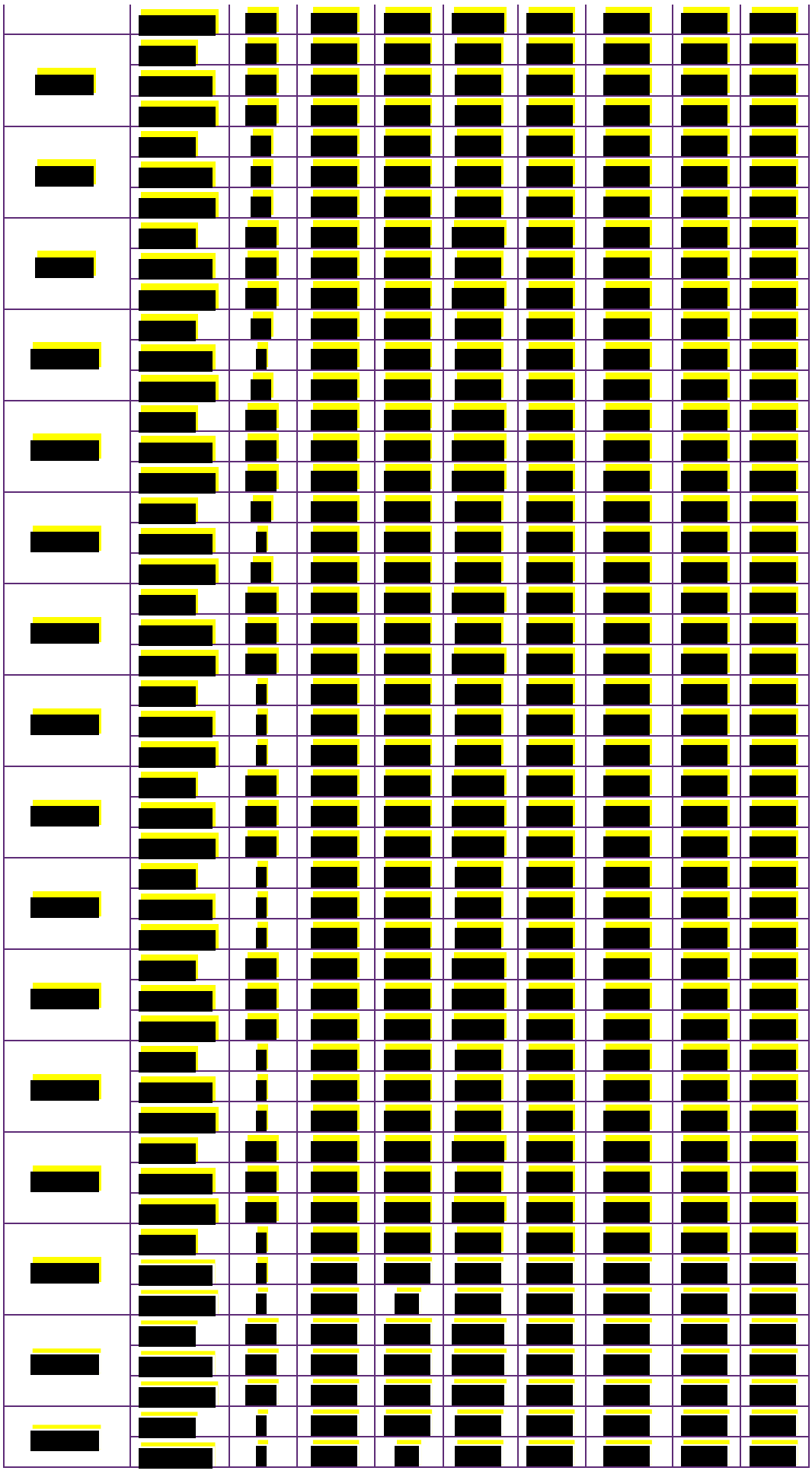

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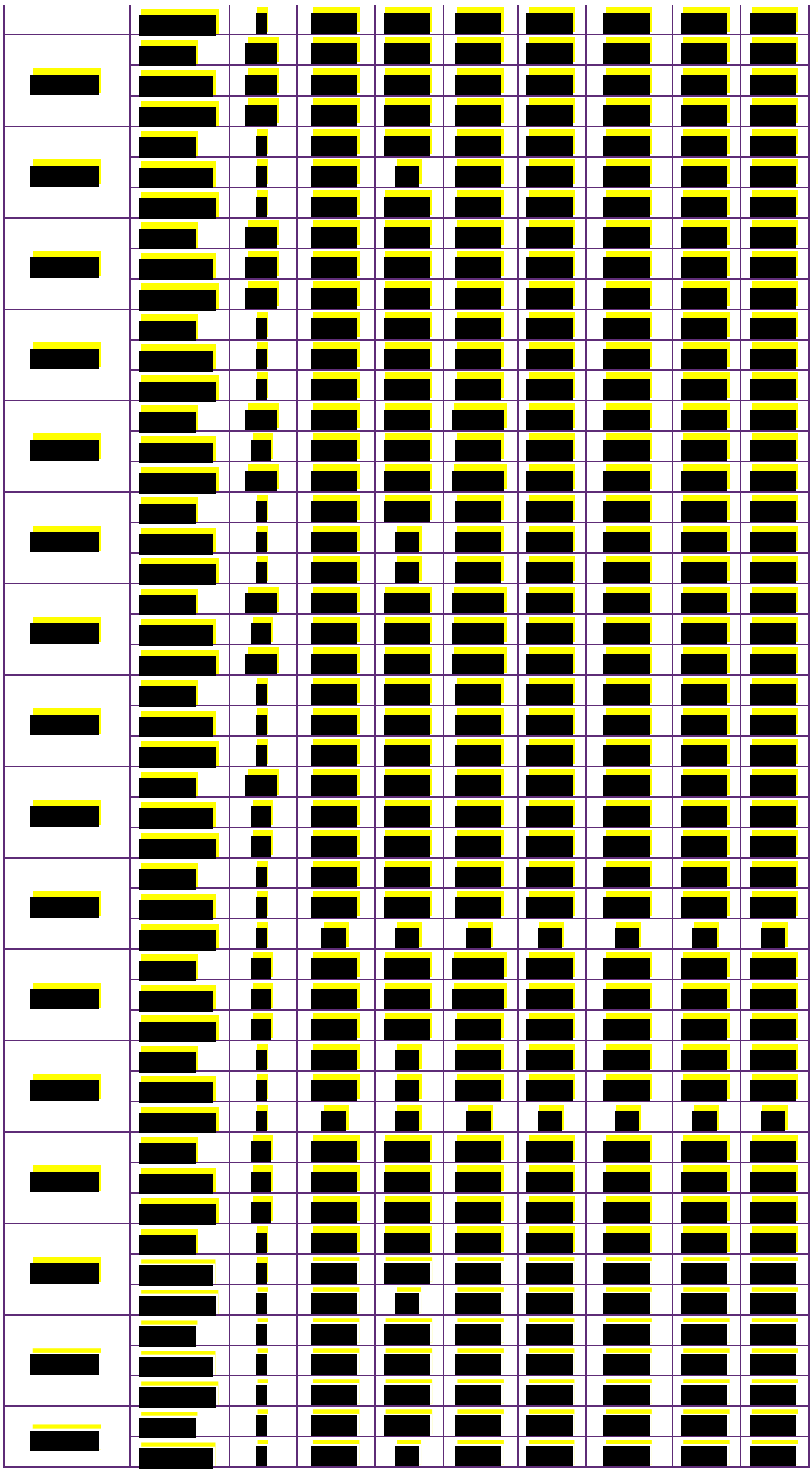

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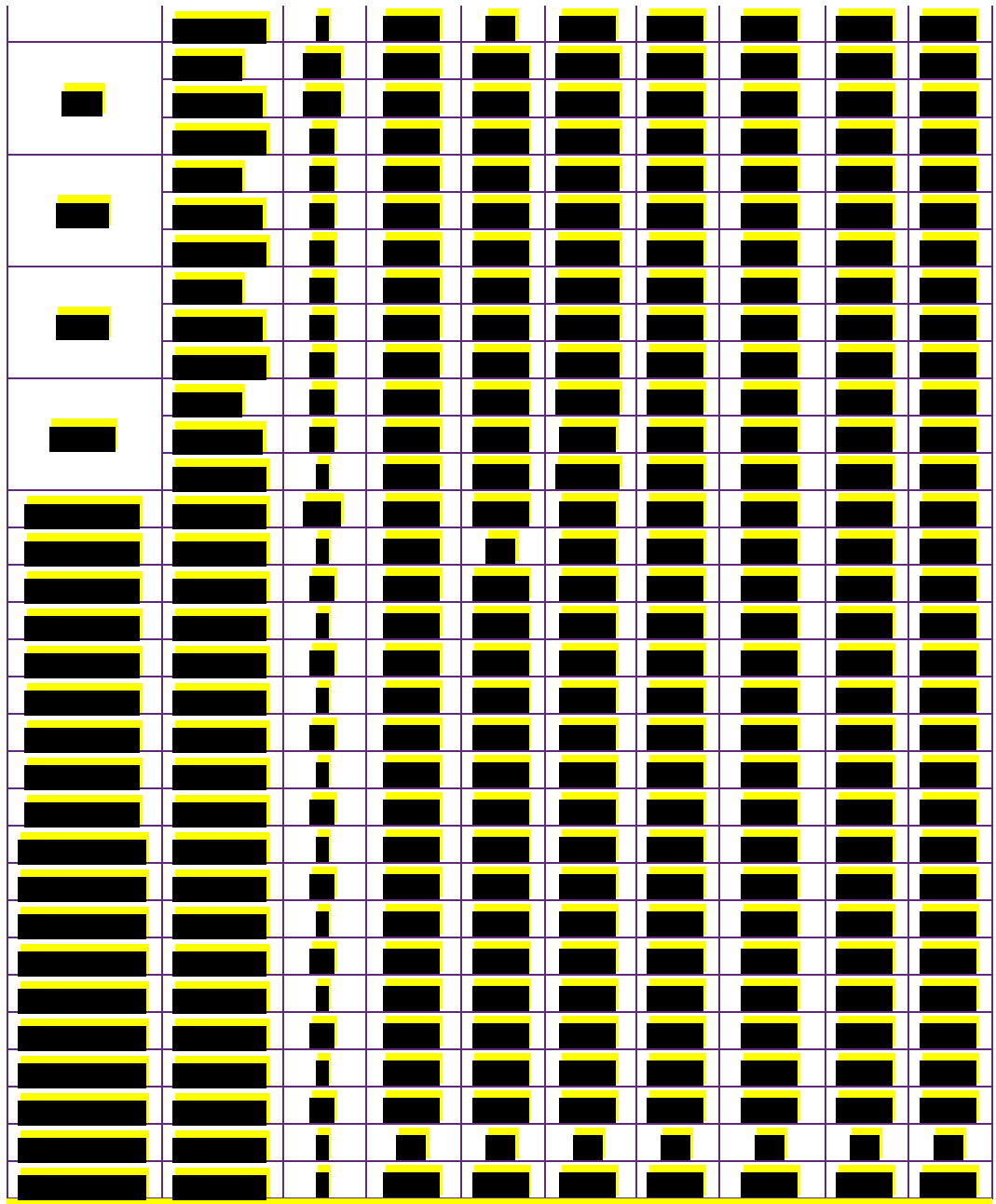

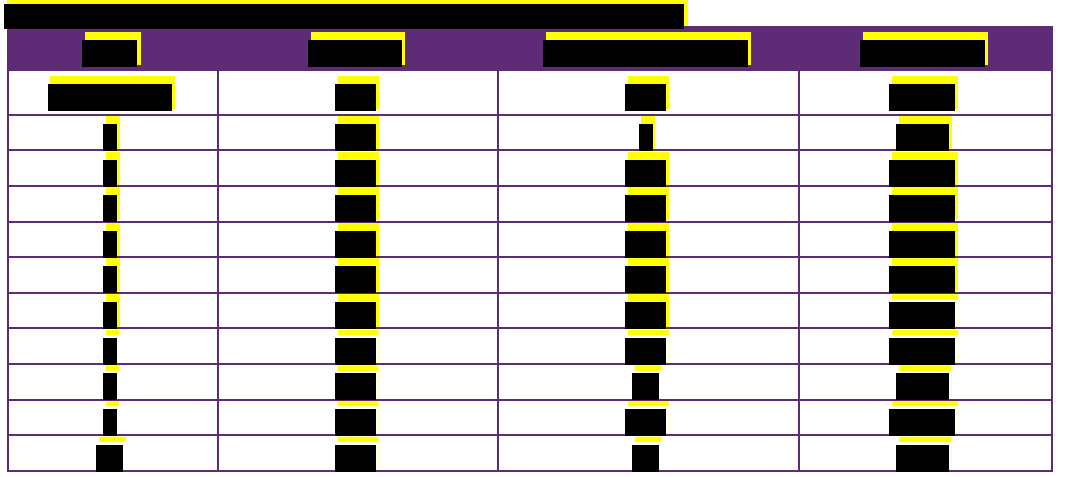

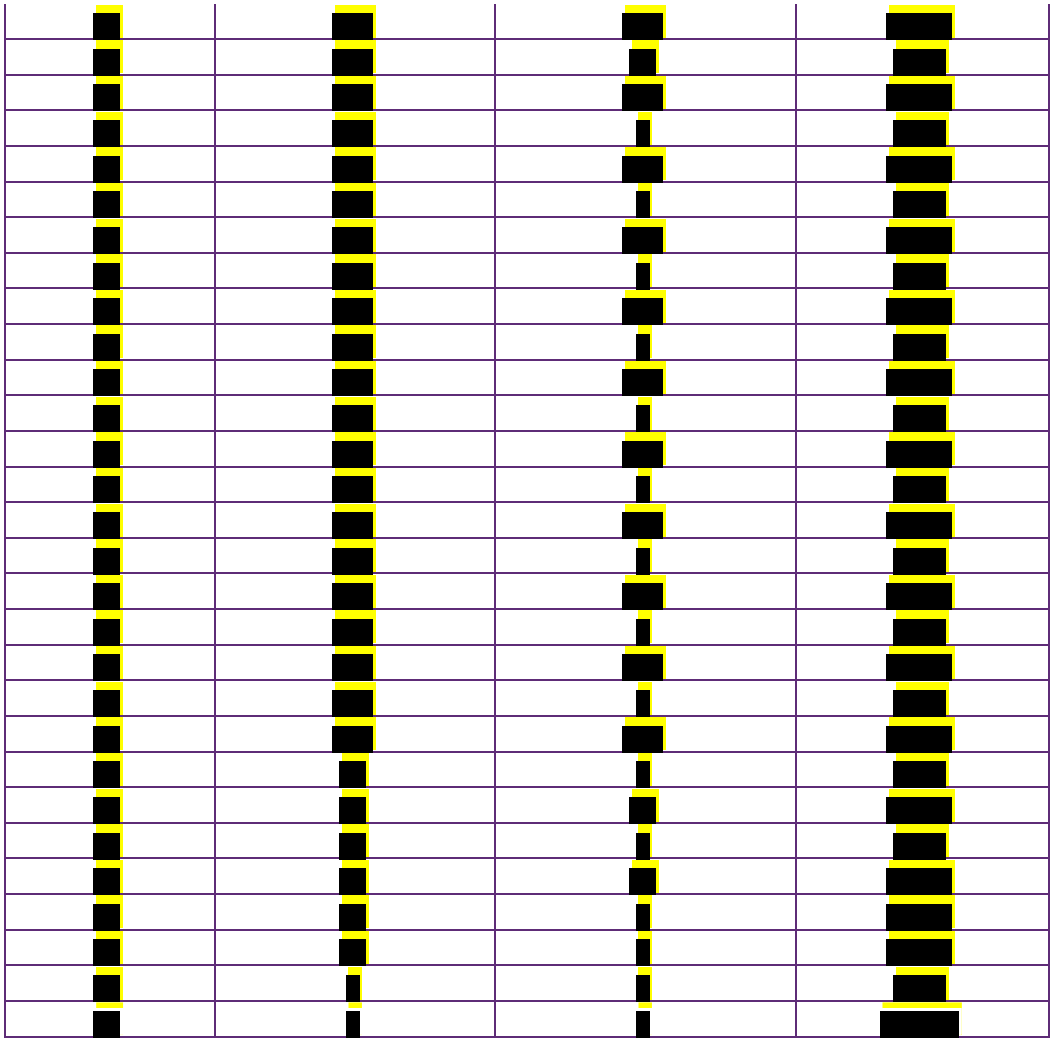

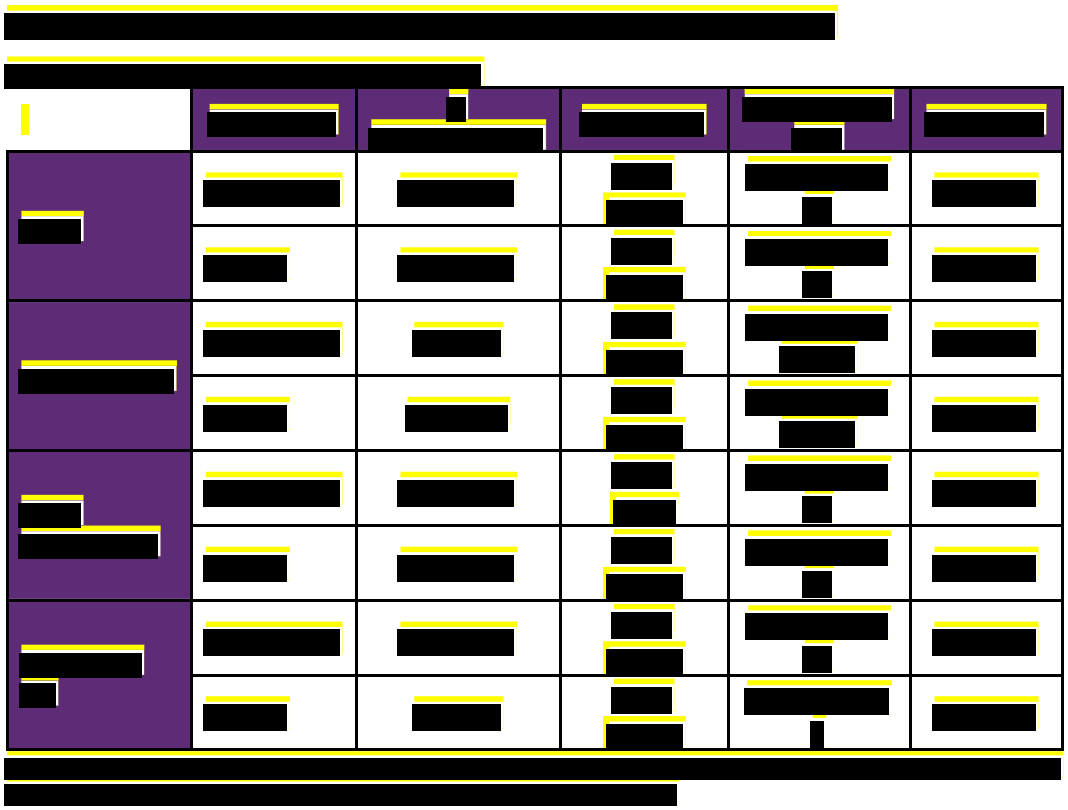

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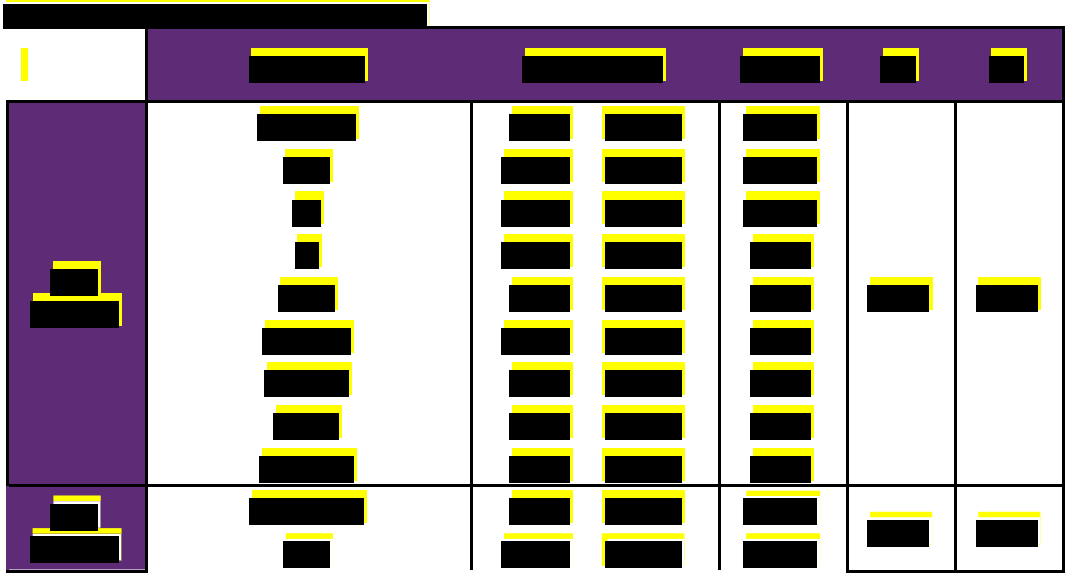

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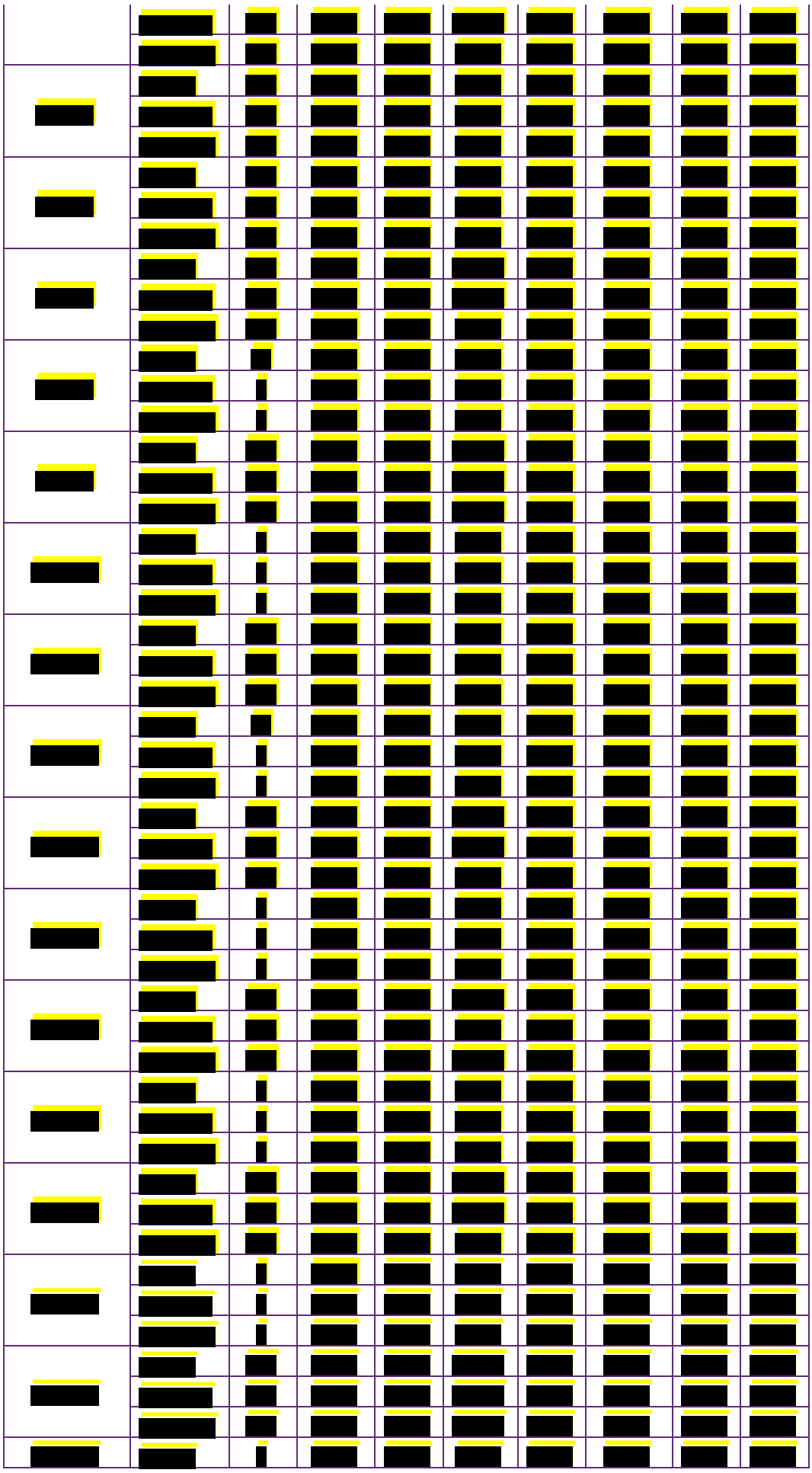

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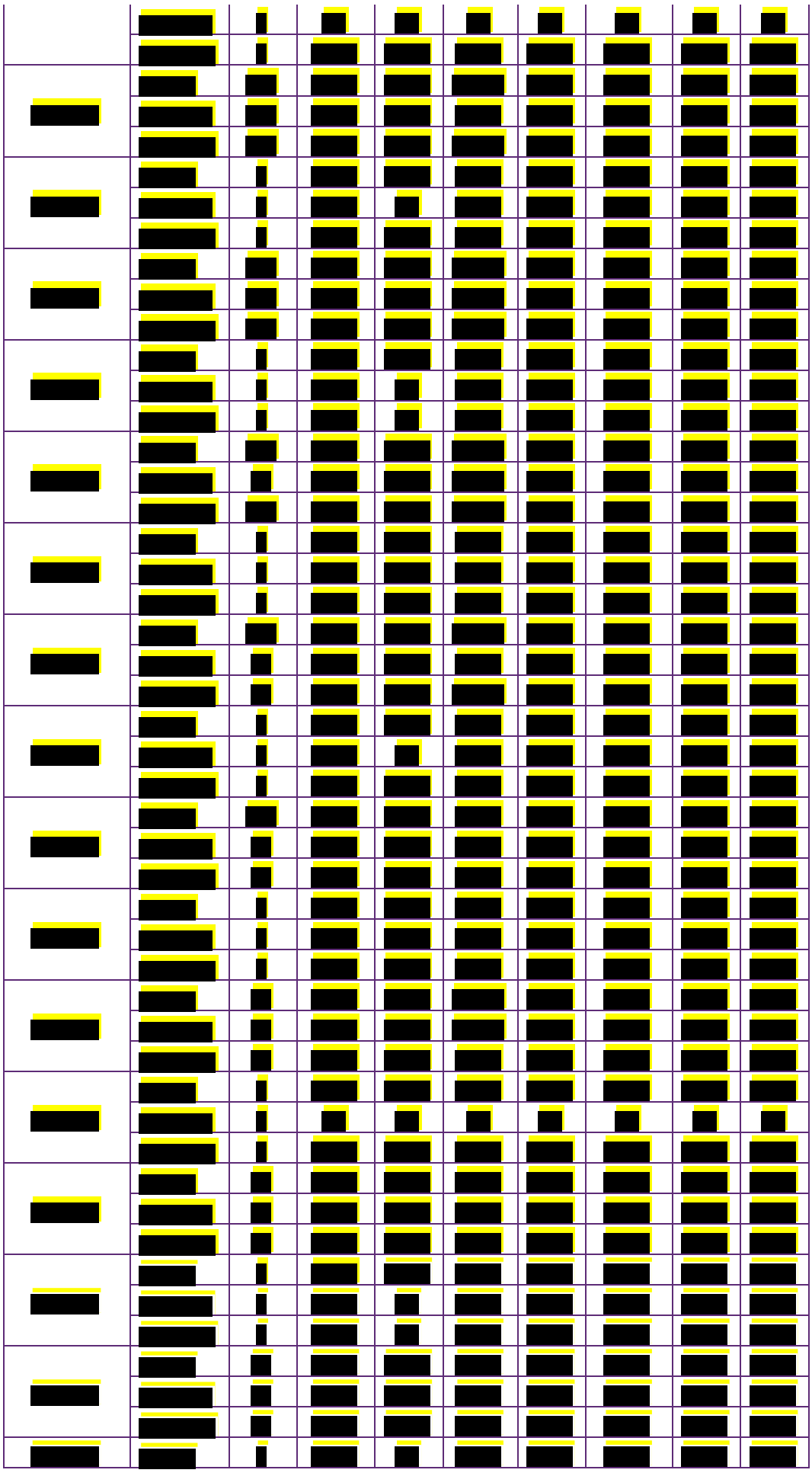

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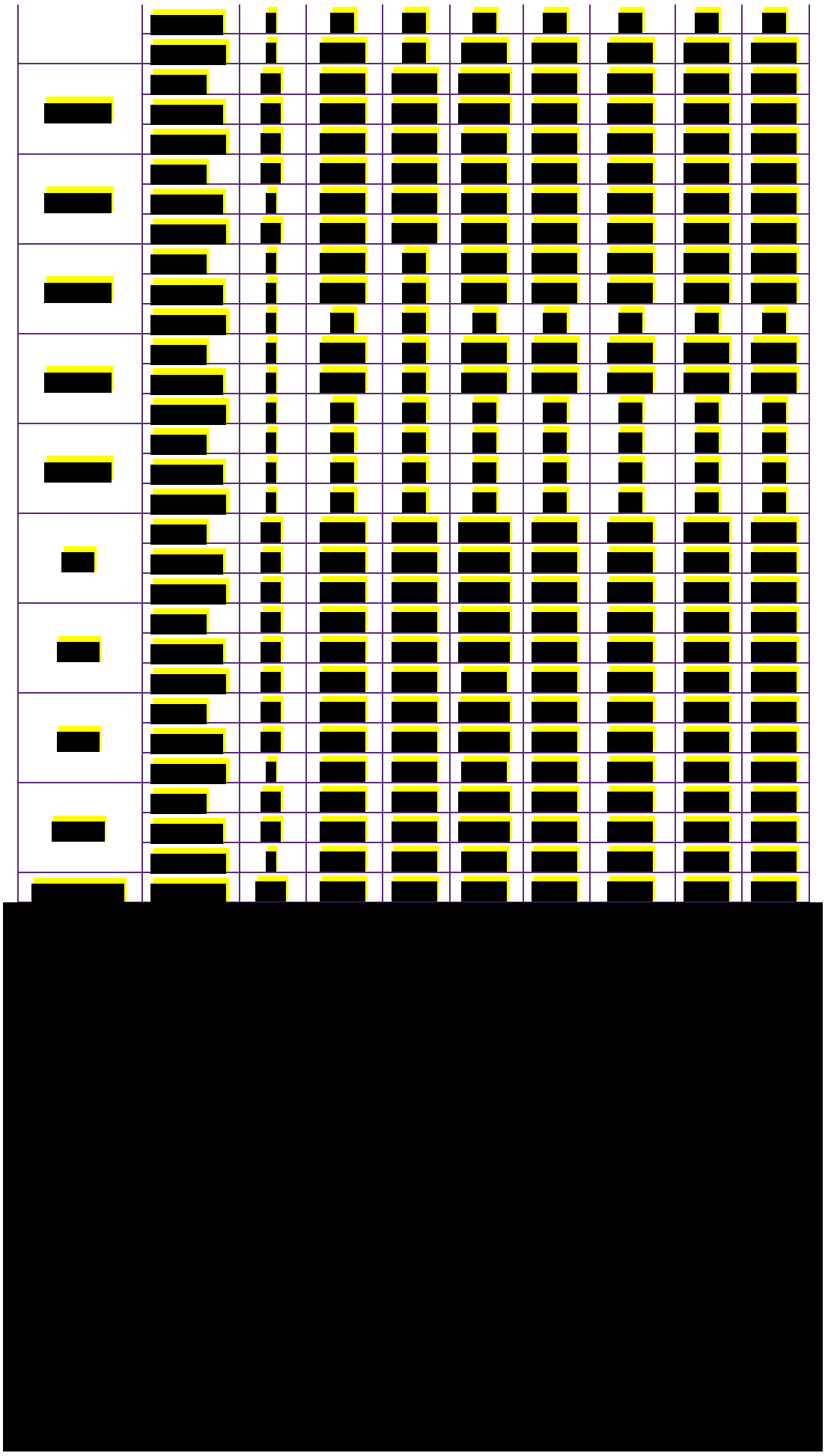

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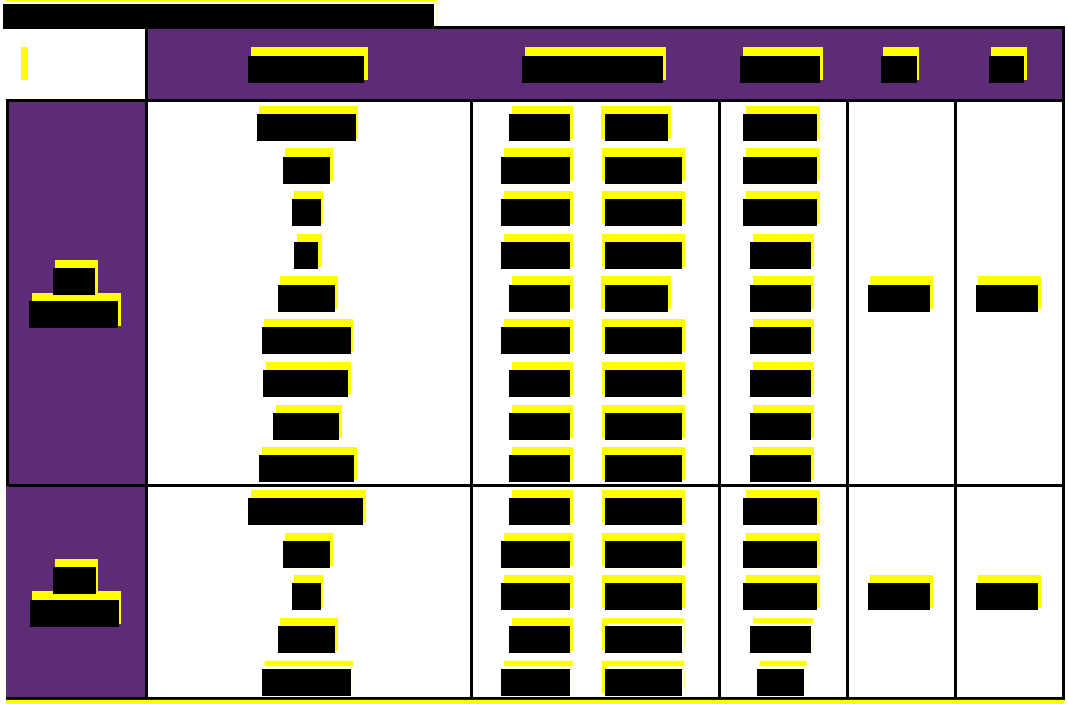

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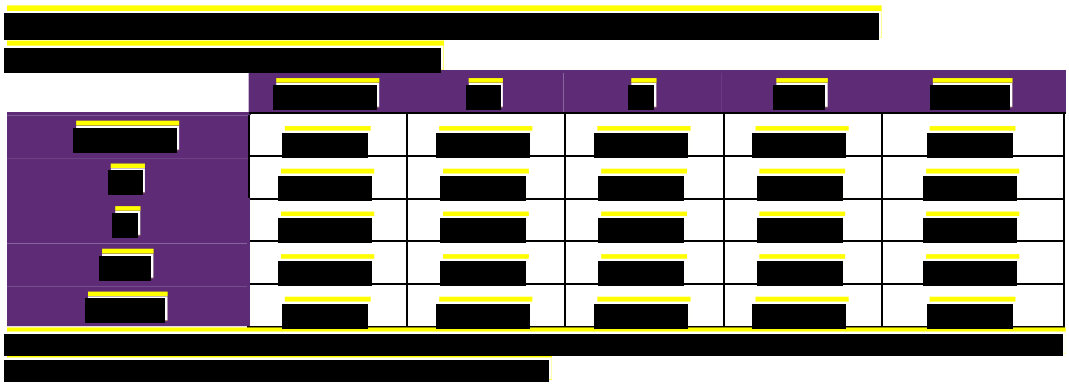

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[14] Jensen CE, Sørensen SS, Gudex C, Jensen MB, Pedersen KM, Ehlers LH. The Danish EQ-5D-5L Value Set: A Hybrid Model Using cTTO and DCE Data. Applied Health Economics and Health Policy. 2021 Feb 2:1-3.

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