Single Technology Appraisal

Darolutamide with androgen deprivation therapy and docetaxel for treating hormone-sensitive metastatic prostate cancer [ID3971]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

Pre-technical engagement documents

1. **Company submission from Bayer:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Prostate Cancer UK
   b. Tackle Prostate Cancer

4. **External Assessment Report** prepared by Southampton Health Technology Assessment Centre

5. **External Assessment Report – factual accuracy check**

Post-technical engagement documents

6. **Technical engagement response from company**

7. **Technical engagement responses and statements from stakeholders:**
   a. Prostate Cancer Research
   b. Prostate Cancer UK
   c. Tackle Prostate Cancer

8. **External Assessment Group critique of company response to technical engagement** prepared by Southampton Health Technology Assessment Centre

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Darolutamide with androgen deprivation therapy and docetaxel for treating hormone-sensitive metastatic prostate cancer [ID3971]

Document B

Company evidence submission

September 2022

File name	Version	Contains confidential information	Date
ID3971_NICE STA_Darolutamide+docetaxel+ADT in mHSPC_Doc B_redacted_FINAL_v2.0_23Nov22	V2.0	Yes	23Nov22

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Abbreviations

Abbreviation	Definition
ADT	Androgen deprivation therapy
AE	Adverse event
AIC	Akaike information criterion
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AR	Androgen receptor
ARTA	Androgen receptor targeted agent
AST	Aspartate aminotransferase
BIA	Budget impact analysis
BIC	Bayesian information criterion
BPI-SF	Brief Pain Inventory – Short Form
CI	Confidence interval
CNS	Central nervous system
CROD	CRPC or death
CRPC	Castration-resistant prostate cancer
DSU	Decision support unit
EAU	European Association of Urology
ECOG	Eastern Cooperative Oncology Group
eGFR	Estimate glomerular filtration rate
ESMO	European Society for Medical Oncology
FAS	Full analysis set
GABAA	γ-aminobutyric acid type A
GnRH	Gonadotropin-releasing hormone
HR	Hazard ratio
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
iNMB	Incremental net monetary benefit
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
LYG	Life years gained
mCRPC	Metastatic castration-resistant prostate cancer
MHRA	Medicines and Healthcare products Regulatory Agency
mHSPC	Metastatic hormone-sensitive prostate cancer
NCCN-FACT-FPSI-17	National Comprehensive Cancer Network Functional Assessment of Cancer Therapy Prostate Symptom Index

Abbreviation	Definition
NE	Not estimable
NHS	National Health Service
NMA	Network meta-analysis
nmCRPC	Non-metastatic castration-resistant prostate cancer
NR	Not reached
OS	Overall survival
OWSA	One-way sensitivity analysis
pDDI	Potential drug-drug interactions
PFS	Progression-free survival
PSA	Prostate-specific antigen
QALY	Quality-adjusted life year
QQ	Quantile-quantile
rPFS	Radiological progression-free survival
SAS	Safety analysis set
SSE	Symptomatic skeletal event
SSE-FS	Symptomatic skeletal event-free survival
SLR	Systematic literature review
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TSD	Technical support document
TTCROD	Time to CRPC or death
ULN	Upper limit of normal

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

This submission covers the technology's full marketing authorization for this indication: 'for the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel'. Further details are provided in the decision problem summary presented in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with hormone-sensitive metastatic prostate cancer	As per final scope	Not applicable
Intervention	Darolutamide with androgen deprivation therapy and docetaxel	As per final scope	Not applicable
Comparator(s)	• Androgen deprivation therapy alone (including orchidectomy, luteinising hormone-releasing hormone agonist therapy, degarelix, monotherapy with bicalutamide) • Docetaxel with androgen deprivation therapy • Enzalutamide with androgen deprivation therapy	As per final scope	Not applicable
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rate	The outcome measures to be considered include: • Overall survival • Time to castration-resistant prostate cancer (CRPC)	Time to CRPC is a secondary endpoint in the ARASENS study and is composed of biochemical progression and radiological progression. Imaging was to be performed on a yearly basis after the end of docetaxel treatment and in case of signs of clinical progression at the investigator's discretion.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Prostate-specific antigen response • Time to prostate-specific antigen progression • Adverse effects of treatment • Health-related quality of life	• Prostate-specific antigen (PSA) response • Time to pain progression • Symptomatic skeletal event-free survival (SSE-FS) • Time to first symptomatic skeletal event (SSE) • Time to initiation of subsequent systemic antineoplastic therapy • Time to worsening of disease-related physical symptoms • Time to initiation of opioid use for ≥ 7 consecutive days • Time to PSA progression • Adverse effects of treatment • Health-related quality of life	Therefore, imaging could be performed at any time in case of PSA progression, symptomatic progressive disease or change of antineoplastic therapy. The rationale for this schedule was to mimic a real-world setting where imaging is driven by clinical signs and symptoms or biochemical progression, compared to rPFS which is based on a fixed assessment schedule every few months. Time to CRPC is therefore more aligned with clinical practice and is the progression-free survival outcome measure that was collected in ARASENS and will be used in the appraisal.
Subgroups	If the evidence allows, the following subgroups of people will be considered: • People with newly diagnosed metastatic prostate cancer • People with high-risk metastatic prostate cancer	The following prespecified subgroups were analysed in ARASENS: • Extent of disease • Alkaline phosphatase (ALP) at baseline • Age category • Race • Geographical region • Prostate-specific antigen (PSA) values • Eastern Cooperative Oncology Group (ECOG) performance status	There is inconsistent use of 'newly diagnosed' and 'high risk' subgroups across all mHSPC trials. These sub-populations would be most relevant to abiraterone, which is specifically licensed for the newly diagnosed, high risk population. However, abiraterone is not a relevant comparator in this appraisal and it has not been approved for use in NHS practice. In the ARASENS study: • Both patients with M1 (synchronous) and M0 (metachronous) disease at initial diagnosis have been included. The

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		• Gleason score • Metastasis at initial diagnosis	majority of patients (86%) were de novo and the results in ARASENS have been consistent across these subgroups • Patients were stratified by extent of disease (i.e. non-regional lymph node metastasis, bone metastasis, and visceral metastasis). The efficacy observed in ARASENS was consistent across these three subgroups. There was no classification by 'high-risk' disease in ARASENS The appraisal is focused on the ITT population on which the ARASENS study was designed and powered to detect an effect, and not on subgroups for which the study was not powered.

Key: ADT, androgen deprivation therapy; ALP, alkaline phosphatase; CRPC, castration-resistant prostate cancer; ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; PSA, prostate-specific antigen; SSE, symptomatic skeletal event; SSE-FS, symptomatic skeletal event-free survival.

B.1.2 Description of the technology being appraised

A summary description of darolutamide is presented in Table 2.

The draft summary of product characteristics (SmPC) for the licence extension to the mHSPC patient population is presented in Appendix C. The UK Public Assessment Report (UKPAR) can be provided on receipt.

Darolutamide in combination with docetaxel and ADT offers the first multimodal, triplet combination therapy option for patients with mHSPC. Darolutamide is a structurally distinct non-steroidal androgen receptor (AR) inhibitor for the treatment of patients with prostate cancer. It binds with high affinity and selectivity to AR when compared to known second-generation anti-androgens.[1] Both darolutamide and its active metabolite inhibit testosterone-induced translocation of AR to the nucleus, decreasing the activation of genes required for the growth and survival of prostate cancer cells.[1, 2] Combining darolutamide with ADT and docetaxel gives a multimodal approach to the treatment of mHSPC: docetaxel targets the androgen-insensitive component of the tumour, thus addressing tumour heterogeneity; the AR axis is targeted centrally with ADT; and by adding darolutamide, a highly effective AR antagonist, targeting of the AR axis is optimized.

The mechanism of action of darolutamide is depicted in Figure 1.

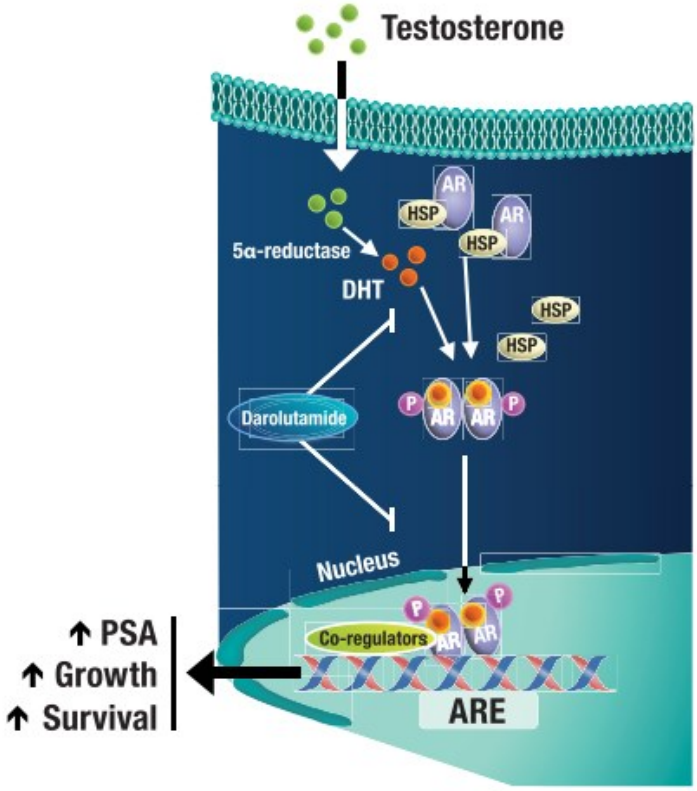
Table 2: Technology being evaluated

UK approved name and brand name	Darolutamide (Nubeqa®)
Mechanism of action	Darolutamide is an androgen receptor (AR) inhibitor with a flexible polar-substituted pyrazole structure that binds with high affinity directly to the receptor ligand binding domain (Figure 1). It competitively inhibits androgen binding, AR nuclear translocation, and AR mediated transcription, which are components of the AR signalling pathway.[1, 3] Its distinct structure offers the potential for fewer and less severe toxic central nervous system (CNS)-related effects due to its low penetration of the blood-brain barrier and low binding affinity for γ-aminobutyric acid type A (GABAA) receptors.[1, 4, 5] Treatment with darolutamide decreases prostate tumour cell survival and proliferation leading to potent antitumour activity. Keto-darolutamide, a major

	metabolite of darolutamide, also exhibits similar in vitro activity to darolutamide.
Marketing authorisation/CE mark status	The application for MHRA filing was submitted in [redacted] for a marketing authorization extension. The marketing authorization for this licence extension was granted in November 2022. The previous indication for darolutamide is the treatment of 'adult men with non-metastatic castration-resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease'. Marketing authorization was granted on 27 March 2020 for this indication.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The new indication for darolutamide is for 'the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel'
Method of administration and dosage	**Darolutamide:** The recommended dose of darolutamide is 600 mg (two 300 mg film-coated tablets) taken orally, twice daily, equivalent to a total daily dose of 1200 mg. Tablets should be swallowed whole and taken with food. In patients with severe renal impairment (eGFR 15–29 mL/min/1.73 m^2) not receiving haemodialysis or moderate/severe hepatic impairment (Child-Pugh Classes B and C), the recommended dose of darolutamide is 300 mg twice daily (equivalent to a total daily dose of 600 mg). Patients receiving darolutamide should also receive a gonadotropin-releasing hormone (GnRH) analogue concurrently or should have had a bilateral orchidectomy. **Docetaxel:** The recommended dose of docetaxel is 75 mg/m^2 as an IV infusion every 3 weeks for 6 cycles. Prednisone or prednisolone 5 mg orally twice daily may be administered continuously. To prevent hypersensitivity reactions and fluid retention, the recommended pre-medication regimen is oral dexamethasone 8 mg, 12 hours, 3 hours and 1 hour before the docetaxel infusion. In patients with serum bilirubin > upper limit of normal (ULN) and/or alanine aminotransferase (ALT) and aspartate aminotransferase (AST) > 3.5 times the ULN associated with alkaline phosphatase > 6 times the

	ULN, no dose reduction can be recommended and docetaxel should not be used unless strictly indicated. Docetaxel should be administered when the neutrophil count is ≥ 1,500 cells/mm^3. In patients who experience either febrile neutropenia, neutrophil count < 500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions or severe peripheral neuropathy during docetaxel therapy, the dose of docetaxel should be reduced to 60 mg/m^2. If the patient continues to experience these reactions at 60 mg/m^2, docetaxel treatment should be discontinued.
Additional tests or investigations	No additional tests or investigations are required. Identification of patients with metastatic hormone-sensitive prostate cancer would occur as part of the regular PSA monitoring and scans within current clinical practice.
List price and average cost of a course of treatment	List price: £4,040.00 (112 x 300mg tablets), for 28 days of treatment.
Patient access scheme (if applicable)	Darolutamide is available to the NHS with a confidential discount of [redacted] on the price per pack
Key: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AR, androgen receptor; CNS, central nervous system; eGFR, estimated glomerular filtration rate; GABAA, γ-aminobutyric acid type A; GnRH, gonadotropin-releasing hormone; IV, intravenous; MHRA, Medicines and Healthcare products Regulatory Agency; mHSPC, metastatic hormone-sensitive prostate cancer; nmCRPC, non-metastatic castration-resistant prostate cancer; ULN, upper limit of normal.	

Figure 1: Darolutamide mode of action



Key: AR, androgen receptor; ARE, androgen-response element; DHT, dihydrotestosterone; HSP, heat shock protein; P, phosphate; PSA, prostate-specific antigen.
Source: Fizazi et al. 2018.[2]

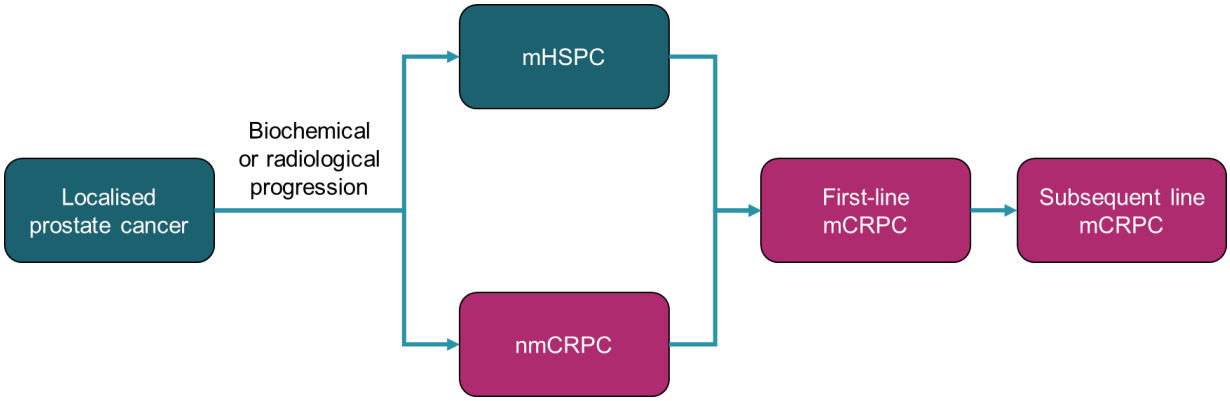
B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

Prostate cancer continues to be the most common cancer diagnosed in males in the UK; it accounted for 1 in 4 (26.3%) male cancer diagnoses in 2017.[6] Risk factors for prostate cancer include age (prostate cancer is most common in men aged 75-79 years), ethnicity (Black African males), a family history of prostate cancer and prostate-specific antigen (PSA) level.[7, 8]

The stages of prostate cancer are shown in Figure 2. In metastatic disease, prostate cancer progresses from the localized site and spreads to more distant parts of the body. The most common site for prostate cancer to spread to is the bones, followed by lymph nodes and viscera (e.g. lung and liver). Patients with metastatic hormone-sensitive prostate cancer (mHSPC) have either not previously received hormone therapy (hormone-naïve), are continuing to respond to hormone therapy, have de novo or synchronous disease, or have metastases after local treatment such as radiotherapy and/or surgery (metachronous).[9, 10] Most patients with mHSPC will develop metastatic hormone-relapsed prostate cancer (mHRPC), defined as disease progression, despite treatment to achieve castrate testosterone levels.[9, 11] This disease state is associated with deterioration in HRQL and poor survival varying from 9 to 30 months.[12] Hormone-relapsed prostate cancer (HRPC) is often used interchangeably with castration-resistant prostate cancer (CRPC).

Figure 2: Stages of prostate cancer



Key: mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; nmCRPC, non-metastatic castration-resistant prostate cancer.
Source: Ng et al. 2020.[9]

Between 2018 and 2020, 13% of prostate cancer patients were diagnosed with metastatic disease in England.[13, 14] In a study of 1,643 patients in the UK with localized prostate cancer, 3.8% (n = 62) developed metastases within 10 years of follow-up.[15] In England, there are estimated to be 7,400 patients diagnosed with mHSPC each year (see budget impact analysis for details of calculation).

Factors associated with poor prognosis in mHSPC patients include a Gleason score ≥ 8, the presence of measurable visceral metastases and ≥ 3 bone metastases.[16] The Gleason score is a common prostate cancer grading system based on the microscopic appearance of cancer cell; the score ranges between 6–10, with higher scores indicating more aggressive disease.

B.1.3.2 Clinical outcomes

The overall median five-year survival rate is 87% for patients with prostate cancer, but when diagnosed at a metastatic stage the five-year survival rate drops to 49%[17] The reduced survival is predominantly due to the progression of mHSPC to mCRPC, highlighting the importance of treatments that prevent progression to mCRPC.[18]

Historically ADT alone was the standard of care (SoC) for mHSPC to achieve castrate levels of testosterone using surgery (e.g. orchiectomy) or medical therapies (e.g. luteinizing hormone releasing hormone [LHRH] agonists/antagonists). However, within approximately 12 months of developing mHSPC, most patients progress

towards mCRPC on ADT alone.[19-21] The prognosis of mHSPC patients treated with ADT alone has been shown to be dependent on whether the disease is de novo or recurrent; median overall survival (OS) is worse for de-novo versus recurrent mHSPC patients, with de-novo high volume disease patients having the worst OS (5-year OS-free: 37%; median OS: 43.2 months) compared to recurrent high volume disease (5-year OS-free: 42%; median OS: 55.2 months).[22]

Adding docetaxel chemotherapy to ADT showed improved outcomes in mHSPC patients, with median OS increasing by approximately 5–14 months compared to ADT alone.[19, 21, 23] However, the majority of patients still progress to mCRPC on docetaxel and ADT; in the CHAARTED long-term study (median follow-up: 53.7 months), 64.7% (n = 257/397) of patients developed mCRPC, with a median time to mCRPC of 19.4 months.[24] A real-world study showed worse progression outcomes, where 82% of patients receiving docetaxel and ADT developed mCRPC over the study duration (median follow-up: 42 months), with a median time to mCRPC of 15.6 months.[25] Of note, this study population was slightly older, had higher PSA at baseline, higher Gleason scores and higher metastatic burden compared to patients in CHAARTED.

Androgen receptor-targeted agents such enzalutamide can also be used in combination with ADT to treat mHSPC. In the ARCHES study, enzalutamide and ADT extended the median radiographic progression-free survival (PFS) by approximately 11 months and reduced the risk of death by 34% compared to placebo and ADT (median OS not reached in either group after a median follow-up of 44.6 months).[26] However, there is no head-to-head data comparing enzalutamide and ADT to docetaxel and ADT.

B.1.3.3 Burden of disease

In patients with metastatic disease, health-related quality of life (HRQL) scores were found to be clinically and statistically significantly lower than in those with localized disease.[27] Both fatigue and pain were found to be the most important factors associated with poor HRQL.[27] The most commonly reported symptoms in metastatic prostate cancer patients include fatigue, urinary symptoms, sexual dysfunction symptoms and bone pain[28], all of which negatively impact the patients' HRQL. Patients reported the most challenging aspect of dealing with advanced prostate

cancer was the decreasing ability to maintain their lifestyle, while caregivers recognized pain management and the emotional impact on the patient's family as the most prominent challenges faced by the patient.[28]

Delaying progression to mCRPC is critical as this disease state is associated with deterioration in HRQL and poorer prognosis.[12] HRQL and well-being are impacted in both mHSPC and mCRPC patients, however, mCRPC patients reported the lowest HRQL scores and highest pain scores.[29] In both disease areas, there is a considerable time burden on caregivers with the majority of care provided by spouses/partners. mCRPC patients with bone metastases are at high risk of skeletal-related events (SREs), including pathological fracture and spinal cord compression, which significantly decrease HRQL.[30]

The consequential psychological burden of inevitable progression to mCRPC is high. Fear of cancer recurrence and PSA anxiety are prominent symptoms for prostate cancer patients; they are associated with poorer quality of life and mental health symptoms such as depression and generalized anxiety.[31] Although the burden of disease for patients with mHSPC is high, it is significantly worse for patients with mCRPC, highlighting the need for treatments that prevent progression to mCRPC without further impacting their HRQL.

B.1.3.4 Clinical pathway of care

The clinical pathway of care for prostate cancer is depicted in Figure 3.

In NHS England, treatment options for mHSPC include ADT alone (LHRH agonists/antagonists [including leuprorelin, goserelin, triptorelin, buserelin and degarelix] or orchidectomy), docetaxel plus ADT (with or without prednisolone), enzalutamide plus ADT and apalutamide plus ADT if docetaxel is not suitable.[32-34] Apalutamide plus ADT is not a relevant comparator for this appraisal, as patients unable to receive docetaxel would be unable to receive darolutamide in combination with docetaxel and ADT. Although the use of docetaxel plus ADT in the hormone-naïve and hormone-sensitive setting was considered an off-label use when the NICE guideline was developed,[32, 33, 35] the SmPC for docetaxel was expanded in November 2019 to include docetaxel plus ADT (with or without prednisone or prednisolone) for the treatment of patients with mHSPC.[36] Clinicians confirmed the

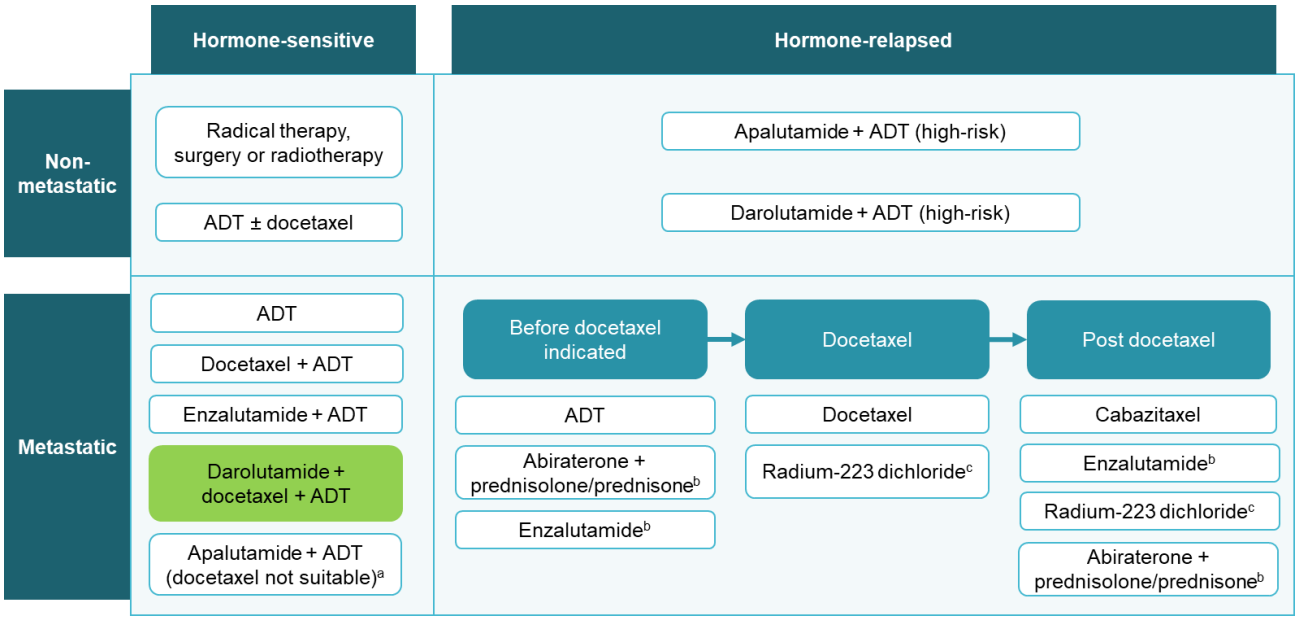
clinical pathway (Figure 3) and the use of docetaxel plus ADT in current NHS England practice.[37]

If patients progressed to mCRPC while on treatment with a novel androgen receptor targeted agent (ARTA; i.e. darolutamide, apalutamide, enzalutamide or abiraterone) it would be expected that the metastatic cancer would be resistant to treatment with another ARTA due to their similar mechanisms of action.[34] Therefore, novel hormonal agents can only be used once in the treatment pathway for prostate cancer.[38, 39]

Other clinical guidelines for the management of metastatic prostate cancer are available from the European Society for Medical Oncology (ESMO) and the European Association of Urology (EAU).[40, 41] In general, these guidelines are consistent with the NICE guidelines for metastatic prostate cancer. However, they also recommend abiraterone with prednisone plus ADT for hormone-naïve and first-line treatment of metastatic disease. In August 2021, abiraterone with prednisone or prednisolone plus ADT was not recommended by NICE for treating newly diagnosed high-risk mHSPC.[42]

Darolutamide in combination with docetaxel and ADT offers the first licensed triplet combination therapy option for patients with mHSPC in NHS, as depicted in Figure 3. As discussed in Section B.1.2, targeting both androgen receptor-dependent and independent mechanisms at initiation of therapy provides an opportunity to prolong survival and delay disease progression without further deterioration in HRQL beyond docetaxel plus ADT. There is a strong recommendation to offer early systemic treatment to metastatic prostate cancer patients in the EAU guidlines[41], which supports adding darolutamide plus docetaxel and ADT early in the treatment pathway.

Figure 3: Clinical pathway of care for prostate cancer and proposed darolutamide plus docetaxel and ADT positioning



Key: ADT, androgen deprivation therapy.
Notes: [a] Recommended only if docetaxel is not suitable; [b] only if a novel anti-hormonal agent (i.e. darolutamide, enzalutamide, apalutamide or abiraterone) has not been used before; [c] only if patients have already had docetaxel, or if docetaxel is contraindicated or is not suitable. Green refers to the proposed positioning of darolutamide plus docetaxel and ADT.
Source: Adapted from NICE prostate cancer: diagnosis and management (NG131)[32]; NHS England commissioning policy statement for docetaxel[33]; BNF treatment summary for prostate cancer.[34]

B.1.3.5 Unmet need

Novel treatment approaches are needed to improve disease control, improve survival and delay progression to mCRPC, which is associated with debilitating symptoms, deterioration in HRQL and poorer prognosis. Approximately 10% to 20% of prostate cancer patients develop CRPC within 5 years and have a poor median survival expectancy of 9 to 30 months.[12] Treatment with docetaxel plus ADT improved survival of mHSPC patients, however, the majority of patients still progress to mCRPC within approximately 20 months.[24, 25]

Newer alternative treatments include AR inhibitors such as enzalutamide. However, enzalutamide has more potential drug-drug interactions (pDDIs) than darolutamide[37, 43] (Section B.2.6.4.1), which may result in sub-optimal treatment of comorbidities while being treated with enzalutamide for mHSPC. This may impact the proportion of patients that are able to successfully receive enzalutamide. Additionally, there is a lack of robust evidence of how enzalutamide performs against docetaxel plus ADT

as there is no head-to-head data directly comparing them. Enzalutamide is not licensed in a triplet combination that would address an early treatment intensification strategy.

A novel treatment approach for mHSPC is required to address this unmet need and delay progression to mHSPC. Treatment approaches that decrease PSA through early treatment intensification and subsequently reduce PSA-related anxiety are also needed. ARASENS demonstrated that the addition of darolutamide to docetaxel and ADT significantly increases OS, significantly increases the time to progression to mCRPC and almost halves the proportion of patients who progressed to mCRPC within 44 months of follow-up (Section B.2.6).[44] This was a large and robust study that compared the treatment against placebo in combination with docetaxel and ADT which is a standard of care comparator more active than other comparators typically used in other mHPSC trials. These superior efficacy results, combined with the acceptable safety (Section B.2.10) and favourable pDDI (Section B.2.6.4.1) profiles, support a positive benefit-risk profile of this first licensed triple combination therapy for patients with mHSPC, and reinforce its use early on in this aggressive metastatic pathway.

B.1.4 Equality considerations

Prostate cancer is more common in Black African men than white men.[7] The introduction of darolutamide plus docetaxel and ADT provides an alternative and more effective treatment option which will support all men with mHSPC.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify all existing evidence assessing the efficacy, safety and tolerability of approved and upcoming treatments of mHSPC. See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

B.2.2 List of relevant clinical effectiveness evidence

Table 3 summarizes the clinical effectiveness evidence supporting darolutamide in addition to standard docetaxel and ADT for the treatment of patients with mHSPC.

Table 3: Clinical effectiveness evidence

Study	ARASENS (NCT02799602)
Study design	ARASENS is an international, randomized, double-blind, placebo-controlled, Phase III efficacy and safety study of darolutamide in addition to standard androgen deprivation therapy (ADT) and docetaxel
Population	Patients with metastatic hormone-sensitive prostate cancer (mHSPC).
Intervention(s)	Darolutamide plus docetaxel and ADT
Comparator(s)	Placebo plus docetaxel and ADT
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in the model	N/A
Reported outcomes specified in the decision problem	• **Overall survival** • **Time to CRPC** • PSA response • Time to PSA progression • **Adverse events from treatment** • Health-related quality of life
All other reported outcomes	• Time to pain progression • SSE-FS • Time to first SSE • Time to initiation of subsequent systemic antineoplastic therapy • Time to worsening of disease-related physical symptoms • Time to initiation of opioid use for ≥ 7 consecutive days
Key: ADT, androgen deprivation therapy; CRPC, castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; PSA, prostate-specific antigen; SSE, symptomatic skeletal event; SSE-FS, symptomatic skeletal event-free survival **Notes:** Bolded outcomes are used in the economic model.	

The study reported by Appukkuttan et al. 2021[43] which investigated the pDDIs of darolutamide, apalutamide and enzalutamide was not used to populate the economic

model but the results are included in Section B.2.6.4.1. The results of this study support the reduced pDDIs of darolutamide in comparison to apalutamide and enzalutamide. This study was not included in the economic model because the relationship between pDDIs, patient HRQL and costs to the NHS is uncertain and there is no precedence of modelling pDDIs in past prostate cancer appraisals.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

Table 4 provides a summary of the trial methodology for ARASENS.

ARASENS is a Phase III international randomized double-blind placebo-controlled trial that evaluates the efficacy and safety of darolutamide in combination with docetaxel and ADT (hereafter termed **darolutamide+docetaxel**) in comparison with placebo in combination with docetaxel and ADT (hereafter termed **placebo+docetaxel**) in patients with mHSPC.[44, 45] The study was conducted in 286 centres in 23 countries, including North America, Asia-Pacific, Europe, Australia, Brazil, Israel and Mexico. In total, 29 patients were randomized across eight trial centres in the UK.

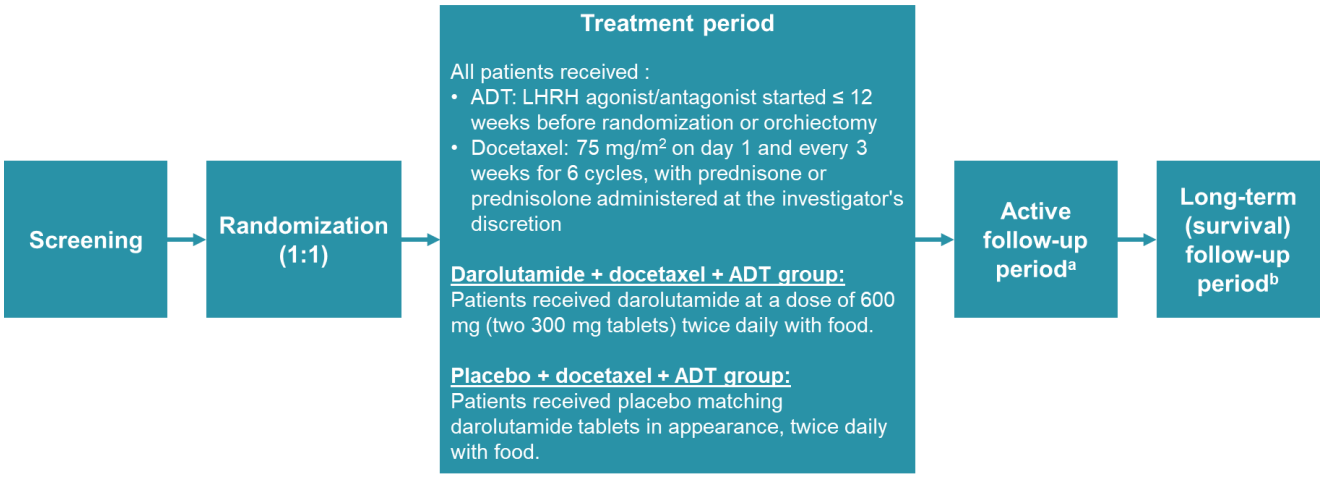
Patients were randomized in a 1:1 ratio to receive one of the study drugs (darolutamide or placebo): darolutamide 600 mg (2 tablets of 300 mg) taken twice daily with food (equal to a total daily dose of 1,200 mg), or placebo that matched darolutamide tablets in appearance taken twice daily with food.[44, 45] Randomization was performed in a double-blind fashion and a randomization number was assigned through the Interactive Voice/Web Response System (IxRS) based on information supplied by the investigator at the time of randomization. All patients were required to receive treatment with ADT of the investigator's choice as standard therapy before randomization. Six cycles of docetaxel were planned to be administered after randomization, with the first cycle to be administered within six weeks after the start of the study drug. Patients continued to receive darolutamide or placebo (treatment period) and were evaluated every 12 weeks until symptomatic disease progression, a change in antineoplastic therapy, unacceptable toxic effects, patient or physician decision, death or nonadherence. After treatment discontinuation, patients entered the active follow-up period where assessments were performed approximately every 12 weeks for up to one year. Patients then entered the long-term (survival) follow-up period until the end of the study (Figure 4).

Patients were stratified at randomization by extent of disease (non-regional lymph nodes metastases only equivalent to TNM M1a; bone metastases with or without lymph node metastases equivalent to TNM M1b; and visceral metastases with or

without lymph node metastases or with or without bone metastases equivalent to TNM M1c) and alkaline phosphatase (ALP) level (ALP < upper limit of normal [ULN] and ALP ≥ ULN).[46] The dose of study drug could be interrupted or reduced to manage clinically significant toxicities. If a dose of the study drug was delayed/missed, the dose could be taken up to 6 hours later. Any discrepancies between actual and expected amount of returned study medication was discussed with the patient at the time of the visit and any explanation documented.

The primary endpoint of the ARASENS trial was OS, defined as the time from the date of randomization until death from any cause.[44] Secondary endpoints included time to CRPC, time to pain progression, symptomatic skeletal event-free survival (SSE-FS), time to first symptomatic skeletal event (SSE), time to initiation of subsequent systemic antineoplastic therapy, time to worsening or disease-related physical symptoms and time to initiation of opioid use for ≥ 7 consecutive days. Exploratory endpoints included time to PSA progression and HRQL measured by the National Comprehensive Cancer Network Functional Assessment of Cancer Therapy Prostate Symptom Index (NCCN-FACT-FPSI-17) and Brief Pain Inventory – Short Form (BPI-SF) questionnaires. See Table 4 for details and definitions of study endpoints.

Figure 4: Study scheme for ARASENS



Key: ADT, androgen deprivation therapy; LHRH, luteinizing hormone releasing hormone; SAE, serious adverse event; SSE, symptomatic skeletal event.
Notes: [a] The following assessments were performed approximately every 12 weeks for up to one year: HRQL, pain assessment, analgesic consumption, survival status, subsequent antineoplastic treatments for prostate cancer, SSEs and study drug–related SAEs; [b] the following assessments were

performed approximately every 12 weeks: antineoplastic treatments for prostate cancer, study drug–related SAEs and survival status.
Source: ARASENS clinical study protocol.[46]

Table 4: Summary of trial methodology for ARASENS

Trial number (acronym)	NCT02799602 (ARASENS)
Location	Multiple investigative sites in 23 countries
Trial design	ARASENS is a randomized, double-blind, placebo-controlled, multicentre Phase III study evaluating the safety and efficacy of darolutamide versus placebo in addition to standard androgen deprivation therapy and docetaxel. Patients will be randomized in a 1:1 ratio to receive one of the following study drugs: • Darolutamide 600 mg (2 tablets of 300 mg) twice daily with food, equivalent to a total daily dose of 1200 mg • Placebo matching darolutamide tablets in appearance, twice daily with food All patients must receive ADT of investigator's choice (LHRH agonist/antagonists or orchiectomy) as standard therapy, started ≤ 12 weeks before randomization. For patients receiving LHRH agonists, treatment in combination with a first generation anti-androgen for at least 4 weeks before randomization is recommended. Six cycles of docetaxel will be administered after randomization. Docetaxel can be administered in combination with prednisone/prednisolone at the discretion of the investigator. Patients will be stratified at randomization by extent of disease and alkaline phosphatase (ALP).
Eligibility criteria for participants	• **Key inclusion criteria:** • Males ≥ 18 years of age • Histologically or cytologically confirmed adenocarcinoma of prostate • Metastatic disease documented either by a positive bone scan, or for soft tissue or visceral metastases, either by contrast–enhanced abdominal/pelvic/chest computed tomography (CT) or magnetic resonance imaging (MRI) scan assessed by investigator and confirmed by central radiology review • Patients must be candidates for docetaxel and ADT therapy per investigator's judgement • Started ADT (LHRH agonist/antagonist or orchiectomy) with or without first generation anti-androgen ≤ 12 weeks before randomization • An ECOG performance status of 0 or 1 • Blood counts at Screening: haemoglobin ≥ 9.0 g/dL, absolute neutrophil count ≥ 1.5×10^9/L, platelet count ≥ 100×10^9/L

	• Screening values of serum alanine aminotransferase and/or aspartate transaminase ≤ 1.5 times upper limit of normal (ULN), total bilirubin ≤ ULN, creatinine ≤ 2.0 times ULN • **Key exclusion criteria:** • Prior treatment with: – LHRH agonist/antagonists started >12 weeks before randomization – Second-generation androgen receptor (AR) inhibitors such as enzalutamide, ARN–509, darolutamide, other investigational AR inhibitors – Cytochrome P 17 enzyme inhibitor such as abiraterone acetate or oral ketoconazole as antineoplastic treatment for prostate cancer – Chemotherapy or immunotherapy for prostate cancer prior to randomization – Treatment with radiotherapy (external beam radiation therapy, brachytherapy, or radiopharmaceuticals) within 2 weeks before randomization • Had any of the following within 6 months before randomization: stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, congestive heart failure (New York Heart Association Class III or IV) • Uncontrolled hypertension as indicated by a resting systolic blood pressure (BP) ≥ 160 mmHg or diastolic BP ≥ 100 mmHg despite medical management • Had a prior malignancy. Adequately treated basal cell or squamous cell carcinoma of skin or superficial bladder cancer that has not spread behind the connective tissue layer (i.e. pTis, pTa, and pT1) is allowed, as well as any other cancer for which treatment has been completed ≥ 5 years before randomization and from which the subject has been disease–free • A gastrointestinal disorder or procedure which is expected to interfere significantly with absorption of study drug • An active viral hepatitis, known human immunodeficiency virus infection with detectable viral load, or chronic liver disease with a need for treatment • Inability to swallow oral medications Note: Other protocol defined Inclusion/Exclusion criteria may apply
Settings and locations where the data were collected	This multinational study was conducted across 23 countries (number of centres in brackets): Australia (5), Belgium (7), Brazil (9), Bulgaria (7), Canada (5), China (36), Czech Republic (7), Finland (7), France (17), Germany (11), Israel (8), Italy (9), Japan (45), South Korea (12), Mexico (6), Netherlands (8), Poland (6), Russian Federation (10), Spain (13), Sweden (5), Taiwan (5), United Kingdom (8), United States (55)
Trial drugs	**Intervention:**

	Darolutamide 600 mg (2 tablets of 300 mg) twice daily with food, equivalent to a total daily dose of 1200 mg, plus ADT (LHRH agonist/antagonist or orchiectomy) and 6 cycles of docetaxel. **Comparator:** Matching placebo with same dosing as the intervention plus ADT (LHRH agonist/antagonist or orchiectomy) and 6 cycles of docetaxel.
Concomitant medication	**Permitted concomitant medication:** • Analgesics • Palliative radiation therapy or surgical intervention as needed are allowed during study treatment. Treatment with bisphosphonates and denosumab is allowed • Switching ADT to an LHRH antagonist is permitted during study treatment. • Supportive care in case of toxicity related to docetaxel including use of biologic response modifiers such as granulocyte colony-stimulating factor or granulocyte–macrophage colony-stimulating factor, should be applied according to standard practice • Concomitant intake of strong CYP3A4 inducers should be avoided. It is strongly recommended to use alternative treatments. Concomitant short term use is allowed • Patients should be closely monitored for signs and symptoms of increased exposure to BCRP, OATP1B1 or OATP1B3 substrates **Disallowed concomitant mediation:** • Any investigational medicinal product • Radiopharmaceuticals • Immunotherapy (e.g. sipuleucel–T) • Cytotoxic chemotherapy other than docetaxel for 6 cycles after randomization • Enzalutamide, ARN–509, bicalutamide, flutamide, nilutamide • Abiraterone acetate, TAK–700, or other CYP17 inhibitors • Systemic ketoconazole as antineoplastic treatment for prostate cancer • ADT switch to LHRH agonist Another systemic antineoplastic therapy may be initiated no sooner than 7 days after the last dose of study drug
Primary outcomes (including scoring methods and timings of assessments)	Overall survival, defined as the time (in days) from date of randomization until death from any cause
Other outcomes used in the economic model/specified in the scope	• Time to CRPC, defined as the time from randomization to the first occurrence of one of the following events: – PSA progression (according to PCWG3 criteria), defined as the date that a 25% increase and an absolute increase of ≥ 2 ng/mL from the nadir (lowest at or after baseline) was document, which was confirmed by a second value

	obtained at least 3 weeks later. This definition required serum testosterone at castrate levels < 0.50 ng/mL and a first assessment date at least 12 weeks from randomization – Radiological progression by soft tissue and visceral lesions, defined according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 based on MRI/CT scans of the chest, abdomen and pelvis (as recommended by PCWG3) – Radiological progression by bone lesions (according to PCWG3 criteria), based on whole body ^{99m}Tc methylene diphosphonate bone scans. Bone lesions were recorded separately from soft tissue and visceral lesions • Time to PSA progression, defined as the time from the date of randomization to the date of first PSA progression with testosterone at castrate level < 0.5 ng/mL. The same definition of PSA progression as was applied to the time to CRPC • PSA response. Absolute PSA response was defined as baseline PSA value above the detection limit and a post-baseline PSA level below 0.2 ng/mL, confirmed by a second subsequent PSA value below 0.2 ng/mL three or more weeks later, with all potential PSA values between the initial date and confirmation date below 0.2 ng/mL. Relative 30% PSA response was defined as baseline PSA value above the detection limit and a post-baseline ≥ 30% reduction in PSA level compared with the baseline value, confirmed by a second subsequent PSA value with a ≥ 30% reduction from baseline 3 or more weeks later, with all potential PSA values between initial date and confirmation date showing a ≥ 30%. Relative 50% and 90% PSA response were defined in the same way reduction from baseline. Relative 50% and 90% PSA response were defined in the same way. • Adverse events from treatment • Health-related quality of life **Other outcomes:** • Time to pain progression, defined as the time from randomization to the first date a patient experienced pain progression. Pain was assessed using the BPI-SF questionnaire and defined as follows: – For asymptomatic patients (WPS = 0 at baseline): an increase of 2 or more points in the 'worst pain in 24 hours' score from nadir observed at 2 consecutive evaluations ≥ 4 weeks apart, or initiation of short- or long-acting opioid use for pain – For symptomatic patients (WPS > 0 at baseline): an increase of 2 or more points in the 'worst pain in 24 hours' score from nadir observed at 2 consecutive evaluations ≥ 4 weeks apart and a WPS of ≥ 4, or initiation of short- or long-acting opioid use for pain

	• Symptomatic skeletal event-free survival (SSE-FS), defined as the time from randomization to the first occurrence of an SSE or death from any cause, whichever occurred first. An SSE was defined as administration of external beam radiation therapy (EBRT) to relieve skeletal symptoms, new symptomatic pathologic bone fracture, spinal cord compression, or tumour-related orthopaedic surgical intervention • Time to first symptomatic skeletal event (SSE), defined as the time from randomization to the first occurrence of an SSE (identical to the definition used for SSE-FS). Death was not considered as an event • Time to initiation of subsequent systemic antineoplastic therapy, defined as the time from randomization to the initiation of first subsequent systemic antineoplastic therapy. Patients may have received subsequent antineoplastic therapy for prostate cancer or for additional primary malignancies • Time to worsening of disease-related physical symptoms, defined as the time from randomization to the first date a patient experienced an increase in disease-related physical symptoms based on the NCCN-FACT-FPSI-17 questionnaire. An increase in disease-related physical symptoms was defined as a 3-point decrease in DRS-P subscale from baseline in the disease-related physical symptoms subscale observed at 2 consecutive evaluations ≥ 4 weeks apart • Time to initiation of opioid use for ≥ 7 consecutive days, defined as the time from randomization to the date of the first opioid use for ≥ 7 consecutive days. Data of opioid use related to cancer pain was included in the analysis, and opioid use for non-malignant causes was excluded
Pre-planned subgroups	Selected efficacy and safety endpoints were performed in subgroups defined by baseline covariates, including extent of disease, ALP at baseline, age, ethnicity, PSA values at baseline and Gleason score

Key: AR, androgen receptor; ADT, androgen deprivation therapy; ALP, alkaline phosphatase; BP, blood pressure; BPI-SF, Brief Pain Inventory – Short Form; CRPC, castration-resistant prostate cancer; CT, computed tomography; DRS-P, disease related symptoms – physical; EBRT, external beam radiation therapy; ECOG, Eastern Cooperative Oncology Group; LHRH, luteinizing hormone-releasing hormone; MRI, magnetic resonance imaging; NCCN-FACT-FPSI-17, National Comprehensive Cancer Network prostate cancer symptom index 17 questionnaire / Functional assessment of cancer therapy; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumours; SSE, symptomatic skeletal event; SSE-FS, symptomatic skeletal event-free survival; ULN, upper limit of normal; WPS, worst pain subscale.
Source: ARASENS CSR.[44]

B.2.3.1 Summary of clinical validation

A clinical advisory board was conducted with nine clinical oncologists from hospitals across the UK managed by the NHS Foundation Trust. The agenda for the session was structured around discussion sessions and presentations of clinical data that were targeted to address questions regarding the health technology assessment (HTA) of darolutamide in combination with docetaxel and ADT in mHSPC. The advisors were posed a number of questions related to UK clinical practice and the generalizability of ARASENS data and asked to formulate a consensus response. The advisors were aware that their names and anonymised responses would be utilized as part of this submission.

B.2.3.2 Baseline characteristics

Table 5 provides a summary of baseline characteristics, including demographics and clinical characteristics.

The characteristics of the patients at baseline were generally well-balanced between the treatment groups.[45] The median age was 67 years in both treatment groups. The majority of patients in both treatment groups (darolutamide+docetaxel versus placebo+docetaxel) presented with bone metastases with or without lymph node metastases (79.4% versus 79.5%), had Stage IV metastatic disease at initial diagnosis (85.7% versus 86.5%) and a Gleason score of ≥ 8 (77.6% versus 78.9%).

Table 5: Baseline characteristics of patients in ARASENS (FAS)

Characteristic	Darolutamide+ docetaxel N = 651	Placebo+ docetaxel N = 654
Age, years		
Mean (SD)	[redacted]	[redacted]
Median	67.0	67.0
Min, max	41, 89	42, 86
Age group in years, n (%)		
< 65	243 (37.3)	234 (35.8)
65–74	303 (46.5)	306 (46.8)
75–84	102 (15.7)	110 (16.8)
≥ 85	3 (0.5)	4 (0.6)
Race, n (%)		
White	345 (53.0)	333 (50.9)

Characteristic	Darolutamide+ docetaxel N = 651	Placebo+ docetaxel N = 654
Black or African American	26 (4.0)	28 (4.3)
Asian	230 (35.3)	245 (37.5)
Other[a]	7 (1.1)	2 (0.3)
Not reported	43 (6.6)	46 (7.0)
Geographical region, n (%)		
North America	125 (19.2)	119 (18.2)
Asia Pacific	229 (35.2)	244 (37.3)
Rest of the world	297 (45.6)	291 (44.5)
Body mass index group in kg/m^2, n (%)		
< 20	[redacted]	[redacted]
20–< 25	[redacted]	[redacted]
25–< 30	[redacted]	[redacted]
≥ 30	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Extent of metastatic disease at study entry using eCRF[b], n (%)		
M1a	23 (3.5)	16 (2.4)
M1b	517 (79.4)	520 (79.5)
M1c	111 (17.1)	118 (18.0)
ALP at baseline – central laboratory using eCRF[c], n (%)		
ALP < ULN	290 (44.5)	291 (44.5)
ALP ≥ ULN	361 (55.5)	363 (55.5)
Stage of prostate cancer at initial diagnosis using TNM classification[d], n (%)		
Stage I	[redacted]	[redacted]
Stage IIA	[redacted]	[redacted]
Stage IIB	[redacted]	[redacted]
Stage III	[redacted]	[redacted]
Stage IV	[redacted]	[redacted]
Stage IV M0	[redacted]	[redacted]
Stage IV M1	558 (85.7)	566 (86.5)
Missing	7 (1.1)	6 (0.9)
Gleason score at initial diagnosis of prostate cancer, n (%)		
< 8	122 (18.7)	118 (18.0)
≥ 8	505 (77.6)	516 (78.9)
Missing	24 (3.7)	20 (3.1)
PSA at baseline – central laboratory, ng/mL		
Mean (SD)	[redacted]	[redacted]
Median	30.30	24.20
Min, max	0.0, 9,219.0	0.0, 11,947.0
Missing, n	[redacted]	[redacted]

Characteristic	Darolutamide+ docetaxel N = 651	Placebo+ docetaxel N = 654
ECOG Performance Status, n (%)		
0	466 (71.6)	462 (70.6)
1	185 (28.4)	190 (29.1)
Missing	[redacted]	[redacted]

Key: ALP, alkaline phosphatase; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; FAS, full analysis set; PSA, prostate-specific antigen; TNM, tumour, node, metastasis; SD, standard deviation; ULN, upper limit of normal.
Notes: [a] Race 'Other' includes “American Indian or Alaska Native”, “Native Hawaiian or other Pacific Islander”, and “Multiple”. [b] TNM classification system categories for the extent of metastatic disease at baseline (M1) were defined as: M1a = Non-regional lymph nodes metastases only; M1b = Bone metastases with or without lymph node metastases; M1c = Visceral metastases with or without lymph node metastases or with or without bone metastases. [c] ALP baseline values were primarily from central laboratory results. For two patients, central laboratory ALP values were not available at baseline and the local laboratory ALP values were selected as baseline instead. One of these patients was randomized to the darolutamide+docetaxel group and the other to the placebo+docetaxel group. [d] According to AJCC 7th edition, Stage IV could be M1 or M0 disease. For the purpose of this analysis, the Stage IV M0 group was defined as the time interval of >3 months between initial diagnosis and initial diagnosis of metastases. The Stage IV M1 group is defined as the time interval of ≤ 3 months between initial diagnosis and initial diagnosis of metastases.
Source: Table 8-3 and Table 8-4 ARASENS CSR[44]; Smith et al. 2022.[45]

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Table 6 provides a summary of the statistical analysis for ARASENS.

The ARASENS study was designed to investigate whether the combination of darolutamide with docetaxel and ADT improves the OS in patients with mHSPC.[44] Approximately 1,300 patients were planned to be randomized to achieve 90% power and to detect a 25% decrease in risk of death with darolutamide compared with placebo with a one-sided test with a Type I error of 0.025. The primary analysis was performed when the targeted number of OS events, approximately 509 deaths, was reached. This submission presents data from the primary analysis of OS with a data cut-off date of 25 October 2021. This constitutes the final analysis of efficacy. The full analysis set (FAS) was used for the primary efficacy analysis, which includes all patients who were randomized.

The secondary efficacy endpoints were tested with a hierarchical gatekeeping procedure; if the prior endpoint in the hierarchy was significant, then the next

endpoint in the order was tested for significance.[44] The hierarchical order was as follows: time to CRPC; time to pain progression; symptomatic skeletal event-free survival (SSE-FS); time to first symptomatic skeletal event (SSE); time to initiation of subsequent systemic antineoplastic therapy; time to worsening of disease-related physical symptoms; time to initiation of opioid use for ≥ 7 consecutive days. An algorithm included in the statistical analysis plan (SAP) was to be used to impute partial or missing event dates.

Table 6: Summary of statistical analysis for ARASENS

Hypothesis objective	The null hypothesis, that there is no difference in OS between treatment arms, which is equivalent to a hazard ratio (HR) of 1, was tested against the alternative hypothesis that the HR of darolutamide over placebo is less than 1.
Statistical analysis	**Main analyses:** Time-to-event endpoints were analysed using a stratified log-rank test with randomization stratification factors using IxRS data. HRs and 95% CIs were provided using the Cox model stratified by the same factors as were used for randomization. Median time, 25th and 75th percentiles, and associated 95% CI of Kaplan–Meier estimates are presented by treatment group, as well as the number and percentage of censored observations. Kaplan–Meier curves were generated for each treatment group. For the primary endpoint (OS), if the p-value from the one-sided log-rank test was less than 0.025 (corresponding to a two-sided log-rank test less than 0.05) with the HR less than 1, the null hypothesis was rejected in favour of the alternative hypothesis. **Sensitivity analyses:** Three sensitivity analyses were planned for OS: one with the unstratified log-rank test and Cox model, one using stratification factors collected from the eCRF, and one using extent of disease stratification factors collected from central imaging review. Four sensitivity analyses were planned for time to pain progression: based on the change from baseline instead of change from nadir; based on the change from nadir after completion of docetaxel; based on the change from baseline after completion of docetaxel; and based on both ePRO device and paper questionnaires, instead of ePRO questionnaires only (change from nadir). The time to worsening of disease-related physical symptoms sensitivity analysis was based on source data from both ePRO device and paper questionnaires. The sensitivity analysis of time to CRPC and time to PSA progression was based on both central and local PSA laboratory data.
Analysis sets	**FAS:** all patients who were randomized were included in the FAS, except for cases with critical GCP violations. Following the intent-to-treat principle, the patients in this set were grouped according to the planned treatment they were allocated to receive at randomization, irrespective of actual treatment.
	SAS: all randomized patients who received at least one dose of darolutamide or placebo were included in the SAS, except for cases with critical GCP violations. This safety population was used in the analyses of

	all safety endpoints and was included in the analyses according to the treatment they actually received. Patients were included in the darolutamide+docetaxel group if they had received any dose of darolutamide and were included in the placebo+docetaxel group if they received only placebo.
Sample size, power calculation	The study was designed to have 90% power to detect a 25% decrease in risk of death with darolutamide compared with placebo with a one-sided test with a Type I error of 0.025 (equivalent to a two-sided test with a Type I error 0.05). The OS data were considered mature when approximately 509 deaths were observed. With the additional assumptions that patients were enrolled at a rate of 50 patients per month, exponential distributions of the OS event times, median time of OS in the placebo group of 60 months, 5% dropout rate of patients, and a 6-months enrolment ramp-up period, it followed that approximately 1,300 patients were required to be randomized to observe 509 deaths after approximately 70 months.
Data management, patient withdrawals	**OS:** patients with no documented death and no contacts after randomization before or at data cut-off were censored to the date of randomization (Day 1). Patients with no documented death before or at data cut-off were censored to the last known alive date or at the data cut-off, whichever comes earlier. **Time to CRPC:** patients with no baseline or post-baseline event assessment for all three components were censored to date of randomization (Day 1). Patients with a PSA progression event immediately after two or more consecutive missing assessments and without any prior radiological progression event before or at data cut-off were censored to the last PSA assessment before the consecutive missed PSA assessments or to the date of the last radiological assessment, whichever was later. Patients with no CRPC (or no event among the three components) before or at data cut-off date were censored to the date of the latest date among the three components' last assessment before discontinuation or randomization date (censored at Day 1 if no follow-up was available), whichever was later. Patients who received subsequent systemic antineoplastic therapy without any prior components event and without post PSA progression event before or at data cut-off were censored to the date of the last radiological assessment before or on subsequent therapy start date or the last PSA assessment date or randomization date (censored at Day 1 if there was no follow-up available), whichever was later. **Time to pain progression:** patients with no baseline or post-baseline event assessment were censored to date of randomization (censored at Day 1 if no follow-up was available). Patients with no pain progression before or at data cut-off date were censored to the date of the last BPS-SF assessment date or randomization date (censored at Day 1 if no follow-up was available), whichever was later. If patients had taken opioids for any reason within 4 weeks before or on randomization they were censored to the date of randomization (Day 1). **SSE-FS and time to first SSE:** patients with no SSE before or at the time of data cut-off were censored to the last SSE assessment date before or at data cut-off. Patients lost to follow-up before or at data cut-off were censored to the date of last SSE assessment or randomization date (censored at Day 1 if no follow-up was available), whichever was later.

	Time to initiation of subsequent antineoplastic therapy: patients with no subsequent antineoplastic therapy before or at data cut-off date were censored to the date of last known alive date, date of death or randomization date (censored at Day 1 if there was no follow-up available), whichever was later. **Time to worsening of disease-related physical symptoms:** patients with no baseline or post-baseline event assessment were censored to the date of randomization (censored at Day 1 if there no follow-up was available). Patients with no worsening of disease-related physical symptoms before or at the data cut-off date were censored to the date of last assessment or randomization date (censored to Day 1 if no follow-up was available), whichever was later. **Time to initiation of opioid use for ≥ 7 consecutive days:** patients with no opioid use for ≥ 7 consecutive days before or at data cut-off date were censored to the date of last visit at which analgesic consumption question was collected or randomization date (censored at Day 1 if no follow-up was available), whichever was later. Patients who used opioids for ≥ 7 consecutive days at or before randomization date were censored to the date of randomization (Day 1). **Time to PSA progression:** patients with no baseline or post-baseline event assessment were censored to the date of randomization (censored at Day 1 if no follow-up was available). Patients with PSA progression even immediately after two or more consecutive missing assessments were censored to the date of the last PSA assessment before the consecutive missed ones. Patients without PSA progression before or of data cut-off were censored at the last PSA assessment before discontinuation or randomization date (censored at Day 1 if no follow-up was available), whichever was later.
Key: BPS-SF, Brief Pain Inventory – Short Form; CI, confidence interval; CRPC, castration-resistant prostate cancer; eCRF; electronic case report form; ePRO, electronic patient-reported outcome; FAS, full analysis set; GCP, good clinical practice; HR, hazard ratio; HRPC, hormone-relapsed prostate cancer; IxRS, Interactive Voice/Web Response System; OS, overall survival; PSA, prostate-specific antigen; SAS, safety analysis set; SSE, symptomatic skeletal event; SSE-FS, symptomatic skeletal event-free survival. **Source:** ARASENS CSR[44] and ARASENS SAP.[47]	

B.2.4.1 Patient disposition data

A total of 1,686 patients were enrolled in the study between November 2016 (first patient first visit) and June 2018 (last patient first visit), of which 1,306 were randomly assigned in a 1:1 ratio to the study drug.[45] One patient was excluded from the analysis due to a GCP violation, leaving 651 patients in the darolutamide+docetaxel group and 654 patients in the placebo+docetaxel group.

Of the randomized patients, 100.0% in the darolutamide+docetaxel group and 99.5% in the placebo+docetaxel group received at least one dose of the study drug.[45] In total, three patients were randomized but were never administered study drug; all of

these patients were in the placebo+docetaxel group. Two of these patients were withdrawn from the treatment period at the investigator's discretion without receiving study drug, entered follow-up, and received docetaxel as subsequent antineoplastic therapy during follow-up. One patient did not receive study drug and did not receive docetaxel; this patient was withdrawn from treatment per patient decision.

At the time of the database cut-off (25 October 2021), 45.9% of patients in the darolutamide+docetaxel group and 19.1% in the placebo+docetaxel group were ongoing with study treatment.[45] A smaller percentage of patients had discontinued study treatment in the darolutamide+docetaxel group (54.1%) than in the placebo+docetaxel group (80.4%). The most commonly reported primary reason for permanent treatment discontinuation was progressive disease (clinical progression), which was reported in a lower percentage of patients in the darolutamide+docetaxel group than in the placebo+docetaxel group (19.5% versus 41.6%, respectively), followed by radiological progression (12.9% versus 20.2%, respectively).

Overall, [redacted]% of patients in the darolutamide+docetaxel group and [redacted]% of patients in the placebo+docetaxel group had entered active follow-up, with [redacted]% and [redacted]% ongoing.[44] The most common primary reason for discontinuation of active follow-up was death, which occurred in [redacted]% of the patients in the darolutamide+docetaxel group and [redacted]% of the patients in the placebo+docetaxel group. For the survival follow-up, [redacted]% of patients in the darolutamide+docetaxel group and [redacted]% of patients in the placebo+docetaxel group had entered survival follow-up, with [redacted]% and [redacted]%, respectively, still ongoing. The most common primary reason for discontinuation of survival follow-up was death, which occurred in [redacted]% of patients in the darolutamide+docetaxel group and [redacted]% of patients in the placebo+docetaxel group.

The Consolidated Standards of Reporting Trials (CONSORT) flow diagrams and summary of patient disposition for the ARASENS study are presented in Appendix D.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

A quality assessment of the ARASENS study was conducted using the NICE checklist; the full details of this checklist are in Appendix D.

The study was approved by the institutional review board and independent ethics committee and was conducted according to good clinical practice. Overall, the study is considered to be a methodologically robust and high-quality study with a comprehensive approach to patient allocation, control of confounding factors, and an overall low risk of bias.

Patients were randomized to receive darolutamide or matching placebo in a double-blind fashion, such that neither the investigator, the sponsor nor the patient knew which agent was being administered. All efficacy and safety parameters, and the methods to measure them, are standard variables and methods used in clinical studies and/or clinical practice. They are widely used and generally recognized as reliable, accurate and relevant.

B.2.6 Clinical effectiveness results of the relevant trials

A summary of the efficacy results from ARASENS is presented in Table 7. Darolutamide in combination with docetaxel and ADT significantly prolonged OS compared with placebo in combination with docetaxel and ADT. Darolutamide was also associated with consistent benefits with respect to secondary endpoints, including time to CRPC. Further details are presented in Section B.2.6.1 and Section B.2.6.2.

Table 7: Summary of primary and secondary endpoint results in ARASENS (FAS)

Endpoint	Darolutamide+ docetaxel (n = 651)[a]	Placebo+ docetaxel (n = 654)[a]	HR (95% CI)	P value
	Median (95% CI), months	Median (95% CI), months		
Primary endpoint				
OS	NR (NE, NE)	48.9 (44.4, NE)	0.68 (0.57, 0.80)	< 0.001
Secondary endpoints				
Time to CRPC	NR (NE, NE)	19.1 (16.5, 21.8)	0.36 (0.30, 0.42)	< 0.001
Time to pain progression	NR (30.5, NE)	27.5 (22.0, 36.1)	0.79 (0.66, 0.95)	0.01
SSE-FS	51.2 ([redacted])	39.7 ([redacted])	0.61 (0.52, 0.72)	< 0.001
Time to first SSE	NR ([redacted])	NR ([redacted])	0.71 (0.54, 0.94)	0.02
Time to initiation of subsequent systemic antineoplastic therapy	NR ([redacted])	25.3 ([redacted])	0.39 (0.33, 0.46)	< 0.001
Time to worsening of disease-related physical symptoms	19.3 ([redacted])	19.4 ([redacted])	1.04 (0.89, 1.22)	0.59
Time to initiation of opioid use for ≥ 7 consecutive days	NR ([redacted])	NR ([redacted])	0.69 (0.52, 0.91)	NA

Key: CI, confidence interval; CRPC, castration-resistant prostate cancer; FAS, full analysis set; HR, hazard ratio; NA, not applicable; NR, not reached; OS, overall survival; SSE, symptomatic skeletal event; SSE-FS, symptomatic skeletal event-free survival.
Notes: [a] One patient who was randomly assigned to the placebo+docetaxel group but received darolutamide was included in the placebo+docetaxel group in the FAS.
Source: Smith et al. 2022[45] and ARASENS CSR.[44]

B.2.6.1 Primary efficacy outcome

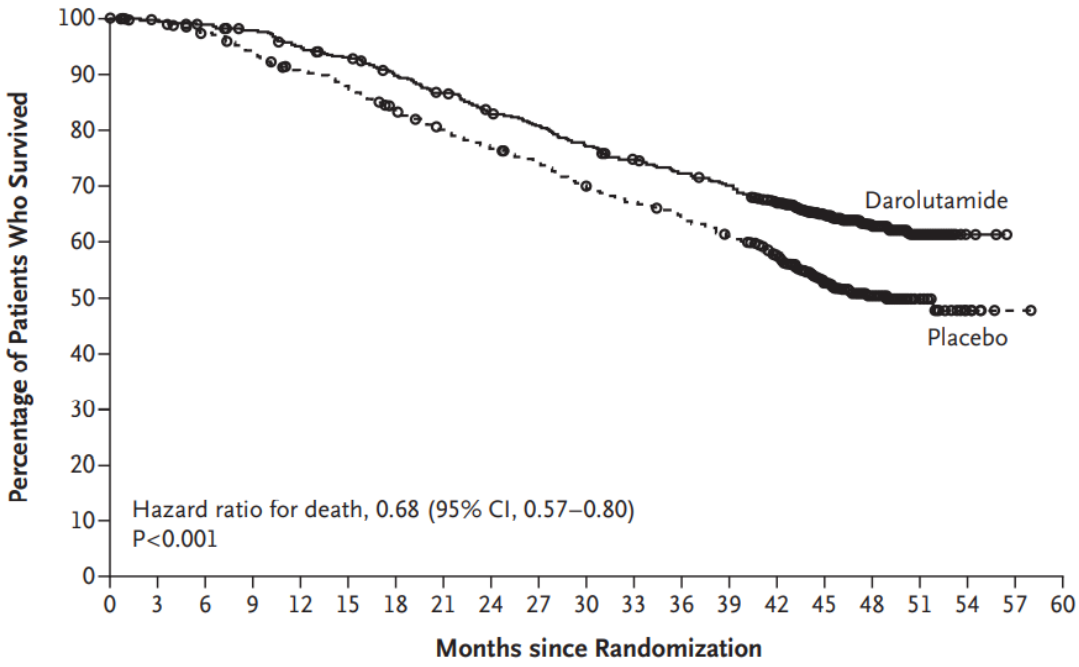
B.2.6.1.1 Overall survival

At the time of the database cut-off date (25 October 2021), a total of 533 OS events had occurred, with 229 deaths in the darolutamide+docetaxel group (35.2% of patients) and 304 deaths in the placebo+docetaxel group (46.5% of patients).[45] The relative risk of death was reduced by 32.5% in the darolutamide+docetaxel group compared with the placebo+docetaxel group (HR: 0.68; 95% CI: 0.57, 0.80; p < 0.001). Median OS was not reached (95% CI: NE [not estimable], NE) in the darolutamide+docetaxel group and was 48.9 months (95% CI: 44.4, NE) in the

placebo+docetaxel group (Figure 5 and Table 8). The median follow-up time from randomization to the last contact or death was 43.7 months in the darolutamide+docetaxel group and 42.4 months in the placebo+docetaxel group.

After approximately 6 months, the survival rate was greater in the darolutamide+docetaxel group than in the placebo+docetaxel group, and continued to be greater throughout the duration of the study.[44] At 48 months, the survival rate was 62.7% in the darolutamide+docetaxel group and 50.4% in the placebo+docetaxel group (Table 8) which is considered a meaningful benefit.[45]

Figure 5: Kaplan–Meier curves of overall survival (FAS)



Key: CI, confidence interval; FAS, full analysis set.
Source: Smith et al. 2022.[45]

Table 8: Overall survival (FAS)

	Darolutamide+docetaxel (N = 651)	Placebo+docetaxel (N = 654)
Patients with event, n (%)	229 (35.2)	304 (46.5)
Patients censored, n (%)	[redacted]	[redacted]
Overall survival, months (95% CI)		
25th percentile	[redacted]	[redacted]
Median	[redacted]	[redacted]
75th percentile	[redacted]	[redacted]
Range including censored values	[redacted]	[redacted]
Overall survival rate (95% CI)		
12 month	[redacted]	[redacted]
24 month	[redacted]	[redacted]
36 month	[redacted]	[redacted]
48 month	[redacted]	[redacted]
HR for darolutamide versus placebo (95% CI)[b]	0.675 (0.568, 0.801)	
One-sided p-value from stratified log-rank test	< 0.0001	

Key: ALP, alkaline phosphatase; CI, confidence interval; FAS, Full analysis set; HR, hazard ratio; NE, not estimable due to censored data; ULN, upper limit of normal.
Notes: Median, percentile and other 95% CIs were computed using Kaplan–Meier estimates. [a] censored observation. [b] HR < 1 indicates superiority of the darolutamide+docetaxel group over the placebo+docetaxel group. The HR and 95% CI were based on a Cox Regression Model, stratified by extent of disease (M1a versus M1b versus M1c) and ALP (<ULN versus ≥ ULN).
Source: Table 9-1. ARASENS CSR.[44]

OS was longer for patients in the darolutamide+docetaxel group despite a higher percentage of patients receiving subsequent life prolonging antineoplastic therapy after discontinuation of study treatment in the placebo+docetaxel group.[45] In the darolutamide+docetaxel group, 56.8% of the 315 patients who entered active or survival follow-up started life-prolonging systemic antineoplastic therapy compared with 75.6% of the 495 patients in the placebo+docetaxel group (Appendix M).

Results of the pre-specific sensitivity analyses and post-hoc sensitivity analysis (using extent of disease stratification data according to central imaging review and by number of docetaxel cycles received) [redacted].[44] A summary of the sensitivity analyses is provided in Appendix M.

B.2.6.2 Secondary efficacy outcome

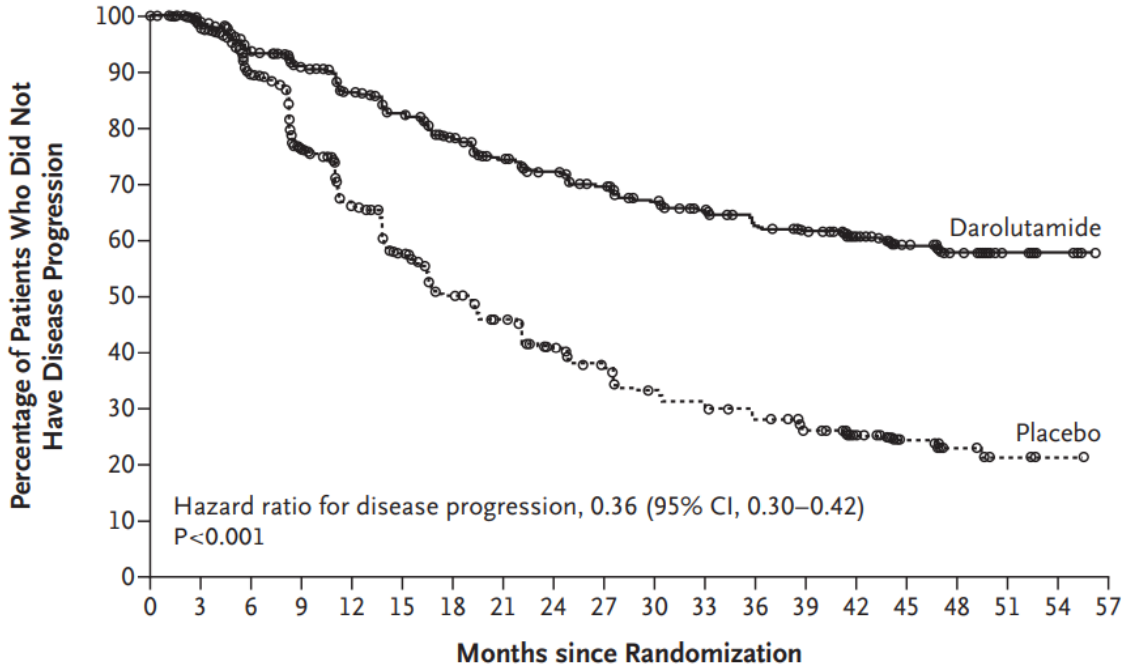
B.2.6.2.1 Time to CRPC

Overall, 225 patients (35%) in the darolutamide+docetaxel group and 391 patients (60%) in the placebo+docetaxel group progressed to CRPC (Appendix M).[45]

A statistically significant prolonged time to CRPC was observed for patients in the darolutamide+docetaxel group compared with the placebo+docetaxel group, with an HR of 0.36 (95% CI: 0.30, 0.42; p < 0.001).[45] The median time to CRPC was not reached (95% CI: NE, NE) in the darolutamide+docetaxel group and was 19.1 months (95% CI: 16.5, 21.8) in the placebo+docetaxel group (Figure 6).

Results of the sensitivity analyses were [redacted], with an HR of [redacted] (95% CI: [redacted], [redacted]; p < [redacted]; Appendix M).[44]

Figure 6: Kaplan–Meier curves of time to CRPC (FAS)



Key: CI, confidence interval; CRPC, castration-resistant prostate cancer; FAS, full analysis set.
Source: Smith et al. 2022.[45]

B.2.6.2.1.1 Time to CRPC or death exploratory outcome

Time to CRPC did not capture death as events, therefore, time to CRPC or death (CROD) was derived from ARASENS CRPC data and used in the partitioned survival model of the economic analysis (Section B.3.3.2). It is defined as the time from randomization to a CRPC event (radiological or PSA progression) or death if a patient has no CRPC event.

A statistically significant prolonged time to CROD was observed for patients in the darolutamide+docetaxel group compared with the placebo+docetaxel group, with an HR of [redacted] (95% CI: [redacted], [redacted]). The median time to CROD was [redacted] months (95% CI: [redacted], [redacted]) in the darolutamide+docetaxel group and [redacted] months (95% CI: [redacted], [redacted]) in the placebo+docetaxel group (Table 9 and Figure 7).

Table 9: Time to CROD summary (FAS)

Treatment	Number of patients	Number of events	Median, months (95% CI)	HR (95% CrI)
Darolutamide+docetaxel	651	[redacted]	[redacted]	[redacted]
Placebo+docetaxel	654	[redacted]	[redacted]	[redacted]

Key: CROD, castration-resistant prostate cancer or death; FAS, full analysis set.

Figure 7: Kaplan–Meier curves of time to CROD (FAS)

Key: CROD, castration-resistant prostate cancer or death; FAS, full analysis set.

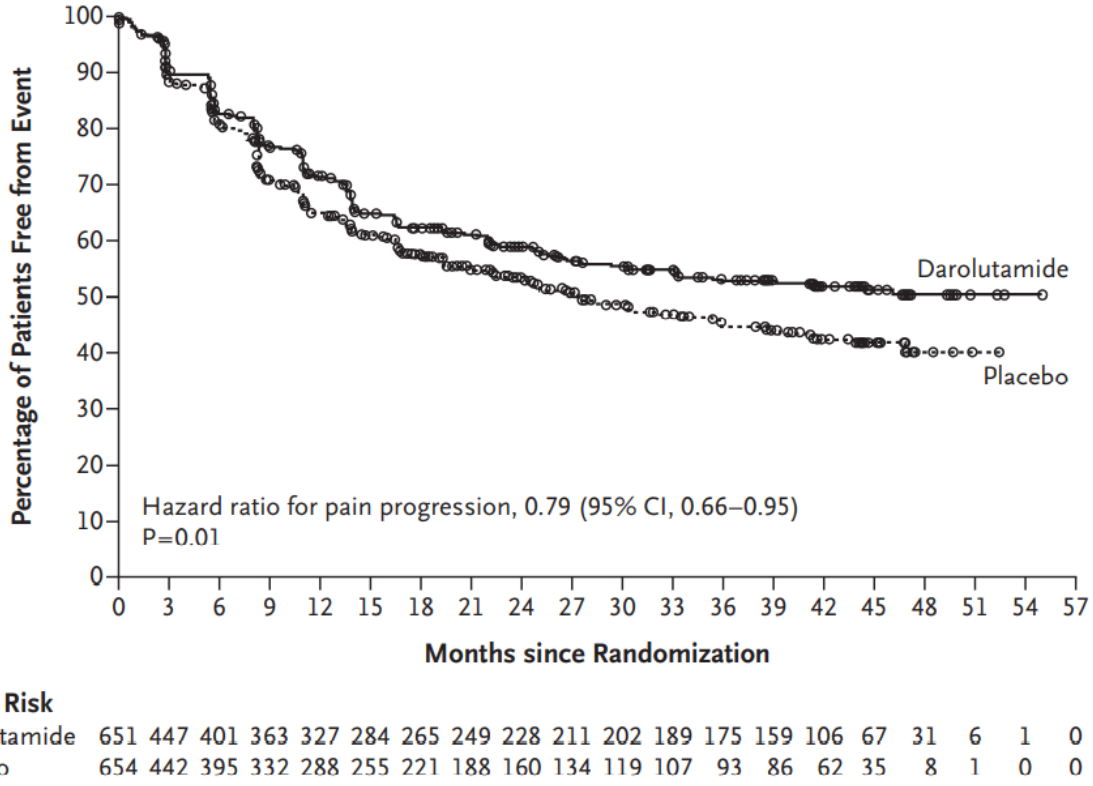
B.2.6.2.2 Time to pain progression

There were 34% of patients in the darolutamide+docetaxel group and 38% in the placebo+docetaxel group with pain progression (Appendix M).[45]

A statistically significant delay in time to pain progression was observed for patients in the darolutamide+docetaxel group, with an HR of 0.79 (95% CI: 0.66, 0.95; p = 0.01).[45] The median time to pain progression was not reached (95% CI: 30.5, NE) in the darolutamide+docetaxel group and was 27.5 months (95% CI: 22.0, 36.1) in the placebo+docetaxel group (Figure 8).

Results of the sensitivity analyses were [redacted].[44] A summary of the sensitivity analyses is provided in Appendix M.

Figure 8: Kaplan–Meier curves of time to pain progression (FAS)



Key: CI, confidence interval; FAS, full analysis set.
Source: Smith et al. 2022.[45]

B.2.6.2.3 Symptomatic skeletal event-free survival

There were 40% of patients in the darolutamide+docetaxel group and 50% in the placebo+docetaxel group with an SSE-FS event, with the majority of events being [redacted] (Appendix M).[44, 45]

SSE-FS was significantly longer in the darolutamide+docetaxel group, with an HR of 0.61 (95% CI: 0.52, 0.72; p < 0.001).[44, 45] The median SSE-FS was 51.2 months (95% CI: [redacted], [redacted]) in the darolutamide+docetaxel group and 39.7 months (95% CI: [redacted], [redacted]) in the placebo+docetaxel group (Figure 9).

Figure 9: Kaplan–Meier curves of SSE-FS (FAS)

Key: FAS, full analysis set; SSE-FS, symptomatic skeletal event-free survival.
Notes: At-risk patient counts were calculated as at start of timepoint.
Source: Figure 9-6. ARASENS CSR.[44]

B.2.6.2.4 Time to first symptomatic skeletal event

Overall, SSEs were reported in 15% of patients in the darolutamide+docetaxel group compared with 17% in the placebo+docetaxel group (Appendix M).[44, 45] The majority of the first SSEs were external beam radiation therapy (EBRT) to relieve skeletal symptoms, reported for [redacted]% of patients with an SSE in the darolutamide+docetaxel group and [redacted]% of patients with an SSE in the placebo+docetaxel group.

Statistically significant delays in time to first SSE were observed for patients in the darolutamide+docetaxel group, with an HR of 0.71 (95% CI: 0.54, 0.94; p = 0.02).[44, 45] The median time to first SSE was not reached (95% CI: [redacted], [redacted]) in either

treatment arm. The results were consistent with the results of SSE-FS, where in addition to SSE, death was considered as an event.

Figure 10: Kaplan–Meier curves for time to first SSE (FAS)

Key: FAS, full analysis set; SSE, symptomatic skeletal event.
Notes: At-risk patient counts were calculated as at start of timepoint.
Source: Figure 9-7. ARASENS CSR.[44]

B.2.6.2.5 Time to initiation of subsequent systemic antineoplastic therapy

There were 34% of patients in the darolutamide+docetaxel group who started a new systemic antineoplastic therapy, compared with 60% in the placebo+docetaxel group (Appendix M).[45]

Statistically significant delays in the time to initiation of subsequent systemic antineoplastic therapy were observed for patients in the darolutamide+docetaxel group compared with the placebo+docetaxel group (HR: 0.39, 95% CI: 0.33, 0.46; p < 0.001).[44, 45] The median time to initiation of subsequent systemic antineoplastic

therapy was not reached (95% CI: [redacted], [redacted]) in the darolutamide+docetaxel group and was 25.3 months (95% CI: [redacted], [redacted]) in the placebo+docetaxel group (Figure 11).

Subsequent systemic antineoplastic therapies were for prostate cancer, however, [redacted] patients in the darolutamide+docetaxel arm and [redacted] patients in the placebo+docetaxel arm received a first antineoplastic therapy for an additional primary malignancy.[44]

Figure 11: Kaplan–Meier curves of time to initiation of subsequent systemic antineoplastic therapy (FAS)

Key: FAS, full analysis set.
Notes: At-risk patient counts were calculated as at start of timepoint.
Source: Figure 9-8. ARASENS CSR.[44]

B.2.6.2.6 Time to worsening of disease-related physical symptoms

The time to worsening of disease-related physical symptoms was based on the results from the FPSI–DRS–P subscale in the NCCN-FACT-FPSI-17 questionnaire. Worsening of disease-related physical symptoms was observed for 54% of patients in the darolutamide+docetaxel group and 47% of patients in the placebo+docetaxel group (Appendix M).[45]

There was no significant difference in time to worsening of disease-related physical symptoms between the treatment arms (HR: 1.04; 95% CI: 0.89, 1.22; p = 0.59).[44, 45] The median time to worsening of disease-related physical symptoms was 19.3 months (95% CI: [redacted], [redacted]) in the darolutamide+docetaxel group and 19.4 months (95% CI: [redacted], [redacted]) in the placebo+docetaxel group (Figure 12). The results indicate that HRQL was maintained in patients in the darolutamide+docetaxel group compared with the placebo+docetaxel group during the study.

The results of the sensitivity analysis [redacted]).[44] Median times to worsening of disease-related physical symptoms were [redacted] months (95% CI: [redacted], [redacted]) in the darolutamide+docetaxel group and [redacted] months (95% CI: [redacted], [redacted]) in the placebo+docetaxel group (Appendix M).

Figure 12: Kaplan–Meier curves of time to worsening of disease-related physical symptoms (FAS)

Key: FAS, full analysis set.
Notes: At-risk patient counts were calculated as at start of timepoint.
Source: Figure 9-9. ARASENS CSR.[44]

B.2.6.2.7 Time to initiation of opioid use for ≥ 7 consecutive days

The secondary endpoints of the study were pre-specified in a hierarchical testing scheme to be tested for significance if the results of all previous endpoints were significant.[44] As the preceding endpoint "Time to worsening of disease-related physical symptoms" did not reach the pre-specified significance level for this analysis, "Time to initiation of opioid use for ≥ 7 consecutive days" was not tested for significance (nominal p-values are provided for information only). However, a benefit in favour of the darolutamide+docetaxel group was observed (HR: [redacted] 95% CI: [redacted], [redacted]; p = [redacted]; Appendix M).

B.2.6.3 Exploratory outcomes

B.2.6.3.1 Time to PSA progression

Baseline PSA values were comparable between the treatment arms (median [redacted] ng/mL in the darolutamide+docetaxel group and [redacted] ng/mL in the placebo+docetaxel group.[44] A smaller percentage of patients in the darolutamide+docetaxel group ([redacted] patients, [redacted]%) than in the placebo+docetaxel group ([redacted] patients, [redacted]%) had PSA progression (Appendix M).

Treatment with darolutamide in combination with docetaxel resulted in a longer time to PSA progression than placebo in combination with docetaxel, with an HR of [redacted] (95% CI: [redacted], [redacted]; p < [redacted].[44] The median time to PSA progression was not reached (95% CI: [redacted], [redacted]) in the darolutamide+docetaxel group and was [redacted] months (95% CI: [redacted], [redacted]) in the placebo+docetaxel group (Figure 13). The results supported the analysis of time to CRPC, as PSA progression was a component event of progression to CRPC.

Results of the sensitivity analyses [redacted].[44] A summary of the sensitivity analyses is provided in Appendix M.

Figure 13: Kaplan–Meier curves of time to PSA progression according to PCWG3 (FAS)

Key: FAS, full analysis set; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PSA, prostate-specific antigen.
Notes: At-risk patient counts were calculated as at start of timepoint.
Source: Figure 9-11. ARASENS CSR.[44]

B.2.6.3.2 PSA response

Patients in the darolutamide+docetaxel group ([redacted]%) demonstrated a significantly higher relative PSA response rate of [redacted]% reduction from baseline at 12 months after randomization than patients in the placebo+docetaxel group ([redacted]%), with a rate difference of [redacted]% (95% CI: [redacted]; [redacted]; p [redacted]). Overall, both absolute PSA response rates (PSA level < 0.2 ng/mL) and relative PSA response rates (≥ 90%, ≥ 50% and ≥ 30% reduction in PSA from baseline) were significantly higher in the darolutamide+docetaxel group than in the placebo+docetaxel group at all evaluated time points.

A summary of the PSA response data is provided in Appendix M.

B.2.6.3.3 Health-related quality of life

B.2.6.3.3.1 NCCN-FACT-FPSI-17

Completion rates of NCCN-FACT-FPSI-17 questionnaires were similar between the treatment groups throughout treatment and follow-up.[44] Other than at Visit 1 ([redacted]%), over [redacted]% of patients completed all the questions at each visit during the study treatment, and at most visits this value was > [redacted]%. During active follow-up, completion rates dropped to > [redacted]%.

At baseline (i.e. Screening or Visit 1/Day 1), disease-related physical symptoms, disease-related emotional symptoms, treatment side effects, function and well-being and total scores were similar between the treatment groups.[44] Changes in mean values from baseline for the disease-related physical symptoms, disease-related emotional symptoms, treatment side effects and total scores were similar in both treatment groups, and there were no clinically meaningful nor statistically significant differences between the treatment groups (Appendix M).

B.2.6.3.3.2 BPI-SF

Completion rates of the BPI-SF questionnaires were comparable between the treatment groups throughout treatment and follow-up.[44] Other than at Visit 1 ([redacted]%), over [redacted]% of patients completed all the questions at each visit during the study treatment, and at most visits this value was > [redacted]%. During active follow-up, the completion rates dropped to > [redacted]%.

At baseline (i.e. Screening or Visit 1/Day 1), the BPI-SF pain interference and pain severity scores were similar between the treatment groups.[44] Changes in mean values from baseline for the pain severity and pain interference scores were observed in both treatment groups, and there were no clinically meaningful differences between the treatment groups (Appendix M). The pain interference score and pain severity score results favoured the darolutamide+docetaxel group (lower scores represent less pain) but were not statistically significant nor clinically meaningful.

B.2.6.4 Additional supporting evidence for darolutamide

B.2.6.4.1 Drug-drug interactions

A retrospective observational cohort study used data from an administrative claims database to compare the risks of pDDIs of darolutamide, enzalutamide and apalutamide among patients with non-metastatic castration-resistant prostate cancer (nmCRPC).[43] Although in a different indication to this appraisal, the theoretical analysis performed in the study is informative for the mHSPC population as both populations are elderly with multiple comorbidities[9, 43], and pDDIs are an important consideration for clinicians.[37]

In total, there was one pDDI for darolutamide in both the Lexicomp and Micromedex compendia (Table 10).[43] For enzalutamide and apalutamide, there were 22 pDDIs each observed in both compendia. There were less frequent severe pDDIs for darolutamide compared with enzalutamide and apalutamide.

In the nmCRPC population (n = 718), a pDDI was identified among 34.5% of patients receiving enzalutamide, 17.1% on apalutamide and 7.0% on darolutamide according to Lexicomp (Figure 14).[43] With respect to Micromedex, a pDDI was identified among 9.3% of nmCRPC patients receiving enzalutamide, 8.5% on apalutamide, and 7.0% on darolutamide.

These results are further supported by additional studies that demonstrate darolutamide has limited DDIs when administered alongside medications commonly used to treat comorbidities in an elderly patient population, such as calcium channel blockers and anticoagulants.[48-50]

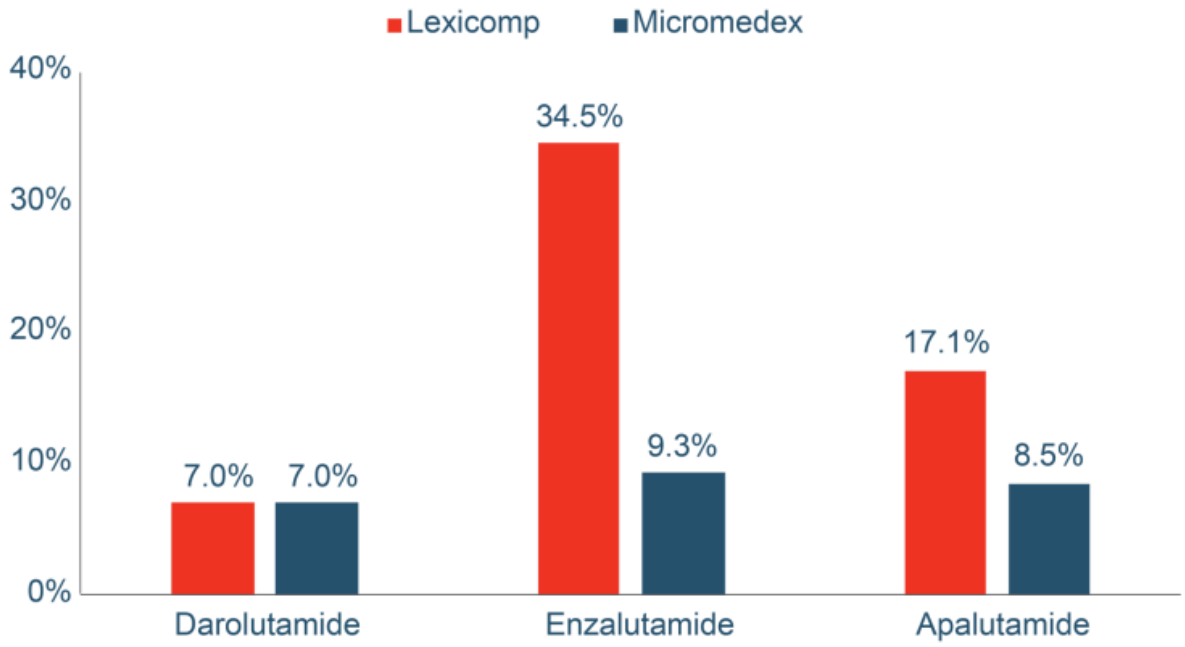
Table 10: Implicated enzymes and interacting drugs for DDIs using Lexicomp and Micromedex compendia

Drug (number of interactions)	DDI severity rating[a]	Implicated enzymes (number of interactions)	Interacting drugs
Lexicomp			
Darolutamide (1)	D: 1	BCRP and OATP1B1/1B3 (1)	Rosuvastatin
Enzalutamide (22)	C: 6 D: 16	CYP3A4 (17) CYP2C19 (1)	Amlodipine, apixaban, atorvastatin, clopidogrel, diltiazem, doxazosin, glimepiride,

Drug (number of interactions)	DDI severity rating[a]	Implicated enzymes (number of interactions)	Interacting drugs
		CYP2C9 (2) CYP2C8 (1) CYP3A4 + CYP2C9 (1)	glipizide, hydrocodone/acetaminophen, isosorbide mononitrate, losartan, losartan/hydrochlorothiazide, mirtazapine, omeprazole, prednisone, rivaroxaban, sertraline, simvastatin, tamsulosin, tramadol, warfarin, zolpidem
Apalutamide (22)	C: 10 D: 9 X: 3	CYP3A4 (17) CYP2C9 (1) CYP2C19 (2) Unknown or not fully investigated (2)	Amlodipine, atorvastatin, clopidogrel, diltiazem, doxazosin, hydrocodone/acetaminophen, isosorbide mononitrate, levothyroxine, losartan, losartan/hydrochlorothiazide, mirtazapine, prednisone, rosuvastatin, sertraline, simvastatin, tamsulosin, tramadol, warfarin, zolpidem
Micromedex			
Darolutamide (1)	Major: 1	BCRP (1)	Rosuvastatin
Enzalutamide (22)	Major: 4	CYP3A4 (3) CYP3A4 + CYP2C9 (1)	Hydrocodone/acetaminophen, mirtazapine, tramadol, warfarin
Apalutamide (22)	Major: 4 Moderate: 2	CYP3A4 (1) SYP3A4 + Pgp (2) CYP3A4 + CYP2C9 (1) CYP3A4 + CYP2C19 + CYP2C9 (2)	Apixaban, mirtazapine, omeprazole, rivaroxaban, simvastatin, warfarin

Key: DDI, drug-drug interaction.
Notes: [a] Lexicomp C rating signifies the patient's therapy must be monitored to identify potential negative effects; D rating signifies the patient's regimen should be modified to minimize the toxicity resulting from the concomitant use of the drugs; X rating signifies the combination of drugs should be avoided as the drugs are contraindicated.
Source: Appukkuttan et al. 2021.[43]

Figure 14: pDDIs identified in nmCRPC patients



Key: nmCRPC, non-metastatic castration-resistant prostate cancer; pDDIs, potential drug-drug interactions.
Source: Appukkuttan et al. 2021.[43]

B.2.7 Subgroup analysis

Pre-specified subgroup analyses were conducted for the primary efficacy endpoint OS, based on the FAS population.[44] Descriptive statistics and HR estimates with 95% CI were given for the subgroups, provided that at least 10 total events were observed within the subgroup across both treatment groups. All subgroup analyses were performed using an unstratified Cox model.

A consistent OS benefit for darolutamide in combination with docetaxel was observed across all pre-specified subgroups including baseline extent of disease, ALP, age, race, geographical region, PSA, ECOG PS, Gleason score, and metastasis at initial diagnosis.[44] For some subgroups there were a low number of events (e.g. extent of disease: non-regional lymph node metastases; race: Black or African American; race: other or not reported; and metastasis at initial diagnosis: no), for which the results must be interpreted with caution.

A summary of results for the analysed subgroups is provided in Appendix E.

B.2.8 Meta-analysis

The main evidence for the use of darolutamide in combination with docetaxel and ADT in the treatment of mHSPC is from ARASENS. No other studies investigating the safety and efficacy of this triplet combination therapy were identified. Therefore, no meta-analysis is required.

B.2.9 Indirect and mixed treatment comparisons

Appendix D include full details of the methodology for the indirect comparison or mixed treatment comparison.

The relative efficacy of darolutamide in combination with docetaxel and ADT was compared with enzalutamide+ADT, docetaxel+ADT and ADT alone for patients with mHSPC using network-meta analysis (NMA) methods.

B.2.9.1 Study selection

A systematic literature review (SLR) was conducted and searches for the SLR were designed to capture relevant studies from a multi-country perspective and to meet the requirements of global HTA agencies (detailed in Appendix D), so comparators that are not relevant for this submission (e.g. radiotherapy and apalutamide) were included. Only studies that included treatments informing the comparisons relevant for this submission are discussed in further detail.

Treatments, trial design and patient characteristics of the identified trials were assessed to determine the suitability of conducting an indirect treatment comparison (ITC) and for informing the appropriate methodology for these analyses. Indirect methods are generally considered acceptable if applied with consideration to the basic assumptions of homogeneity, similarity and consistency as reported in Song et al. 2009.[51] The appropriateness of an NMA was considered in terms of these criteria for each endpoint.

The SLR identified 27 studies as potentially relevant for darolutamide + docetaxel + ADT NMAs, presented in Table 11. The STAMPEDE trial was a multi-arm platform randomized controlled trial (RCT), and each stage of the platform design was

considered as a separate study in this NMA in line with the enzalutamide technology appraisal (TA).[38]

Table 11: Overview of studies included in the systematic literature review

Study name	Trial name	Treatment/comparator
Agarwal 2021[52]	SWOG S1216	Bicalutamide + ADT
		Orteronel (TAK-700) + ADT
Armstrong 2019[53]	ARCHES	Enzalutamide + ADT
		ADT
Boccon-Gibod 1997[54]	NR	Orchiectomy
		Flutamide
Bruun 1996[55]	NR	Buserelin
		Conventional antiandrogenic treatment (oestrogens or bilateral orchiectomy)
Chang 1996[56]	NR	Flutamide
		Diethylstilbestrol
Chi 2019[57]	TITAN	Apalutamide + ADT
		ADT
Chodak 1995[58]	NR	Bicalutamide
		Castration (medical or surgical)
Clark 2013[59]	STAMPEDE-6	ADT
Clarke 2019[60]	STAMPEDE-3	ADT
		Docetaxel + ADT
Davis 2019[61]	ENZAMET	Enzalutamide + ADT ± docetaxel
		SNA + ADT ± docetaxel
Eisenberger 1998[62]	SWOG study-S8894	Bilateral orchiectomy + flutamide
		Bilateral orchiectomy
Ferrari 1996[63]	NR	Leuprolide
		Leuprolide + flutamide
Fizazi 2017[16]	LATITUDE	Abiraterone acetate + prednisone + ADT
		ADT
Fizazi 2021[64]	PEACE-1	Abiraterone + docetaxel + ADT
		Radiotherapy + SoC
		Abiraterone + radiotherapy + SoC
		Docetaxel + ADT
Gravis 2013[19]	GETUG-AFU 15	Docetaxel + ADT
		ADT
Iversen 1996[65]	NR	Bicalutamide
		Bilateral orchiectomy
James 2016[23]	STAMPEDE-1	ADT
		Zoledronic acid + ADT
		Docetaxel + ADT

Study name	Trial name	Treatment/comparator
		Docetaxel + zoledronic acid + ADT
James 2012[66]	STAMPEDE-7	Celecoxib + ADT
		ADT
James 2017[67]	STAMPEDE-2	ADT
		Abiraterone acetate + prednisone + ADT
Kaisary 1995[68]	NR	Bicalutamide
		Castration (medical or surgical)
Kirby 1999[69]	NR	Goserelin + flutamide
		Goserelin + finasteride
		Finasteride + flutamide
Klijn 1993[70]	EORTC-TRIAL 30843	Orchiectomy
		Buserelin + cyproterone acetate 2wk
		Buserelin + cyproterone acetate 2wk
Kulkarni 2003[71]	NR	Bilateral orchiectomy + Flutamide
		Bilateral orchiectomy
Parker 2018[72]	STAMPEDE-5	Radiotherapy + ADT
		ADT
Saltzstein 2021[73]	HERO Study	Leuprolide
		Relugolix
Schröder 2004[74]	EORTC-30892	Flutamide
	EORTC-30892	Cyproterone acetate
Sweeney 2015[21]	CHAARTED	Docetaxel + ADT
		ADT
Sydes 2018[75]	STAMPEDE-4	Docetaxel + prednisolone + ADT
		Abiraterone acetate + prednisone + ADT
Thorpe 1996[76]	NR	Goserelin
		Cyproterone acetate
		Goserelin + cyproterone acetate
Vaishampayan 2021[77]	NR	Enzalutamide + ADT
		Bicalutamide + ADT
Vogelzang 1995[78]	NR	Goserelin
		Orchiectomy
Zalcberg 1996[79]	NR	Bilateral orchiectomy
		Bilateral orchiectomy + Placebo

Key: ADT, androgen deprivation therapy; NA, not reported; NR, not reported; SNA, nonsteroidal antiandrogen.

B.2.9.1.2 Treatments

To assess trial comparability of the 27 studies identified, the differences and similarities between treatments of interest, treatment dosing, frequency, delivery, and treatment cycle were investigated (tables summarizing treatments are included in Table 7 Appendix D). The relevant comparators for darolutamide+docetaxel+ADT are enzalutamide+ADT, docetaxel+ADT and ADT alone. Abiraterone+ADT is not considered a relevant comparator, but, as it has been a treatment studied in STAMPEDE against both docetaxel+ADT and ADT alone (two of the comparators in this appraisal), studies that investigated abiraterone were considered if they provided indirect evidence to enrich the network through the formation of loops.

35 treatments were identified across 27 trials in the evidence base. 14 trials did not include relevant comparators of interest and were excluded (Boccon-Gibod 1997, Chang 1996, Chodak 1995, EORTC-30892, EORTC-TRIAL 30843, Kaisary 1995, Kirby 1999, PEACE-1, STAMPEDE-5, STAMPEDE-6, STAMPEDE-7, SWOG S1216, Thorpe 1996 and TITAN). All ADT treatments were grouped into one node, and four trials comparing ADT versus ADT were excluded as they did not provide comparisons of interest (Brunn 1996, the HERO study, Iverson 1996 and Vogelzang 1995 between them include buserelin, goserelin, LHRH analogues and orchiectomies, which are all forms of ADT).

STAMPEDE-1 included metastatic and non-metastatic patients whereas STAMPEDE-3 included only the metastatic patients from STAMPEDE-1, so STAMPEDE-1 was excluded.

ENZAMET compared enzalutamide+ADT±docetaxel or standard nonsteroidal antiandrogen (SNA)+ADT±docetaxel, and the administration of docetaxel was applied as a stratification factor. About 45% of patients received enzalutamide+ADT+docetaxel (not a comparator of interest) or SNA+ADT+docetaxel, and the remaining patients received enzalutamide+ADT (comparator of interest) or SNA+ADT. Baseline characteristics were not available for each treatment group (treated with docetaxel versus not treated with non-docetaxel), but it is assumed that patients who receive docetaxel have a worse prognosis than those who do not, as docetaxel is a form of chemotherapy (Kaplan–Meier curves presented in Davis 2019 suggested that patients who were not treated with

docetaxel appeared to have better survival than those treated with docetaxel[61]). Due to lack of availability of baseline characteristics for the docetaxel/non-docetaxel treatment groups in ENZAMET, it was not possible to assess the presence of heterogeneity as any characteristics of the overall trial population would probably be skewed. Therefore, ENZAMET has been excluded from the base case NMA but included in a scenario analysis. Similarly to ENZAMET, Vaishampayan 2021 compared enzalutamide + ADT with SNA + ADT; this study was excluded from the base case due to the high risk of bias, low power, early stop in patient accrual, and short follow-up, but was included in scenario analysis around the NMA network.

A further four studies included SNA+ADT (compared to ADT) which is not a treatment of interest but were relevant to the scenario analysis including ENZAMET and Vaishampayan 2021 as they provide an indirect link between these trials and ADT. These studies are Ferrari 1996, Kulkarni 2003, SWOG study S8894, and Zalcberg 1996. Out of these four studies, Ferrari 1996 and Kulkarni 2003 were excluded as outcome data were not reported.

Detailed reasons for exclusion of each study included in the SLR are detailed in Table 8 Appendix D.

Eight trials (ARASENS, ARCHES, CHAARTED, GETUG-AFU 15, LATITUDE, STAMPEDE-2, STAMPEDE-3 and STAMPEDE-4) were included in the base case NMA as they included relevant treatments. All trials were evaluated and found to be similar in terms of dose, frequency, delivery and treatment cycles of docetaxel, except GETUG-AFU 15 where patients could receive up to nine cycles (as detailed in Appendix D). GETUG-AFU 15 was included in the base case NMA, but a sensitivity analysis was performed excluding GETUG-AFU 15.

B.2.9.1.3 Trial heterogeneity assessment

After excluding studies based upon the investigated treatments, there were eight trials remaining for the base case NMA (including three studies from the STAMPEDE trial) whose trial design was considered for comparability. A summary of trial design is presented in Table 12; the STAMPEDE trial has been included as a single trial in this table due to the multi-arm, multi-stage platform design. Studies were either double-blind or open label. All studies were multi-centre RCTs. Five studies (83.3%)

were Phase III and one study was Phase II/III. Half of the studies had placebo-/best supportive care (BSC)-controlled comparators (50%), 33.3% had active and placebo-/BSC-controlled comparators and one had an active controlled comparator.

Trial population was defined slightly differently across the studies. Our focus was on patients with mHSPC. Studies used the interchangeable terms ‘metastatic hormone-sensitive prostate cancer’ (ARASENS, ARCHES, CHAARTED) and ‘metastatic castration-sensitive prostate cancer’ (LATITUDE). The trial population in STAMPEDE was defined as ‘hormone-naïve prostate cancer’, and patients who had metastatic, non-metastatic and high-risk hormone-naïve prostate cancer were included in this trial. However, only results from the metastatic subgroup have been included in the NMA. The trial population in GETUG-AFU 15 was described as ‘non-castrate metastatic prostate cancer’. Both metastatic hormone-naïve prostate cancer and non-castrate metastatic prostate cancer are classified as mHSPC. The HRs from the overall trial population were used in the NMA from all trials in the evidence base, except STAMPEDE where results from the metastatic subgroup only was used.

Table 12: Detailed trial design of studies identified by clinical SLR and included in the base case NMA

Trial name	Sample size	Blinding	Phase	Population	Comparator	Median length of follow up in weeks
ARASENS	1,305	Double blind	III	Darolutamide in addition to standard androgen deprivation therapy (ADT) and docetaxel in metastatic hormone–sensitive prostate cancer	Placebo/BSC	303
ARCHES	1,150	Double blind	III	A randomized, Phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer	Active and placebo/BSC controlled	193.8
CHAARTED	790	Open label	III	Chemohormonal therapy in metastatic hormone-sensitive prostate cancer	Active controlled	233.34
GETUG-AFU 15	385	Open label	III	Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomized, open-label, phase 3 trial	Placebo/BSC controlled	364.5
LATITUDE	1,199	Double blind	III	Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer	Placebo/BSC controlled	225
STAMPEDE	2,962	Open label	II/III	Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multi-arm, multistage, platform randomized controlled trial.*	Active and placebo/BSC controlled	339.8

Key: ADT, androgen deprivation therapy; BSC, best supportive care; NR, not reported.
Notes: *Only results from the metastatic subgroup was considered for this analysis.

The trial inclusion/exclusion criteria and baseline characteristics of the patient populations were compared for the eight trials considered for inclusion in the NMAs (STAMPEDE 2, 3 and 4 are each considered to be their own study). Inclusion/exclusion criteria and baseline characteristics by study are presented in detail in Appendix D, Section D.1.6.4.

No studies were excluded due to the inclusion/exclusion criteria or due to the baseline characteristics.

Exploratory analysis was performed with the ARASENS trial patient-level data to identify potential treatment effect modifiers. There was no evidence of treatment effect modification from the exploratory analysis of the ARASENS trial data (Appendix D, Figures 7 and 8). This was confirmed by HTA and clinical expert input.[37, 80]

Most studies were similar to ARASENS in terms of inclusion and exclusion criteria. Eastern Cooperative Oncology Group (ECOG) inclusion/exclusion criteria varied slightly; ARASENS and ARCHES included 0–1, and LATITUDE, GETUG-AFU 15 and CHAARTED included 0-2. However, baseline characteristics showed that no study was a clear outlier for ECOG. Age ranges across the studies were similar and the method of confirmed disease was similar between the studies. Some of the studies had different inclusion criteria to ARASENS, with some allowing the patient to have received prior chemotherapy before beginning trials. This is a source of heterogeneity in the evidence base that occurs in a minority of the selected studies. Patients in all studies used in the base case NMA received prior treatment. A variety of prior treatments were given, such as docetaxel, ADT, prostatectomy, surgery, hormone therapy and antiandrogen treatments. Duration of prior treatment was not well reported in the evidence. Since prior docetaxel was administered to only 17.8% of patients in ARCHES and the results of the overall population and the ‘no prior docetaxel treated’ subgroup are similar, the HR from the overall population has been used in the analysis.

Table 13: Summary of studies identified by clinical SLR and included in the NMA

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
Primary NMA evidence network				
NCT02799602 (ARASENS)	Darolutamide + docetaxel + ADT	Placebo + docetaxel + ADT	Patients with metastatic hormone-sensitive prostate cancer (mHSPC).	Smith et al., 2022
CHAARTED	Docetaxel + ADT	ADT	Patients with metastatic hormone-sensitive prostate cancer	Sweeney 2015
GETUG-AFU 15	Docetaxel + ADT	ADT	Patients with non-castrate metastatic prostate cancer	Gravis et al., 2013
STAMPEDE-3	Docetaxel + ADT	ADT	Patients with metastatic hormone-naive prostate cancer (mHNPC)	Clarke et al., 2020
STAMPEDE-4	Abiraterone acetate + ADT	Docetaxel + ADT	Patients with metastatic hormone-naive prostate cancer (mHNPC)	Sydes et al., 2018
LATITUDE	Abiraterone acetate + Prednisone + ADT	ADT	Men with metastatic, castration-sensitive prostate cancer	Fizazi et al., 2017
STAMPEDE-2	Abiraterone acetate + Prednisone + ADT	ADT	Patients with metastatic hormone naive prostate cancer (mHNPC)	James et al., 2017
ARCHES	Enzalutamide + ADT	ADT	Men with metastatic hormone-sensitive prostate cancer (mHSPC).	Armstrong et al., 2019
Scenario analyses included				
ENZAMET	Enzalutamide + ADT	SNA + ADT	Patients receiving first-line therapy in	Davis et al., 2019

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
			metastatic prostate cancer	
Vaishapayan 2021	Enzalutamide + ADT	SNA + ADT	Men with metastatic hormone-sensitive prostate cancer	Vaishapayan et al., 2021
Zalcberg 1996	SNA + ADT	ADT	Newly diagnosed patients with metastatic carcinoma of the prostate	Zalcberg et al., 1996
Kaulkarni 2003*	SNA + ADT	ADT	Previously untreated histologically proven adenocarcinoma of prostate with metastasis to bones with or without metastasis to lymph nodes or other sites	Kaulkarni et al., 2003
SWOG-study-S8894	SNA + ADT	ADT	Patients with metastatic prostate cancer	Eisenberger et al., 1998
Ferrari 1996*	SNA + ADT	ADT	Patients with advanced prostatic cancer	Ferrari et al., 1996
Key: ADT, androgen deprivation therapy; SNA, nonsteroidal antiandrogen **Note:** * Kaulkarni 2003 and Ferrari 1996 did not report relevant outcome data for NMAs.				

B.2.9.1.4 Outcomes

Two outcomes were considered for the NMAs: OS and PFS. Kaulkarni 2003 and Ferrari 1996 did not report relevant outcome data for NMAs, so they were excluded from the evidence base. Outcomes from the ITT study populations were used throughout these analyses (results from STAMPEDE from the metastatic only subgroup were used).

B.2.9.1.4.1 Overall survival

OS was defined similarly across all trials.

B.2.9.1.4.2 Progression

The PFS outcome definitions were not fully aligned across the trials, so we have conducted two progression NMAs:

- A base PFS network based on time to CROD from ARASENS (CROD is an endpoint that captures both progression and death) and using the best matching progression outcomes across the other trials. The following data were used for each trial:
  - Time to CROD was used for ARASENS
  - Radiological PFS (rPFS) was used for ARCHES, LATITUDE, and GETUG-AFU 15
  - Clinical PFS (cPFS) was used for CHAARTED
  - Failure-free survival (FFS) was used for STAMPEDE-2, STAMPEDE-3 and STAMPEDE-4
- To test the robustness of the base PFS network, we also ran an alternative PFS network based on time to CRPC from ARASENS. This network used the most closely aligned best matching progression outcomes across the other trials where time to CRPC was not reported. Time to CRPC was not reported in LATITUDE, GETUG-AFU 15, STAMPEDE-2, STAMPEDE-3 and STAMPEDE-4, so the following data were used instead:
  - Time to CRPC for ARASENS, ARCHES, and CHAARTED
  - Time to subsequent prostate cancer therapy for LATITUDE
  - Biochemical PFS for GETUG-AFU 15
  - FFS for STAMPEDE-2, STAMPEDE-3 and STAMPEDE-4

Differences and similarities between definitions are summarized in Table 14 and Table 15, based on the information available in the publications that were identified in the SLR.

Table 14: Summary of similarities and differences of definitions used for base case PFS network

Study	PFS NMA data				
	Definition	**PSA progression**	**Clinical progression**	**Radiographic progression**	**Death**
ARASENS	Time to CROD: defined as the time to PSA progression with serum testosterone being at castrate level < 0.50 ng/mL, or the time to radiological progression by soft tissue/visceral lesions or bone lesions or death, whatever comes first.	✓		✓	✓
ARCHES	rPFS: defined as the time from the date of randomization to the first objective evidence of rPD at any time or death up to 24 weeks after study drug discontinuation without documented radiographic progression, whichever occurred first. rPD was defined as progressive disease by RECIST 1.1 for soft tissue disease or by appearance of 2 or more new lesions on bone scan compared to baseline or week 13 according to PCWG2 criteria, as assessed by ICR or death.			✓	✓
LATITUDE	rPFS: defined as the time interval from randomization to the first date of radiographic progression or death. Radiographic progression included progression by bone scan (according to modified PCWG2 criteria), defined as at least 2 new lesions on bone scan and progression of soft tissue lesions by computed tomography (CT) or magnetic resonance imaging (MRI) (according to RECIST 1.1 criteria). As per the RECIST 1.1 guideline, progression requires a 20 percent (%) increase in the sum of diameters of all target lesions and a minimum absolute increase of 5 millimetre (mm) in the sum as compared to nadir sum of diameter.			✓	✓
GETUG-AFU 15	rPFS: In patients with measurable lesions, radiographic progression was defined using RECIST v.1.0 criteria. In patients with bone lesions only, radiographic progression was defined as one or more new bone lesions on bone scan. Radiographic progression was the occurrence of new bone lesions or RECIST progression, whichever happened first. Death was considered as an event			✓	✓
CHAARTED	Time to clinical progression: defined as the time from randomization to clinical progression. Clinical progression is defined as increasing		✓	✓	

Study	PFS NMA data				
	Definition	PSA progression	Clinical progression	Radiographic progression	Death
	symptomatic bone metastases, progression per RECIST criteria or clinical deterioration due to cancer per investigator's opinion				
STAMPEDE	FFS: defined as time from randomization to first evidence of at least one of: biochemical failure; progression either locally, in lymph nodes, or in distant metastases; or death from prostate cancer*	✓		✓	✓
Key: CROD, castration-resistant prostate cancer or death; NMA, network meta-analysis; PCWG2, Prostate Cancer Working Group 2; PFS, progression-free survival; PSA, prostate-specific antigen; rPD, radiographic progression disease; rPFS, radiograph progression-free survival.					
Note: Radiographic progression was defined as either Response Evaluation Criteria In Solid Tumors (RECIST) or bone scan progression. *Biochemical assumed to be PSA, distant metastases assumed to be radiographic progression. Tick marks are based on information available in the SLR identified studies and publications.					

Table 15: Summary of similarities and differences of definitions used for alternative PFS network

Study	Alternative PFS network NMA data				
	Definition	PSA progression	Clinical progression	Radiographic disease progression	Death
ARASENS	Time to CRPC: defined as the time to PSA progression with serum testosterone being at castrate level < 0.50 ng/mL, or the time to radiological progression by soft tissue/visceral lesions or bone lesions, whatever comes first.	✓		✓	
ARCHES	Time to CRPC: defined as the time from randomization to the first castration-resistant event. A castration resistance event was defined as any of the following in the presence of castrate levels of testosterone (< 50 ng/dL): radiographic disease progression, PSA progression or symptomatic skeletal event, whichever occurred first.	✓		✓	
LATITUDE	Time to subsequent prostate cancer therapy: defined as time from randomization to initiation of any subsequent therapy for prostate			✓	

Study	Alternative PFS network NMA data				
	Definition	**PSA progression**	**Clinical progression**	**Radiographic disease progression**	**Death**
	cancer, including hormonal therapy, chemotherapy, surgery, or radiotherapy. Subsequent therapy in this study was allowed after radiographic progression assessed by the investigators. Similar to the real-world setting, treatment was initiated only after multiparametric verification of castration-resistant prostate cancer progression, especially when disease progressed from a castration-sensitive to castration-resistant state (Fizazi 2019).*				
GETUG-AFU 15	Biochemical PFS: defined as time to PSA progression, clinical progression, or death	✓	✓		✓
CHAARTED	Time to CRPC: defined as the time from randomization to PSA progression or clinical progression, whichever occurred first.	✓	✓	✓	
STAMPEDE	FFS: defined as time from randomization to first evidence of at least one of: biochemical failure; progression either locally, in lymph nodes, or in distant metastases; or death from prostate cancer.**	✓		✓	✓

Key: CRPC, castration-resistant prostate cancer; FFS, failure free survival; NMA, network meta-analysis; PFS, progression free survival; PSA, prostate-specific antigen.

Note: Radiographic progression was defined as either Response Evaluation Criteria In Solid Tumors (RECIST) or bone scan progression.
*Distant metastases assumed to be radiographic progression.
Tick marks are based on information available in the SLR identified studies and publications.

Proportional hazards assumption

Proportionality of hazards was assessed for time-to-event outcomes that were included in the NMA for all outcomes with an available Kaplan–Meier curve. If Kaplan–Meier curves were available, these were digitized using the method of Guyot et al. (2012) to generate pseudo patient-level data.[81] The proportionality of hazards assumption check was performed using a log-cumulative hazards plot, a Schoenfeld residuals plot and Schoenfeld's global test ($p < 0.05$ suggests a possible violation of proportional hazards [PH]). These findings are described in Appendix D, Section D.1.6.6. Where possible, the PH assumption was assessed in detail across all trials and endpoints. For OS, the PH assumption was borderline implausible for one study of interest (CHAARTED) and a sensitivity analysis removing this study was performed. For both PFS networks, the PH assumption was considered plausible for all trials reporting Kaplan–Meier curves and no sensitivity analyses were deemed necessary.

Data used in the NMA

Table 16 summarizes the available data for the endpoints of interest for the NMAs and whether proxy data were used for specific endpoints. All data were identified from the SLR.

Table 16: Data used in NMAs

Study name	Trial name	Trt 1	Trt 2	N Trt1	N Trt2	OS		PFS base case		PFS alternative	
						Endpoint used	HR (95% CI)	Endpoint used	HR (95% CI)	Endpoint used	HR (95% CI)
Studies included in base case NMA											
Bayer 2021	ARASENS	Darolutamide + docetaxel + ADT	Docetaxel + ADT	651	654	OS	0.675 (0.568, 0.801)	CROD	0.42 (0.36, 0.48)	CRPC	0.36 (0.3, 0.42)
Armstrong 2019	ARCHES	Enzalutamide + ADT	ADT	574	576	OS	0.66 (0.53, 0.81)	rPFS	0.39 (0.3, 0.5)	CRPC	0.28 (0.22, 0.36)
Sweeney 2015	CHAARTED	Docetaxel + ADT	ADT	397	393	OS	0.72 (0.59, 0.89)	Time to clinical progression	0.62 (0.51, 0.75)	CRPC	0.61 (0.52, 0.73)
Gravis 2013	GETUG-AFU 15	Docetaxel + ADT	ADT	192	193	OS	0.88 (0.68, 1.14)	rPFS	0.69 (0.55, 0.87)	bPFS	0.67 (0.54, 0.84)
Fizazi 2017	LATITUDE	Abiraterone acetate + ADT	ADT	597	602	OS	0.66 (0.56,0.78)	rPFS	0.47 (0.39, 0.55)	Time to subsequent prostate cancer therapy	0.45 (0.38, 0.53)
James 2017	STAMPEDE-2	Abiraterone acetate + ADT	ADT	500	502	OS	0.60 (0.50, 0.71)	FFS	0.31 (0.26, 0.37)	FFS	0.31 (0.26, 0.37)
Clarke 2019	STAMPEDE-3	Docetaxel + ADT	ADT	362	724	OS	0.81 (0.69, 0.95)	FFS	0.66 (0.57, 0.76)	FFS	0.66 (0.57, 0.76)

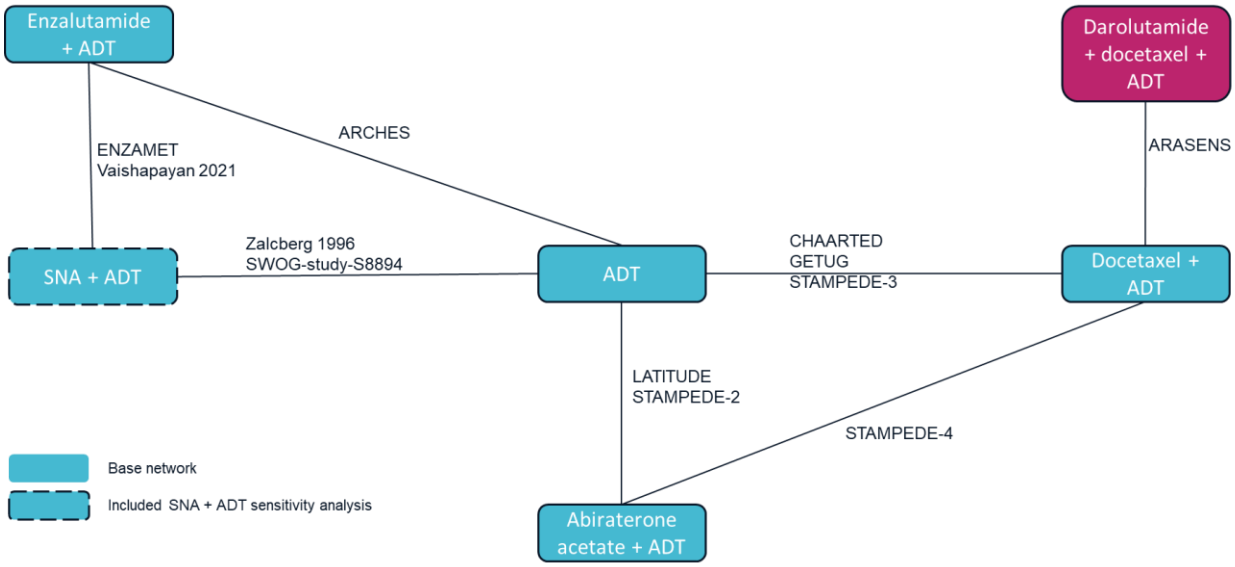
Study name	Trial name	Trt 1	Trt 2	N Trt1	N Trt2	OS		PFS base case		PFS alternative	
						Endpoint used	HR (95% CI)	Endpoint used	HR (95% CI)	Endpoint used	HR (95% CI)
Sydes 2018	STAMPEDE-4	Abiraterone acetate + ADT	Docetaxel + ADT	277	115	OS	1.13 (0.77, 1.66)	FFS	0.56 (0.42, 0.75)	FFS	0.56 (0.42, 0.75)
Studies included in sensitivity NMA											
Davis 2019	ENZAMET	Enzalutamide + ADT	SNA + ADT	309	313	OS	0.53 (0.37, 0.75)	cPFS	0.34 (0.26, 0.44)	PSA progression-free survival	0.34 (0.26, 0.44)
Vaishampayan 2021	NR	Enzalutamide + ADT	SNA + ADT	697	685	OS	0.31 (0.13, 0.74)			PSA progression	0.15 (0.05, 0.47)
Eisenberger 1998	SWOG-study-S8894	SNA + ADT	ADT	697	685	OS	1 (0.88, 1.14)				
Zalcberg 1996	NR	SNA + ADT	ADT	111	110	OS	1.14 (0.85, 1.53)				

Key: AE, adverse events; ADT, androgen deprivation therapy; bPFS Biochemical progression-free survival; CI, confidence interval; CROD, CRPC or death; CRPC; castration-resistant prostate cancer; FFS, failure-free survival; HR; hazard ratio; N, number of patients; NMA, Network meta-analysis; NR, not reported; OS; overall survival; PFS; Progression free survival; PSA, prostate-specific antigen; rPFS; radiographic progression free survival; SNA, nonsteroidal antiandrogen; TrT, treatment.

B.2.9.1.5 Studies included and excluded from NMA

The eight studies identified for inclusion in the base case NMA and those included in sensitivity analyses are presented in Figure 15.

Figure 15: NMA network diagram



Key: ADT, androgen deprivation therapy; NMA, network meta-analysis ; SNA, nonsteroidal antiandrogen

B.2.9.2 Methods

B.2.9.2.1 Network meta-analysis

The NMA was carried out using a Bayesian approach, as this captures the uncertainty in model parameters while preserving correlation between treatment effects. All NMA methods are consistent with the NICE Decision Support Unit (DSU) Technical Support Documents (TSD) 2–4.[82-85] Relative treatment effects were estimated using Markov chain Monte Carlo (MCMC) methods. One fixed-effects (FE) model and one random-effects (RE) model were fitted with a prior distribution for the RE which was non-informative and in line with those specified in NICE DSU TSD 2, as this allowed the posterior distribution to be primarily driven by the data. For each of the RE models, a non-informative uniform (0, 5) distribution was used as the prior distribution for the between-study standard deviation. This prior distribution assumes that any values between 0 and 5 are equally probable. The Unif(0, 5) was used as it indicates a vague prior on the between-trial standard deviation. This was in agreement with HTA expert input and in line with TA712.[38, 80]

Based on the advice from HTA experts, the preferred model was selected based on clinical plausibility of the estimated relative treatment effects and by assessing the residual deviance statistic and the deviance information criterion (DIC).[86] Inconsistency was assessed with a 'node-splitting' technique, which used the method of van Valkenhoef et al. (2016).[87]

For each NMA, treatments were ranked based on their surface under the cumulative ranking curve (SUCRA) values. SUCRA is a numerical presentation of the overall ranking and presents a single number associated with each treatment. SUCRA values range from 0 to 100%. The larger the SUCRA, the higher the treatment in the hierarchy according to the outcome. Rankings are presented alongside the NMA results.

B.2.9.2.2 Time-to-event endpoints

For time-to-event endpoints, the analysis used the reported hazard ratio (HR) and an associated variance estimate such as the standard error or 95% confidence interval (CI) to derive the input data for the analysis.

The time-to-event endpoints included in these analyses were:

- OS
- PFS:
  - The base PFS network was based on time to CROD from ARASENS and used the best matching progression outcomes from across the other trials
  - The alternative PFS network was based on time to CRPC from ARASENS and used the best matching progression outcomes from across the other trials

B.2.9.2.3 NMAs conducted

The NMAs conducted are summarized in Table 17. A base case NMA and different sensitivity analyses were performed to explore the limitations described in the conclusions and uncertainties in the indirect and mixed treatment comparisons section (Section 2.9.4).

Table 17: NMAs conducted

Outcome	Effect measure	Analyses
OS	HR	Base case NMA
		Sensitivity NMA Including SNA + ADT node
		Sensitivity NMA Excluding GETUG-AFU 15
		Sensitivity NMA Excluding CHAARTED
PFS base network	HR	Base case NMA
		Sensitivity NMA Including SNA + ADT node
		Sensitivity NMA excluding GETUG-AFU 15
PFS alternative network	HR	Base case NMA
		Sensitivity NMA Including SNA + ADT node
		Sensitivity NMA excluding GETUG-AFU 15

Key: ADT, androgen deprivation therapy; CRPC, castration-resistant prostate cancer; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival; SNA, nonsteroidal antiandrogen; rPFS, radiographic progression-free survival.

B.2.9.3 Results

The HR (for time-to-event outcomes) are reported with 95% credible intervals (CrI). Results focus on the comparisons of darolutamide+docetaxel+ADT to enzalutamide+ADT, docetaxel+ADT and ADT alone due to the relevance to the decision problem. Results for abiraterone acetate+ADT have been included in tables for completeness. NMA sensitivity analyses results and fit statistics are reported in detail in Appendix D, Section D.1.6.9.

B.2.9.3.1 Overall survival

Results of the NMAs for OS are presented in Table 18. This includes HRs and 95% CIs for the relative effect of darolutamide+docetaxel+ADT compared to each treatment. The FE model was selected as the base case model based on model fit; it had the lowest DIC when compared with the RE model. Model fit is summarized in Appendix D.

Darolutamide+docetaxel+ADT had a [redacted] and was [redacted]. The SUCRA rankings of this analysis suggest that

darolutamide+docetaxel+ADT is [redacted]. The inconsistency assessment for OS, which is presented in Appendix D, showed no evidence of statistically significant inconsistency. A number of sensitivity analyses were carried out as described in Table 17, the direction of effect remained consistent in all analyses conducted. (Appendix D Section D.1.6.9).

Table 18: Relative effect of darolutamide+docetaxel+ADT compared to all treatment – OS

Treatment	NMA models		Rank SUCRA (%)
	Base case FE HR (95% CrI)	RE, Unif(0,5) HR (95% CrI)	Base case FE
Darolutamide + docetaxel + ADT			[redacted]
Enzalutamide + ADT	[redacted]	[redacted]	[redacted]
Abiraterone acetate + ADT*	[redacted]	[redacted]	[redacted]
Docetaxel + ADT	[redacted]	[redacted]	[redacted]
ADT	[redacted]	[redacted]	[redacted]

Key: ADT, androgen deprivation therapy; CrI, credible interval; FE, fixed effect; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival; RE, random effect; SUCRA; surface under the cumulative ranking
Notes: *Abiraterone acetate + ADT is not a treatment of interest but was included in the network to provide additional indirect evidence for the relative treatment effects.

B.2.9.3.2 PFS base network

Results for PFS base network NMAs are presented in Table 19 for each treatment in relation to darolutamide+docetaxel+ADT. The random-effect Unif(0,5) model was selected as the base case, as it had the lowest DIC when compared with the FE model (model fit is summarized in Appendix D, Section D.1.6.9). Selecting the RE model for this outcome acknowledges the heterogeneity caused by using proxy outcomes in the analysis.

For the PFS base network, darolutamide+docetaxel+ADT had a [redacted] It was also [redacted] The SUCRA values suggest that darolutamide+docetaxel+ADT is [redacted]. The inconsistency assessment for the PFS base network, which is presented in Appendix D, showed no evidence of statistically significant inconsistency.

Table 19: Relative effect of darolutamide+docetaxel+ADT compared to all treatment – PFS base network

Treatment	NMA models		Rank SUCRA (%)
	Base case RE, Unif(0,5) HR (95% CrI)	FE HR (95% CrI)	RE model
Darolutamide + docetaxel + ADT	[redacted]	[redacted]	[redacted]
Enzalutamide + ADT	[redacted]	[redacted]	[redacted]
Abiraterone acetate + ADT*	[redacted]	[redacted]	[redacted]
Docetaxel + ADT	[redacted]	[redacted]	[redacted]
ADT	[redacted]	[redacted]	[redacted]

Key: ADT, androgen deprivation therapy; CrI, credible interval; FE, fixed effect; HR, hazard ratio; OS, overall survival; NMA, network meta-analysis; OS, overall survival; RE, random effect; SUCRA; surface under the cumulative ranking.
Note: *Abiraterone acetate + ADT is not a treatment of interest but was included in the network to provide additional indirect evidence for the relative treatment effects.

B.2.9.3.3 PFS alternative network

Results for the alternative PFS network are presented in Table 20 for each treatment in relation to darolutamide+docetaxel+ADT. The random-effect Unif(0,5) model was selected as the base case as this model had the lowest DIC when compared with the FE model (model fit is summarized in Appendix D). Selecting the RE model for this outcome acknowledges the heterogeneity caused by using proxy outcomes in the analysis.

For the alternative PFS network, darolutamide+docetaxel+ADT had [redacted] It was also [redacted]. The SUCRA values suggest that darolutamide+docetaxel+ADT is the [redacted]. The inconsistency assessment for the alternative PFS network, which is presented in Appendix D, showed no evidence of statistically significant inconsistency.

Table 20: Relative effect of darolutamide+docetaxel+ADT compared to all treatment – PFS alternative network

Treatment	NMA models	NMA models	Rank SUCRA (%)
	Base case RE, Unif(0,5) HR (95% CrI)	FE HR (95% CrI)	RE
Darolutamide + docetaxel + ADT	[redacted]	[redacted]	[redacted]
Enzalutamide + ADT	[redacted]	[redacted]	[redacted]
Abiraterone acetate + ADT*	[redacted]	[redacted]	[redacted]
Docetaxel + ADT	[redacted]	[redacted]	[redacted]
ADT	[redacted]	[redacted]	[redacted]

Key: ADT, androgen deprivation therapy; CrI, credible interval; FE, fixed effect; HR, hazard ratio; OS, overall survival; NMA, network meta-analysis; OS, overall survival; RE, random effect; SUCRA; surface under the cumulative ranking.
Note: *Abiraterone acetate + ADT* is not a treatment of interest but was included in the network to provide additional indirect evidence for the relative treatment effects.

B.2.9.4 Conclusions and uncertainties in the indirect and mixed treatment comparisons

The NMAs indicates that darolutamide+docetaxel+ADT has [redacted]. These results should be considered alongside the limitations of this NMA analysis.

Two NMAs on progression outcomes were conducted. The base PFS network used time to CROD (also used in the cost-effectiveness model) from ARASENS and the best matching progression outcomes from across the other trials. This prioritized outcomes that included death as an event (where possible) in order to be consistent with the modelling. To test the robustness of the base PFS network, an alternative PFS network using time to CRPC from ARASENS was conducted using best matching progression outcomes from across the other trials. The PFS base and PFS alternative network NMAs provided relatively comparable results. Similarities and differences between best matching progression outcomes are further summarized in Section B.2.9.1.1.2 and Appendix D.

Two trials in the NMA evidence base, ARCHES and LATITUDE, allowed for crossover of patients. Cross-over typically occurs when patients whose disease progresses under the comparator treatment are crossed over into the experimental arm. The methods for crossover adjustments are associated with numerous uncertainties, ARCHES and LATITUDE both used the rank preserving structure failure time modelling (RPSFTM). Using the unadjusted approach aligns with the Committee recommendations from NICE TA741[88], which stated that an analysis that did not adjust survival estimates for crossover could be reasonable, as patients receiving placebo plus ADT in clinical practice would probably be offered enzalutamide plus ADT as their first subsequent treatment.

An investigation of the studies' baseline characteristics can be found in Appendix D. In general, studies were considered reasonably comparable. There was no evidence of treatment effect modification from the exploratory analysis of the ARASENS trial data. The amount of missing data varied across the studies, which made it difficult to assess the heterogeneity for all studies robustly. It was also not appropriate to exclude studies due to outliers in these baseline characteristics as none of them were identified as treatment effect modifiers (see Appendix D). Furthermore, all studies reported various prior treatments, but duration of prior treatment received was poorly reported across the evidence base and could not be fully assessed. However, no studies were excluded on this basis.

GETUG-AFU 15 was the only study in which the treatment dose varied (see Section B.2.9.1). This was investigated in a sensitivity analysis that excluded GETUG-AFU

15 from the network. However, the results from this analysis were nevertheless consistent with the base case NMA (see Appendix D).

Proportionality of hazards was assessed for all outcomes that had a Kaplan–Meier curve available. The assumption held for all cases except CHAARTED, where borderline plausibility was assumed. A sensitivity analysis was therefore performed excluding CHAARTED from the base case, and results were consistent with the base case NMA (see Appendix D).

B.2.10 Adverse reactions

B.2.10.1 Safety summary

Table 21 presents an overview of the safety data from ARASENS up to the data cut-off date (25 October 2021).

The overall incidence of treatment-emergent adverse events (TEAE) was comparable between the treatment groups.[45] At least one TEAE was reported in nearly all patients during the study; 99.5% of patients experienced TEAEs in the darolutamide+docetaxel group and 98.9% in the placebo+docetaxel group. Similar incidences were observed for TEAEs with a worst grade of ≥ 3 in both treatment groups (70.2% versus 67.5%, respectively). The incidences of Grade 5 TEAEs were similar in both treatment groups (4.1% versus 4.0%, respectively). [redacted] Grade 5 TEAEs were considered to be study drug-related by the investigator in the darolutamide+docetaxel group.[44] Overall, treatment-emergent serious adverse events (TESAE) were reported with a similar incidence between the darolutamide+docetaxel and placebo+docetaxel treatment groups (44.8% versus 42.3% of patients, respectively).[45]

TEAEs that resulted in permanent discontinuation of study drug occurred at a comparable incidence in both the darolutamide+docetaxel group and the placebo+docetaxel group (13.5% versus 10.6%, respectively).[45] The incidences of TEAEs that resulted in permanent discontinuation of docetaxel were also comparable between the treatment groups (8.0% versus 10.3%, respectively).

Table 21: Overview of TEAEs (SAS)

	Darolutamide+ docetaxel N = 652	Placebo+ docetaxel N = 650
Any TEAE, n (%)[a]	649 (99.5)	643 (98.9)
Worst Grade 1 or 2	190 (29.1)	204 (31.4)
Worst Grade ≥ 3	458 (70.2)	439 (67.5)
Worst Grade 5	27 (4.1)	26 (4.0)
TESAE	292 (44.8)	275 (42.3)
TEAE leading to study drug dose modification[b]	[redacted]	[redacted]
TEAE leading to permanent discontinuation of study drug[c]	88 (13.5)	69 (10.6)
TEAE leading to docetaxel dose modification[b]	[redacted]	[redacted]
TEAE leading to permanent discontinuation of docetaxel[c]	52 (8.0)	67 (10.3)
Related to protocol-required procedure	[redacted]	[redacted]
Any study drug-related TEAE, n (%)[a,d]	[redacted]	[redacted]
Worst Grade 1 or 2	[redacted]	[redacted]
Worst Grade ≥ 3	[redacted]	[redacted]
Worst Grade 5	[redacted]	[redacted]
Study drug-related TESAE	[redacted]	[redacted]
Study drug-related TEAE leading to study drug dose modification[b]	[redacted]	[redacted]
Study drug-related TEAE leading to permanent discontinuation of study drug[c]	[redacted]	[redacted]
Any docetaxel-related TEAE, n (%)	[redacted]	[redacted]
Worst Grade 1 or 2	[redacted]	[redacted]
Worst Grade ≥ 3	[redacted]	[redacted]
Worst Grade 5	[redacted]	[redacted]
Docetaxel-related TESAE	[redacted]	[redacted]
Docetaxel-related TEAE leading to docetaxel dose modification[b]	[redacted]	[redacted]
Docetaxel-related TEAE leading to permanent discontinuation of docetaxel[c]	[redacted]	[redacted]

Key: AE, adverse event; SAS, safety analysis set; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.
Notes: [a] Any TEAE also includes patients with grade not available for all AEs. [b] Modifications include dose interruptions/delays and reductions. [c] Discontinuation of study drug (darolutamide/placebo) and docetaxel due to an AE was calculated for AEs where action taken was checked as 'Drug Withdrawn'. [d] Based on investigator's assessment.
Source: Table 10-4 ARASENS CSR[44] and Smith et al. 2022.[45]

B.2.10.2 Extent of exposure

B.2.10.2.1 Study drug exposure

Most patients in both treatment groups received the planned dose of study drug (the median was [redacted]% and the mean was above [redacted]% in both treatment groups).[44] The median treatment duration at the time of the database cut-off was longer in the darolutamide+docetaxel group (41.0 months) than in the placebo+docetaxel group (16.7 months; Appendix F).[45] The proportion of patients staying on study drug treatment for over 42 months was more than 2-fold higher in the darolutamide+docetaxel group than in the placebo+docetaxel group (45.9% versus 19.1%, respectively).

After the last dose of docetaxel, patients continued on study drug treatment for a median time of [redacted] months in the darolutamide+docetaxel group and [redacted] months in the placebo+docetaxel group.[44]

B.2.10.2.2 Docetaxel exposure

The majority of the patients in both treatment groups, 87.6% in the darolutamide+docetaxel group and 85.5% in the placebo+docetaxel group, received full six cycles of docetaxel (Appendix F).[45] The median total number of cycles was [redacted] in both treatment arms.[44] There were [redacted] patients ([redacted]%) in the darolutamide+docetaxel group and [redacted] patients ([redacted]%) in the placebo+docetaxel group who never received docetaxel. These patients were initially assessed by the investigator to be candidates for docetaxel and ADT. After randomization and start of study drug, they were no longer considered to be eligible to receive concomitant docetaxel within six weeks after start of study drug.

B.2.10.2.3 Dose modifications

The full dose of study drug was tolerated by the majority of patients in both treatment groups without any dose modifications during the treatment period.[44] At least one study drug dose modification (interruption/delay or reduction) was reported for [redacted]% of patients in the darolutamide+docetaxel group and [redacted]% in the placebo+docetaxel group (Appendix F). The total number of study drug dose modifications was higher in the darolutamide+docetaxel group ([redacted]) than in the placebo+docetaxel group ([redacted]). The number of study drug dose modifications per

patient was generally similar in both treatment groups, with most patients having either one or two dose modifications; however, there were slightly more patients with ≥ 10 dose modifications per patient in the darolutamide+docetaxel group ([redacted]%) than in the placebo+docetaxel group ([redacted]%). The most common reason for dose modification was patient error for [redacted]% of events in the darolutamide+docetaxel group and [redacted]% of events in the placebo+docetaxel group. Most patient errors were reported as single dose interruptions; however, the single missed dose did not impact the overall compliance with the study drug. TEAE was a reason for drug dose modification in [redacted]% and [redacted]% of dose modification events, respectively. Study drug dose reductions (for any reason) were reported for [redacted]% of patients in the darolutamide+docetaxel group and [redacted]% in the placebo+docetaxel group. Study drug dose was re-escalated in [redacted]% and [redacted]% of patients with dose reduction, respectively.

Overall, docetaxel dose modifications were reported at a similar level between the treatment groups.[44] At least one docetaxel dose modification (interruption/delay or reduction) was reported for [redacted]% of patients in the darolutamide+docetaxel group and [redacted]% of patients in the placebo+docetaxel group (Appendix F). The primary reason for docetaxel dose modifications was TEAE in [redacted]% and [redacted]% of patients in the darolutamide+docetaxel and placebo+docetaxel group, respectively. Docetaxel dose was interrupted or delayed in [redacted]% and [redacted]% of patients in the darolutamide+docetaxel and placebo+docetaxel groups, respectively, and a dose reduction was reported in [redacted]% and [redacted]% of patients, respectively. Docetaxel was withdrawn in [redacted]% versus [redacted]% of patients, respectively.

B.2.10.3 Common treatment-emergent adverse events

Table 22 presents the most common TEAEs occurring in ≥ 10% of patients in either treatment group. To adjust for potential differences in study drug treatment duration between the treatment groups, exposure-adjusted incidence rates (EAIRs) per 100 patient year (PY) are also summarized.

The most commonly reported TEAEs were generally comparable between the treatment groups.[44] The most common events (≥ 25% of patients in either treatment group) included alopecia, fatigue, anaemia, arthralgia, oedema peripheral, neutrophil count decreased, and diarrhoea. The most common TEAEs reported with ≥ 3%

higher incidence in the darolutamide+docetaxel group than in the placebo+docetaxel group were decreased appetite, hypertension, aspartate aminotransferase (AST) increased, and pain in extremity. When adjusted for the difference in study drug treatment duration, the EAIRs of these events were comparable between the treatment groups. Based on the analysis of common TEAEs over time, the incidences for the majority of events were highest during the first 6 months after the start of study treatment in both treatment groups, corresponding to the docetaxel treatment period.[89] After that, a trend towards lower incidence and reduced severity of TEAEs was observed in both treatment arms for most TEAEs.

Overall, events with a worst grade of ≥ 3 were reported with low incidences within the most common TEAEs, with the exception of the following Grade 3 or 4 TEAEs that occurred in ≥ 5% of patients in either treatment group: neutrophil count decreased, white blood cell count decreased, hypertension, and neutropenia.[44] Many of the common TEAEs in the study (such as alopecia, anaemia, neutropenia) are known to be commonly associated with docetaxel treatment. For the events known to be associated with both darolutamide and docetaxel (such as fatigue, neutrophil count decreased, and neutropenia), the incidences were similar between the treatment groups.

Table 22: Incidences and exposure-adjusted incidence rates of the most common TEAEs by MedDRA PT occurring in ≥ 10% of patients in either treatment group (SAS)

MedDRA PT v 24.1	Darolutamide+docetaxel N = 652					Placebo+docetaxel N = 650				
	Total, n (%)	EAIR per 100 PY[a]	Worst CTCAE grade			Total, n (%)	EAIR per 100 PY[a]	Worst CTCAE grade		
			Grade 3, n (%)	Grade 4, n (%)	Grade 5, n (%)			Grade 3, n (%)	Grade 4, n (%)	Grade 5, n (%)
Alopecia	264 (40.5)	15.3				264 (40.6)	22.0			
Fatigue	216 (33.1)	12.5				214 (32.9)	17.8			
Anaemia	181 (27.8)	10.5				163 (25.1)	13.6			
Arthralgia	178 (27.3)	10.3				174 (26.8)	14.5			
Oedema peripheral	173 (26.5)	10.0				169 (26.0)	14.1			
Decreased neutrophil count										
Diarrhoea	167 (25.6)	9.6				156 (24.0)	13.0			
Decreased white blood cell count										
Constipation	147 (22.5)	8.5				130 (20.0)	10.8			
Hot flush	124 (19.0)	7.2				122 (18.8)	10.2			
Back pain	123 (18.9)	7.1				123 (18.9)	10.2			
Decreased appetite	121 (18.6)	7.0				85 (13.1)	7.1			
Weight increased	116 (17.8)	6.7				102 (15.7)	8.5			
Nausea	115 (17.6)	6.6				133 (20.5)	11.1			
Increased alanine aminotransferase	102 (15.6)	5.9				84 (12.9)	7.0			
Pain in extremity	98 (15.0)	5.7				78 (12.0)	6.5			

MedDRA PT v 24.1	Darolutamide+docetaxel N = 652					Placebo+docetaxel N = 650				
	Total, n (%)	EAIR per 100 PY[a]	Worst CTCAE grade			Total, n (%)	EAIR per 100 PY[a]	Worst CTCAE grade		
			Grade 3, n (%)	Grade 4, n (%)	Grade 5, n (%)			Grade 3, n (%)	Grade 4, n (%)	Grade 5, n (%)
Increased aspartate aminotransferase	91 (14.0)	5.3				68 (10.5)	5.7			
Pyrexia	86 (13.2)	5.0				90 (13.8)	7.5			
Hypertension	85 (13.0)	4.9				59 (9.1)	4.9			
Cough	84 (12.9)	4.9				73 (11.2)	6.1			
Bone pain	81 (12.4)	4.7				84 (12.9)	7.0			
Neuropathy peripheral	76 (11.7)	4.4				67 (10.3)	5.6			
Hyperglycaemia	74 (11.3)	4.3				61 (9.4)	5.1			
Insomnia	74 (11.3)	4.3				81 (12.5)	6.7			
Myalgia	73 (11.2)	4.2				63 (9.7)	5.2			
Dysgeusia	69 (10.6)	4.0				80 (12.3)	6.7			
Asthenia	68 (10.4)	3.9				65 (10.0)	5.4			
Neutropenia										
Stomatitis	66 (10.1)	3.8				57 (8.8)	4.7			
Peripheral sensory neuropathy	65 (10.0)	3.8				67 (10.3)	5.6			
Urinary tract infection	61 (9.4)	3.5				67 (10.3)	5.6			
Dyspnoea	59 (9.0)	3.4				71 (10.9)	5.9			
Malaise	57 (8.7)	3.3				66 (10.2)	5.5			

Key: CTCAE, Common Terminology Criteria for Adverse Events; EAIR, exposure-adjusted incidence rate; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; PY, patient year; SAS, safety analysis set; TEAE, treatment-emergent adverse event.
Notes: A patient may have more than one entry. The total column also includes patients with a missing CTCAE grade (two patients with white blood cell count decreased and one patient with oedema peripheral in the darolutamide+docetaxel group, and one patient with hypertension in the placebo+docetaxel

MedDRA PT v 24.1	Darolutamide+docetaxel N = 652					Placebo+docetaxel N = 650				
	Total, n (%)	EAIR per 100 PY[a]	Worst CTCAE grade			Total, n (%)	EAIR per 100 PY[a]	Worst CTCAE grade		
			Grade 3, n (%)	Grade 4, n (%)	Grade 5, n (%)			Grade 3, n (%)	Grade 4, n (%)	Grade 5, n (%)
group. [a] EAIR of TEAEs, defined as the number of patients with a given TEAE divided by the total study drug treatment duration of all patients in years. The rate is expressed in number of patients with events per 100 PYs. **Source:** Table 10-6 ARASENS CSR[44] and Smith et al. 2022.[45]										

B.2.10.4 Treatment-emergent adverse events by severity

Table 23 presents the incidence of worst Grade 3 or 4 TEAEs.

Overall, TEAEs with Grade 3 or 4 as the worst grade were reported at a similar incidence in the darolutamide+docetaxel group (66.1%) and in the placebo+docetaxel group (63.5%).[45] The most common TEAEs with worst Grade of 3 or 4 (≥ 5% of patients in either treatment arm) in the darolutamide+docetaxel and placebo+docetaxel groups, respectively, were neutrophil count decreased ([redacted]% versus [redacted]%), WBC count decreased ([redacted]% versus [redacted]%), neutropenia ([redacted]% versus [redacted]%), febrile neutropenia (7.8% versus 7.4%), hypertension (6.4% versus 3.2%) and anaemia (4.8% versus 5.1%).[44, 45] Hypertension was reported with ≥ 3% higher incidence in the darolutamide+docetaxel group than in the placebo+docetaxel group, which is discussed in more detail in Section B.2.10.6.

Table 23: Incidence of worst Grade 3 or 4 TEAEs by MedDRA PT occurring in ≥ 1.5% of patients in either treatment group (SAS)

MedDRA PT v24.1	Darolutamide+ docetaxel N = 652	Placebo+ docetaxel N = 650
Neutrophil count decreased	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Febrile neutropenia	51 (7.8)	48 (7.4)
Hypertension	42 (6.4)	21 (3.2)
Anaemia	31 (4.8)	33 (5.1)
Pneumonia	21 (3.2)	20 (3.1)
Hyperglycaemia	18 (2.8)	24 (3.7)
Alanine aminotransferase increased	18 (2.8)	11 (1.7)
Aspartate aminotransferase increased	17 (2.6)	7 (1.1)
Leukopenia	[redacted]	[redacted]
Weight increased	14 (2.1)	8 (1.2)
Urinary tract infection	13 (2.0)	12 (1.8)
Back pain	[redacted]	[redacted]
Syncope	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]

MedDRA PT v24.1	Darolutamide+ docetaxel N = 652	Placebo+ docetaxel N = 650
Blood alkaline phosphatase increased	[redacted]	[redacted]
Bone pain	[redacted]	[redacted]

Key: SAS; safety analysis set; TEAE, treatment-emergent adverse event.
Source: Table 10-9 ARASENS CSR[44] and Smith et al. 2022.[45]

B.2.10.5 Treatment-related adverse events

Overall, TEAEs assessed as study drug-related by the investigator were reported with a slightly higher incidence in the darolutamide+docetaxel group ([redacted]%) than in the placebo+docetaxel group ([redacted]%; Table 21).[44] Study drug-related TEAEs that were reported in ≥ 5% of patients in either the darolutamide+docetaxel or placebo+docetaxel treatment group included fatigue ([redacted]% versus [redacted]%, respectively), hot flush ([redacted]% in both groups), ALT increased ([redacted]% versus [redacted]%), AST increased ([redacted]% versus [redacted]%), and anaemia ([redacted]% versus [redacted]%). These events were reported mostly with Grade 1 or 2 as the worst grade. Study drug-related Grade 4 ALT and AST increases were both observed in [redacted] patient ([redacted]%) in the darolutamide+docetaxel group and [redacted] Grade 4 events were reported in the placebo+docetaxel group (Table 24).

Overall, TEAEs that were assessed as docetaxel-related by the investigator occurred with a similar incidence between the treatment arms, in [redacted]% of patients in the darolutamide+docetaxel group and in [redacted]% of patients in the placebo+docetaxel group (Table 21).[44] Docetaxel-related events reported in ≥ 20% of patients in either the darolutamide+docetaxel or placebo+docetaxel treatment group included alopecia ([redacted]% versus [redacted]%, respectively), neutrophil count decreased ([redacted]% versus [redacted]%), fatigue ([redacted]% versus [redacted]%), and WBC count decreased ([redacted]% versus [redacted]%) (Table 24).

Table 24: Study drug and docetaxel-related TEAEs by MedDRA and worst CTCAE grade occurring in ≥ 5% of patients (SAS)

	Darolutamide+docetaxel N = 652						Placebo+docetaxel N = 650					
Preferred term	**Total**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Total**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Darolutamide/placebo-related												
Anaemia												
Fatigue												
Increased alanine amino-transferase												
Increased aspartate amino-transferase												
Hot flush												
Docetaxel-related												
Anaemia												
Neutropenia												
Febrile neutropenia												
Diarrhoea												
Nausea												
Stomatitis												

	Darolutamide+docetaxel N = 652						Placebo+docetaxel N = 650					
Preferred term	**Total**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Total**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Constipation												
Vomiting												
Fatigue												
Oedema peripheral												
Malaise												
Asthenia												
Pyrexia												
Decreased neutrophil count												
Decreased white blood cell count												
Increased alanine amino-transferase												
Decreased appetite												
Arthralgia												
Myalgia												
Dysgeusia												
Peripheral neuropathy												

	Darolutamide+docetaxel N = 652						Placebo+docetaxel N = 650					
Preferred term	**Total**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Total**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Peripheral sensory neuropathy												
Paraesthesia												
Alopecia												
Nail discolouration												

Key: CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; SAS, safety analysis set; TEAE, treatment-emergent adverse event.
Notes: Ordered by system organ class. CTCAE version 4.03 and MedDRA version 24.1. Any adverse events with missing CTCAE grade are not included in this summary table.
Source: Table 14.3.1/31 and Table 14.3.1/38. ARASENS CSR.[44]

B.2.10.6 Adverse events of special interest

Adverse events of special interest were defined as events/disorders representing potential risks known to be associated with ADT or with anti-androgens. Most of the reported events were comparable in both treatment groups with no major differences (Table 25).[44, 45] The majority of events reported for fatigue/asthenic conditions, bone fractures, fall, vasodilatation and flushing, breast disorders/gynaecomastia, rash, mental impairment disorders, depressed mood disorders, seizure and decreased weight were Grade 1 or 2 in both treatment groups (Appendix F). A general trend of decreasing incidence of TEAEs of special interest was observed in both treatment arms after the first 6 months of study treatment, with the exception of hypertension.

Table 25: Incidences and exposure-adjusted incidence rates of TEAEs of special interest associated with ADT or anti-androgens (SAS)

Grouped TEAE term	Darolutamide+ docetaxel (N = 652)		Placebo+ docetaxel (N = 650)		Incidence risk ratio for EAIR
	Total, n (%)	EAIR per 100 PY[a]	Total, n (%)	EAIR per 100 PY[a]	
Fatigue/asthenic conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bone fractures (excluding pathological fractures)	49 (7.5)	2.8	33 (5.1)	2.7	1.03
Fall	43 (6.6)	2.5	30 (4.6)	2.5	1.00
Vasodilatation and flushing	133 (20.4)	7.7	141 (21.7)	11.7	0.66
Breast disorders/gynaecomastia	21 (3.2)	1.2	10 (1.5)	0.8	1.46
Rash	108 (16.6)	6.2	88 (13.5)	7.3	0.85
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	71 (10.9)	4.1	76 (11.7)	6.3	0.65
Cardiac arrhythmias	52 (8.0)	3.0	55 (8.5)	4.6	0.66
Coronary artery disorders	19 (2.9)	1.1	13 (2.0)	1.1	1.01
Heart failures	4 (0.6)	0.2	13 (2.0)	1.1	0.21
Diabetes mellitus and hyperglycaemia	99 (15.2)	5.7	93 (14.3)	7.7	0.74
Mental impairment disorders	23 (3.5)	1.3	15 (2.3)	1.2	1.06
Depressed mood disorders	21 (3.2)	1.2	24 (3.7)	2.0	0.61
Cerebral ischaemia	8 (1.2)	0.5	8 (1.2)	0.7	0.69
Cerebral and intracranial haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Seizure	4 (0.6)	0.2	1 (0.2)	0.1	2.78

Grouped TEAE term	Darolutamide+ docetaxel (N = 652)		Placebo+ docetaxel (N = 650)		Incidence risk ratio for EAIR
	Total, n (%)	EAIR per 100 PY[a]	Total, n (%)	EAIR per 100 PY[a]	
Weight decreased	22 (3.4)	1.3	35 (5.4)	2.9	0.44

Key: ADT, androgen deprivation therapy; EAIR, exposure-adjusted incidence rate; PT, preferred term; PY, patient year; SAS, safety analysis set; TEAE, treatment-emergent adverse event.
Notes: If a patient experienced more than one episode of a TEAE, the patient was counted only once within a grouped term. [a] EAIR of grouped events, defined as the number of patients with a given TEAE divided by the total study drug treatment duration of all patients in years. The rate is expressed in number of patients with events per 100 PYs.
Source: Table 10-31 ARASENS CSR[44] and Smith et al. 2022.[45]

The majority of adverse events (AEs) of special interest with incidences slightly higher in the darolutamide+docetaxel group compared to the placebo+docetaxel group exhibited similar EAIRs when adjusted for the difference in study drug treatment duration, demonstrating no increased risk.[44] For other AEs of special interest where the incidence risk ratio for EAIR was > 1 or there was a disproportionality in their incidence between treatment groups:[44]

- **Breast disorders/gynaecomastia:** the observed slight difference in the incidence of breast disorders/gynaecomastia was not considered clinically relevant. All events of breast disorders/gynaecomastia were either Grade 1 or 2 as the worst grade in both treatment groups. No TESAEs, study drug or docetaxel discontinuations, dose interruptions or dose reductions were reported due to breast disorders/gynaecomastia in the darolutamide+docetaxel group
- **Rash:** rash events resulting in dose modification or permanent discontinuation of study drug or docetaxel treatment, and events with Grade 3 or 4 as the worst grade were more common in the darolutamide+docetaxel group
- **Hypertension:** the incidence of Grade 3 events were consistently higher in the darolutamide+docetaxel group regardless of history of hypertension; however, these events did not lead to dose modifications or permanent discontinuation of darolutamide
- **Coronary artery disorders:** [redacted] fatal events of myocardial infarction were reported in the darolutamide+docetaxel group. In both treatment groups,

coronary artery disorders were more commonly reported in patients who had a medical history of cardiac disorders. With the known history of patients who experienced cardiac disorders along with the known side effects of ADT causing metabolic changes contributing to these events, no evidence was seen to link the events to darolutamide

- **Cerebral haemorrhage:** all [redacted] reports of cerebrovascular accident (CVA) in the darolutamide+docetaxel group were confounded by preceding surgery, trauma, and underlying comorbidities. No evidence was found for an increased risk of cerebral and intracranial haemorrhage for patients treated with darolutamide compared with placebo, both in combination with docetaxel and ADT
- **Seizure:** considering the low number of seizure events reported, with none leading to permanent discontinuation of darolutamide, and confounding factors reported in [redacted] of the patients, it is concluded that there is not sufficient evidence for an increased risk of seizure with darolutamide in combination with docetaxel and ADT

B.2.10.7 Safety overview

The data from ARASENS demonstrated that darolutamide in combination with docetaxel and ADT had an acceptable safety profile in the target indication, characterized by AEs that were mostly predictable and reversible.[44] Treatment with darolutamide did not adversely affect the overall safety of docetaxel and ADT, and it did not add to the toxicity profile that is driven by the six cycles of docetaxel.[89] Discontinuation rates due to AEs with darolutamide plus docetaxel and ADT were similar to those with docetaxel and ADT, highlighting the favourable tolerability profile of darolutamide. Furthermore, adding darolutamide to docetaxel and ADT did not affect the ability of patients to complete the full six cycles of docetaxel treatment.

In general, the incidence, severity, and nature of the most commonly reported TEAEs in patients treated with darolutamide in combination with docetaxel were consistent with those expected of the individual compounds in the target population (patients with advanced age and underlying disease).[44] Importantly, the incidences of these events were similar between the treatment groups; there was a higher incidence of hypertension in the darolutamide+docetaxel group compared with the placebo+docetaxel group, however, the EAIRs were similar when adjusted for the

difference in study drug treatment duration. The combination of darolutamide with docetaxel did not show an increase in most of the known expected toxicities of either drug, or specific safety concerns which are known to be associated with the currently existing therapeutic options for mHSPC. Based on the analysis of common TEAEs over time, the incidences for the majority of events were highest during the first 6 months after the start of study treatment in both treatment groups, corresponding to the docetaxel treatment period. After that, a trend towards lower incidence and reduced severity of TEAEs was observed in both treatment groups for most TEAEs.

As recommended in the SmPC for docetaxel, patients should be monitored for signs of neutropenia, gastrointestinal toxicity, worsening pulmonary symptoms and tumour lysis syndrome.[90] Hypersensitivity reactions may occur within a few minutes following initiation of the infusion of docetaxel, therefore facilities for the treatment of hypotension and bronchospasm should be available. No additional monitoring is warranted with the addition of darolutamide to docetaxel and ADT.

B.2.11 Ongoing studies

The ARASENS study is complete; no other studies are investigating darolutamide in combination with docetaxel and ADT in mHSPC patients. The primary analysis in ARASENS focused on OS as the primary outcome, the follow-up duration was sufficient to provide mature data and there will be no further data cuts.

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Principal findings from the clinical evidence

The ARASENS study met its primary objective, showing a statistically significant improvement of OS in patients treated with darolutamide in combination with docetaxel and ADT compared with placebo in combination with docetaxel and ADT.[44, 45] The risk of death was 32.5% lower in the darolutamide+docetaxel group than in the placebo+docetaxel group. This result was observed despite a higher percentage of patients receiving life-prolonging subsequent therapy after discontinuation of study treatment in the placebo+docetaxel group (75.6%) compared with the darolutamide+docetaxel group (56.8%). A consistent OS benefit

for darolutamide in combination with docetaxel was observed across all pre-specified subgroups, including baseline extent of disease, ALP, age, ethnicity, geographical region, PSA, ECOG PS, Gleason score and metastasis at initial diagnosis. Treatment compliance was high in both treatment groups, where more than [redacted]% of patients received planned dose of study drug and more than 85% of patients completed the full 6 cycles of docetaxel.

In addition to the OS improvement, a consistent benefit in secondary endpoints also favoured darolutamide plus docetaxel and ADT.[44, 45] The time to CRPC was significantly longer in the darolutamide+docetaxel group compared to the placebo+docetaxel group (64% reduction in risk), and almost half the amount of patients progressed to CRPC (35% versus 60%, respectively). This significantly reduces the burden on patients, as progression leads to deterioration of HRQL and poorer prognosis (see Section B.1.3.3). Additionally, treatment with darolutamide plus docetaxel and ADT resulted in significantly longer time to pain progression, SSE-FS, time to first SSE and time to first subsequent antineoplastic therapy, all of which are key to maintaining patients HRQL and reducing the burden on both patients and the NHS. Results of the exploratory endpoints further supported the conclusion of clinical benefit for patients in the darolutamide+docetaxel group compared with the placebo+docetaxel group, including a longer time to PSA progression in the darolutamide+docetaxel group. HRQL (measured by NCCN-FACT-FPSI-17 and BPI-SF) was maintained in patients from both treatment groups while receiving study treatment.

Darolutamide in combination with docetaxel and ADT is the first multimodal, triplet therapy with demonstrated prolonged survival and delayed disease progression in patients with mHSPC. By delaying progression to mCRPC, darolutamide is likely to reduce the high levels of psychological burden associated with the inevitable progression to a disease state with worse prognosis with current SoC. The added benefit of darolutamide in combination with docetaxel therapy outweighed any additional toxicity, which was transient and did not affect overall HRQL.[44] Darolutamide in combination with docetaxel and ADT has an acceptable safety profile in the target indication, characterized by AEs that are mostly predictable and reversible. Furthermore, darolutamide exhibits fewer pDDIs compared to

enzalutamide or apalutamide,[43] which may drive clinical decisions in situations where these considerations are clinically important.[37]

Results from NMAs of OS, PFS base and alternative networks reported that darolutamide + docetaxel + ADT is the most efficacious treatment in the evidence base. For OS, darolutamide + docetaxel + ADT had a [redacted] and when compared to [redacted] the HR was in [redacted] This effect was consistent for the progression outcomes (PFS base and alternative networks).

B.2.12.2 Strengths and limitations of the evidence base

ARASENS was a large RCT that investigated the efficacy and safety of the first triplet combination therapy, darolutamide plus docetaxel and ADT, for the treatment of patients with de novo and recurrent mHSPC. It was a high-quality study with an overall low risk of bias, that investigated outcomes that are relevant to clinicians and patients, and are commonly used in clinical practice.[37] It is the only study in mHSPC which included a more active comparator widely used as part of the SoC (docetaxel plus ADT). ARASENS provided robust data directly relevant to the decision problem being addressed, which demonstrated that darolutamide plus docetaxel and ADT significantly improved survival for patients with mHSPC and significantly reduced the time progression to mCRPC in comparison to placebo plus docetaxel and ADT.

There remains an unmet need for a treatment approach that prolongs survival and delays disease progression to mCRPC beyond current SoC, without compromising tolerability or patients' HRQL. Therefore, darolutamide plus docetaxel and ADT, as demonstrated by ARASENS, has the potential to improve patient outcomes and change the landscape of current clinical practice.

Although the ARASENS study did not capture EQ-5D questionnaire data, HRQL data were reported using validated instruments (NCCN–FACT FPSI–17 and BPI-SF). The NCCN–FACT FPSI–17 questionnaire assesses symptoms of prostate cancer, symptoms of treatment of prostate cancer, and HRQL of prostate cancer patients, while the BPI-SF is a widely used tool to assess patient-reported levels of pain. The HRQL evaluation in ARASENS demonstrated that HRQL was maintained

in both treatment groups and the addition of darolutamide to docetaxel and ADT had no detriment to patients HRQL.

A notable limitation of the evidence base is that there are no head-to-head data for darolutamide plus docetaxel and ADT versus enzalutamide and ADT or ADT alone, which are listed as comparators in the scope of this appraisal. The ARASENS study was started before regulatory and NICE approval of enzalutamide and ADT[38], and therefore did not include it as a comparator. To address this limitation, an ITC was conducted, and the findings demonstrate that darolutamide plus docetaxel and ADT is the most efficacious treatment in the evidence base for OS and PFS (Section B.2.9).

B.2.12.3 Applicability of clinical evidence to practice

As confirmed by clinical experts, ARASENS provides head-to-head data for the relevant comparator used in clinical practice, which is docetaxel and ADT.[37] A real-world treatment pattern study demonstrated that ADT alone and docetaxel plus ADT were the most common initial mHSPC treatments received in the UK in 2020 (47.2% and 40.2%, respectively), while novel hormonal agents plus ADT were used the least (12.6%).[91] However, as part of a clinical advisory board, clinicians noted that the lockdowns caused by the COVID-19 pandemic resulted in a decrease in docetaxel prescribing in a number of centres from April 2020, in some cases falling below 5%. At the same time, some centres also saw an increase in prescribing of enzalutamide+ADT. This is likely due to enzalutamide being easier to manage and requiring less resource use; therefore, the significant staffing issues associated with the pandemic resulting in some clinicians making different treatment choices. It is important to note, however, that there was significant inter-regional variation,[14] with some centres not changing their practice at all during this time. Clinicians estimated that androgen receptor targeting agents (ARTAs) are currently prescribed in > 50% of patients, and therefore could arguably be considered current SOC.[37] However, rapid access data for the UK in 2021 will be available later this year, which will confirm the current situation and how things have changed. It is estimated that with resourcing issues returning more closely to normal approaching the end of the COVID pandemic, prescribing decisions may also have returned to their pre-pandemic levels, with docetaxel plus ADT remaining as SoC.

As part of a clinical advisory board, a consensus was gained that the ARASENS population was reflective of other clinical trials and reflective of the population that would be considered suitable for chemotherapy in UK clinical practice.[37] In total, [redacted] patients were enrolled across [redacted] UK trial centres in ARASENS, with [redacted] patients in the darolutamide+docetaxel group and [redacted] patients in the placebo+docetaxel group being included in the FAS.[44] This is a reasonable proportion for an international study, enabling meaningful representation of UK clinical practice in trial outcomes and clinical efficacy results which we would expect in clinical practice in England. The outcomes in ARASENS are relevant to patients and commonly used in clinical practice, and efficacy data for the docetaxel plus ADT group was considered to be in line with other publications and evidence.[37]

The addition of darolutamide to the combination of docetaxel plus ADT is not associated with any significant NHS clinical service changes; darolutamide plus ADT is already reimbursed for the treatment of adult patients with nmCRPC at high risk of developing metastatic disease, and docetaxel plus ADT is reimbursed for mHSPC.[92, 93]

Darolutamide has been reported to exhibit fewer pDDIs compared to enzalutamide or apalutamide[43], and limited DDIs have been seen when darolutamide was administered alongside medications commonly used to treat comorbidities in an elderly patient population, such as calcium channel blockers and anticoagulants.[48-50] Enzalutamide and apalutamide are potent enzyme inducers, therefore interaction with many common medicinal products that are substrates of enzymes is expected.[94, 95] This can lead to reduction in plasma concentrations, lost or reduced clinical effect and also increase the risk of formation of active metabolites; all of which may lead to sub-optimal treatment of comorbidities while being treated for mHSPC. This is particularly important as most mHSPC patients are elderly (> 65 years) and a considerable proportion will have comorbidities, some of which may be life limiting.[9, 96] Due to polypharmacy in mHSPC patients, some potential drug-drug interactions could be missed, which is a major concern for clinicians.[37] In this regard, clinicians were reassured by the reduced DDIs observed with darolutamide as it would result in less resource intensive monitoring of any interactions.[37]

As demonstrated in ARASENS, darolutamide in combination with docetaxel and ADT significantly increases OS, significantly increases the time to mCRPC, maintains patients' HRQL and has an acceptable safety profile in patients with mHSPC (Section B.2.6).[44] The very positive benefit-risk ratio of this first triple combination therapy reinforces its use early on in this aggressive metastatic pathway.

B.3 Cost-effectiveness

B.3.1 Published cost-effectiveness studies

A systematic literature review (SLR) was conducted to identify cost-effectiveness studies in mHSPC. Full details of the search methods and results are presented in Appendix G. The search identified 30 publications that met the inclusion criteria. As some studies were associated with multiple publications, secondary publications were combined, leaving 23 unique studies. However, for the purpose of this submission, only details from the UK studies are discussed below (Table 26).

Searching the NICE website identified three previous STAs for adults with mHSPC. These appraisals are summarized in Table 27 and include:

- NICE TA712[38], which assessed the cost-effectiveness of enzalutamide plus ADT for treating mHSPC in the UK
- NICE TA721[42], which assessed the cost-effectiveness of abiraterone with prednisone or prednisolone and ADT in newly diagnosed high-risk mHSPC
- NICE TA741[88], which assessed the cost-effectiveness of apalutamide plus ADT for treating mHSPC in the UK

Table 26: Summary list of published cost-effectiveness studies

Study	Year	Patient population (average age in years)	Summary of model	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)
SMC [Abiraterone] (Scotland)[97]	2021	Newly diagnosed high-risk metastatic hormone sensitive prostate cancer in adult men in combination with ADT (NR)	Semi-Markov model (Partitioned Survival Model)	Incremental QALYs: AAP + ADT versus ADT alone: 0.987 AAP + ADT versus Docetaxel + ADT: 0.401	NR	Base case results: list price ICER (£/QALY): • AAP + ADT versus ADT alone: £90,483 • AAP + ADT versus Docetaxel + ADT: £201,527
Lu (UK)[98]	2021	NR	Decision tree and a Markov submodel.	QALY: Degarelix: 2.4548 Triptorelin + anti-androgen: 2.4419 Incremental (Degarelix vs Triptorelin + anti-androgen): 0.0128	Total cost (£) Degarelix: 3883 Triptorelin + anti-androgen: 3125 Incremental (Degarelix vs Triptorelin + anti-androgen): £758 Disaggregated cost (Base case) Costs of drugs (£) Degarelix: 3617 (93.2%) Triptorelin + anti-androgen: 1965 (62.9%) Costs of drug administration (£) Degarelix: 266 (6.8%) Triptorelin + anti-androgen: 92 (2.9%) Costs for treating SCC (£) Degarelix: 0	ICER (£ per QALY gained): Degarelix vs Triptorelin + anti-androgen: 59 012

Study	Year	Patient population (average age in years)	Summary of model	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)
					Triptorelin + anti-androgen: 57 (1.8%) Costs for treating BOO (£) Degarelix: 0 Triptorelin + anti-androgen: 283 (9.0%) Costs for care as a result of SCC symptoms (£) Degarelix: 0 Triptorelin + anti-androgen: 728 (23.3%)	
Woods (UK)[99]	2018	NR	Patient-level simulation approach	QALYs (discounted): Total QALY: • SOC: 3.01 • SOC + Doc: 3.51 • SOC+Docetaxel vs SOC alone: 0.51	Metastatic prostate cancer Costs (UK pounds, discounted): Total: • SOC: 52,466 • SOC + Doc: 55,253 •SOC+Docetaxel vs SOC alone: 2787 Disaggregated results Docetaxel • SOC: NA • SOC + Doc: 1761 • SOC+Docetaxel vs SOC alone: 1761 Monitoring • SOC: 5471 • SOC + Doc: 5641 • SOC+Docetaxel vs SOC alone: 170 Management including toxicities: • SOC: 14,415	Metastatic prostate cancer ICER (UK pounds/QALY): SOC+Docetaxel vs SOC alone: £5514/QALY

Study	Year	Patient population (average age in years)	Summary of model	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)
					• SOC + Doc: 16,555 •SOC+Docetaxel vs SOC alone: 2139 Life-extending therapies: • SOC: 27,716 • SOC + Doc: 26,611 •SOC+Docetaxel vs SOC alone: -1105 End-of-life care: • SOC: 4864 • SOC + Doc: 4687 •SOC+Docetaxel vs SOC alone: -177	

Key: ADT, androgen deprivation therapy, DOC, docetaxel, ICER, incremental cost-effectiveness ratio, NR, not reported, QALY, quality-adjusted life-years, SCC, symptomatic skeletal, SOC, standard of care.

Table 27: Previous NICE TAs

	TA712[38]	TA721[42]	TA741[88]
Year	2021	2021	2021
Summary of model	Partitioned survival model	Partitioned survival model (after initially submitted STM was critiqued for being too complex for the decision problem)	Partitioned survival model
Patient population	mHSPC	mHSPC	mHSPC
Average age (years)	70	67	
Time horizon	30 years (lifetime)	20 years	32 years (lifetime)
Treatment waning effect	Not included in company base case, but explored by ERG	Not included in company base case, but explored by ERG	Not included in company base case, but explored as a scenario
Source of efficacy data	ARCHES, LATITUDE, ENZAMET	LATITUDE	TITAN
Source of utilities	LATITUDE, NICE TA387	LATITUDE	TITAN
Source of costs	NHS reference costs	NHS reference costs	NHS reference costs
QALYs (intervention, comparator)	Redacted	Redacted	Redacted
Costs (currency, intervention, comparator)	Redacted	Redacted	Redacted
FAD outcome	Recommended	Not recommended	Recommended

Key: ADT; Androgen deprivation therapy, FAD, final appraisal determination, ICER; incremental cost-effectiveness ratio, mHSPC; metastatic hormone sensitive prostate cancer, NHS; National Health Service, QALYs; quality-adjusted life-years, SMC, Scottish Medicines Consortium, TA; technology appraisal.

B.3.2 Economic analysis

As no relevant economic studies investigating the cost-effectiveness of darolutamide+docetaxel+ADT in adult men with mHSPC were identified, a de novo model was developed. The design of this model is described below.

B.3.2.1 Patient population

In line with the ARASENS trial and anticipated marketing authorization for darolutamide, the patient population considered in this analysis is adult men with mHSPC.[46]

Population characteristics in the model are aligned with those of the ARASENS trial population; the mean age at baseline is 66.8 years. Section B.2.3.1 provides further details on the baseline characteristics of patients participating in the ARASENS trial. As discussed in Section B.2.12.3, clinical experts confirmed that the ARASENS population, and therefore the population in the model, was reflective of the population that would be considered suitable for chemotherapy in UK clinical practice.[37].

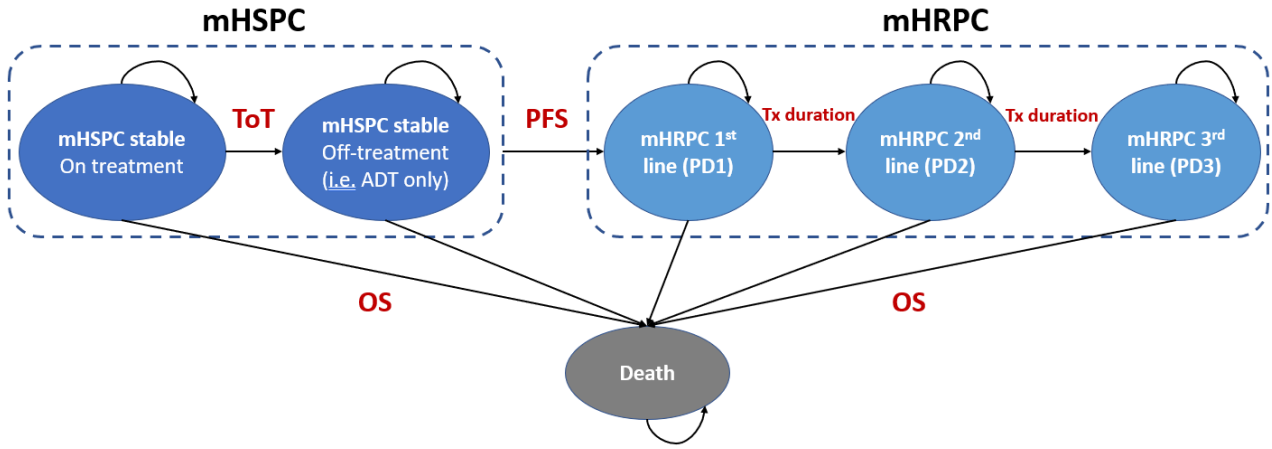
B.3.2.2 Model structure

A de novo cost-effectiveness model was developed in Microsoft Excel®. A partitioned survival model with three health states (pre-progression, post-progression and death) was selected as the model structure. The three-state partitioned survival model is widely used in oncology modelling, including in previous NICE TAs for mHSPC and the darolutamide model in nmCRPC.[38, 42, 88, 100] In TA660, TA712 and TA741, a partitioned survival model structure was considered most appropriate. In TA721, a more complex, multi-state modelling approach was used initially; however, this was subsequently criticized by the Evidence Review Group (ERG) and the model was rebuilt during the appraisal to follow a partitioned survival structure. A partitioned survival model was therefore deemed most appropriate for NICE decision-making.

The model structure, as shown in Figure 16 below, is fully aligned with the NHS treatment pathway and with the primary objectives of treatment in mHSPC: delaying

disease progression to progressed mHRPC, and avoiding debilitating symptoms and reduced HRQL, as discussed in Section B.1.3

Figure 16: Model structure



Key: mHRPC, metastatic hormone-relapsed prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival; PD1, progressed disease – first line; PD2, progressed disease – second line; PD3, progressed disease – third line; PFS, progression-free survival; ToT, time on treatment; Tx, treatment.

The model has three mutually exclusive health states:

- **mHSPC, progression-free:** all patients enter the model in the mHSPC health state. In this state, the disease is stable and responding to treatment. For the darolutamide and enzalutamide treatment arms, the mHSPC health state is further partitioned into active treatment and no active treatment, based on modelled time on treatment (ToT). In line with current UK clinical practice, background ADT continued indefinitely[37]
- **mHRPC, progressed disease**: it is assumed patients who have progressed to hormone-relapsed disease to have moved onto subsequent treatment. To model this progression across treatment lines, the mHRPC health state is divided into three lines of treatment (first line [1L], second line [2L] and third line [3L], respectively) that patients subsequently progress through. This reflects the multiple lines of therapy available in the NHS (see Section B.1.3.4)
- **Dead**: this is an absorbing state

Health state occupancy in a partitioned survival model is dictated by the area under the curves for the different survival inputs. Progression was modelled using time to CRPC, which was taken from ARASENS. This was considered to be better aligned

with UK clinical practice than rPFS, as time to CRPC consists of multiple criteria used to assess disease progression in UK practice and does not rely on a set assessment schedule like rPFS (see Section B.3.3 for more details).[37] However, the definition of time to CRPC used in ARASENS did not include death as an event. To account for patients leaving the pre-progression health state by either progression or death, an additional analysis was conducted to derive an amended secondary endpoint in which death was included as an event to measure all risks in pre-progressed patients, as discussed in Section B.2.6.2.1.1. For this analysis, PFS is therefore defined as time to castration resistance or death (TTCROD). This approach was validated by expert clinicians at an advisory board meeting, who agreed that rPFS is more reflective of how progression was assessed in other mHSPC trials rather than clinical practice, and that TTCROD is a more clinically reflective progression endpoint.[37]

OS is based on the ARASENS primary endpoint. TTCROD was used directly to estimate the proportion of patients in the mHSPC, mHRPC and death health states over time, where

- mHSPC = TTCROD
- mHRPC = OS - TTCROD
- Dead = 1 - OS

All post-progression treatment costs are applied as a single weighted lump-sum cost upon progression, based on publicly available data for time to progression or treatment discontinuation. This approach is most aligned with a partitioned survival model structure, which relies on survival curves to model progression, since there are no direct trial data or survival curves to inform progression between the different post-progression health states (PD1-3). This approach is also in line with the approached used in the previous darolutamide model in nmCRPC (TA660).

B.3.2.3 General model settings

The analysis perspective is that of the NHS and Personal Social Services (PSS) in England for costs and direct health effects on individual patients for outcomes, in line with the NICE reference case.[101]

The model uses a 28-day cycle length. A half-cycle correction is applied throughout the model to both costs and health outcomes to better account for the fact that some costs can occur at any point during the cycle, while other health outcomes are spread across time. The analysis assumes a lifetime time horizon (34 years), which is sufficient to capture the plausible maximum life expectancy for the ARASENS intention-to-treat (ITT) population (mean age 66.8 years). Shorter time horizons are explored in the scenario analysis in Section B.3.11. A discount rate of 3.5% per year is applied to costs and quality-adjusted life years (QALYs), which is also specified in the NICE reference case.[101] All costs are presented in British pounds sterling (GBP) and the cost year is 2021.

General model settings, along with a comparison of settings used in past appraisals in mHSPC and a brief justification for our approach, are summarized in Table 28. Not all previous appraisals are equally representative, as they either cover treatments that were not approved in the UK (abiraterone, TA721)[42], or approved in a different patient population (apalutamide, TA741).[88] The enzalutamide+ADT appraisal, TA712, is therefore the most relevant source of comparison and validation for this appraisal.[38, 42, 88]

Table 28: Features of the economic analysis

Factor	Previous appraisals			Current appraisal	
	TA712[38]	TA741[88]	TA721[42]	Chosen values	Justification
Time horizon	Lifetime horizon implemented as 30 years	Lifetime horizon implemented as 32 years	Lifetime horizon implemented as 20 years	Lifetime horizon implemented as 34 years	A lifetime horizon was used (34 years, given the mean patient age in the cost-effectiveness model based on the ARASENS trial is 66.8 years and assuming a maximum life expectancy of 100). This is considered to be adequately long that all the patients would have died by the end of the model time horizon so that the model is able to capture relevant benefits and costs for the darolutamide + docetaxel in line with the NICE reference case[101]
Cycle length	1 month	1 week	1 week for first year, every 28 days thereafter	28 days	Cycles lasting up to a month were accepted in previous appraisals. A 28-day cycle was chosen, as it algins well with darolutamide dosing, and overall clinical practice, considering that most treatments and assessment schedules are defined as multi-week cycles
Health states	• PF (on-tx) and PF (off-tx) • PD (mHRPC), divided by treatment (1L, 2L and 3L)	• PF • PD (mHRPC), split into: 1L (pre) and (on-tx) mHRPC, 2L (pre) and (on-	• PF (on-tx) and PF (off-tx) • PD (mHRPC), divided by treatment (1L, 2L and 3L)	• PF (mHSPC) subdivided on-tx and off-tx • PD (mHRPC), divided by	The health states are in line with all previous mHSPC appraisals. There are multiple lines of therapy available for patients in mHRPC, and QoL is expected to deteriorate as patients progress

Factor	Previous appraisals			Current appraisal	
	TA712[38]	TA741[88]	TA721[42]	Chosen values	Justification
	• Death	tx) mHRPC, 3L mHRPC • Death	• Death	treatment (1L, 2L and 3L) • Death	through these treatment lines. This decline is accounted for in the mHRPC calculations to accurately capture costs and QALYs in mHRPC.
Comparators	• ADT alone (including orchidectomy, luteinising hormone-releasing hormone agonist therapy) or monotherapy with bicalutamide • Docetaxel + ADT	• ADT alone • Docetaxel + ADT	• ADT alone (including LHRH agonist therapy) • Docetaxel + ADT	• Docetaxel + ADT • Enzalutamide + ADT • ADT alone	Aligned with NICE scope, as discussed in Section B.1.1, and standard of treatments for patients with mHSPC
Health effects measure	QALYs	QALYs	QALYs	QALYs	Consistency with NICE reference case[101]
Discount for utilities and costs	3.5%	3.5%	3.5%	3.5%	Consistency with NICE reference case[101]
Perspective (NHS/PSS)	NHS and PSS in England	NHS and PSS in England	NHS and PSS in England	NHS and PSS in England	Consistency with NICE reference case[101]
Half-cycle correction applied?	Not applied	Not stated	Not applied	Yes	Consistency with NICE reference case[101]
Treatment waning effect?	Excluded from company base case	Excluded from company base case	Not discussed	Exclude	None of the previous mHSPC appraisals included treatment waning

Factor	Previous appraisals			Current appraisal	
	TA712[38]	TA741[88]	TA721[42]	Chosen values	Justification
Source of utilities	ARCHES, AFFIRM	SPARTAN, TITAN	The LATITUDE EQ-5D -5L data is cross walked to EQ-5D-3L using the van Hout et al algorithm which the company describes as being recommended by the DSU.	ERG preferred utilities from TA712	The QoL measurements captured in ARASENS were NCCN-FACT-FPSI-17 and BPI-SF To identify if there were any suitable mapping algorithms to EQ-5D-3L, we carried out a targeted literature review replicating the methodology (search strategy and database/websites) used by HERC database,[102] and manually screened for NCCN-FACT-FPSI-17 or BPI-SF. There were no mapping algorithms identified for either of these measures. Therefore, data from ARASENS are not suitable for utility value calculation, hence literature values are required. Of the publicly available information the ERG preferred values from TA712, and TA741 were considered the most reliable sources, as they reported very similar utility values, and were accepted by the ERG in past mHSPC submissions. Of these, TA712 was chosen as the base-case, as this TA assessed a direct comparator in this population.
Source of costs	NHS reference	NHS reference	NHS reference	NHS reference costs	In line with NICE reference

Factor	Previous appraisals			Current appraisal	
	TA712[38]	TA741[88]	TA721[42]	Chosen values	Justification
	costs	costs	costs		case[101]

Key: 1L, first line; 2L, second line; 3L, third line; AC, Appraisal Committee; ADT, androgen deprivation therapy; ERG; Evidence Review GroupEQ-5D-5L; Euro-QoL 5 dimension 5 levels, HERC; Health Economics Research Centre, LHRH; Luteinizing hormone-releasing hormone, mHRPC, metastatic hormone-relapsed prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; MSM, multi-state model; NHS, National Health Service; NICE; National Institute for Health and Care Excellence; PD, progressed disease; PF, progression-free; PSS; Personal Social Services, QALY, quality-adjusted life year; QoL; quality of life, TA; technology appraisal, tx; treatment.

B.3.2.4 Intervention technology and comparators

B.3.2.4.1 Intervention

The intervention, darolutamide, is implemented in the model as per the expected marketing authorization, which is for 'for the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel'. This is reflective of the decision problem described in Section B.1.1. Darolutamide is an AR inhibitor that binds with high affinity directly to the receptor ligand binding domain. It competitively inhibits androgen binding, AR nuclear translocation and AR mediated transcription, which are components of the AR signalling pathway.[1, 3] Both darolutamide and its active metabolite inhibit testosterone-induced translocation of AR to the nucleus, decreasing the activation of genes required for the growth and survival of prostate cancer cells.[1, 2 12]

The recommended dose of darolutamide in mHSPC is 600 mg (two 300 mg film-coated tablets) taken orally twice daily, equivalent to a total daily dose of 1,200 mg. In mHSPC, darolutamide is given in combination with docetaxel at a dose of 75 mg/m^2 every 21 days for a maximum of 6 cycles, with patients receiving ADT as background therapy. This is in line with the ARASENS trial and expected licence for darolutamide. Darolutamide is administrated until disease progression or unacceptable toxicity.

B.3.2.4.2 Comparator

As per the final scope, the following comparators have been included in the model:

- Docetaxel with ADT
- Enzalutamide with ADT
- ADT alone

Docetaxel is a cytotoxic agent that targets fast-growing cells, and thereby inhibits prostate cancer cell growth. Docetaxel dosing is based on body surface area (BSA), and it is included at the recommended dose of 75 mg/m^2. Enzalutamide has a similar mechanism of action to darolutamide and acts as an AR inhibitor to inhibit testosterone-induced growth and survival of prostate cancer cells. It is included at its recommended dose of 160 mg per day.

ADT is a collective term that comprises LHRH agonists and antagonists. ADT is considered a background therapy, and is therefore continued indefinitely for all patients, in line with the approach used in past mHSPC appraisals.[38, 42, 88] It is also included as standalone treatment in the model as a comparator. ADT is included in the model as a weighted average of ADT used in UK clinical practice. Clinical experts informed the treatment distribution for ADT as 30:30:40 leuprorelin: goserelin: triptorelin.[37] Degarelix was not included as ADT, as clinical experts stated that it was only used in the short term to treat patients with spine compression, not as a long-term ADT therapy. The ADT options used in the model and their corresponding market shares used to derive ADT costs are presented in Table 29. This ADT distribution is the same for all health states.

Table 29: Breakdown of ADT treatments used in the model

Androgen deprivation therapies	Market shares used to derive ADT cost
Leuprorelin	30%
Goserelin	30%
Triptorelin	40%
Key: ADT, androgen deprivation therapy.	

B.3.3 Clinical parameters and variables

The pivotal ARASENS trial provides key efficacy, safety and baseline characteristics data for the mHSPC population. The model used the following clinical inputs from the ARASENS trial: PFS (modelled using TTCROD, as described below), OS and ToT. A summary of the methods used is available in the sections below.

As the model time horizon (i.e. 34 years) is longer than the duration of follow-up in ARASENS, time to event outcomes are extrapolated to estimate survival over the time horizon of the model. For each outcome, seven standard parametric models (i.e. exponential, log-normal, log-logistic, Weibull, generalized gamma, Gompertz and gamma) were fitted to the ARASENS data. To determine the best model fit in line with the recommendations of the NICE DSU TSD 14,[103] the following steps were followed:

- The validity of the proportional hazards and accelerated failure time assumptions was assessed using log-cumulative hazards, Schoenfeld residuals, QQ plots and hazard plots (shown in Appendix N)
- Statistical fit was assessed using the Akaike information criterion (AIC) and Bayesian information criterion (BIC). Lower AIC and BIC figures are indicative of a better statistical fit of the survival function to the Kaplan–Meier data
- Visual inspection was carried out by plotting the projected survival curves overlaid with the Kaplan–Meier survival functions
- The clinical plausibility of the estimated patients alive at different time points was compared against external reference data and validated by expert opinion

In the base case, PFS and OS were modelled by extrapolating docetaxel data from the ARASENS trial, and by applying the ITC HR to the extrapolated docetaxel data to generate OS and PFS for all other treatments. Details of the ITC are described in Section B.2.9. Although direct darolutamide data are also available from ARASENS, docetaxel was preferred as an anchor because there are a number of publications providing long-term data to validate the docetaxel extrapolations, increasing the reliability of the extrapolated survival estimates.[21,60] In addition, applying an HR to the docetaxel data for all treatments, including darolutamide, ensures that darolutamide is modelled consistently with the other comparators (i.e. enzalutamide and ADT alone). This approach was also validated with health economics experts, who agreed that it would be most consistent and robust to model all treatments based on the docetaxel data, and that this approach would avoid potential discrepancies in estimating the treatment effects of docetaxel and darolutamide.[104] Similarly to TA712, the extrapolated trial data overestimated enzalutamide's survival relative to ADT. The ERG for TA712 therefore argued that it would be more appropriate to model enzalutamide by applying an HR to the ADT arm, to ensure the relative treatment effect was modelled properly.[38, 105]

The sections below will discuss the docetaxel OS and PFS extrapolations. The darolutamide extrapolations are shown in Appendix N, and will be explored as anchor for the efficacy input in the scenarios.

B.3.3.1 Overall survival modelling, ARASENS

As described above, OS was modelled using extrapolated docetaxel data, which was then used as an anchor arm to apply HR for all other treatments.

B.3.3.1.1 Docetaxel OS extrapolation

Docetaxel OS data from ARASENS were extrapolated to match the time horizon of the model. The assumption of proportional hazards for OS was assessed using log-cumulative hazard and Schoenfeld residuals plots, as shown in Appendix N. These plots showed that the proportional hazards assumption holds for OS, which validates the approach to model comparator OS by applying ITC HRs to docetaxel, as confirmed by consulted health economic experts.[104] Docetaxel data were therefore extrapolated using independent models (discussed below). The dependent extrapolations are available in Appendix N, and were explored as a scenario analyses.

Standard parametric models fitted to docetaxel OS from ARASENS are presented in Figure 17. All the modelled OS extrapolations were adjusted to ensure that the hazard of OS would not be lower than that of the UK age and gender-matched general population mortality hazard.[106] The statistical fit was assessed using the AIC and BIC data, as shown in Table 30. Based on the AIC and BIC data, the gamma extrapolation showed the best fit to the ARASENS Kaplan–Meier data. However, this AIC/BIC ranking should be interpreted with caution, as all extrapolations had comparable AIC/BIC values to those of the gamma curve, except for the exponential and Gompertz extrapolations. So, overall these data indicate all curves had comparable statistical fit to the ARASENS data, except for the exponential and Gompertz curves which fitted the data poorly.

Figure 17: Docetaxel OS extrapolations using independent standard parametric models

Table 30: AIC and BIC statistical fit statistics for docetaxel OS

Model	AIC	Rank	BIC	Rank
Exponential				
Gamma				
Gen. gamma				
Gompertz				
Log-logistic				
Log-normal				
Weibull				

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; Gen., generalized; OS, overall survival.

The clinical validity of the docetaxel OS extrapolations was compared against published long-term OS data from STAMPEDE-3 and CHAARTED.[21,60] These studies provided the most reliable long-term OS estimates for docetaxel, as they both captured up to 9 years of follow-up data, and both study characteristics were broadly similar to ARASENS (as discussed in Section B.2.9 and Appendix D). Most notably, STAMPEDE-3 is a good source to validate OS as it was a UK study, so the observed survival is likely to be representative of survival in the UK. STAMPEDE-3 will therefore be used to validate the darolutamide OS extrapolations, with CHAARTED used as additional validation.

Table 31 shows OS extrapolations of the docetaxel arm of ARASENS at different time points compared to survival estimates from ARASENS and digitized Kaplan–Meier data from CHAARTED and STAMPEDE-3. At 5 and 7 years. The Gompertz, gamma, and Weibull extrapolations are the least aligned with these external OS data. These curves are likely to underestimate long-term survival as they predict substantially lower survival than STAMPEDE-3 at 5, 7, and 9 years. The exponential and log-normal extrapolations align most closely with the external STAMPEDE-3 data. However, the exponential extrapolation showed a poor statistical and visual fit to the ARASENS data, as it underestimated ARASENS survival at Years 1 and 2, as shown by the survival data below. At 9 years, the STAMPEDE survival drops and is more closely aligned with the log-logistic extrapolation. However, low patient numbers toward the end of the curve decrease the reliability of these data. The log-normal OS extrapolation was therefore selected in the base case, with log-logistic explored as a scenario. This is also in line with the CHAARTED OS data, with log-normal showing a good alignment to the 5- and 9-year CHAARTED OS estimates (Table 31).

Table 31: Comparison of docetaxel OS extrapolations and published data

Docetaxel+ADT	**Predicted % alive at**					
	1 year	**2 years**	**3 years**	**5 years**	**7 years**	**9 years**
Exponential	[redacted]					
Log-normal						
Log-logistic						
Gompertz						
Weibull						

Docetaxel+ADT	Predicted % alive at					
	1 year	2 years	3 years	5 years	7 years	9 years
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHAARTED	*94.9%*	*83.6%*	*71.7%*	*46.5%*	*23.9%*	*23.9%*
STAMPEDE	*91.7%*	*76.9%*	*65.4%*	*48.8%*	*35.2%*	*21.4%*
ARASENS	*90.3%*	*76.8%*	*63.8%*	*N/A*	*N/A*	*N/A*

Key: ADT, androgen deprivation therapy; N/A, not available; OS, overall survival.
Note: Bold (log-normal) reflects base case OS input.

As noted above, HRs derived from the ITC were applied to the docetaxel OS extrapolations to estimate the OS for all other treatments in the model.

Table 32 shows the HRs used in the base case and predicted OS over time for each treatment option in the model. As discussed in Section B.2.9, some uncertainty surrounded the ITC, and different ITC sensitivity analyses were performed. These alternative HRs will also be explored as scenario analyses.

Table 32: OS estimates over time for all modelled treatments

OS	*HR*	Predicted % alive at				
		2 years	5 years	10 years	20 years	30 years
Darolutamide + Docetaxel + ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide + ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADT alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ADT, androgen deprivation therapy; HR, hazard ratio; OS, overall survival

B.3.3.2 Progression-free survival modelling (time to castration resistance or death), ARASENS

As discussed in Section B.3.2.2, progression in the model was based on TTCROD, which combines time to CRPC and pre-progression OS from ARASENS. The reason for this was twofold. Firstly, both clinical experts and past appraisals indicated that rPFS is not reflective of how progression is assessed in UK clinical practice.[38, 42, 88] In UK clinical practice, clinical progression is assessed using a combination of tests including PSA progression and rPFS.[37] rPFS alone, which is commonly used in trials, is therefore not an accurate metric to model progression in mHSPC, as it only

considers one aspect of the clinical progression definition. In UK clinical practice, castration resistance can occur before rPFS, for example due to biochemical progression, so using rPFS alone is likely to underestimate progression. In addition, rPFS from trials is based on a fixed clinical trial assessment schedule. This is also not reflective of UK clinical practice, where imaging is driven by clinical signs and symptoms or biochemical progression, instead of a fixed schedule every few months. Secondly, rPFS was not a pre-specified endpoint in ARASENS; radiographic investigations were undertaken in ARASENS based on signs for clinical progression at the investigator's discretion. Imaging could therefore be performed at any time in case of PSA progression, symptomatic progressive disease or change of antineoplastic therapy, to mimic a real-world setting. Time to CRPC from ARASENS was therefore considered a more representative measure of progression, as it combines both rPFS and PSA progression, and does not rely on a set scanning frequency. The model therefore uses TTCROD as PFS input to best reflect clinical practice.

The chosen approach for progression modelling was validated by UK clinical experts who confirmed that rPFS is not commonly used to define progression in practice. [37] In addition, this approach is in line with past appraisals in mHSPC, in which the ERG critiqued the use of rPFS to define progression, in part because it was not reflective of UK practice.[38]

B.3.3.2.1 Docetaxel TTCROD extrapolation

Similar to OS, docetaxel TTCROD from ARASENS was extrapolated to align with the 34-year time horizon of the model. The assumption of proportional hazards for TTCROD was confirmed using log-cumulative hazard and Schoenfeld residuals plots, shown in Appendix J. In addition, the validity of assuming proportional hazards for TTCROD was validated by consulted health economic experts, based on the plots in Appendix J.[104] As with OS, HRs were applied to docetaxel data to inform PFS for all treatments. The independent docetaxel extrapolations are therefore discussed below, with the darolutamide and dependent extrapolations discussed in Appendix N and explored in scenario analyses.

As per OS, seven standard parametric models were fitted to docetaxel TTCROD from ARASENS for the extrapolation period (Figure 18). Similar to OS, the TTCROD

extrapolations were adjusted to ensure that the hazard of progression would not be lower than the hazard of death from the selected OS extrapolation or the UK age and gender-matched general population mortality hazard. Table 33 shows the statistical fit based on AIC/BIC. Based on the AIC and BIC data, the generalised gamma extrapolation showed the best fit to the ARASENS Kaplan–Meier data.

Figure 18: Docetaxel TTCROD extrapolations using independent standard parametric models

Table 33: AIC and BIC statistical fit statistics for docetaxel TTCROD

Model	AIC	Rank	BIC	Rank
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gen. gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; Gen., generalized; TTCROD, time to castration resistance or death.

The clinical validity of the extrapolated docetaxel data was also validated against the published docetaxel data from STAMPEDE-3 and CHAARTED.[21,60] Table 34 shows TTCROD extrapolations of the docetaxel arm of ARASENS at different time points compared to progression data from STAMPEDE-3 and CHAARTED. Both CHAARTED and STAMPEDE-3 predicted a higher percentage of progression-free patients al all assessed timepoints (Table 34). However, this may be explained by the difference in endpoint definition. STAMPEDE-3 reported rPFS, and CHAARTED reported time to clinical progression (defined as time to radiographic progression or worsening of symptoms) and time to CRPC (defined as time to PSA progression or worsening of symptoms), whereas the model uses TTCROD from ARASENS. As discussed above, it is likely that these endpoints underestimate progression in clinical practice, as it only looks at one or two progression criteria, whereas multiple criteria are assessed in TTCROD and UK clinical practice. In addition, none of the endpoints assessed in CHAARTED included death as an event, which was included in TTCROD. It is therefore expected that TTCROD from ARASENS would be lower than the progression estimates from CHAARTED and STAMPEDE-3, as shown in Table 34. Nevertheless, the consulted clinical experts flagged that most docetaxel progression predictions of the extrapolation were lower than what they observed in clinical practice, and preferred the generalized gamma TTCROD extrapolation followed by log-logistic as the second-best choice, as they provided the highest progression estimates. Based on this input and the statistical fit, the generalized gamma curve was used in the base case, and the log-logistic curve was explored as a scenario.

Table 34: Comparison of docetaxel TTCROD extrapolations and published data

Docetaxel+ADT	Predicted % alive at					
	1 year	2 years	3 years	5 years	7 years	9 years
Exponential	[redacted]					
Log-normal	[redacted]					
Log-logistic	[redacted]					
Gompertz	[redacted]					
Weibull	[redacted]					
Generalized gamma	[redacted]					
Gamma	[redacted]					
CHAARTED cPFS	*77.5%*	*60.0%*	*46.2%*	*36.6%*	*30.5%*	*N/A*
CHAARTED TTCRPC	*67.1%*	*44.7%*	*32.9%*	*29.9%*	*22.4%*	*N/A*
STAMPEDE rPFS	*81.5%*	*61.5%*	*49.6%*	*36.6%*	*29.0%*	*21.3%*
ARASENS	*63.1%*	*37.8%*	*25.0%*	*N/A*	*N/A*	*N/A*

Key: ADT, androgen deprivation therapy; cPFS, clinical progression-free survival; N/A, not available; rPFS, radiographic progression-free survival; TTCROD, time to castration resistance or death; TTCRPC, time to castration-resistant prostate cancer
Note: Bold (generalized gamma) reflects base case TTCROD input

As noted above, HRs derived from the base PFS ITC were applied to the docetaxel TTCROD extrapolations to estimate the TTCROD for all other treatments in the model.

Table 35 shows the HRs used in the base case and predicted TTCROD over time for each treatment option in the model. As discussed in Section B.2.9, some uncertainty surrounded the progression definition in the ITC and different ITC sensitivity analyses were performed. These alternative HRs will also be explored as scenario analyses.

Table 35: TTCROD estimates over time for all modelled treatments

OS	*HR*	Predicted % progression-free at				
		2 years	5 years	10 years	20 years	30 years
Darolutamide + Docetaxel + ADT	[redacted]					
Docetaxel + ADT	[redacted]					
Enzalutamide + ADT	[redacted]					
ADT alone	[redacted]					

Key: ADT, androgen deprivation therapy; HR, hazard ratio; OS, overall survival

B.3.3.3 Time on treatment, ARASENS

For ToT, the model uses darolutamide data from ARASENS instead of docetaxel data. In ARASENS, docetaxel was only given for six treatment cycles, followed by placebo+ADT. Consequently, docetaxel ToT data from ARASENS would mostly be informed by the patient's adherence to placebo. ToT was therefore modelled using extrapolated darolutamide data from ARASENS as an anchor, and the ITC HR versus darolutamide was used to model ToT for enzalutamide which has similar mode of action.

B.3.3.3.1 Darolutamide ToT extrapolation

Darolutamide ToT was informed by post-hoc analysis of ARASENS data. ToT was extrapolated to align with the 34-year time horizon of the model. The assumption of proportional hazards for ToT was confirmed using log-cumulative hazard and Schoenfeld residuals plots, which is presented in Appendix N. In line with TTCROD and OS, the model uses independent extrapolations, with dependent models discussed in Appendix N and explored in scenario analyses.

Standard parametric models fitted to darolutamide ToT in ARASENS are presented in Figure 19. Similar to OS and TTCROD, the ToT extrapolations were adjusted to ensure that the hazard of discontinuation would not be lower than the hazard of death or progression. All adjusted extrapolations showed a good visual fit to the ARASENS data (Figure 19). The statistical fit was assessed using the AIC and BIC data, as shown in Table 36. Based on the AIC and BIC data, the log-logistic and exponential extrapolations showed the best statistical fit.

Figure 19: Darolutamide ToT extrapolations using independent standard parametric models

Key: ADT, androgen deprivation therapy; ToT, time on treatment.

Table 36: AIC and BIC statistical fit statistics for darolutamide ToT

Model	AIC	Rank	BIC	Rank
Exponential				
Gamma				
Gen. gamma				
Gompertz				
Log-logistic				
Log-normal				
Weibull				

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; Gen., generalized; ToT, time on treatment.

The clinical validity of the ToT extrapolations could not be validated with external data, as no publicly available long-term ToT data were available. However, there was a broad consensus from both the clinical advisory board and past mHSPC appraisals that it is not clinically plausible to have a large gap between ToT and progression.[37,38] The plausibility of the ToT extrapolations was therefore assessed by comparing the darolutamide ToT extrapolations to the observed ToT from ARASENS and the modelled darolutamide TTCROD (Table 37). Based on the proximity to the modelled TTCROD, log-normal and log-logistic are likely to be the most clinically plausible, followed by Gompertz. However, the log-normal extrapolations showed a poor statistical fit and deviated the most from the observed ARASENS data, as shown in Table 37. Therefore, the log-logistic ToT extrapolation will be used in the base case, with Gompertz explored as a scenario, as they provided the best combination of clinical plausibility and statistical fit.

Table 37: Comparison of darolutamide ToT extrapolations with ARASENS ToT and modelled darolutamide TTCROD data

Darolutamide + docetaxel + ADT		**Predicted % on treatment at**				
	1 year	**2 years**	**3 years**	**5 years**	**7 years**	**9 years**
Exponential						
Log-normal						
Log-logistic						
Gompertz						
Weibull						
Generalized gamma						

Darolutamide + docetaxel + ADT		Predicted % on treatment at				
	1 year	2 years	3 years	5 years	7 years	9 years
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARASENS	*82.5%*	*63.1%*	*53.1%*	*#N/A*	*#N/A*	*#N/A*
Modelled TTCROD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ADT, Androgen deprivation therapy; PFS, progression-free survival; NR, not reported
Note: Bold (generalized-gamma) reflects base case TTCROD input

As described above, HRs derived from the ITC were applied to the darolutamide ToT to estimate the ToT for all other treatment options in the model. For ToT, the only indirect comparator in the model is enzalutamide, as docetaxel is given for a fixed number of cycles, and ADT continued indefinitely. Since no enzalutamide ToT data were available, the model uses the HR from the base PFS ITC as a proxy for ToT. This approach assumes that the relative difference in progression is comparable to the relative difference in treatment discontinuation, as most patients are treated until progression. However, this is likely to represent a conservative approach. As darolutamide is given as a triple therapy, which includes docetaxel, it is plausible that patients receiving darolutamide+docetaxel+ADT show higher discontinuation rates than patients taking enzalutamide+ADT. The model will therefore also explore an optimistic scenario that assumes the ToT of enzalutamide is equal to PFS, with the true enzalutamide treatment use likely falling somewhere between these two estimates. Table 38 shows the predicted ToT over time for enzalutamide when applying the PFS HR to the extrapolated darolutamide ToT data. A large discrepancy between darolutamide and enzalutamide in treatment discontinuations is observed, with roughly twice as many patients continuing treatment with darolutamide compared to enzalutamide past 10 years. This lacks clinical face validity since both treatments are ARIs and have a similar mode of action. Therefore, the modelled enzalutamide ToT is likely overly conservative.

Table 38: ToT estimates over time for all modelled treatments

OS	*HR*	Predicted % on treatment at				
		2 years	5 years	10 years	20 years	30 years

Darolutamide + Docetaxel + ADT	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide + ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: ADT, androgen deprivation therapy; HR, hazard ratio; OS, overall survival.						

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality of life data from clinical trials

The ARASENS trial did not capture EQ-5D data. Disease-specific HRQL measurements from ARASENS included NCCN-FACT-FPSI-17 and BPI-SF. A targeted literature review was undertaken to identify if suitable mapping algorithms from NCCN-FACT-FPSI-17 and BPI-SF to EQ-5D could be found. The search strategy was informed by methodology used by the Health Economics Research Centre (HERC) database, and consisted of a targeted literature review of known sources for mapping algorithms and manually screening for NCCN-FACT-FPSI-17 or BPI-SF.[102] Details on the databases and search terms used are available in Appendix O. No mapping algorithms were identified for either of these measures. Consequently, the disease-specific HRQL measures, NCCN-FACT-FPSI-17 and BPI-SF, from ARASENS were deemed unsuitable for the cost-effectiveness model. The model therefore relied on external data to inform the utilities per health state.

B.3.4.2 Mapping

As discussed above, we did not identify a suitable mapping algorithm to map the NCCN-FACT-FPSI-17 and BPI-SF measurements from ARASENS to EQ-5D.

B.3.4.3 Health-related quality of life studies

A systematic search was performed to identify all relevant published HRQL studies in adults with mHSPC. Full details of the search methods and results are reported in Appendix H. In summary, 20 studies met the full inclusion criteria. Studies reporting a de novo utility analysis were prioritized, and this resulted in extractions of eight studies from 12 publications. Out of the eight studies, only Hall 2019[107], TA712[38] and TA741[88] reported utilities that were generated using a UK tariff and can therefore be considered relevant to decision-making in the UK. Of these, Hall 2019 was a vignette study, whereas TA712 and TA741 were past TAs with utilities directly based on clinical trial data. There are some important limitations to vignette studies. The

vignette methodology may not accurately reflect the extent to which patients learn to cope with and adjust to their disease. In addition, the utilities derived from vignette studies rely heavily upon the accuracy of the descriptions that are included, so can lead people to overly focus on certain aspects of the description, which could lead to bias. Utilities directly derived from patient-reported outcomes captured in a clinical trial, as reported in TA712 and TA741, are therefore more reliable than utilities from a vignette study. The remainder of this section will therefore discuss the utilities from TA712 and TA741. However, a full overview of the studies included in the SLR is also included in Appendix H. In addition, utility values in TA721 may have been relevant to this appraisal, but these were redacted throughout the Committee papers.

Utility values used in TA712 and TA741 are summarized in Table 39. The utilities in the TA712 base case analysis were obtained from the EQ-5D-5L data in the key enzalutamide clinical trials (ARCHES and AFFIRM). Mean utilities derived from all pre-progression measurements and all post-progression values from both arms of ARCHES were used in the mHSPC and progressed disease (PD) 1 health states, respectively. Baseline utility values from the AFFIRM study were used to inform utility values in PD3. To calculate the PD2 value, a mean of the PD1 and PD3 values were used. Based on the last utility assessment before death conducted in both arms of ARCHES, it was assumed that patients had a lower utility value in the last 3 months of life.[38] However, the ERG critiqued utilities in TA712, stating that the utility values for progressive disease are higher than values used in previous mHRPC appraisals. It therefore applied a utility decrement of 0.093 between the sub-states (i.e. PD2 0.63, PD3 0.53), based on the decrement observed in other appraisals.

Progression-based utility values were also used in TA741. The utility values used for pre-progression and post-progression (1L mHRPC) were taken from the company trials (SPARTAN and TITAN) using the EQ-5D-3L. As a limited number of patients completed the EQ-5D-3L questionnaire after developing metastases in SPARTAN, the company derived the utility values for 2L and 3L mHRPC by applying a relative decline ratio, which was estimated by dividing the 2L mHRPC utility by the 1L mHRPC utility from TA387. This ratio was then multiplied by the utility from the post-progression health state (1L mHRPC) from the company's trials. This process was repeated to estimate the 3L mHRPC utility. The company adjusted the derived utility

values to account for population differences between SPARTAN and TA387 in line with TSD12.[108] In response, the ERG considered that a more appropriate approach would be not to adjust second- and third-line utilities by applying a relative decline ratio to the first-line mHRPC utility value (that is, 0.625 for second-line mHRPC treatment and 0.5 for third-line mHRPC treatment) as this assumes that the utility values would decrease by the same relative proportion between 1L and 2L treatments of mHRPC (as in TA387). The Committee also considered that this assumption may not be appropriate given the different starting populations in this appraisal. In its base case, the ERG used the utility values from TA387 without adjusting them.

Overall, the utility approach and values per health state from TA712 and TA741 were broadly similar. In both appraisals, the Committee accepted progression-based utilities. In addition, the ERG preferred treatment-agnostic utilities for all treatments, with the exception of docetaxel, for which the effect of an on-treatment docetaxel utility decrement was explored in TA741. This docetaxel disutility was not modelled in our base-case, as clinical experts did not see any clinical grounds for applying a specific docetaxel disutility, based on data from STAMPEDE suggesting that docetaxel improves HRQL.[44] In addition, any negative impacts of docetaxel therapy due to tolerability are already explicitly captured through the adverse event disutilities, as described in Section B.3.4.5. However, the impact of applying a docetaxel disutility will be explored as a scenario.

Table 39: Health-related quality of life results for TAs identified by the SLR

Study name (treatment), date	Population	Method of elicitation	Utility data
Hall et al. (docetaxel + ADT and ADT alone), 2019	High-risk mHSPC	Vignette study, using: • Elicitation: EQ-5D • Valuation: VAS, TTO TTO methodology with members of the UK general public was used	ADT alone: TTO value mean (SD): 0.71 (0.26) Receiving docetaxel + ADT: TTO value mean (SD): 0.64 (0.27) Completed docetaxel + on ADT; not progressed: TTO value mean (SD): 0.68 (0.26) AEs (Base State 2 + specific AE), TTO value (n = 200) Mean (SD): • Fatigue: 0.54 (0.34) • Nausea and vomiting: 0.41 (0.36) • Reduced immunity: 0.48 (0.33) • Fluid retention: 0.58 (0.29) • Alopecia: 0.58 (0.29) • Diarrhoea: 0.40 (0.38)
NICE TA712 (Enzalutamide + ADT and ADT alone), 2021	mHSPC	• EQ-5D-5L • EQ-5D-3L	Companies' treatment-agnostic utility values: mHSPC: 0.806 (ARCHES pre-progression) 1L mHRPC : 0.723 (ARCHES post-progression) 2L mHRPC: 0.702 (Average of 1L and 3L) 3L mHRPC: 0.688 (AFFIRM) End of life: 0.457 ERG-preferred utility values: mHSPC: 0.806 (unchanged) 1L mHRPC: 0.723 (unchanged) 2L mHRPC: 0.630 (-0.093 from 1L) 3L mHRPC: 0.537 (-0.093 from 2L) End of life: 0.457 (unchanged)

Study name (treatment), date	Population	Method of elicitation	Utility data
NICE TA741 (Apalutamide + ADT and ADT alone), 2021	nmCRPC / mHSPC	EQ-5D-3L	Companies' treatment-agnostic utility values: mHSPC: 0.8047 (TITAN pre-progression) 1L mHRPC: 0.6981 (TITAN post-progression) 2L mHRPC: 0.5257 (TA384 1L:2L ratio applied to 1L) 3L mHRPC: 0.4206 (TA384 2L:3L ratio applied to 2L) ERG-preferred utility values: • mHSPC: 0.8047 (unchanged) 1L mHRPC: 0.6981 (unchanged) 2L mHRPC: 0.625 (TA387) 3L mHRPC: 0.500 (TA387)
Key: 1L, first line 2L, second line, 3L, third line, AE, adverse event, EQ-5D-5L, Euro-QoL 5 dimension 5 levels, ERG, Evidence Review Group, mHSPC, metastatic hormone-sensitive prostate cancer, mHRPC, metastatic hormone-relapsed prostate cancer, nmCRPC, non-metastatic castration-resistant prostate cancer, SLR, systematic literature review, TA; technology appraisal, TTO, time trade-off.			

B.3.4.4 Adverse reactions and symptomatic skeletal events

mHSPC AE incidences and durations used in the model for the darolutamide and docetaxel arms were taken from the ARASENS trial. Enzalutamide and ADT alone AE incidence was informed from ARCHES.[53] mHRPC AE incidences and durations were taken from TA712 and confirmed using the respective trial publications, which ensured consistency with TA712. The model considers AEs of Grade 3 and higher that occurred in at least 5% of patients in any treatment in the model. This cut-off was chosen to ensure that infrequent but costly or severe AEs were captured in the model. However, it should be noted that this approach may underestimate AEs for enzalutamide and ADT alone. ARCHES only reported AEs that occurred in ≥5% of patients, so data were not available for all AEs that were included in the model.[53] It could be that less frequent AEs, that were included for darolutamide and docetaxel based on the patient level data, should have been included for ARCHES as well if all ARCHES data were available. However, without access to the ARCHES patient level data, it is impossible to assess the magnitude of this underestimate.

The average AE rate per treatment across the different trials was calculated by combining the observed number of AE events and the number of patients per arm for the different trials. This is presented in Table 40 and Table 41 for mHSPC and mHRPC treatments, respectively.

Table 40: mHSPC adverse event rates used in economic model

Adverse event	Darolutamide (ARASENS) (N = 652)		Docetaxel (ARASENS) (N = 650)		Enzalutamide (ARCHES) (N = 572)		ADT alone (ARCHES) (N = 574)	
	N	rate	N	rate	N	rate	N	rate
ALT increased	[redacted]							
Anaemia								
Decreased neutrophil count								
Decreased white blood cell count								
Diarrhoea								
Febrile neutropenia								
Hypertension					19	3.3%	10	2%
Neutropenia								

Adverse event	Darolutamide (ARASENS) (N = 652)		Docetaxel (ARASENS) (N = 650)		Enzalutamide (ARCHES) (N = 572)		ADT alone (ARCHES) (N = 574)	
	N	rate	N	rate	N	rate	N	rate
Source	ARASENS CSR				ARCHES (Armstrong (2019)			
Key: ADT, androgen deprivation therapy; ALT, alanine aminotransferase; N, total number.								

Table 41: mHRPC adverse event rates used in economic model

Adverse event	Enzalutamide (PREVAIL) (N = 871)		ADT alone (PREVAIL) (N = 844)		Abiraterone (COU-AA-302) (N = 652)		Docetaxel (TAX-327) (N = 332)		Cabazitaxel (TROPIC) (N = 378)		Radium-223 (ALSYMPCA) (N = 600)	
	N	rate	N	rate	N	rate	N	rate				
ALT increased												
Anaemia	29	3%	25	3%			17	5%	39	10%	76	13%
Bone pain	12	1%	20	2%					3	1%	125	21%
Decreased neutrophil count									253	67%		
Decreased white blood cell count												
Diarrhoea									23	6%	9	2%
Febrile neutropenia							10	3%	28	7%		
Hypertension	59	7%	19	2%	23	4%						
Hypokalaemia					14	2%						
Hepatotoxicity												
Neutropenia							106	32%	303	80%	13	2%
Thrombocytopaenia									15	4%	39	7%
Source	NICE TA712,						TAX-302 (Tannock (2004),		NICE TA712,		ALSYMPCA (Parker (2013),	

Key: ADT, androgen deprivation therapy; ALT, alanine aminotransferase; N, total number.

The model does not include the impact of SSEs in the base case, as individual SSE data were only available from ARASENS, so there was no data to reliably estimate the impact of SSEs for enzalutamide or ADT alone. However, a scenario exploring the impact of SSEs was performed for the comparison with docetaxel+ADT only, using the ARASENS SSE rates as reported in Table 42.

Table 42: mHSPC symptomatic skeletal event rates used in a scenario analysis versus docetaxel

Symptomatic skeletal event	Darolutamide (ARASENS) (N = 651)		Docetaxel (ARASENS) (N = 654)	
	N	rate	N	rate
EBRT to relieve skeletal symptoms	[redacted]	[redacted]	[redacted]	[redacted]
New symptomatic pathologic bone fracture	[redacted]	[redacted]	[redacted]	[redacted]
Spinal cord compression	[redacted]	[redacted]	[redacted]	[redacted]
Tumour-related orthopaedic surgical intervention	[redacted]	[redacted]	[redacted]	[redacted]

Key: EBRT, external beam radiation therapy; N, total number.

B.3.4.5 Adverse event and symptomatic skeletal events utility decrements

As discussed in Section B.2.10, adverse events for darolutamide+docetaxel+ADT were infrequent and mostly associated with docetaxel. This is also supported by ARASENS, as the majority of AEs observed in ARASENS were observed during docetaxel treatment.[89] As docetaxel is only given at the start of treatment, AEs are expected to occur in the short term after initial treatment.[89] AE disutilities were therefore applied in the model as a one-off QALY decrement in the first model cycle. As no utility data from ARASENS were available, utility decrements and durations used in the model were aligned with the decrements used in TA712. The durations were based on the durations used in the ERG report on pre-chemotherapy enzalutamide for TA377, in line with TA712.

Table 43: Adverse event disutilities

Adverse event	Disutility	Duration	Source
Alanine aminotransferase increased	0.000	28.0	Assumed to be 0
Anaemia	-0.119	10.5	Swinburn 2019[109]
Bone pain	-0.069	10.5	Doyle 2008[110]
Decreased neutrophil count	-0.090	10.5	Nafees 2008[107]
Decreased white blood cell count	-0.090	10.5	Assumed equal to neutropenia
Diarrhoea	-0.137	10.5	Nafees 2008[111], Swinburn2019, [109] and Lloyd 2006[107] (as reported in TA712)
Febrile neutropenia	-0.120	10.5	Lloyd 2006 and Nafees 2008[111, 112]
Hypertension	-0.153	10.5	Swinburn 2010[109]
Hypokalaemia	0.000	28.0	Assumed to be 0
Hepatotoxicity	-0.131	91.3	Assumed equal to fatigue in Lloyd 2006, Nafees 2008 and Swinburn 2010 (as reported in NICE TA712)[105, 109, 111, 112]
Neutropenia	-0.090	10.5	Nafees 2008[111]
Thrombocytopaenia	-0.09	10.5	Assumed the same as neutropenia: Nafees 2008[111] (as reported in TA712)

Key: N/A, not applicable, NICE, National Institute for Health and Care Excellence, TA, technology appraisal.

Table 44: Symptomatic skeletal event disutilities

Symptomatic skeletal event	Disutility	Duration	Source
EBRT to relieve skeletal symptoms	-0.056	30.42	Botteman 2011[113]
New symptomatic pathologic bone fracture	-0.201	30.42	Botteman 2011[113]
Spinal cord compression	-0.237	30.42	Botteman 2011[113]
Tumour-related orthopaedic surgical intervention	-0.056	30.42	Botteman 2011[113]

Key: EBRT, external beam radiation therapy.

B.3.4.6 Health-related quality of life data used in the cost-effectiveness analysis

As discussed above, the HRQL data captured in ARASENS were not suitable to determine health state utilities for the model, so external utility data were used in the model base case. Out of all identified studies, TA712 was considered most appropriate for use in the base case. Although TA741 also provided a robust utility input, it was considered less relevant, as apalutamide was eventually restricted to patients for whom docetaxel is not suitable. The model therefore uses the ERG-preferred utilities from TA712 as the base case (Table 45). In addition, all utilities used in the model were adjusted for age, using the UK general population utility values by Hernández Alava et al.[114]

Table 45: Health state utilities used in the model base case

Health state	Utility value	Source
mHSPC	0.806	NICE TA712 (Technical response form, page 26)[105]
mHRPC 1L	0.723	
mHRPC 2L	0.630	
mHRPC 3L+	0.530	
Key: 1L, first line, 2L, second line, 3L, third line, mHRPC, metastatic hormone-relapsed prostate cancer, NICE, National Institute for Health and Care Excellence, TA, technology appraisal.		

B.3.5 Cost and healthcare resource use identification, measurement and valuation

Costs included in the model reflect the UK NHS and PSS perspective. As such, only direct medical costs were considered, consisting of the following components:

- Drug acquisition and administration costs
- Monitoring costs
- Costs associated with the management of AEs
- Subsequent treatment costs
- End-of-life care costs

Resource use and unit costs for the economic model were obtained from NHS reference costs,[115] Personal Social Services Research Unit (PSSRU) costs and previous technology appraisals in prostate cancer, which are described in more

detail below. All model costs were inflated to 2021–2022 costs where appropriate, using inflation indices from the 2021 PSSRU.[116]

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Drug acquisition costs

This section details drug acquisition costs for the treatments used in mHSPC and after progression to mHRPC. A breakdown of costs for the intervention and comparator treatments is provided in Table 46, and a breakdown of treatment dosing schedules is presented in Table 47.

Table 46: Drug acquisition costs

Treatment	Pack size x formulation	Unit cost (£)	Source
Darolutamide	112 x 300 mg	£4,040.00	MIMS, accessed 11 Feb 2022[117]
Docetaxel	1 x 20 mg	£3.56	eMIT, January 2021, accessed 11 Feb 2022[118]
	4 x 20 mg	£8.90	
	8 x 20 mg	£17.38	
Enzalutamide	112 x 40 mg	£2,734.67	MIMS, accessed 11 Feb 2022[117]
Abiraterone (mHRPC)	56 x 500 mg	£2,735.00	MIMS, accessed 11 Feb 2022[117]
Radium-223 (mHRPC)	6.0 ml (6000 kBq)	£4,040.00	NICE TA412[119]
Cabazitaxel (mHRPC)	60 mg / 1.5 mL	£3,696.00	MIMS, accessed 11 Feb 2022[117]
ADT treatments			
Leuprorelin	1 x 3.75 mg	£75.24	MIMS, accessed 11 Feb 2022[117]
Goserelin	1 x 3.6 mg	£70.00	MIMS, accessed 11 Feb 2022[117]
Triptorelin (Decapeptyl)*	1 x 3 mg	£69.00	MIMS, accessed 11 Feb 2022[117]

Key: ADT, androgen deprivation therapy, eMIT, electronic market information tool, mHRPC, metastatic hormone-relapsed prostate cancer; MIMS, Monthly Index of Medical Specialities, TA, technology appraisal.
Note: * Assumed Decapeptyl as cheaper than Gonapeptyl

Table 47: Treatment dosing schedules

Treatment	Dose per administration	Dosing schedule	Source
Darolutamide	1200 mg	Daily	Label
Docetaxel	75 mg/m^2	1 dose per 21 days	Label
Enzalutamide	160 mg	Daily	Label
Abiraterone (mHRPC)	1000 mg	Daily	Label
Radium-223 (mHRPC)	55 kBq/kg	Once per 28 days	NICE TA412[119]
Cabazitaxel (mHRPC)	25 mg/m2	Once per 21 days	Label
ADT			
Leuprorelin	3.75 mg	Monthly	Label
Goserelin	3.60 mg	Once per 28 days	Label
Triptorelin (Decapeptyl)*	3 mg	Once per 28 days	Label
Key: ADT, androgen deprivation therapy; mHRPC, metastatic hormone-relapsed prostate cancer; TA, technology appraisal.			

B.3.5.1.1.1 Intervention

As per the recommended licence, the model uses a fixed dose of 600 mg (two 300 mg film-coated tablets) of darolutamide taken orally twice daily, equivalent to a total daily dose of 1200 mg. The list price for a pack of 112 300 mg tablets of darolutamide is £4,040, equating to a cost per dose of £72.14.[120] The model results also take into account a confidential discount of [redacted] applied as a simple discount on the price per pack, resulting in a modelled cost per dose of [redacted].

B.3.5.1.1.2 Comparators

Drug acquisition costs for the generic products were sourced from the electronic Market Information Tool (eMIT).[118] The remainder of drug acquisition costs for treatments in the model were sourced from the Monthly Index of Medical Specialities (MIMS).[120] For intravenous and subcutaneous treatments, drug doses were calculated per patient weight or BSA. Wastage was considered by rounding up the number of vials required per administration, assuming no vial sharing, in line with NHS clinical practice. Where multiple strengths of a drugs were available, the distribution of vial sizes was assumed to be optimal, assuming minimal wastage.

B.3.5.1.1.3 Relative dose intensity, missed doses and dose reductions

Overall, treatment compliance in ARASENS was high, with darolutamide patients receiving an average 97.2% of the darolutamide planned dose.[44] Docetaxel dose intensity was also high, with patients receiving 96.0% and 95.8% of the planned dose in the darolutamide and docetaxel arms, respectively. This illustrates the good tolerability of darolutamide+docetaxel+ADT. In addition, this high compliance is in line with other ARTA, with enzalutamide showing an observed mean dose of 158.3 mg (98.9% of label dose). To ensure that the dosing in the model reflects the efficacy data from the respective trials, and to accurately model the expected treatment costs in the UK, darolutamide and enzalutamide treatment costs in mHSPC were adjusted by the reported relative dose intensity (RDI) in the modelled base case.

B.3.5.1.1.4 Treatment durations

ToT data from ARASENS was used in the model and captured treatment discontinuations as a result of early withdrawal due to AEs and any other reasons for discontinuation before progression. Additional weeks of treatment that patients may have received while waiting for confirmation of progression was also included (see Section B.3.3). In addition, some treatments had maximum durations in line with their licences. For a breakdown of the maximum treatment durations implemented in the model, see Table 48.

Table 48: Treatment stopping rules

Treatment	Stopping rule	Source
Darolutamide	ToT, no maximum duration	Expected label: Continued until disease progression (evidence of radiographic progression, a skeletal related event, or clinical progression) or until unacceptable toxicity.
Docetaxel	6 treatment cycles	ARASENS trial design
Enzalutamide	ToT, no maximum duration	Continued until disease progression (evidence of radiographic progression, a skeletal related event, or clinical progression) or until unacceptable toxicity.[94]
ADT		
Leuprorelin	None (all ADT assumed to be used indefinitely)	Assumption, in line with previous appraisals and confirmed by clinical experts[37, 38, 42, 88]
Goserelin		
Triptorelin (Decapeptyl)*		
Key: ADT, androgen deprivation therapy; mHSPC; metastatic hormone sensitive prostate cancer; ToT, time on treatment.		

B.3.5.1.1.5 Wastage

In line with past appraisals, the base case considered drug wastage for drugs administered intravenously, assuming a full vial would be used without vial sharing.[42] This is a conservative assumption, as it raises the costs for docetaxel, which is given in combination with darolutamide and ADT as the intervention.

B.3.5.1.2 Treatment administration costs

Drug administration costs include the cost of therapy infusions required at each treatment administration. Costs are sourced from NHS 2020–2021 reference costs[115] and PSSRU 2021 costs.[116] Administration costs are applied so that drug administration occurs during the ToT curve for each intervention. For the base case, it is assumed that oral treatments have no administration costs. The relevant administration modes and corresponding costs by treatment are outlined in Table 49.

Table 49: Drug administration costs

Mode of administration	Drug administration cost	Source
Intravenous infusion	£258.56	Deliver more complex parenteral chemotherapy at first attendance, outpatient (SB13Z), NHS reference costs 2020/2021
Subcutaneous injection	£32.00	Cost per working hour for Band 4 hospital based nurses, PSSRU 2021, page 138
Oral	NA	Assumption, in line with past mHSPC appraisals[38, 42, 88]
Key: mHSPC, metastatic hormone-sensitive prostate cancer, NA, not applicable; NHS, national health service; PSSRU, Personal Social Services Research Unit.		

B.3.5.2 Health-state unit costs and resource use

An SLR was conducted to identify relevant cost and resource use evidence for the cost-effectiveness model. The SLR identified 38 unique studies from 49 publications that met the inclusion criteria, including three HTAs.[38, 42, 88] During the extractions, studies conducted in Europe, Canada and the US were prioritized, which resulted in extractions of 26 studies from 37 publications. These papers are presented in Appendix H.

As the three HTAs in mHSPC identified by the SLR are closely aligned with the population and decision problem of this appraisal, particular consideration was given to the healthcare resource use (HRU) reported in these publications. Previous TAs used similar HRU assumptions, based on the publicly reported HRU estimates. TA712 was deemed to be the best source for HRU rates, as it evaluated three competitors in scope for this appraisal (enzalutamide+ADT, docetaxel+ADT and ADT alone). It also used an HRU approach that was in line with this model structure, with a constant HRU rate per health state (rather than an HRU declining over time, as in TA741).[38, 42, 88]

In the model, HRU costs are implemented per cycle and differ between the pre-progression (mHSPC) and post-progression (mHRPC) health states. Pre-progression HRU costs differ by treatment arm, owing to the variation in resource use frequencies and distributions between patients in different treatment arms. As docetaxel is only administered for the first six treatment cycles, docetaxel resource

use costs were only applied for the first six treatment cycles while patients were receiving treatment. After that, it was assumed that patients would switch to darolutamide HRU or ADT HRU in the darolutamide and docetaxel arms of the model, respectively.

The following direct medical costs have been considered in the model, based on the costs used in TA712: cost of outpatient treatment (e.g. visits to urologist and/or oncologist, laboratory examinations, and emergency treatment); cost of drug therapies and concomitant medications if applicable; administration costs; monitoring costs; hospitalization costs; all follow-up treatment costs; and costs for nursing care. The resource use and corresponding unit costs used in the model are presented in Table 50.

Table 50: Resource use costs used in the model

Resource	Unit cost	Source
Outpatient visit oncologist	£158.01	NHS reference cost 2020/2021 Total HRGs WF01A – Non-Admitted Face-to-Face Attendance, Follow-up
Outpatient visit nurse	£41.00	Cost per hour for Band 5 hospital based nurses, Section 13 in PSSRU 2021 page 138
Community nurse visit	£44.00	Cost per hour for Band 5 community based nurses, Section 10.1 in PSSRU 2021 page 108
CT scan	£144.59	NHS reference cost 2020/2021: IMAGOP RD22Z, Computerised Tomography Scan of One Area, with Pre- and Post-Contrast
Radiographic or MRI scan	£300.56	NHS reference cost 2020/2021: IMAGOP RD03Z, Magnetic Resonance Imaging Scan of One Area, with Pre- and Post-Contrast
Bone scan	£524.27	NHS reference cost 2020/2021: NM IMAGOP RN16A, Nuclear Bone Scan of Other Phases, 19 years and over
Full blood count	£3.63	NHS reference cost 2020/2021: DAPS, Haematology: DAPS05
Liver function test	£1.85	NHS reference cost 2020/2021: DAPS, clinical biochemistry: DAPS04
Kidney function test	£1.85	NHS reference cost 2020/2021: DAPS, clinical biochemistry: DAPS04
PSA test	£1.85	NHS reference cost 2020/2021: DAPS, clinical biochemistry: DAPS04
Testosterone test	£1.85	NHS reference cost 2020/2021: DAPS, clinical biochemistry: DAPS04

Key: CT, computed tomography, ERG, Evidence Review Group, mHRPC, metastatic hormone-relapsed prostate cancer, MRI, magnetic resonance imaging, no., number, PD, progressed disease, PSA, prostate-specific antigen, PSSRU, Personal Social Services Research Unit, pts: patients, TA, technology appraisal.

The rates of the HRU applied in the model were based on HRU rates from TA712. In addition, the HRU rates applied in the model were also validated by UK clinical experts, who indicated that docetaxel patients should alternate outpatient oncologist and nurse visits on a 50/50 basis (in contrast to 67% oncologist visits and 33% nurse visits, as used in TA712). The clinical experts flagged that the MRI scans for docetaxel were too low, indicating that at least 50% of patients would receive one MRI scan per year. Finally, the experts flagged that darolutamide patients were likely to require fewer outpatient oncologist or nurse visits than enzalutamide, as they expected less toxicity and fewer DDIs than enzalutamide. The experts therefore recommended one visit every 12 weeks visits for darolutamide after the final docetaxel cycle, in contrast to one visit every 8 weeks recommended in TA712. All this input was combined and the resource use frequencies and distributions among patients for each treatment arm is presented in Table 51 to Table 53.

Table 51: Visits and testing frequencies included as HRU for patients receiving darolutamide+docetaxel+ADT or docetaxel+ADT in mHSPC

mHSPC	mHSPC darolutamide plus docetaxel and ADT and docetaxel plus ADT			Reference
	% of patients	No. of visits	Every x weeks	
Outpatient visit oncologist	50%	1.00	3.00	TA712, updated to reflect input given during clinical advisory board[37,38]
Outpatient visit nurse	50%	1.00	3.00	
Community nurse visit	100%	0.00	3.00	
CT scan	100%	1.00	18.00	
Radiographic or MRI scan	50%	1.00	52.00	
Bone scan	100%	1.00	18.00	
Full blood count	100%	1.00	3.00	
Liver function test	100%	1.00	3.00	
Kidney function test	100%	1.00	3.00	
PSA test	100%	1.00	3.00	

Key: ADT, androgen deprivation therapy, CT, computed tomography, HRU, health-care resource use, mHSPC, metastatic hormone-sensitive prostate cancer, no., number, MRI, magnetic resonance imaging, PSA, prostate-specific antigen, TA, technology appraisal.

Table 52: Visits and testing frequencies included as HRU for patients receiving darolutamide+ADT (i.e. after the last cycle of docetaxel) in mHSPC

Service mHSPC	mHSPC darolutamide + ADT			Reference
	% of patients	No. of visits	Every x weeks	
Outpatient visit oncologist	50%	1.00	12.00	TA712, updated to reflect darolutamide + ADT HRU, based on clinical input [38, 37]
Outpatient visit nurse	50%	1.00	12.00	
Community nurse visit	100%	0.00	6.00	
CT scan	80%	1.00	39.00	
Radiographic or MRI scan	5%	1.00	12.00	
Bone scan	80%	1.00	39.00	
Full blood count	100%	1.00	8.00	
Liver function test	100%	1.00	8.00	
Kidney function test	100%	1.00	8.00	
PSA test	100%	1.00	8.00	
Key: ADT, androgen deprivation therapy, CT, computed tomography, HRU, health-care resource use, mHSPC, metastatic hormone-sensitive prostate cancer, no., number, MRI, magnetic resonance imaging, NSAA: non-steroidal anti-androgens, PSA, prostate-specific antigen, TA, technology appraisal.				

Table 53: Visits and testing frequencies included as HRU for patients receiving enzalutamide+ADT, and ADT alone in mHSPC in the model

Service mHSPC	mHSPC enzalutamide + ADT and ADT alone			Reference
	% of patients	No. of visits	Every x weeks	
Outpatient visit oncologist	50%	1.00	8.00	TA712[38,
Outpatient visit nurse	50%	1.00	8.00	
Community nurse visit	100%	0.00	6.00	
CT scan	80%	1.00	39.00	
Radiographic or MRI scan	5%	1.00	12.00	
Bone scan	80%	1.00	39.00	
Full blood count	100%	1.00	8.00	
Liver function test	100%	1.00	8.00	
Kidney function test	100%	1.00	8.00	
PSA test	100%	1.00	8.00	
Key: ADT, androgen deprivation therapy, CT, computed tomography, HRU, health-care resource use, mHSPC, metastatic hormone-sensitive prostate cancer, no., number, MRI, magnetic resonance imaging, NSAA: non-steroidal anti-androgens, PSA, prostate-specific antigen, TA, technology appraisal.				

In mHRPC, HRU costs are based on the subsequent treatments used throughout the mHRPC health states. HRU rates for each individual subsequent treatment option are reported in Table 54 to Table 57 below. As docetaxel, cabazitaxel and radium-223 can only be used for a fixed number of cycles in mHRPC, the HRU rates in the model were adjusted for the expected time spent on treatment, assuming that patients switch to ADT treatment and HRU after discontinuation. These HRU costs per subsequent treatment were then combined with the overall expected subsequent treatment use per mHRPC treatment (as reported in Section B.3.5.3) and adjusted for the modelled time spent per mHRPC treatment line, to calculate the average HRU costs per treatment arm in mHRPC.

Table 54: Visits and testing frequencies included as HRU for patients receiving docetaxel+ADT in mHRPC in the model while on treatment

Service mHRPC (PD1–3)	mHRPC all treatments			Reference
	% of patients	No. of visits	Every x weeks	
Outpatient visit oncologist	50%	1.00	3.00	TA712, updated to reflect input given during clinical advisory board[38,37]
Outpatient visit nurse	50%	1.00	3.00	
Community nurse visit	100%	0.00	3.00	
CT scan	100%	1.00	18.00	
Radiographic or MRI scan	50%	1.00	52.00	
Bone scan	100%	1.00	18.00	
Full blood count	100%	1.00	3.00	
Liver function test	100%	1.00	3.00	
Kidney function test	100%	1.00	3.00	
PSA test	100%	1.00	3.00	

Key: CT, computed tomography, ERG, Evidence Review Group, HRU, health-care resource use, mHRPC, metastatic hormone-relapsed prostate cancer, no., number, MRI, magnetic resonance imaging, PSA, prostate-specific antigen, TA, technology appraisal.

Table 55: Visits and testing frequencies included as HRU for patients receiving enzalutamide+ADT, and ADT alone in mHRPC in the model

Service mHRPC (PD1–3)	mHRPC all treatments			Reference
	% of patients	No. of visits	Every x weeks	
Outpatient visit oncologist	50%	1.00	8.00	TA712[38]
Outpatient visit nurse	50%	1.00	8.00	
Community nurse visit	100%	0.00	6.00	
CT scan	100%	1.00	39.00	
Radiographic or MRI scan	5%	1.00	12.00	
Bone scan	100%	1.00	39.00	
Full blood count	100%	1.00	8.00	
Liver function test	100%	1.00	8.00	
Kidney function test	100%	1.00	8.00	
PSA test	100%	1.00	8.00	

Key: CT, computed tomography, ERG, Evidence Review Group, HRU, health-care resource use, mHRPC, metastatic hormone-relapsed prostate cancer, no., number, MRI, magnetic resonance imaging, PSA, prostate-specific antigen, TA, technology appraisal.

Table 56: Visits and testing frequencies included as HRU for patients receiving abiraterone+ADT in mHRPC in the model

Service mHRPC (PD1–3)	mHRPC all treatments			Reference
	% of patients	No. of visits	Every x weeks	
Outpatient visit oncologist	50%	1.00	4.00	TA712[38,]
Outpatient visit nurse	50%	1.00	4.00	
Community nurse visit	50%	1.00	4.00	
CT scan	100%	3.00	66.70	
Radiographic or MRI scan	-	-	-	
Bone scan	20%	1.00	12.00	
Full blood count	100%	1.00	4.00	
Liver function test	50%	1.00	4.00	
Kidney function test	100%	1.00	4.00	
PSA test	100%	1.00	4.00	

Key: CT, computed tomography, ERG, Evidence Review Group, HRU, health-care resource use, mHRPC, metastatic hormone-relapsed prostate cancer, no., number, MRI, magnetic resonance imaging, PSA, prostate-specific antigen, TA, technology appraisal.

Table 57: Visits and testing frequencies included as HRU for patients receiving cabazitaxel+ADT or radium-223+ADT in mHRPC in the model while on treatment

Service mHRPC (PD1–3)	mHRPC all treatments			Reference
	% of patients	No. of visits	Every x weeks	
Outpatient visit oncologist	50%	1.00	8.00	TA712[38]
Outpatient visit nurse	50%	1.00	8.00	
Community nurse visit	100%	0.00	6.00	
CT scan	100%	1.00	39.00	
Radiographic or MRI scan	5%	1.00	12.00	
Bone scan	100%	1.00	39.00	
Full blood count	100%	1.00	8.00	
Liver function test	100%	1.00	8.00	
Kidney function test	100%	1.00	8.00	
PSA test	100%	1.00	8.00	

Key: CT, computed tomography, ERG, Evidence Review Group, HRU, health-care resource use, mHRPC, metastatic hormone-relapsed prostate cancer, no., number, MRI, magnetic resonance imaging, PSA, prostate-specific antigen, TA, technology appraisal.

B.3.5.3 Post-progression treatments

As discussed in Section B.3.2, the model includes the option to model up to three lines of subsequent treatment. To calculate the subsequent treatment costs in mHRPC, subsequent treatment distributions were sourced from the UK clinical advisory board.[37] During the meeting, clinicians noted that in the UK, only one ARTA (i.e. darolutamide, abiraterone, apalutamide or enzalutamide) is permitted for use in the prostate cancer treatment pathway. This is also covered in more detail in Section B.1.3. The model therefore assumes that subsequent treatment use is dependent on whether a patient has received an ARTA in mHSPC and goes on to receive the same subsequent treatment distributions for darolutamide and enzalutamide, and for docetaxel and ADT alone. The distribution of treatments by mHRPC treatment line reached by consensus in the meeting is presented in Table 58.

Table 58: Subsequent treatment distribution per received mHSPC treatment

Treatment	Darolutamide + docetaxel + ADT in mHSPC			Docetaxel + ADT in mHSPC			Enzalutamide + ADT in mHSPC			ADT alone in mHSPC		
	1L	2L	3L	1L	2L	3L	1L	2L	3L	1L	2L	3L
ADT												
Abiraterone												
Enzalutamide												
Docetaxel												
Radium-223												
Cabazitaxel												

Key: 1L, first line, 2L, second line, 3L, third line, ADT, androgen deprivation therapy, BSC, best supportive care, mHRPC, metastatic hormone-relapsed prostate cancer, mHSPC, metastatic hormone-sensitive prostate cancer, N/A, not available.

The total lump-sum post-progression treatment costs which a patient is expected to incur over a lifetime were then modelled using treatment distributions shown in Table 58 combined with the reported ToT per subsequent treatment (Table 59) and the subsequent treatment costs and admin costs (Table 46 and Table 49). These costs were adjusted for the average proportion of patients expected to reach each line of treatment, based on the % alive at each subsequent treatment line, using the reported PFS per subsequent treatment (Table 59). Finally, these costs were also adjusted to account for any future discounting after the time of progression. This resulted in the total subsequent treatment and administration cost estimates as shown in Table 60, which were applied as a lump-sum cost upon progression.

Table 59: Subsequent treatment durations and PFS used for the subsequent treatment calculations

Subsequent treatment	Mean* PFS (weeks)	Mean* treatment duration (weeks)	Source

ADT	24.5	28.9	Estimated using median ToT and PFS from PREVAIL[121]
Abiraterone	103.5	86.6	Estimated using median time on treatment of clinical trial, TA387 (Table 67 pg 150 of manufacturer's submission[122] and median rPFS TA387 page 79 of 308[122])
Enzalutamide	123.6	111.1	Estimated using median time to treatment discontinuation and median rPFS, TA377 (page 16 of NICE pre-meeting briefing)[123]
Docetaxel	73.4	41.1	Estimated using median ToT 9.5 cycles of 21 days, TAX 327, Table 2[124] and median PFS, Bajranada et al. (2016).[125]
Radium 223	89.0	29.3	ToT Bayer internal data [Data on file] PFS estimated from median PFS, TA412 slide 28.[119]
Cabazitaxel	55.2	26.0	Estimated using median TTP: TA391 (pg 71 of ACD)[126] and median ToT: TROPPIC 6 cycles of 21 days (as stated in TA712, Table 48)[105]
Key: ADT, androgen deprivation therapy, PFS, progression-free survival, pg., page, rPFS, radiographic progression-free survival, TA, technology appraisal, ToT, time-on-treatment			

Table 60: One-off lump-sum subsequent treatment and administration costs per mHSPC treatment, applied upon progression

mHSPC treatment	One-off lump-sum subsequent treatment costs	One-off lump-sum subsequent admin costs
Darolutamide + Docetaxel + ADT	[redacted]	[redacted]
Docetaxel + ADT	[redacted]	[redacted]
Enzalutamide + ADT	[redacted]	[redacted]
ADT alone	[redacted]	[redacted]
Key: ADT, androgen deprivation therapy; mHSPC, metastatic hormone-sensitive prostate cancer.		

B.3.5.3.1 Survival adjustments for subsequent treatment use

As the ARASENS trial was a multi-centre study, subsequent treatments used in the trial may not reflect UK clinical practice. This is illustrated by the subsequent treatments observed in ARASENS (Table 62), which deviated from the UK subsequent treatments distribution recommended by the clinical advisory board (Table 58). Most notably, there was some abiraterone and enzalutamide use in mHRPC after darolutamide, which is not permitted in UK clinical practice.

Table 62: Subsequent treatment distribution from ARASENS

Treatment	Darolutamide + docetaxel + ADT	Docetaxel + ADT

	All lines	All lines
BSC	[redacted]	[redacted]
ADT	[redacted]	[redacted]
Abiraterone	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]
Radium-223	[redacted]	[redacted]
Cabazitaxel	[redacted]	[redacted]
Olaparib	[redacted]	[redacted]
Bicalutamide	[redacted]	[redacted]

Key: ADT, androgen deprivation therapy; BSC, best supportive care.
Note: ARASENS Clinical Study Report, Table 9–3.

Although there was some abiraterone and enzalutamide use in mHRPC after darolutamide, both the advisory board clinicians and health economic experts who were consulted considered that no adjustment to OS was necessary, as the OS benefit demonstrated by ARASENS did not appear to be driven by additional ARTAs.[37] This is illustrated by an ARASENS post-hoc analysis of darolutamide and docetaxel post-progression survival (PPS), stratified per subsequent treatment (Figure 20 and Figure 21). For the darolutamide arm, no difference in PPS was observed between patients receiving an ARTA, or another subsequent treatment (Figure 20). In contrast, for the docetaxel arm, a clear PPS benefit was observed for patients receiving either abiraterone or enzalutamide (Figure 21). This shows that subsequent use of ARTAs after darolutamide is unlikely to have affected the observed survival, confirming that no adjustment of OS was necessary. The subsequent treatments and distributions in the model therefore only affect the costs and utilities and no additional OS adjustments for subsequent treatment use were deemed appropriate.

Figure 20: ARASENS darolutamide + docetaxel + ADT post-progression survival stratified by post-progression treatment

Figure 21: ARASENS docetaxel + ADT post-progression survival stratified by post-progression treatment

B.3.5.4 Adverse reaction and symptomatic skeletal event unit costs and resource use

AE- and SSE-related costs used in the model are presented in Table 63 and Table 64. AE and SSE cost information has been obtained from NHS 2020–2021 reference costs and TA712. AE costs are applied as one-off costs on the first model cycle for

each treatment arm. AE costs differ between treatment arms owing to different AE rates between treatment arms (see Section B.3.4 for more details). SSE costs were only applied for darolutamide and docetaxel as a scenario analysis, as no SSE information was publicly available for enzalutamide and ADT alone (see Section B.3.4.4 for more details).

Table 63: TEAE-related unit costs

AEs	Unit cost	Source
Alanine aminotransferase increased	£0.00	Assumed to have no costs, in line with TA712
Anaemia	£3,200.84	NHS reference costs 2020-2021; NEL: Weighted average of SA04G, SA04H, SA04J, SA04K, SA04L
Bone pain	£1,186.21	NHS reference costs 2020-2021; NES: Weighted average of HD40D, HD40E, HD40F, HD40G, HD40H
Decreased neutrophil count	£667.35	Assumed to be equal to decreased white blood cell count, NHS Reference cost 2020-2021; NES. Weighted average of SA08G, SA08H and SA08J
Decreased white blood cell count	£667.35	NHS Reference cost 2020-2021; NES. Weighted average of SA08G, SA08H and SA08J
Diarrhoea	£952.61	NHS Reference cost 2020-2021; NES. Weighted average of PF26A, PF26B, PF26C
Febrile neutropenia	£11,841.96	NHS reference costs 2020-2021: NEL: Weighted average of PM45A, PM45B, PM45C, PM45D
Hypertension	£537.86	NHS Reference cost 2020/2021; NES. EB04Z (Hypertension)
Hypokalaemia	£393.35	NHS reference costs 2020-2021; HCDr: PHCD00331 (Outpatients; Parenteral Nutrition)
Hepatotoxicity	£898.78	NHS Reference cost 2020-2021; NES. Weighted average of GC01C, GC01D, GC01E, GC01F
Neutropenia	£667.35	Assumed to be equal to decreased white blood cell count, NHS Reference cost 2019/2020; NES. Weighted average of SA08G, SA08H and SA08J
Thrombocytopaenia	£881.88	NHS reference costs 2020-2021; NES: Weighted average of SA12G, SA12H, SA12J, SA12K

AEs	Unit cost	Source
Key: AE, adverse event, ALT, Alanine aminotransferase, AST, Aspartate aminotransferase, ERG, evidence review group, NEL, non-elective long stay, NES, non-elective short stay, NICE, National Institute for Health and Care Excellence, NHS, National Health Service, TA, technology appraisal, TEAE, treatment-emergent adverse events.		

Table 64: SSE-related unit costs

SSEs	Unit cost	Source
EBRT to relieve skeletal symptoms	£697.29	Ford et al (2013) (as reported in TA712, inflated to 2021)[127]
New symptomatic pathologic bone fracture	£987.48	Ford et al (2013) (as reported in TA712, inflated to 2021) [127]
Spinal cord compression	£7,700.74	Ford et al (2013) (as reported in TA712, inflated to 2021) [127]
Orthopaedic surgical intervention	£7,656.50	Ford et al (2013) (as reported in TA712, inflated to 2021) [127]
Key: EBRT, external beam radiation therapy; SSE, symptomatic skeletal event.		

B.3.5.5 Miscellaneous unit costs and resource use

Terminal care costs: end-of-life or terminal treatment costs have been included as one composite cost for the last three months of life. Terminal care costs were based on Georghiou and Bardsley 2014[128] and inflated to 2021 costs, resulting in an average one-off cost of £7,999.65.

Concomitant medication: clinicians did not anticipate the darolutamide triplet combination therapy to impact the use of concomitant therapies, so it was therefore assumed to be equal and was not included in the model.[37] However, we will explore a scenario in which granulocyte-colony stimulating factor (G-CSF) is used prophylactically for 7 days in 8.1% of the total number of patients who are receiving docetaxel, cabazitaxel or radium-223, in line with TA712.

B.3.6 Severity

Due to redacted overall results in the NICE appraisal of enzalutamide+ADT, estimates of QALY shortfall have been made using outcomes from the economic

model described above, and results are displayed below. This was compared to the expected QALYs of the general population to assess the severity of mHSPC.

To estimate the general population QALYs, we used the sex distribution and starting age from the ARASENS population and patient population described in Section B.3.2.1, as detailed in Table 65. This was then combined with the life expectancy UK life tables and expected utility for the general UK population reported by Hernández Alava et al.[114], which provided an estimate that the general population was expected to incur 10.5 discounted lifetime QALYs (Table 66).[114, 129] The expected discounted QALYs for people living with mHSPC on current treatment are also detailed in Table 66, based on the model results described in Section B.3.10 below. This resulted in an absolute QALY shortfall of [redacted] and proportional shortfall of [redacted], depending on the mHSPC treatment. As the absolute QALY shortfalls are all below 12 and the proportional QALY shortfalls are all less than 85%, no multiplier for disease severity is considered appropriate for any of the comparisons.[101]

Table 65: Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Sex distribution	100% male	N/A
Starting age	66.8 years	Section B.3.2.1
Key: QALY, quality-adjusted life year, N/A, not applicable.		

Table 66: Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment		QALY shortfall (absolute/proportional)
10.5	ADT	[redacted]	[redacted]
10.5	Docetaxel + ADT	[redacted]	[redacted]
10.5	Enzalutamide + ADT	[redacted]	[redacted]
Key: ADT, androgen depletion therapy; QALY, quality-adjusted life year.			

B.3.7 Uncertainty

We aim to present an analysis that is as robust as we consider technically feasible, with the data and resources available. Nevertheless, some uncertainties remain,

mostly due to limitations in the available data. These uncertainties are discussed below. In addition, the impact of these uncertainties is further explored through sensitivity analyses where possible, as discussed in Section B.3.11.

One source of uncertainty relates to the differences in how progression is defined between trials. As discussed in Section B.3.3, our model uses TTCROD from ARASENS to model progression. This was considered to be better aligned with UK clinical practice than rPFS, as TTCROD consists of multiple criteria used to assess disease progression in UK practice, whereas rPFS only considers radiographic progression, and TTCROD from ARASENS is not reliant on a set assessment. In addition, both clinical experts and past appraisals indicated that rPFS is not reflective of clinical practice.[38] However, as the progression definitions differed across comparator trials, and none of the comparator trials reported an identical outcome to TTCROD, the base PFS ITC used comparator progression data as a proxy for TTCROD. An alternative PFS network that looked at time to CRPC was performed, which compared darolutamide's time to CRPC from ARASENS to the time to CRPC of the indirect comparators, as time to CRPC was reported more consistently across trials. To investigate the impact of the progression definition used in the ITC, we explored a scenario using the alternative PFS network ITC results to model comparator progression. Overall, using the alternative PFS network ITC had a positive impact on the results versus all comparators as discussed in Section B.3.11. This indicated that the risk of the difference in progression definition leading to an over-estimate of the cost-effectiveness is limited.

In addition, the issue raised above also points to a broader uncertainty; namely the lack of direct evidence comparing darolutamide+docetaxel+ADT to enzalutamide+ADT or ADT alone. The model therefore relies on an ITC, as discussed above. However, there were some uncertainties around this ITC, most notably around which studies to include, as there was some variation between trial design and consistency of outcomes. As discussed in Section B.2.9, all these uncertainties were explored in a series of ITC scenarios, which resulted in similar HRs to the base case ITC. To explore the impact of these ITC scenarios on the model outcomes, a series of model scenarios were performed using the different ITC scenarios as input. Overall, these scenarios had a minor impact on model results, as discussed in Section B.3.11.

Another uncertainty is the lack of darolutamide-specific utility data from ARASENS. The model therefore relies on the ERG-preferred utilities from TA712 to inform the quality of life per health state.[38] Although it would be preferable to use darolutamide-specific inputs, using data from TA712 is not likely to have a big impact on model outcomes. Across previous appraisals, treatment-agnostic utilities were used, indicating that utility values are not likely to differ between treatments or appraisals. This is also confirmed by TA741, which reported similar utility values per health state, indicating that there is a good consensus on how to model patients' quality of life in mHSPC.[88] Nevertheless, this uncertainty was explored in a scenario, using the utilities reported in TA741. In addition, any structural uncertainty around the utility input is also explored in the one-way sensitivity analysis (OWSA). Both are discussed in Section B.3.11.

B.3.8 Managed access proposal

A managed access proposal is not considered relevant for this appraisal.

B.3.9 Summary of base case analysis inputs and assumptions

B.3.9.1 Summary of base case analysis inputs

Table 67 gives a summary of the main variables applied in the economic model.

Table 67: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
General settings			
Time horizon (years)	34 (lifetime)	N/A	Full information of general setting provided in Section B.3.2
Model cycle length (days)	28	N/A	
Discount rate for costs	3.50%	N/A	
Discount rate for life years	3.50%	N/A	
Discount rate for QALYs	3.50%	N/A	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Patient characteristics			
Mean age	66.8	N/A	Full breakdown provided in Section B.2.3.1, Table 5.
Mean body weight (kg)	77.51	N/A	BMI information provided in Section B.2.3.1, Table 5
Mean body surface area (m^2)	1.79	N/A	
Efficacy			
Docetaxel OS curve in use	Log-normal Meanlog: [redacted] Sdlog: [redacted]	Varied together using covariance	Section B.3.3
Docetaxel TTCROD curve in use	Generalized gamma Mu[redacted] Sigma: -[redacted] Q: -[redacted]	Varied together using covariance	
Darolutamide ToT curve in use	Log-logistic Shape: [redacted] Scale:[redacted]	Varied together using covariance	
PFS hazard ratio – darolutamide vs docetaxel	[redacted]	Varied using CODA samples	
PFS hazard ratio – enzalutamide vs docetaxel	[redacted]	Varied using CODA samples	
PFS hazard ratio – ADT vs docetaxel	[redacted]	Varied using CODA samples	
OS hazard ratio – darolutamide vs docetaxel	[redacted]	Varied using CODA samples	
OS hazard ratio – enzalutamide vs docetaxel	[redacted]	Varied using CODA samples	
OS hazard ratio – ADT vs docetaxel	[redacted]	Varied using CODA samples	
ToT hazard ratio – enzalutamide vs darolutamide	[redacted]	Varied using CODA samples	
Drug costing			
Cost per package: regorafenib 300 mg tablet, pack of 112	£4,040	N/A	Full information is provided in Section B.3.5.1.1. A

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Cost per package: Docetaxel 20 mg 1ml vial	£3.56	N/A	breakdown of drug acquisition costs is provided in Table 46. A breakdown of treatment dosing schedules is provided in Table 47.
Cost per package: Docetaxel 20 mg 4ml vial	£8.90	N/A	
Cost per package: Docetaxel 20 mg 8ml vial	£17.38	N/A	
Cost per package: Abiraterone 500mg tablet, pack of 56	£2,735.00	N/A	
Cost per package: Enzalutamide 40mg tablet, pack of 112	£2,734.67	N/A	
Cost per package: Leuprorelin 3.75mg powder	£75.24	N/A	
Cost per package: Goserelin 3.6mg implant	£70.00	N/A	
Cost per package: Triptorelin (Decapeptyl) 3mg injection	£69.00	N/A	
Cost per package: Radium-223 1000 mg 6ml vial	£4,040	N/A	
Cost per package: Cabazitaxel 60 mg 1.5ml vial	£3,696	N/A	
Administration costs			
Oral	£0.00	£0, £0 (Gamma)	Full information on drug administration costs is provided in B.3.5.1.2, Table 49
Intravenous infusion (IV)	£258.56	£210.38, £311.64 (Gamma)	
Subcutaneous injection (SI)	£32.00	£26.04, £38.57 (Gamma)	
Healthcare resource use			
mHSPC HRU: Darolutamide	£305.11	£248.25, £367.75 (Gamma)	Aggregate value, calculated based on HRU rates and
mHSPC HRU: Darolutamide off Tx	£97.65	£79.45, £117.70 (Gamma)	
mHSPC HRU: Docetaxel	£305.11	£248.25, £367.75 (Gamma)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
mHSPC HRU: Enzalutamide	£114.23	£92.95, £137.68 (Gamma)	costs, in Section B.3.5. Individual HRU rates varied in OWSA and probabilistic sensitivity analysis
mHSPC HRU: ADT	£114.23	£92.95, £137.68 (Gamma)	
Terminal cost	£7,999.65	£6508.83, £9641.89 (Gamma)	
Average one-off AE costs			
Darolutamide	[redacted]	£1,036.65, £1,535.64 (Gamma)	Aggregate value, calculated based on AE rates in Section B.3.4 and AE costs in Section B.3.5
Docetaxel	[redacted]	£927.42, £1,373.84 (Gamma)	
Enzalutamide	[redacted]	£14.54, £21.53 (Gamma)	
ADT	[redacted]	£3.02, £4.48 (Gamma)	
Average one-off AE disutilities			
Darolutamide	[redacted]	-0.00127, -0.00188 (Beta/Multinormal)	Aggregate value, calculated based on AE rates and disutilities in Section B.3.4
Docetaxel	[redacted]	-0.00123, -0.00182 (Beta/Multinormal)	
Enzalutamide	[redacted]	-0.00012, -0.00018 (Beta/Multinormal)	
ADT	[redacted]	-0.00002, -0.00003 (Beta/Multinormal)	
Utilities			
mHSPC	0.806	0.6259, 0.9362 (Beta/Multinormal)	A breakdown of health state utilities used in model base case provided in Section B.3.4.6, Table 45
mHRPC 1L	0.723	0.5711, 0.8522 (Beta/Multinormal)	
mHRPC 2L	0.630	0.5028, 0.7487 (Beta/Multinormal)	
mHRPC 3L	0.530	0.4257, 0.633 (Beta/Multinormal)	
mHRPC off Treatment	0.530	0.4257, 0.633 (Beta/Multinormal)	

Key: 1L, first line, 2L, second line, 3L, third line, ADT, androgen deprivation therapy, AE, adverse event, CI, confidence interval, HRU, health-care resource use, IV, intravenous, m2, metres squared, mg, milligram, mHRPC, metastatic hormone-relapsed prostate cancer, mHSPC, metastatic hormone-sensitive prostate cancer, ml, millilitre, N/A, not applicable, OWSA, one-way sensitivity analysis, QALY, quality-adjusted life year, SI, subcutaneous injection, Tx, treatment.

B.3.9.2 Assumptions

An overview of the most important model assumptions are shown in Table 68 below.

Table 68: Key model assumptions

Assumption	Justification/reason
ARASENS trial design, patient characteristics, and treatment use are sufficiently reflective of UK practice to inform darolutamide's efficacy in mHSPC.	Clinical experts confirmed that ARASENS is likely to be reflective of UK practice, both in terms of patient characteristics and extrapolated survival estimates.[37] This was further validated by external UK-specific data from STAMPEDE-3, which showed comparable survival to the extrapolated ARASENS OS.[60]
ADT is continued indefinitely regardless of the health state or treatment arm	In line with UK clinical expert input who confirmed that ADT is continued indefinitely in UK practice, and with the approach used in past mHSPC TAs.[37, 38, 88]
TTCROD more accurately reflects how progression is defined in UK practice than rPFS	UK clinical experts confirmed that progression in the UK is assessed using a diverse range of clinical criteria, and that assessment is performed based on the patients test outcomes and symptoms rather than at a set assessment schedule.[37] TTCROD from ARASENS was therefore considered to be more in line with UK practice than rPFS, as it considers multiple criteria used to assess disease progression in UK practice, whereas rPFS only looks at radiographic progression, and is not reliant on a set assessment schedule like rPFS
Subsequent treatment distribution used in the model is reflective of UK practice, and no further corrections for subsequent treatment use are needed.	Subsequent treatment distribution used in the model is reflective of UK practice, as it was informed by UK clinical experts.[37] Although there was some abiraterone and enzalutamide use in mHRPC after darolutamide in ARASENS, this is unlikely to have affected the observed OS, as no difference in post-progression survival was observed for any of the post-progression treatments received after darolutamide. In addition, both the consulted UK clinical experts and health economic experts considered that no adjustment to OS was necessary, and that adjusting for post-progression treatment use would only increase the uncertainty.[37, 104]
The ERG-preferred utilities from TA712 accurately reflect QoL for mHSPC patients, as darolutamide-specific utilities from ARASENS were not available.	Two past mHSPC TAs reported publicly available utility values, TA741 and TA712.[38, 88] In both TA, the used utilities were thoroughly assessed by the ERG, and both ERG used comparable health state utilities in their final preferred analysis. This provides a well-validated precedent for the expected utility of UK mHSPC patients. Out of these options, TA712 was used in the base case, as it assessed a more relevant patient population. However, the choice in utility input did not have a major impact on model results, as explored in the scenario analyses below.

Assumption	Justification/reason
The comparator trials included in the ITC are defined sufficiently similar in terms of endpoint definition and trial design to allow for an indirect comparison of darolutamide + docetaxel + ADT and docetaxel + ADT, to the indirect comparators enzalutamide + ADT and ADT alone.	Although there was some variation in trial design and endpoint definitions in the ITC trials, most notably in terms of patient characteristics and endpoint definitions, none of those differences were identified as treatment effect modifiers, so they should not affect the observed treatment effects of those comparator trials. In addition, several ITC sensitivity analyses were performed to explore the impact of including and excluding different comparator trials. These explored sensitivity analysis only had a minor impact on both the ITC results (as discussed in Section B.2.9) and model outcomes (as discussed in Section B.3.11.3).
Patients have a short gap between mHSPC and first-line mHRPC in which they only receive ADT. This is informed by ToT in the model	In ARASENS a short gap between ToT and TTCROD was observed, indicating that patients spend a short time off-treatment before progression. This was also confirmed by UK clinical experts, who agreed that there could indeed be a short gap in which patients would only receive ADT, while preparations are made for the next line of treatment.[104] In addition, this modelling approach is in line with how treatment was modelled in past mHSPC appraisals.[38, 88]
Applying the ITC HRs to the extrapolated docetaxel data reflects the most accurate and consistent method of modelling the OS and TTCROD for all treatments in the model.	Docetaxel was preferred as an anchor because of availability of external data to validate long term docetaxel extrapolations. In addition, applying the ITC HRs to the extrapolated docetaxel OS and TTCROD data from ARASENS ensures that all treatments in the model are modelled consistently, and that all efficacy data accurately reflects the relative efficacy estimated by the ITC. This approach was also validated by health economic experts who agreed that using docetaxel as an anchor for all treatments would be the most robust and consistent approach.[104] In addition, this approach is in line with ERG critique in TA712.[38]
Key: ADT, androgen deprivation therapy, HR, hazard ratio, ITC, indirect treatment comparison, mHRPC, metastatic hormone-relapsed prostate cancer, mHSPC, metastatic hormone-sensitive prostate cancer, OS, overall survival, QoL, quality of life, ToT, time on treatment, TTCROD, time to castration resistance or death.	

B.3.10 Base case results

B.3.10.1 Base case incremental cost-effectiveness analysis results

The results reported below include a confidential discount of [redacted] on the darolutamide price per pack. As no comparator discounts are publicly available, all other treatment costs are based on the UK list prices and do not include any confidential discounts that are used in practice.

The base case deterministic cost-effectiveness results (darolutamide+docetaxel+ADT versus each comparator) are presented in Table 69, with the disaggregated results shown in Appendix J. Using a 34-year time horizon, the discounted incremental QALYs for darolutamide+docetaxel+ADT were largest versus ADT alone ([redacted] QALYs gained), followed by docetaxel+ADT and enzalutamide+ADT ([redacted] and [redacted] QALYs gained, respectively). The discounted incremental costs were [redacted] versus ADT alone, [redacted] versus docetaxel+ADT, and [redacted] versus enzalutamide. Consequently, darolutamide was cost-effective versus both docetaxel+ADT and ADT alone, with ICERs of £14,950 and £10,915, respectively, and incremental net monetary benefits (iNMB) of [redacted] and [redacted], respectively. Compared to enzalutamide+ADT, darolutamide was dominant (i.e. less costly and more effective then enzalutamide) with an iNMB of [redacted]. However, as stated above, these results do not include the confidential discounts that are in place for enzalutamide or any of the subsequent treatments. Including these discounts will decrease the cost-effectiveness of darolutamide, but the extent of this difference is not known.

Table 69: Base case results

Treatments	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER (daro + Doc + ADT vs comparator)	iNMB (daro + Doc + ADT vs comparator)

Daro + Doc + ADT	[redacted]						
Doc + ADT	[redacted]					£14,950	[redacted]
Enza + ADT	[redacted]					Darolutamide dominant	[redacted]
ADT alone	[redacted]					£9,216	[redacted]
Key: ADT, androgen deprivation therapy, daro, darolutamide; Doc, docetaxel, ICER, incremental cost-effectiveness ratio, incr., incremental; Lys, life years, QALYs, quality-adjusted life years.							

B.3.11 Exploring uncertainty

B.3.11.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was performed to account for multivariate and stochastic uncertainty in the model. The uncertainties in the individual parameters for treatment effect, costs and utilities were characterized using probability distributions and analysed using a Monte Carlo simulation with 2,000 simulations. This number of iterations was sufficient to achieve stabilization, as shown by the stabilization plots in Appendix N (Table 70) presents the probabilistic pairwise results. A comparison of the ICERs from the probabilistic and deterministic analyses is presented in Table 71.

Overall, the probabilistic sensitivity analysis results are broadly aligned with the deterministic model outcomes, with a difference of approximately £1,000 between the deterministic and probabilistic ICERs.

Table 70: Probabilistic sensitivity analysis results: pairwise comparison

Treatments	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
Darolutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,560
Docetaxel + ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,763
Enzalutamide + ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Daro. dominant

Key: ADT, androgen deprivation therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; LYs, life years; QALYs, quality-adjusted life years.

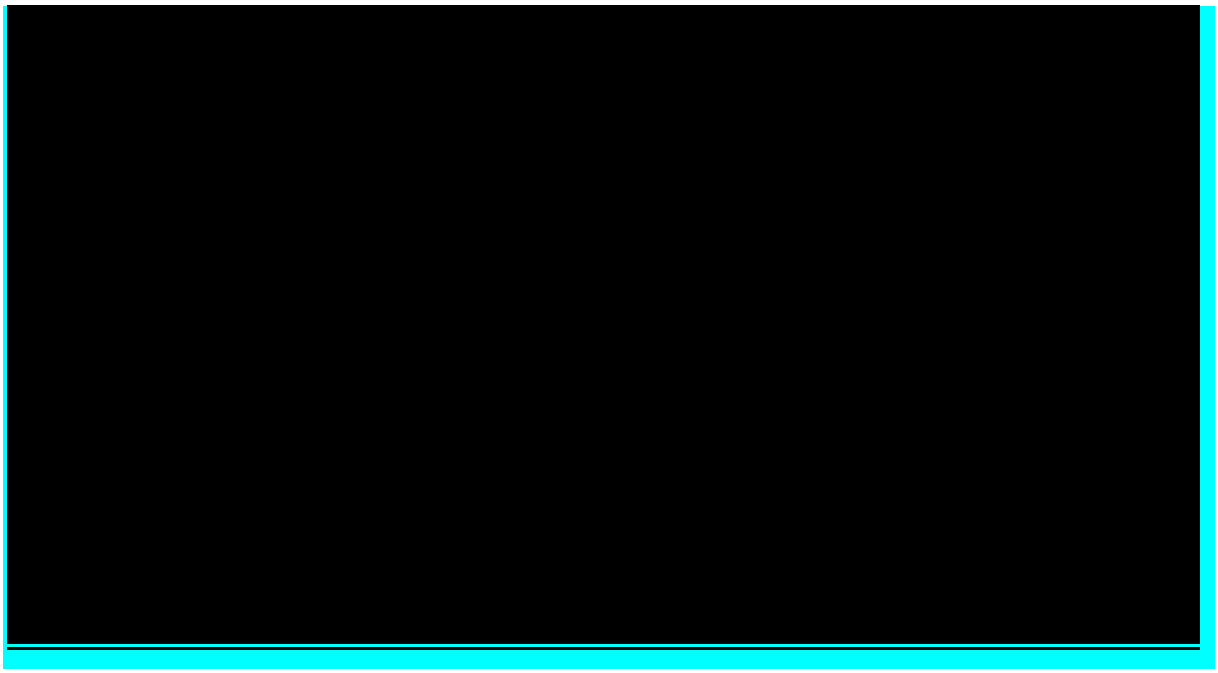
Table 71: Comparison of deterministic and probabilistic ICERs

Analysis	Darolutamide + Doc + ADT	Docetaxel + ADT	Enzalutamide + ADT	ADT alone
Deterministic ICER	-	£14,950	Darolutamide dominant	£9,216
Probabilistic ICER		£13,763	Darolutamide dominant	£8,560
Difference (%)	-	-£1.187 (-7.9%)	N/A	-£656 (-7.1%)

Key: ADT, androgen deprivation therapy; Doc, docetaxel; ICER, incremental cost-effectiveness ratio.

The cost-effectiveness scatterplot for each treatment is presented in Figure 22, Figure 23 and Figure 24. For all analyses, the majority of the cost-effectiveness plane is situated in the north-east quadrant below the £30,000 willingness-to-pay (WTP) threshold. This indicates that darolutamide treatment resulted in increased costs and increased QALY benefit and was cost-effective for most model iterations for all treatments. The cost-effectiveness acceptability curve shows that darolutamide has a [redacted] and [redacted] probability of being cost-effective versus all comparators when considering a £20,000 and £30,000 WTP threshold, respectively (Figure 25).

Figure 22: Cost-effectiveness plane – darolutamide+docetaxel+ADT vs docetaxel+ADT



Key: ADT, androgen deprivation therapy; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

Figure 23: Cost-effectiveness plane – darolutamide+docetaxel+ADT vs enzalutamide+ADT

Figure 24: Cost-effectiveness plane – darolutamide+docetaxel+ADT vs ADT alone

Key: ADT, androgen deprivation therapy; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

Figure 25: Cost-effectiveness acceptability curve

Key: ADT, androgen deprivation therapy; QALY, quality-adjusted life year.

B.3.11.2 Deterministic sensitivity analysis

During the univariate OWSAs, each input parameter was varied to explore the impact of each parameter on model outcomes. Variables for which no CI and/or standard deviation or error was available have been varied using an assumed standard error of 10% of the mean. Parameters with no associated uncertainty, such as drug costs, are excluded from the analysis. Interdependent variables that cannot be varied individually, such as efficacy extrapolation parameters, were also excluded.

The top 10 parameters with the biggest impact on iNMB for darolutamide+docetaxel+ADT versus each comparator are shown in Table 72, Table 73 and Table 74 below, with tornado diagrams shown in Figure 26, Figure 27 and Figure 28. Results are presented as iNMB values, as for some comparisons, negative ICER results limited the interpretability of the results. The WTP threshold used for calculating iNMB was assumed to be £30,000 per QALY.

The parameter with the largest effect on iNMB for docetaxel+ADT and ADT alone was mHSPC health state utility. This is mostly driven by the substantial PFS benefit darolutamide has over these comparators. Other important drivers are the inputs from the ITC, with ITC HRs making up two, and three of the five most impactful parameters versus docetaxel and ADT alone respectively. Other impactful parameters included subsequent treatment durations, post progression utilities, and HRU inputs, albeit with a much smaller impact on the model results then the mHSPC utility or ITC HRs.

For the comparison to enzalutamide+ADT, the top four parameters that had the biggest impact all related to ITC HRs, with the ToT HR having the biggest impact on the enzalutamide results. The OS and PFS HR for enzalutamide also had a considerable impact on the base case results. Besides the ITC HRs, the mHSPC utilities also had a big impact on the results versus enzalutamide+ADT, in line with the other comparisons. This shows that the model is most sensitive to the ITC and utility input, most notably the utility used for mHSPC.

Overall, the OWSA shows that the analysis is robust, with a narrow spread in outcomes for most model inputs. In addition, [redacted] However, the model was very sensitive to variations in the utility and ITC HR inputs, with the OWSA showing a large spread in iNMB results when the utility and ITC HR inputs were varied within their respective 95% confidence intervals. Any uncertainty around the utility and ITC inputs was therefore further explored in the scenarios in Section B.3.11.3 below.

Table 72: Top 10 most influential parameters for darolutamide+docetaxel+ADT versus docetaxel+ADT

Parameter	iNMB results vs Docetaxel + ADT		
Base case			
	Lower iNMB	**Upper iNMB**	**Difference**
Utilities: mHSPC			£29,238
OS Hazard ratio - Darolutamide			£20,296
PFS Hazard ratio - Darolutamide			£9,212
Subsequent Tx. duration - Enzalutamide			£7,600
Subsequent treatment duration - Abiraterone			£6,020
Utilities: mHRPC 1L			£5,404
Utilities: mHRPC 3L			£4,143
mHSPC HRU: Darolutamide off Tx			£3,431
mHRPC HRU: Docetaxel + ADT			£2,241
Subsequent treatment PFS - Enzalutamide			£1,376

Key: 1L, first-line, 3L, third line, ADT, androgen deprivation therapy, HRU, healthcare resource use, iNMB, incremental net monetary benefit, mHRPC, metastatic hormone-relapsed prostate cancer, mHSPC, metastatic hormone-sensitive prostate cancer, OS, overall survival, PFS, progression-free survival, Tx, treatment.

Table 73: Top 10 most influential parameters for darolutamide+docetaxel+ADT versus enzalutamide+ADT

Parameter	iNMB results vs Enzalutamide + ADT		
Base case			
	Lower iNMB	**Upper iNMB**	**Difference**
ToT Hazard ratio - Enzalutamide			£93,048
PFS Hazard ratio - Enzalutamide			£24,835
OS Hazard ratio - Enzalutamide			£24,560
OS Hazard ratio - Darolutamide			£20,296
Utilities: mHSPC			£13,171
PFS Hazard ratio - Darolutamide			£9,212
mHSPC HRU: Darolutamide off Tx			£3,431
mHSPC HRU: Enzalutamide			£2,428
mHRPC HRU: Enzalutamide + ADT			£1,500
mHRPC HRU: Darolutamide + Docetaxel + ADT			£1,132

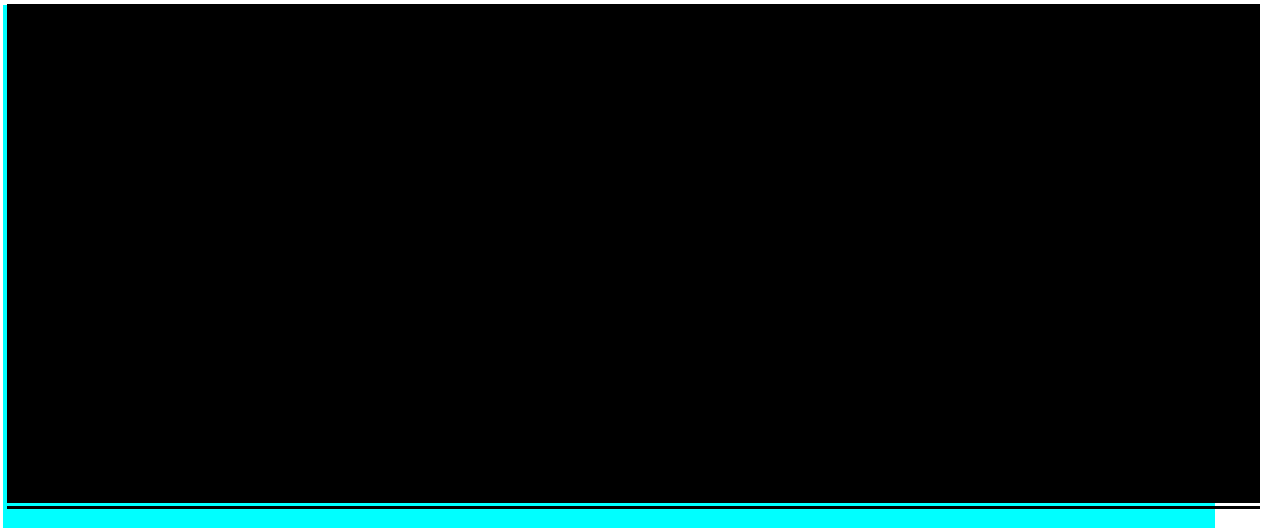
Key: ADT, androgen deprivation therapy, HRU, healthcare resource use, iNMB, incremental net monetary benefit, mHSPC, metastatic hormone-sensitive prostate cancer, OS, overall survival, PFS, progression-free survival, ToT, time-on-treatment, Tx, treatment.

Table 74: Top 10 most influential parameters for darolutamide+docetaxel+ADT versus ADT alone

Parameter	iNMB results vs ADT alone		
Base case	[redacted]		
	Lower iNMB	**Upper iNMB**	**Difference**
Utilities: mHSPC	[redacted]	[redacted]	£36,974
OS Hazard ratio - Darolutamide	[redacted]	[redacted]	£20,296
PFS Hazard ratio - ADT	[redacted]	[redacted]	£19,635
Subsequent treatment duration - Enzalutamide	[redacted]	[redacted]	£9,338
PFS Hazard ratio - Darolutamide	[redacted]	[redacted]	£9,212
Subsequent treatment duration - Abiraterone	[redacted]	[redacted]	£7,396
Utilities: mHRPC 1L	[redacted]	[redacted]	£7,157
OS Hazard ratio - ADT	[redacted]	[redacted]	£6,429
mHSPC HRU: Darolutamide off Tx	[redacted]	[redacted]	£3,431
Subsequent treatment PFS - Enzalutamide	[redacted]	[redacted]	£2,302

Key: 1L, first-line, ADT, androgen deprivation therapy, HRU, healthcare resource use, iNMB, incremental net monetary benefit, mHSPC, metastatic hormone-sensitive prostate cancer, OS, overall survival, PFS, progression-free survival, ToT, time-on-treatment, Tx, treatment.

Figure 26: Tornado plot of most influential parameters for darolutamide+docetaxel+ADT vs docetaxel+ADT



Key: 1L, first-line, ADT, androgen deprivation therapy, HRU, healthcare resource use, iNMB, incremental net monetary benefit, mCRPC, metastatic castration-resistant prostate cancer, mHRPC, metastatic hormone-relapsed prostate cancer, mHSPC, metastatic hormone-sensitive prostate cancer, OS, overall survival, PFS, progression-free survival, Tx, treatment.

Figure 27: Tornado plot of most influential parameters for darolutamide+docetaxel+ADT vs enzalutamide+ADT

Key: ADT, androgen deprivation therapy, HRU, healthcare resource use, iNMB, incremental net monetary benefit, mHSPC, metastatic hormone-sensitive prostate cancer, OS, overall survival, PFS, progression-free survival, ToT, time-on-treatment, Tx, treatment.

Figure 28: Tornado plot of most influential parameters for darolutamide+docetaxel+ADT vs ADT alone

Key: 1L, first-line, ADT, androgen deprivation therapy, HRU, healthcare resource use, iNMB, incremental net monetary benefit, mHSPC, metastatic hormone-sensitive prostate cancer, OS, overall survival, PFS, progression-free survival, ToT, time-on-treatment, Tx, treatment.

B.3.11.3 Scenario analysis

To further explore the uncertainty around the modelled results in terms of key inputs and assumptions, a series of scenario analyses with alternative modelling assumptions were performed. All performed scenario analyses are briefly summarized in Table 75 below.

Table 75: Scenarios explored in the cost-effectiveness model

No.	Scenario analysis	Scenario description
1	Using darolutamide as the anchor curve for all treatments, including docetaxel	Run the base case analysis using darolutamide data from ARASENS to extrapolate OS, TTCROD and ToT as an anchor for all treatments
2	Using dependent docetaxel extrapolations	Run the base case analysis using docetaxel OS and TTCROD data from ARASENS extrapolated using dependent extrapolations (i.e. treatment effect models)
3	Next best OS fit: log-logistic	Run the base case analysis using the log-logistic ARASENS OS curve to model survival
4	Next best TTCROD fit: log-logistic	Run the base case analysis using the log-logistic ARASENS TTCROD curve to model progression
5	Next best ToT fit: Gompertz	Run the base case analysis using the Gompertz ARASENS ToT curve to model treatment use
6	Enzalutamide ToT modelled equal to PFS[a]	Assume enzalutamide ToT is equal to PFS, rather than applying the PFS HR to the ToT data
7	Without GETUG-AFU 15 trial	Use the resulting hazard from the ITC when GETUG-AFU 15 trial is excluded.
8	Including SNA node	Include studies using SNA which may have indirectly contributed to the ITC
9	Without non-proportional hazard study	Exclude CHARTERED from the ITC, as it did not show proportional hazards for OS.
10	Using the alternative PFS network ITC results as TTCROD HR	Use the alternative PFS network ITC hazards to model progression for indirect comparators
11	Excluding RDI	Exclude RDI
12	Using utilities from TA741	Use health state utilities for pre-progression, 1L, 2L and 3L+ from those reported in TA741.
13	Include docetaxel disutility	Include an on-treatment disutility for patients treated with docetaxel.
14	Including G-CSF costs	Include prophylactic G-CSF costs as concomitant treatment for patients

No.	Scenario analysis	Scenario description
		receiving docetaxel, cabazitaxel or radium-223
15	Include SSEs (only for daro vs doc)[b]	Include SSE costs and disutilities for darolutamide and docetaxel only
16	20-year time horizon	A time horizon of 20 years is used instead of the lifetime time horizon
17	25-year time horizon	A time horizon of 25 years is used instead of the lifetime time horizon

Key: ADT, androgen deprivation therapy; G-CSF, granulocyte-colony stimulating factor; HR; hazard ratio; ICER, incremental cost-effectiveness ratio, ITC, indirect treatment comparison; iNMB, incremental net monetary benefit, mHRPC, metastatic hormone-relapsed prostate cancer, OS, overall survival, PH, proportional hazards; PFS, progression-free survival, RDI, relative dose intensity, SNA; nonsteroidal antiandrogen; ToT, time on treatment; TTCRPC, time to castration-resistant prostate cancer.
Note: (a) Scenario only performed versus enzalutamide + ADT, as comparator ToT was not modelled for other treatments, (b) scenario only performed versus docetaxel + ADT, as SSE data were only available for docetaxel.

An overview of the deterministic and probabilistic scenario analysis results for the cost-effectiveness of darolutamide+docetaxel+ADT versus versus docetaxel+ADT, enzalutamide+ADT and ADT alone are shown in Table 76 to Table 81. Overall, all scenarios resulted in a positive iNMB (at a WTP threshold of £30,000), indicating that darolutamide is cost-effective across all scenarios tested versus all comparators. In addition, the deterministic and probabilistic results were aligned, which further highlighted the robustness of the model. Scenarios with the largest impact on results and scenarios exploring key model inputs are discussed in further detail below.

Table 76: Deterministic scenario results versus docetaxel, ranked by difference in iNMB

Rank	Scenario	ICER	Δ ICER	iNMB	Δ iNMB
Deterministic base case		**£14,950**			
1	Gompertz ToT				
2	Using the alternative PFS network as PFS HR				
3	Daro as anchor				
4	Excluding RDI				
5	Log-logistic OS				
6	Log-logistic PFS				
7	Using utilities from TA741				
8	Dependent docetaxel extrapolations				

Rank	Scenario	ICER	Δ ICER	iNMB	Δ iNMB
9	Time horizon (20 years)				
10	Time horizon (25 years)				
11	Include SSEs*				
12	Including G-CSF costs				
13	Without GETUG AFU-15 trial				
14	Without non-non-PH studies				
15	Including SNA node				
16	Include docetaxel disutility				

Key: ADT, androgen deprivation therapy; alt. alternative; G-CSF, granulocyte-colony stimulating factor; HR; hazard ratio; ICER, incremental cost-effectiveness ratio, ITC, indirect treatment comparison; iNMB, incremental net monetary benefit, mHRPC, metastatic hormone-relapsed prostate cancer, OS, overall survival, PH, proportional hazards; PFS, progression-free survival, RDI, relative dose intensity, SNA; nonsteroidal antiandrogen; ToT, time on treatment; TTCRPC, time to castration-resistant prostate cancer.
Note: *Scenario only performed versus docetaxel + ADT, as SSE data were only available for docetaxel.

Table 77: Probabilistic scenario results versus docetaxel, ranked by difference in iNMB

Rank	Scenario	ICER	Δ ICER	iNMB	Δ iNMB
	Probabilistic base case	**£13,763**			
1	Daro as anchor				
2	Gompertz ToT				
3	Excluding RDI				
4	Using the alternative PFS network as PFS HR				
5	Log-logistic PFS				
6	Log-logistic OS				
7	Dependent docetaxel extrapolations				
8	Time horizon (20 years)				
9	Including G-CSF costs				
10	Time horizon (25 years)				
11	Including SNA node				
12	Without GETUG AFU-15 trial				
13	Include docetaxel disutility				
14	Using utilities from TA741				
15	Without non-proportional hazard study				
16	Include SSEs*				

Key: ADT, androgen deprivation therapy; alt. alternative; G-CSF, granulocyte-colony stimulating factor; HR; hazard ratio; ICER, incremental cost-effectiveness ratio, ITC, indirect treatment

Rank	Scenario	ICER	Δ ICER	iNMB	Δ iNMB
comparison; iNMB, incremental net monetary benefit, mHRPC, metastatic hormone-relapsed prostate cancer, OS, overall survival, PH, proportional hazards; PFS, progression-free survival, RDI, relative dose intensity, SNA; nonsteroidal antiandrogen; ToT, time on treatment; TTCRPC, time to castration-resistant prostate cancer. **Note**: *Scenario only performed versus docetaxel + ADT, as SSE data were only available for docetaxel.					

Table 78: Deterministic scenario results versus enzalutamide, ranked by difference in iNMB

Rank	Scenario	ICER	Δ ICER	iNMB	Δ iNMB
	Deterministic base case	**Enz dom.**			
1	Using the alternative PFS network as PFS HR				
2	Comparator ToT modelled with PFS*				
3	Gompertz ToT				
4	Including SNA node				
5	Dependent docetaxel extrapolations				
6	Time horizon (20 years)				
7	Log-logistic PFS				
8	Without non-PH studies				
9	Daro as anchor				
10	Log-logistic OS				
11	Time horizon (25 years)				
12	Including G-CSF costs				
13	Include docetaxel disutility				
14	Using utilities from TA741				
15	Without GETUG AFU-15 trial				
16	Excluding RDI				
Key: ADT, androgen deprivation therapy; alt. alternative; enz. dom., enzalutamide dominated by darolutamide; G-CSF, granulocyte-colony stimulating factor; HR; hazard ratio; ICER, incremental cost-effectiveness ratio, ITC, indirect treatment comparison; iNMB, incremental net monetary benefit, mHRPC, metastatic hormone-relapsed prostate cancer, OS, overall survival, PH, proportional hazards; PFS, progression-free survival, RDI, relative dose intensity, SNA; nonsteroidal antiandrogen; ToT, time on treatment; TTCRPC, time to castration-resistant prostate cancer. **Note**: *Scenario only performed versus enzalutamide + ADT, as comparator ToT was not modelled for other treatments.					

Table 79: Probabilistic scenario results versus enzalutamide, ranked by difference in iNMB

Rank	Scenario	ICER	Δ ICER	iNMB	Δ iNMB
	Probabilistic base case	**Enz dom.**			
1	Comparator ToT modelled with PFS*				
2	Using the alternative PFS network as PFS HR				
3	Including SNA node				
4	Gompertz ToT				
5	Time horizon (20 years)				
6	Log-logistic PFS				
7	Without non-proportional hazard study				
8	Log-logistic OS				
9	Including G-CSF costs				
10	Time horizon (25 years)				
11	Dependent docetaxel extrapolations				
12	Daro as anchor				
13	Using utilities from TA741				
14	Excluding RDI				
15	Include docetaxel disutility				
16	Without GETUG AFU-15 trial				

Key: ADT, androgen deprivation therapy; alt. alternative; enz. dom., enzalutamide dominated by darolutamide; G-CSF, granulocyte-colony stimulating factor; HR; hazard ratio; ICER, incremental cost-effectiveness ratio, ITC, indirect treatment comparison; iNMB, incremental net monetary benefit, mHRPC, metastatic hormone-relapsed prostate cancer, OS, overall survival, PH, proportional hazards; PFS, progression-free survival, RDI, relative dose intensity, SNA; nonsteroidal antiandrogen; ToT, time on treatment; TTCRPC, time to castration-resistant prostate cancer.
Note: *Scenario only performed versus enzalutamide + ADT, as comparator ToT was not modelled for other treatments.

Table 80: Deterministic scenario results versus ADT, ranked by difference in iNMB

Rank	Scenario	ICER	Δ ICER	iNMB	Δ iNMB
	Deterministic base case	**£9,216**			
1	Daro as anchor				
2	Using the alternative PFS network as PFS HR				
3	Gompertz ToT				
4	Log-logistic OS				

Rank	Scenario	ICER	Δ ICER	iNMB	Δ iNMB
5	Time horizon (20 years)				
6	Excluding RDI				
7	Without GETUG AFU-15 trial				
8	Without non-non-PH studies				
9	Dependent docetaxel extrapolations				
10	Using utilities from TA741				
11	Including G-CSF costs				
12	Time horizon (25 years)				
13	Log-logistic PFS				
14	Include docetaxel disutility				
15	Including SNA node				

Key: ADT, androgen deprivation therapy; alt. alternative; G-CSF, granulocyte-colony stimulating factor; HR; hazard ratio; ICER, incremental cost-effectiveness ratio, ITC, indirect treatment comparison; iNMB, incremental net monetary benefit, mHRPC, metastatic hormone-relapsed prostate cancer, OS, overall survival, PH, proportional hazards; PFS, progression-free survival, RDI, relative dose intensity, SNA; nonsteroidal antiandrogen; ToT, time on treatment; TTCRPC, time to castration-resistant prostate cancer.

Table 81: Probabilistic scenario results versus ADT, ranked by difference in iNMB

Rank	Scenario	ICER	Δ ICER	iNMB	Δ iNMB
	Probabilistic base case	**£8,560**			
1	Daro as anchor				
2	Gompertz ToT				
3	Using the alternative PFS network as PFS HR				
4	Log-logistic OS				
5	Excluding RDI				
6	Time horizon (20 years)				
7	Dependent docetaxel extrapolations				
8	Including G-CSF costs				
9	Without GETUG AFU-15 trial				
10	Without non-proportional hazard study				
11	Time horizon (25 years)				
12	Include docetaxel disutility				
13	Log-logistic PFS				
14	Using utilities from TA741				
15	Including SNA node				

Key: ADT, androgen deprivation therapy; alt. alternative; G-CSF, granulocyte-colony stimulating factor; HR; hazard ratio; ICER, incremental cost-effectiveness ratio, ITC, indirect treatment comparison; iNMB, incremental net monetary benefit, mHRPC, metastatic hormone-relapsed prostate cancer, OS, overall survival, PH, proportional hazards; PFS, progression-free survival, RDI, relative dose intensity, SNA; nonsteroidal antiandrogen; ToT, time on treatment; TTCRPC, time to castration-resistant prostate cancer.

The most impactful scenario versus docetaxel was the scenario that explored the use of the Gompertz ToT extrapolation for darolutamide. This resulted in a more favourable ICER compared to docetaxel ([redacted]). Similarly, it also lead to a more favourable ICER compared to ADT [redacted], the third most impactful scenario). iNMB was also changed by a similar magnitude, increasing by [redacted] for both the comparison versus docetaxel + ADT and ADT alone, while only slightly decreasing for enzalutamide [redacted]). Overall, this shows that the model is sensitive to the ToT input, especially for the comparisons versus docetaxel and ADT, due to the big mHSPC cost-difference between darolutamide and these treatments.

Compared to ADT alone, the most impactful scenario was the scenario in which darolutamide data from ARASENS is used as the anchor arm to model all other treatments. Compared to ADT, modelling clinical inputs using a darolutamide anchor increased the ICER by [redacted] and decreased iNMB by [redacted] compared to the base case. In comparison to docetaxel, this was the third most impactful scenario with a higher ICER (+[redacted]) and a lower iNMB ([redacted]). However, it should be noted that there was broad consensus during the economic validation meetings that using docetaxel as a reference curve and applying an HR to the docetaxel extrapolation for all comparators was the most robust approach. This is because docetaxel extrapolations can be validated using external long-term trial data, and using docetaxel as a reference ensures that all the efficacy data that are used in the model are fully reflective of the ITC results, and that darolutamide is modelled consistently with all the indirect comparators.[104] In addition, this approach is in line with the ERG critique on TA712.

The results versus enzalutamide were most sensitive to changes in the PFS and ToT input, and the scenarios using the alternative PFS network as PFS HR input and that used PFS as enzalutamide ToT input were ranked as the most impactful scenarios. This is understandable, considering the high treatment costs of enzalutamide at list price. However, it should be noted that the PFS as enzalutamide ToT scenario is

likely to overestimate the treatment costs for enzalutamide. As discussed in Section B.3.3, no enzalutamide ToT HR was publicly available, so no ToT ITC could be performed. In absence of an enzalutamide ToT HR, the model base case therefore assumes that the PFS HR is equal to that of ToT. However, it is plausible that our base case approach underestimates the actual ToT, as it assumes the same relation between ToT and PFS as darolutamide, which is given in combination with docetaxel. As the true ToT for enzalutamide is not known and the base case likely underestimates ToT, this scenario was performed to explore the upper bound for ToT by assuming enzalutamide ToT is equal to PFS. These results show that the likely range of the enzalutamide iNMB is between [redacted] and [redacted], depending on the ToT assumptions used. Similarly, it should be noted the alternative PFS network is less aligned with the PFS input for the model, as it uses TTCRPC from ARASENS, whereas the model uses TTCROD. The results from this alternative PFS network should therefore be interpreted with caution. However, as all the alternative PFS network scenarios had a positive impact on the ICER and NMB results, it can be stated that there's limited uncertainty around using TTCROD in the ITC, as it likely represents a conservative approach.

In addition, all comparisons were sensitive to the choice in parametric model used for docetaxel. Most of the scenarios that explored second-best fitting PFS, OS, and ToT extrapolations fell within the top 10 most impactful scenarios for all comparisons. This is understandable given the importance of survival input in the model and the inherent uncertainty around long-term extrapolations. However, it should be noted that there was no clear bias observed in these scenarios and the modelled base case is likely to represent an appropriate median estimation of all plausible survival input options.

Finally, considering that the OWSA identified the mHSPC utility input and ITC HRs used as the most impactful outcome drivers for all comparisons, several scenarios exploring different utility approaches or ITC option inputs were explored. Two alternative utility scenarios were performed, one using TA741 as utility input and one including docetaxel disutilities. However, neither had a big impact on model results for any of the comparisons. For the ITC, several scenarios were performed that explored all the different ITC sensitivity analyses reported in Section B.2.9 as HR inputs, again with a minimal impact on model outcomes. This indicates that, although

the model is sensitive to variations in the individual utility and ITC input values, there is little structural uncertainty associated with the choice of utility and ITC approach in the model.

B.3.12 Subgroup analysis

No subgroup analysis has been conducted.

B.3.13 Benefits not captured in the QALY calculation

As discussed in Section B.2, darolutamide has fewer pDDIs than enzalutamide[37, 43] (Section B.2.6.4.1), which may result in sub-optimal treatment of comorbidities while being treated with enzalutamide for mHSPC. This may impact the proportion of patients that are able to successfully receive enzalutamide. In addition, darolutamide exhibited low penetration of the blood-brain barrier in preclinical and human studies, which may be associated with a low potential for central nervous system AEs.[1, 4] However, as the exact impact of this favourable profile on the clinical effectiveness and cost-effectiveness is unknown, and there is no precedent for including DDIs in mHSPC appraisals, these benefits were not included in the company base case. It is likely that explicitly including these benefits would improve the cost-effectiveness versus enzalutamide.

B.3.14 Validation

B.3.14.1 Quality control

The economic model was extensively quality checked by an independent health economist who was not involved in the model's construction. The model was reviewed for coding errors, inconsistencies and the plausibility of inputs. The model was tested using a an internal checklist of known modelling errors, based on publicly available checklists such as Drummond and Philips as a guide.[130, 131] The checklist also includes all checks listed in the published technical verification (TECH-VER) checklist.[132]

B.3.14.2 Clinical and economic validation

A clinical advisory board was conducted with nine clinical oncologists from hospitals across the UK managed by the NHS Foundation Trust. The agenda for the session was structured around discussion sessions and presentations of clinical data that

were targeted to address questions regarding the HTA of darolutamide in combination with docetaxel and ADT in mHSPC. The experts were posed a number of questions and asked to formulate a consensus response. The experts were aware that their names and anonymised responses would be used as part of this submission.

The clinical experts confirmed that the baseline characteristics of the ARASENS trial aligned with what they would expect to see in UK clinical practice, so they considered these data to be reflective of the UK population. The validity of clinical assumptions such as current treatment practice, utility, HRU and the validity of long-term survival estimates were tested and confirmed as discussed in this submission. Full details of this meeting, including meeting notes, are available in the submission references.

Economic validation of the methodology was conducted at three video conference interviews with key health economic experts. The areas validated included the suitability and robustness of the ITC approach, the suitability of the ITC studies, the model structure, and the most methodologically sound approach to survival modelling. Full details of this meeting, including meeting notes, are available in the submission references.

B.3.14.3 Validation versus external data

Long-term survival data from STAMPEDE-3 and CHAARTED were used to validate the docetaxel survival input. Most notably, STAMPEDE-3 provides a good source to validate the expected docetaxel survival in the UK, as it is a UK-specific study with 9 years of follow-up data available, so this further validates the survival data used in the model. Median docetaxel OS from the model was compared against the available median OS from ARASENS, STAMPEDE-3, and CHAARTED (Table 82). The modelled median OS falls between the medians from ARASENS and STAMPEDE, indicating that it is close to the expected UK survival, while still showing a good fit to the ARASENS data. These steps further increase the robustness of the survival data used in the model.

Table 82: Comparison of median OS from the model to available docetaxel trial data

Median OS analysis	Docetaxel
Modelled OS, median, months	[redacted]
ARASENS OS, median, months	48.9
STAMPEDE-3 OS, median, months	59.1
CHAARTED OS, median, months	57.6
Key: OS, overall survival	

B.3.14.4 Validation versus past technology appraisals

Limited publicly available model results from past technology appraisals were available to further validate the model results, as all disaggregated results were redacted in most past TAs. The only available data that were identified to validate the model outcomes are the discounted life years gained (LYG) results from TA741. To provide a like-for-like comparison, the LYG results from our model were also discounted at 3.5% and compared with the results from TA741 in Table 83. Overall, the results are well aligned, with both models reporting comparable total LYGs, indicating that our survival predictions are in line with those used in TA741 and further increasing the robustness of our results.

Table 83: Discounted LYG results of the current model compared to the results reported in TA741

Treatment	Discounted LYG (current model)	Discounted LYG (TA741)
Darolutamide + docetaxel + ADT	[redacted]	N/A
Docetaxel + ADT	[redacted]	5.501
Enzalutamide + ADT	[redacted]	N/A
Apalutamide + ADT	N/A	6.023
ADT alone	[redacted]	4.588
Key: ADT, androgen deprivation therapy, LYG, life years gained, N/A, not available.		

B.3.15 Interpretation and conclusions of economic evidence

B.3.15.1 Conclusions

The base case analysis shows that darolutamide+docetaxel+ADT is a cost-effective option to treat patients with mHSPC, compared to all current available treatments. Darolutamide showed a higher mean survival in comparison to all comparators resulting in [redacted] total QALYs, compared to [redacted] and [redacted] QALYs for docetaxel+ADT, enzalutamide+ADT, and ADT alone, respectively. Compared to docetaxel+ADT and ADT alone, the total cost of darolutamide+docetaxel+ADT was higher, with a difference of [redacted] and [redacted] respectively. There is a cost saving compared with enzalutamide+ADT. This resulted in an ICER of £14,950 and £9,216 compared to docetaxel+ADT and ADT alone, respectively, leading to enzalutamide+ADT being dominated by darolutamide.

The uncertainty of the model parameters was explored in a series of sensitivity analyses. The probabilistic sensitivity analysis resulted in similar outcomes to the deterministic results, indicating that there was no major bias in the parametric uncertainty of the input parameters. The OWSA identified that the parameters with the largest effect on the model outcomes were the mHSPC utility input and ITC HRs for all comparisons. However, all scenarios exploring different utility approaches had a limited impact on the model outcomes. This shows that, although the model is sensitive to variations the utility input, it is not sensitive to the overall assumptions guiding the utility approach. In addition, the structural uncertainty of the model was further explored over a range of scenarios. The scenarios with the biggest impact on model outcomes were the scenarios that explored alternative survival extrapolations, an alternative PFS input, and using darolutamide as anchor arm for the ITC. However, darolutamide remained cost-effective across all scenarios. Altogether, these results show that, although there is some structural uncertainty in the model, it is likely that darolutamide is a cost-effective treatment option in mHSPC

B.3.15.2 Generalizability to the UK

The base case analysis was designed to provide a cost-effectiveness estimate that is as generalizable to UK practice as practically feasible. The efficacy input in the

model was based on ARASENS, which included 37 patients enrolled across eight UK trial centres, and was confirmed by UK clinical experts to be in line with mHSPC in the UK, both in terms of trial design and patient characteristics.[37] In addition, all model inputs and assumptions were validated by UK clinical experts who confirmed that the ARASENS population reflected the current patient population in the UK. Finally, the ARASENS docetaxel extrapolations were validated using the UK-specific data from STAMPEDE-3 to ensure that our representation of mHSPC reflected current UK practice.

B.3.15.3 Strengths and weaknesses

Several steps were undertaken to increase the reliability of the analysis with the key strengths as follow:

- The model structure was built upon the previously accepted and thoroughly reviewed nmCRPC model used in TA660.[100] In addition, the modelled approach was guided by precedent set by three past mHSPC TAs[38, 42, 88]
- The modelled efficacy of darolutamide+docetaxel+ADT and docetaxel+ADT was informed by a large multicentre Phase III trial, ARASENS, and validated using long-term UK-specific data from STAMPEDE-3. In addition, the modelled LYG results were consistent with the publicly available results from TA741[88]
- The model assumptions and inputs were extensively validated by UK clinical experts. In addition, any structural uncertainty was further explored across a range of sensitivity analyses, further supporting the validity of the model results

Nevertheless, some uncertainties remain because of limitations in the available data. The key uncertainties are discussed in more detail in Section B.3.7 and are outlined below:

- The definition of PFS was different in our model compared with what is reported for comparator trials
- Heterogeneity in endpoint definitions and trial designs for the studies included in the ITC
- There was a lack of darolutamide-specific utility data from ARASENS

However, as discussed in Section B.3.7 and Section B.3.11.3, all these uncertainties were explored in a series of scenario analyses, and darolutamide remained cost-effective across all scenarios. This shows that, although there is some uncertainty in the model, it is likely that darolutamide is a cost-effective treatment option in mHSPC.

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B.5 Appendices

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Darolutamide with androgen deprivation therapy and docetaxel for treating hormone-sensitive metastatic prostate cancer [ID3971]

Summary of Information for Patients (SIP)

September 2022

File name	Version	Contains confidential information	Date
ID3971_NICE STA_Darolutamide+docetaxel+ADT in mHSPC_SIP_FINAL_v1.0_09Sep22.docx	V1.0	No	09Sep22

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the Summary of Information for Patients (SIP)?

The SIP is written by the company who is seeking approval from National Institute for Health and Care Excellence (NICE) for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The Summary of Information for Patients template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

UK approved name: darolutamide **Brand name:** Nubeqa®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

The patient population is adults with metastatic hormone-sensitive prostate cancer (mHSPC). Metastatic means the cancer has spread to other parts of the body, and hormone-sensitive means the cancer can be treated with hormone therapy (e.g. androgen deprivation therapy [ADT]).

1c) Authorization: Please provide marketing authorization information, date of approval and link to the regulatory agency approval. If the marketing authorization is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Darolutamide was approved by the European Medicines Agency in March 2020 for the treatment of adult men with non-metastatic castration-resistant prostate cancer who are at high risk of the cancer spreading elsewhere in the body.[1] The marketing authorization extension to include the indication for metastatic hormone-sensitive prostate cancer is pending. Anticipated dates for approval are shown in Document B Section B.1.2 page 13.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Bayer has provided £16,000 in grant financial support to Prostate Cancer UK to support its 2022 Care Improvement Programme. The programme helps clinicians involved in treating prostate cancer with professional training and support to lead quality improvements within and beyond their service. Launched in Men's Health Week in June 2022, Bayer worked with the UK Men's Sheds Association on the 'Manversation', the campaign for prostate cancer conversation. The campaign aims to raise awareness of the symptoms of advanced prostate cancer and to equip and motivate men with a diagnosis of prostate cancer to have important conversations about their condition. Bayer has contributed £1,743 to this campaign. Please note, the collaborations listed are within the last 12 months only, and only existing collaborations and projects are listed. All details of Bayer partnerships and financial payments to patient organisations are listed on the Bayer website here.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England. Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.
Prostate cancer continues to be the most common cancer diagnosed in males in the UK; it accounted for 1 in 4 (26.3%) male cancer diagnoses in 2017.[2] When disease is

metastatic, the cancer progresses from the localized site (the prostate) and spreads to more distant parts of the body (e.g. bones, lymph nodes and internal organs). Patients with metastatic hormone-sensitive prostate cancer have either not previously received hormone therapy, are continuing to respond to hormone therapy, or have had cancer spread after local treatment such as radiotherapy and/or surgery.[3, 4] It is estimated that approximately 7,400 men are diagnosed with metastatic hormone-sensitive prostate cancer each year in England.[5-7]

The majority of patients with metastatic hormone-sensitive prostate cancer develop metastatic castration-resistant prostate cancer (prostate cancer that does not respond to hormone therapy) within approximately 20 months.[8, 9] This disease stage is associated with deterioration in health-related quality of life, and most patients die within 9 to 30 months[10], highlighting the importance of treatments that prevent progression.

The most commonly reported symptoms in patients with metastatic prostate cancer include fatigue, urinary symptoms, sexual dysfunction symptoms and bone pain[11], all of which negatively impact patients' health-related quality of life and affect daily life. Furthermore, the psychological burden of inevitable progression to metastatic castration-resistant prostate cancer is high. Fear of cancer recurrence and prostate-specific antigen anxiety are prominent symptoms for people with prostate cancer and can have a profound impact on patients' mental health (e.g. they can contribute to depression and anxiety).[12]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Metastatic hormone-sensitive prostate cancer is diagnosed using imaging tests (e.g. bone scan, computed tomography [CT] scan, magnetic resonance imaging [MRI]) to assess if the cancer has spread around the body and blood tests to assess the prostate-specific antigen levels. Identification of patients with metastatic hormone sensitive cancer would occur as part of the regular prostate-specific antigen monitoring and scans in current clinical practice. No additional tests or investigations are required for patients to receive treatment with darolutamide plus docetaxel and ADT.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP
- Please also consider:

- if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data
- are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are

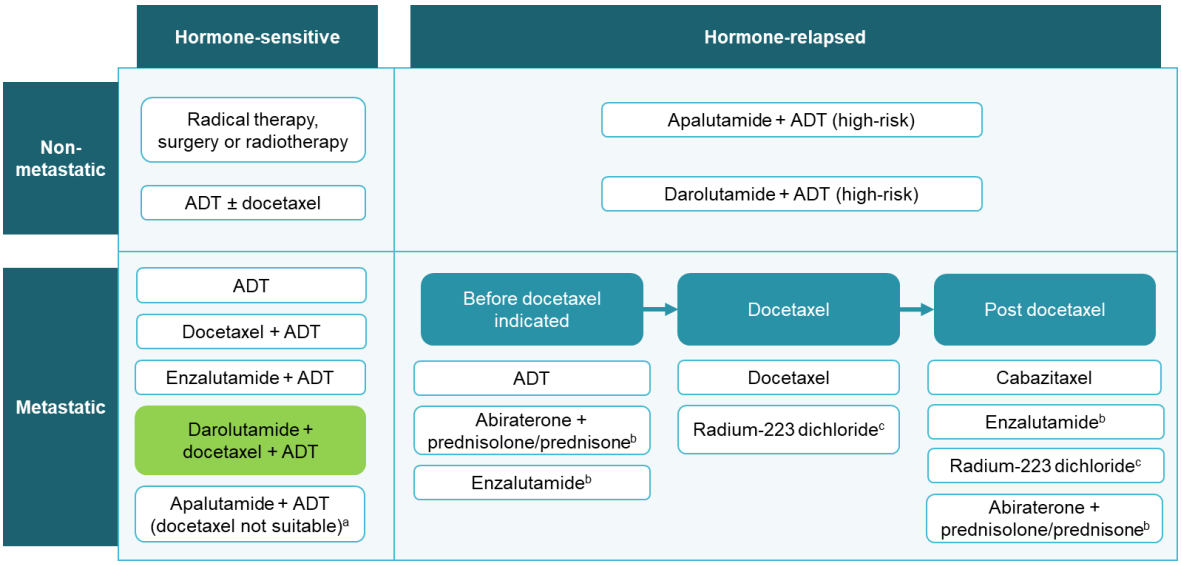
Figure 1 illustrates the treatment pathway for prostate cancer in England based on guidance issued by the National Institute for Health and Care Excellence. The proposed positioning of darolutamide plus docetaxel and ADT is highlighted.

Treatment options for metastatic hormone-sensitive prostate cancer include ADT alone (e.g. leuprorelin, goserelin, triptorelin, buserelin, degarelix or orchidectomy), docetaxel plus ADT for newly diagnosed patients who do not have any other significant health problems, and enzalutamide plus ADT.[13-15]

Enzalutamide and apalutamide has more potential drug–drug interactions than darolutamide.[16, 17] This may result in sub-optimal treatment of other diseases while being treated with enzalutamide or apalutamide for metastatic hormone-sensitive prostate cancer, and it may impact the proportion of patients that are able to successfully receive these treatments.

Darolutamide in combination with docetaxel and ADT offers the first licensed triplet combination therapy option for patients with metastatic hormone-sensitive prostate cancer in the NHS.

Figure 1: Clinical pathway for prostate cancer and proposed positioning of darolutamide plus docetaxel and ADT



Key: ADT, androgen deprivation therapy; BNF, British National Formulary; NG, NICE guideline; NHS, National Health Service; NICE, National Institute for Health and Care Excellence.
Notes: [a] Recommended only if docetaxel is not suitable; [b] Only if a novel anti-hormonal agent (i.e. darolutamide, enzalutamide, apalutamide or abiraterone) has not been used before; [c] Only if patients have already received docetaxel, or if docetaxel is contraindicated or is not suitable.

Green refers to the proposed positioning of darolutamide plus docetaxel and ADT.
Source: Adapted from NICE prostate cancer: diagnosis and management (NG131)[13]; NHS England commissioning policy statement for docetaxel[14]; BNF treatment summary for prostate cancer.[15]

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

In patients with metastatic disease, health-related quality of life scores were found to be clinically and statistically significantly lower than in those with cancer only in the prostate.[18] Both fatigue and pain were found to be the most important factors associated with poor health-related quality of life.[18] Patients reported via a survey that the most challenging aspect of dealing with advanced prostate cancer was the decreasing ability to maintain their lifestyle, while caregivers recognized pain management and the emotional impact on the patient's family as the most prominent challenges faced by the patient.[11]

Although the burden of disease for patients with metastatic hormone-sensitive prostate cancer is high, it is significantly worse for patients with metastatic castration-resistant prostate cancer.[19] For example, patients with metastatic castration-resistant prostate cancer reported the lowest health-related quality of life scores and highest pain scores. This reiterates the need for treatments that delay progression. Furthermore, there is a considerable burden on caregivers with the majority of care provided by spouses/partners.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Darolutamide is a treatment for patients with prostate cancer. Darolutamide binds to androgen receptors in the cell more efficiently and more specifically than other anti-androgen treatments.[20] When darolutamide binds to these receptors it leads to a decrease in the activation of genes required for the growth and survival of prostate cancer cells.[20, 21] As darolutamide has a different biological structure than other drugs in the same class (androgen receptor inhibitors), it has a low toxicity profile and has fewer interactions with other drugs. A summary of product characteristics is available for darolutamide.[1]

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Darolutamide is intended to be used in combination with docetaxel and ADT. Darolutamide binds to androgen receptors and prevents the activation of genes required for the growth and survival of prostate cancer cells; ADT lowers the levels of androgens; and docetaxel is a chemotherapy agent that targets the components of the tumour that are insensitive to androgen levels. Targeting both androgen receptor-dependent and independent mechanisms at initiation of treatment for metastatic hormone-sensitive prostate cancer provides an opportunity to prolong survival and delay disease progression early on in this aggressive metastatic pathway.

All components of the combination therapy are available in the NHS: darolutamide plus ADT is already reimbursed for the treatment of adult patients with non-metastatic castration-resistant prostate, and docetaxel plus ADT is reimbursed for metastatic hormone-sensitive prostate cancer.[22, 23]

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

The recommended dose of darolutamide is 600 mg (two 300 mg film-coated tablets) taken orally twice daily to achieve a total daily dose of 1,200 mg. Tablets should be swallowed whole and taken with food. Darolutamide treatment should be continued for as long as the benefit is observed, which can typically be for many years. The recommended dose of

docetaxel is 75 mg/m^2 as an intravenous infusion every 3 weeks for six cycles. Docetaxel treatment can be stopped if any unacceptable side effects (adverse events) occur.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates, etc. Please provide references to further information about the trials or publications from the trials.

Table 1 summarizes the clinical effectiveness evidence supporting darolutamide plus docetaxel and ADT for the treatment of adult patients with metastatic hormone sensitive prostate cancer.

Table 1: Summary of completed clinical trials for darolutamide plus docetaxel and ADT

Study name	**ARASENS (NCT02799602)**
Location	Global: multiple investigative sites in 23 countries
Population	Adults (≥ 18 years) with metastatic hormone-sensitive prostate cancer
Patient group size	1,306 patients were randomized
Comparators	Placebo plus docetaxel and ADT
Key inclusion criteria	• Histologically or cytologically confirmed adenocarcinoma of prostate (i.e. prostate cancer confirmed by looking at affected tissues) • Metastatic disease documented either by a positive bone scan, or computed tomography or magnetic resonance imaging for cancer in the soft tissue or internal organs • Patients must be candidates for docetaxel and ADT
Key exclusion criteria	• Prior treatment with: – Luteinizing hormone-releasing hormone agonists/antagonists started > 12 weeks before randomization – Second-generation androgen receptor inhibitors such as enzalutamide or darolutamide – Cytochrome P 17 enzyme inhibitor such as abiraterone acetate – Chemotherapy or immunotherapy for prostate cancer prior to randomization – Treatment with radiotherapy within 2 weeks before randomization • Uncontrolled high blood pressure

	• Had any of the following within 6 months before randomization: stroke, myocardial infarction (heart attack), severe/unstable angina pectoris, coronary/peripheral artery bypass graft, congestive heart failure
Completion dates	October 2021
Primary publication	Smith et al., 2022[24]

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Data from the ARASENS study clearly demonstrated clinically meaningful improvements in survival and delayed progression for patients treated with darolutamide plus docetaxel and ADT compared with placebo plus docetaxel and ADT. ARASENS is the only trial of patients with metastatic hormone-sensitive prostate cancer which includes a more active comparator widely used as part of standard of care (docetaxel plus ADT).

Treatment with darolutamide reduced the risk of dying by 32.5%, reduced the risk of cancer becoming castration-resistant by 64%, reduced the risk of pain becoming worse by 21%, reduced the risk of bone fractures and related symptoms by 29% and reduced the risk of needing additional therapies for cancer by 61% compared with placebo. All of these factors are key to maintaining patient health-related quality of life and reducing the burden on both patients and the NHS.

Table 2: Summary of clinical outcomes in ARASENS

Outcome	Median		Statistically significant difference in favour of darolutamide?
	Darolutamide+ docetaxel and ADT	Placebo+ docetaxel and ADT	
Primary endpoint			
Overall survival	Not reached	48.9 months	Yes
Secondary endpoints			
Time to castration-resistant prostate cancer	Not reached	19.1 months	Yes
Time to pain progression	Not reached	27.5 months	Yes
Symptomatic skeletal event-free survival	51.2 months	39.7 months	Yes
Time to first symptomatic skeletal event	Not reached	Not reached	Yes
Time to initiation of subsequent systemic antineoplastic therapy	Not reached	25.3 months	Yes
Time to worsening of disease-related physical symptoms	19.3 months	19.4 months	No

Key: ADT, androgen deprivation therapy.

A limitation of the evidence base is that there are no clinical trials which directly compare darolutamide plus docetaxel and ADT with all other treatments which are currently used in the NHS: enzalutamide plus ADT or ADT alone. To address this, a statistical analysis using the trial data for both treatments has been conducted, looking at the impact of these treatments on the survival and progression of patients with metastatic hormone-sensitive prostate cancer. The analysis suggested that darolutamide plus docetaxel and ADT is the most clinically effective treatment in the evidence base.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used, does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient-reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

There were two questionnaires used to assess health-related quality of life throughout the ARASENS trial. One questionnaire assessed the symptoms of prostate cancer, and the other assessed levels of pain. Both showed that darolutamide plus docetaxel and ADT and placebo plus docetaxel and ADT were comparable in terms of impact on quality of life.

Preference studies with patients, caregivers and physicians in non-metastatic castration-resistant prostate cancer have reported a preference for treatments with lower adverse event burdens and a willingness to trade substantial amounts of survival to avoid adverse events.[25, 26] This emphasizes the importance of balancing therapies' benefits and risks to optimize the overall quality of the patients survival, which is expected to transcend across the prostate cancer space.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies, etc.

Although most patients experienced at least one adverse event while on treatment in both the darolutamide plus docetaxel and ADT (99.5%) and placebo (98.9%) groups, the events were mostly predictable and reversible. Many of the common adverse events while on treatment in the study (such as alopecia, anaemia, neutropenia) are known to be commonly associated with docetaxel treatment. For the events known to be associated with both darolutamide and docetaxel, the incidences were similar between the darolutamide plus docetaxel and ADT and placebo plus docetaxel and ADT groups: fatigue (33.1% versus 32.9%, respectively) and neutropenia (39.3% versus 33.8%, respectively).

In summary, treatment with darolutamide did not adversely affect the overall safety of docetaxel and ADT and it did not add to the toxicity profile that is driven by the six cycles of docetaxel. Furthermore, adding darolutamide to docetaxel and ADT did not affect the ability of patients to complete the full six cycles of docetaxel treatment.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

• Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments. • Please include benefits related to the mode of action, effectiveness, safety and mode of administration
Darolutamide in combination with docetaxel and ADT offers the first licensed triplet combination therapy option for patients with metastatic hormone-sensitive prostate cancer in the NHS. Data from the ARASENS trial showed that patients taking darolutamide plus docetaxel and ADT were less likely to die (reduced the risk by 32.5%) and less likely to develop castration-resistant prostate cancer (reduced the risk by 64%) compared with placebo. By delaying progression to metastatic castration-resistant prostate cancer, darolutamide is likely to reduce the high levels of psychological burden associated with the inevitable progression to a disease state with worse prognosis with current standard of care. The added benefit of darolutamide in combination with docetaxel therapy outweighed any additional toxicity, which was transient and did not affect overall health-related quality of life. Docetaxel is administered every 3 weeks for six cycles, whereas darolutamide is typically taken for several years (as observed in ARASENS). Furthermore, darolutamide exhibited fewer interactions with other drugs compared with enzalutamide or apalutamide.[17] Treatment with darolutamide would therefore result in less resource-intensive monitoring of any interactions, reduce the risk of sub-optimal treatment of other diseases while being treated for metastatic hormone-sensitive prostate cancer, and offer a greater proportion of patients the chance to effectively delay progression.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response: • Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers? • Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration • What is the impact of any disadvantages highlighted compared with current treatments
A disadvantage is that most patients experienced at least one adverse event while on treatment with darolutamide plus docetaxel and ADT treatment, although this was also the case for patients treated with placebo plus docetaxel and ADT. The incidences for the majority of events were highest during the first 6 months after the start of study treatment in both treatment groups, corresponding to the docetaxel treatment period. After that, a trend towards lower incidence and reduced severity of adverse events was observed in both treatment groups for most adverse events. The darolutamide component is taken for several years, therefore the long-term favourable toxicity profile and few drug–drug

interactions is key to ensure maximum efficacy and to maintain health-related quality of life while on treatment.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g. whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g. travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Cost-effectiveness model approach

To assess the value and economic considerations of using darolutamide in combination with docetaxel and ADT in mHSPC compared to docetaxel plus ADT, enzalutamide plus ADT, or ADT alone, a cost-effectiveness model was developed. This model uses a simplified representation of mHSPC, in which a patient's progression across distinct health states relevant to mHSPC patient is simulated. Each of these health states is associated with a certain amount of costs and a certain quality of life. The following health states were used in our cost-effectiveness model:

- **Progression-free (mHSPC)**: a patient's disease is stable or responding to treatment, and not actively progressing. Costs in this health state are associated with treatment received, treatment administration costs, management of disease and adverse events. Quality of life is higher compared with patients with progressed disease
- **Progressed (metastatic hormone-relapsed prostate cancer)**: a patient's disease is assumed to have progressed to a hormone-relapsed state. This state is split into three lines of treatment to simulate all the subsequent treatments a patients with mHSPC could receive. Costs in this health state are associated with subsequent treatment

received, treatment administration costs, management of disease and adverse events. Patients have a lower quality of life than in the progression-free state

- **Death**: an absorbing health state

The cost-effectiveness model uses the clinical data available for darolutamide and the relevant comparators to estimate how fast a patient progresses through these different health states. More specifically, it uses the data on progression from clinical trials to estimate how long patients spend in the progression-free mHSPC state, and the overall survival data to estimate how fast patients progress to death. This time spend per health state is then adjusted for the quality of life of a patient in that health state to estimate the total amount of quality-adjusted life years (QALYs) gained by a patient, as a result of their received mHSPC treatment. This is then compared with the total costs associated with that treatment (consisting of treatment costs, subsequent treatment costs, adverse event costs, and general costs associated to management of mHSPC such as routine visits and testing), to assess whether the costs associated with using darolutamide in combination with docetaxel and ADT is justifiable based on the additional QALYs patients gain.

Clinical benefits included in the model

The model predicted that treatment with darolutamide in combination with docetaxel and ADT would lead to more clinical benefit (QALYs) gained than treatment with all other comparators (exact QALY results are confidential). This benefit was mainly driven by progression-free survival and overall survival benefit that darolutamide has over these comparators. This resulted in a longer time spent in the progression-free health state, which was associated with a better overall quality of life, and a longer survival overall.

Costs included in the model

Both darolutamide, enzalutamide, and some subsequent treatments such as abiraterone and Radium-223 are subject to confidential price agreements with the NHS, so full cost information cannot be presented. However, broadly, treatment with darolutamide plus docetaxel and ADT was associated with higher costs than treatment with docetaxel plus ADT or ADT alone. This was mostly driven by higher treatment costs of darolutamide. Compared with enzalutamide plus ADT, darolutamide plus docetaxel and ADT was cost saving, due to the lower treatment costs of darolutamide compared with enzalutamide. However, this is mainly because the exact enzalutamide discount is unknown, and therefore not included in the analysis.

Model results

Overall, the model determined that treatment with darolutamide was associated with sufficient additional benefit to patients (QALYs) to justify any additional costs compared with all of the relevant comparators. Therefore, in addition to offering a meaningful clinical benefit to patients, darolutamide is also considered a cost-effective treatment option for patients with mHSPC. Darolutamide remained cost-effective across a range of sensitivity analyses which tested the model's assumptions and confirmed the robustness of the results.

Uncertainty

Although darolutamide plus docetaxel and ADT was consistently cost-effective compared with all relevant comparators over a range of sensitivity analyses, some uncertainties remain. The key uncertainties are:

- **The clinical benefit compared with treatments not included in ARASENS:** Because there is no study that compares darolutamide plus docetaxel and ADT with enzalutamide plus ADT, or ADT alone. The relative efficacy of these comparators was informed by a statistical analysis which compared results across different trials. Although the model results were sensitive to the specific enzalutamide and ADT alone efficacy input used, darolutamide was still cost-effective for all different enzalutamide and ADT alone input options
- **The generalizability to the UK:** As no UK-specific clinical data are available for darolutamide plus docetaxel and ADT, docetaxel plus ADT, enzalutamide plus ADT, or ADT alone, all efficacy data in the model is informed largely by global trials. Although these trials are broadly aligned with UK practice, some of the patients in these trials received treatments which are not currently used in the UK. However, these were not shown to affect the observed clinical benefits, so are unlikely to affect the model results

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative, please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see Section 3f).

Darolutamide in combination with docetaxel and ADT offers the first licensed triplet combination therapy option for patients with metastatic hormone-sensitive prostate cancer in the NHS. The multi-targeted approach provides an opportunity to prolong survival and delay disease progression at initiation of therapy, without further deterioration in health-related quality of life beyond docetaxel and ADT. The docetaxel component is limited to six cycles (one cycle every 3 weeks), whereas treatment with darolutamide is anticipated to continue for multiple years as observed in ARASENS. Furthermore, darolutamide exhibited fewer potential drug–drug interactions compared with enzalutamide or apalutamide.[17] This would result in less resource-intensive monitoring of any interactions and reduce the risk of sub-optimal treatment of comorbidities while being treated for metastatic hormone-sensitive prostate cancer.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.
Prostate cancer is more common in Black/African men than white men.[27] The introduction of darolutamide plus docetaxel and ADT provides an alternative and more effective treatment option which will support all men with metastatic hormone-sensitive prostate cancer.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials, etc. Where possible, please provide open-access materials or provide copies that patients can access.
Further information on darolutamide: • Plain language summary of publication Darolutamide and survival in metastatic, hormone-sensitive prostate cancer: a patient and caregiver perspective and plain language summary of the ARASENS trial Further information on prostate cancer: • Cancer research UK prostate cancer statistics: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer#:~:text=There%20are%20around%2052%2C300%20new,UK%20(2016%2D2018).

- Prostate cancer UK: https://prostatecanceruk.org/prostate-information/about-prostate-cancer
- Manversation campaign: https://www.manversation.co.uk/

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Adverse event – an unexpected medical problem that occurs when a patient administers a treatment

Androgen – a sex hormone (e.g. testosterone) that regulates the development of male characteristics

Computed tomography scan – a procedure that uses x-rays to generate internal images of the body (bones, blood vessels and soft tissue)

Drug–drug interactions – when you take a medication it can interfere with the way other medications work. This may result in a medication not working effectively.

Health-related quality of life – an assessment of how the mental and physical health of patients affect their daily life (e.g. energy levels, any pain experienced, mobility)

Magnetic resonance imaging – a procedure that uses a magnetic field to generate internal images of the body (organs and tissues)

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Darolutamide with androgen deprivation therapy and docetaxel for treating hormone-sensitive metastatic prostate cancer [ID3971]

Clarification questions

September 2022

File name	Version	Contains confidential information	Date
ID3971 Darolutamide for mHSPC EAG clarification Qs from EAG to company_Bayer response_AIC	1.0	Yes	18OCT22

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Treatment effect modifiers

A1. Company submission (CS) Appendix D Figures 7 and 8 include five patient variables from the ARASENS trial which were assessed to identify any potential effect modification. These five appear to be selected from a wider set of patient subgroups from the ARASENS trial (Figure 16, Appendix E).

> **A1a.** Please comment on the rationale for selecting variables to be assessed to determine effect modification.
>
> **A1b.** Please comment on the evidence for/against effect modification for each of the remaining variables in Figure 16, Appendix E.

Bayer response

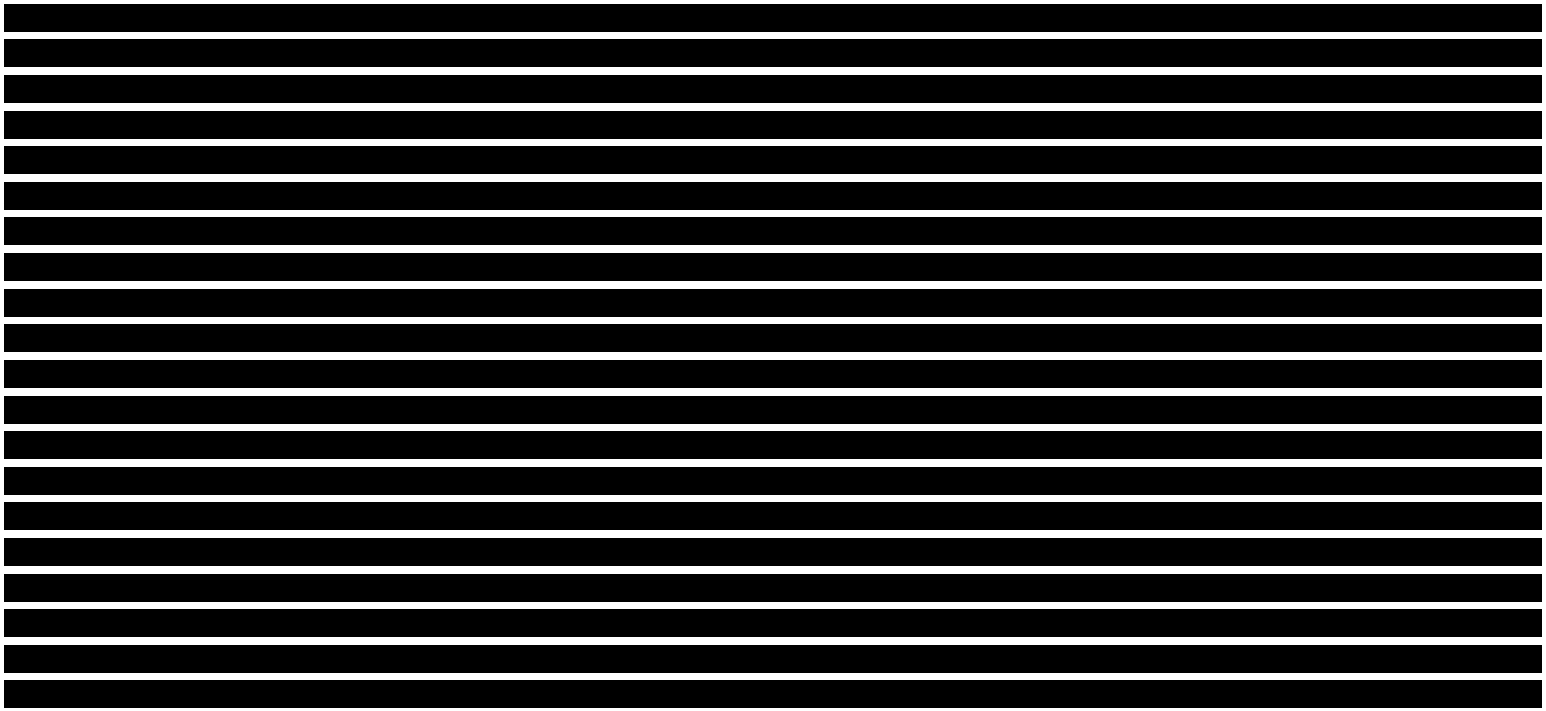
The following baseline characteristics were presented in Appendix D Figures 7 and 8: age, cancer stage, ECOG, Gleason score, and PSA level. These five variables were investigated as an additional investigation to the CSR Figure 16, Appendix E, for both the outcomes of overall survival and progression free survival. These were selected as they were considered to be the variables most clinically likely to have an impact on treatment effect and thereby relative treatment effect, as well as being the

variables most consistently reported across the other trials in the network which was needed to assess similarity.

The following additional variables were provided in Figure 16 Appendix E: extent of disease (location of metastases), alkaline phosphatase stratification factor, race, geographic region, and metastasis at initial diagnosis. The results of Figure 16 Appendix E do not indicate that any of these variables are relative treatment effect modifiers for OS. We have included additional subgroup analysis results for both OS and time to CRPC in ARASENS trial in Figure 1-Figure 4. There does not appear to be good evidence of treatment effect modification for any of the variables presented in these forest plots. The forest plots show the relative effect (darolutamide + docetaxel vs placebo + docetaxel) is consistent in the direction of effect across all subgroups for OS (as concluded in the ARASENS CSR) with hazard ratios all less than one and overlapping confidence intervals. These are also consistent across almost all subgroups for CRPC with hazard ratios all less than one and overlapping confidence intervals, other than [redacted] (however, small sample size in some of these groups make it difficult to interpret).

It is important to consider that typically these subgroup comparisons are not based on randomised comparisons (in cases where the randomisation was not stratified for that subgroup) and clinical trials are not adequately powered to investigate subgroup effects. Therefore, findings from multiple subgroup analyses may be misleading as false negative and false positive significance tests increase in likelihood as more subgroup analyses are performed.

Figure 1: Forest plot of subgroup analysis results for overall survival in ARASENS trial (1/2)



Key: ALPBL, alkaline phosphatase baseline; BL, baseline; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group performance status; HR; hazard ratio; ULN, upper limit of normal.

Notes: *, Non-regional. HR <1 indicates superiority of the darolutamide+docetaxel group over the placebo+docetaxel group. HRs and CIs were obtained from univariate analysis using Cox regression (unstratified).

Figure 2: Forest plot of subgroup analysis results for overall survival in ARASENS trial (2/2)

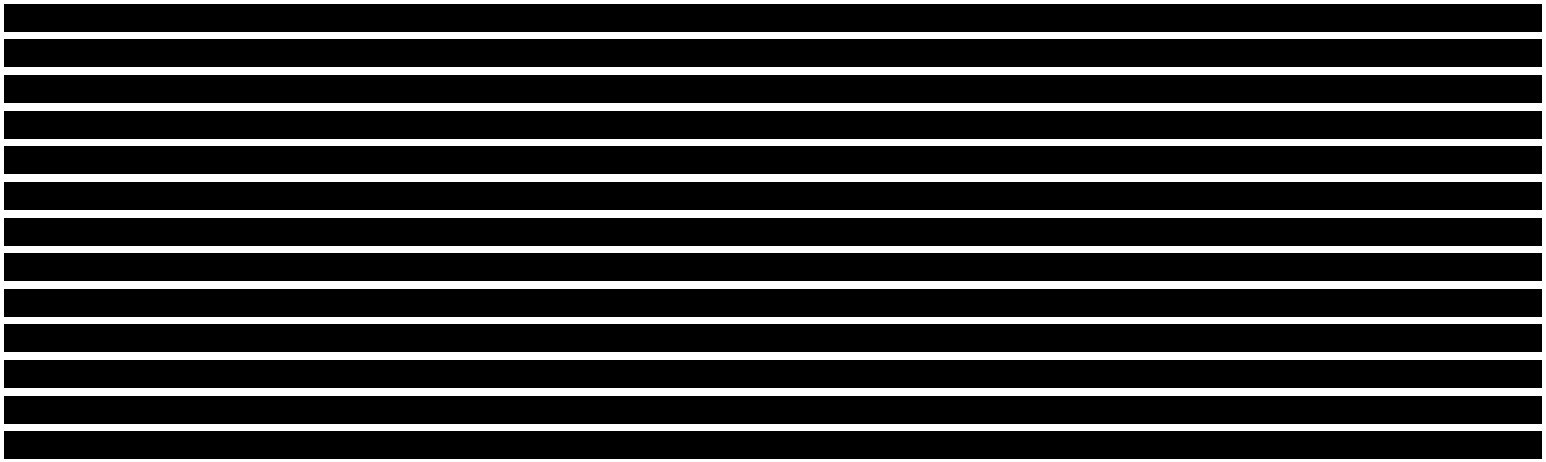
[redacted]

Key: ALPBL, alkaline phosphatase baseline; BL, baseline; CI, confidence interval; HR; hazard ratio; PSA, prostate-specific antigen.

Notes: For metastasis we used a slightly different definition to that provided by the CSR (we used No or NR when the CSR used No, this was chosen due to the data available, and this resulted in a similar number of events and hazard ratios to that of the CSR. HR <1 indicates superiority of the darolutamide+docetaxel group over the placebo+docetaxel group. HRs and CIs were obtained from univariate analysis using Cox regression (unstratified).

Figure 3: Forest plot of subgroup analysis results for time to CRPC in ARASENS trial (1/2)

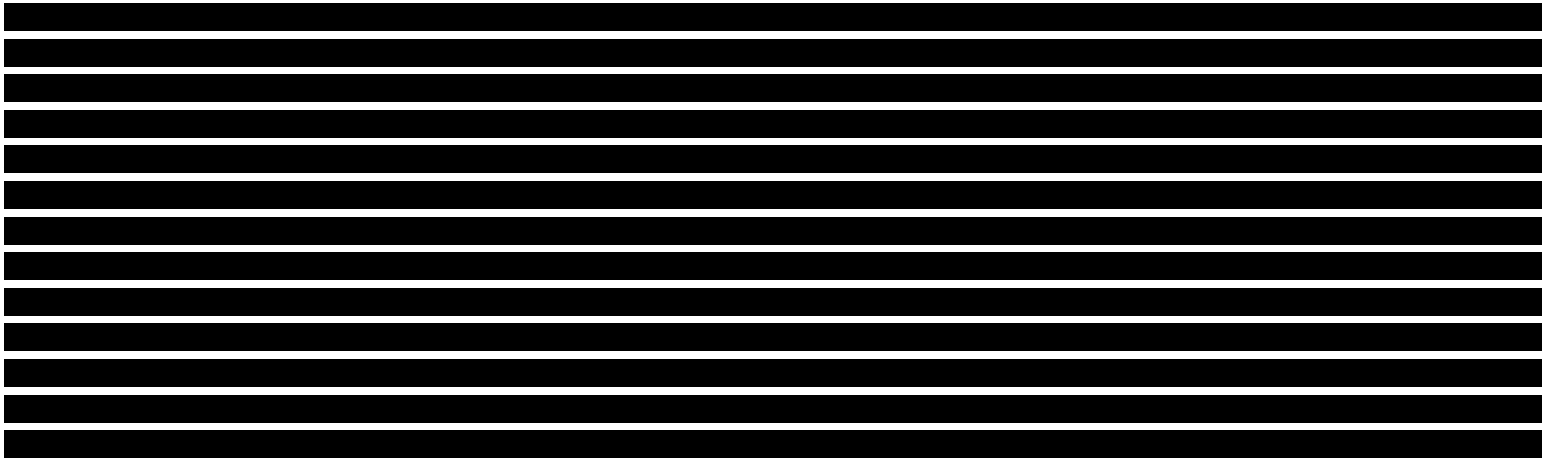
[redacted]



Key: ALPBL, alkaline phosphatase baseline; BL, baseline; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group performance status; HR; hazard ratio; ULN, upper limit of normal.

Notes: *, Non-regional. HR <1 indicates superiority of the darolutamide+docetaxel group over the placebo+docetaxel group. HRs and CIs were obtained from univariate analysis using Cox regression (unstratified).

Figure 4: Forest plot of subgroup analysis results for time to CRPC in ARASENS trial (2/2)



[redacted]

Key: ALPBL, alkaline phosphatase baseline; BL, baseline; CI, confidence interval; HR; hazard ratio; PSA, prostate-specific antigen.

Notes: HR <1 indicates superiority of the darolutamide+docetaxel group over the placebo+docetaxel group. HRs and CIs were obtained from univariate analysis using Cox regression (unstratified).

A2 Please provide an assessment of potential effect modifiers in each of the comparator trials included in the network meta-analysis.

Bayer response

We are unable to systematically assess treatment effect modifiers in other trials as we do not have access to the trial patient level data, therefore, we need to rely on available evidence reported in the trial publications. We have reviewed key trial publications from the evidence base included in the base NMA network to identify relevant reported subgroup outcome information. Some forest plots presented were based on shorter follow-up than the outcome data used in the NMAs. Where the relative effect is consistent across subgroups with overlapping confidence intervals this suggests there is no evidence for treatment effect modification for this subgroup, The limitations of subgroup analyses discussed in response Question A1 to apply here also.

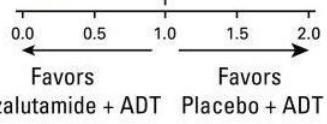
We identified subgroup analyses (including tables of results or forest plots) for relevant outcomes and patient populations for ARCHES – Armstrong 2019(1), CHAARTED - Sweeney 2015(2), GETUG-AFU 15 - Gravis 2013(3), LATITUDE - Fizazi 2017(4), and STAMPEDE-3- Clarke 2019(5). For most trials and variables identified there does not appear to be good evidence of treatment effect modification. Subgroup results were identified for ENZAMET – Davis 2019(6), STAMPEDE-2 – James 2017(7), Vaishampayan 2021(8), and SWOG-study-S8894 – Eisenberger 1998(9) however, these identified were not available for relevant populations and/or endpoints used in the NMA.

Figure 5 present a forest plot of the primary outcome rPFS for subgroups in the ARCHES trial (1) The treatment effect of enzalutamide + ADT was consistent across all prespecified subgroups in ARCHES suggesting none of the subgroups presented in Figure 5 were identified as treatment effect modifiers. Figure 6 present a forest plot of OS of the CHAARTED trial (2), there was no strong evidence of treatment effect modification in these. Figure 8 presents a forest plot of OS for subgroups in LATITUDE (4), the treatment effect of abiraterone acetate + ADT was consistent across all subgroups suggesting none of the subgroups presented were identified as treatment effect modifiers. Figure 9 presents a forest plot of OS for subgroups in STAMPEDE-3 (5), there was some change in direction of effect for the treatment

effect of docetaxel + ADT however there was no good evidence that the docetaxel effect varies across any of the sub-groups included. Figure 7 presents the forest plot for OS for subgroups in the GETUG-AFU 15 trial (3). There was some evidence that Gleason score may have an impact on treatment effect, however, this is inconclusive and Figure 7 uses an earlier data-cut from GETUG-AFU 15 to the HR used in the NMA. In addition, GETUG-AFU 15 was included in the base case NMA, however, a sensitivity analysis was performed excluding GETUG-AFU 15 which showed very similar results to the base case NMA, substantiating the limited effect of Gleason score on relative treatment effects.

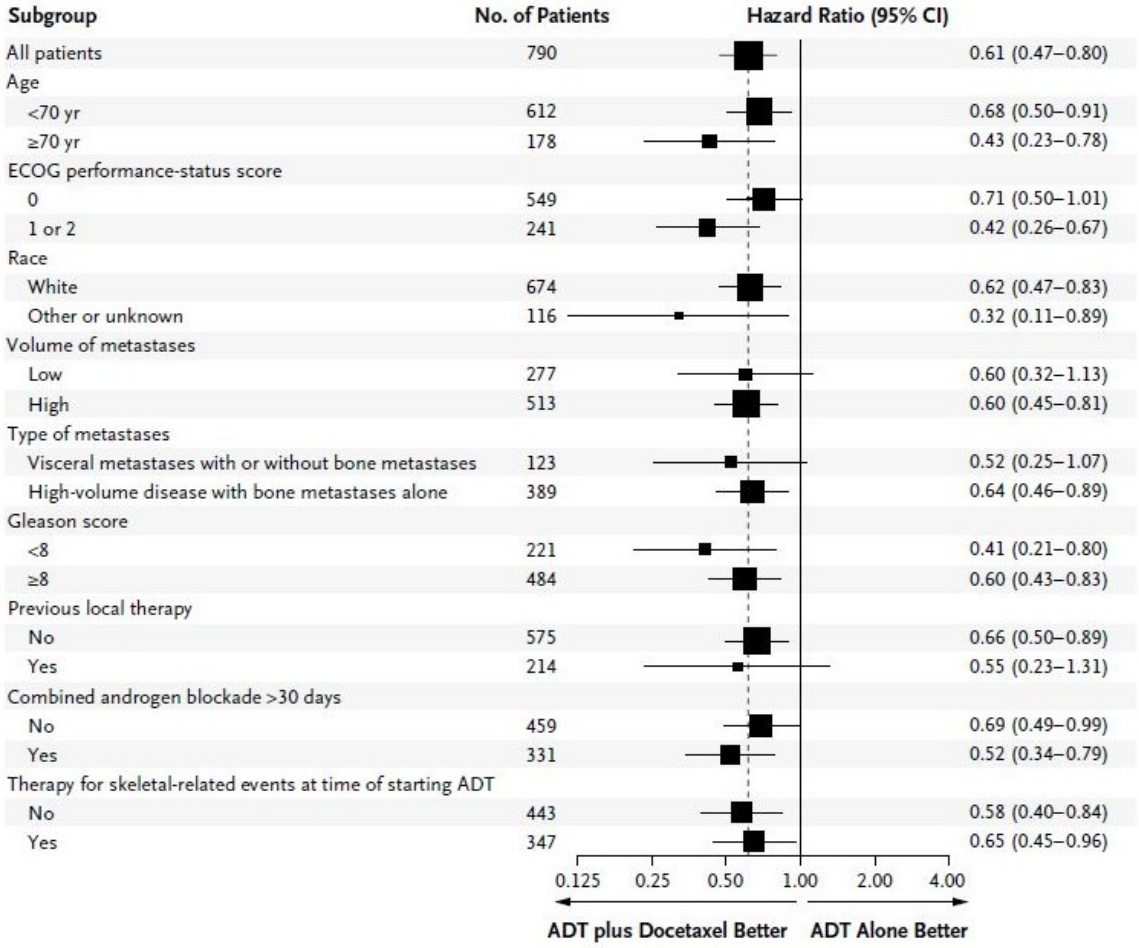
Figure 5: ARCHES trial forest plot of rPFS for subgroups

Subgroup	Enzalutamide + ADT No. of patients (E)	Placebo + ADT No. of patients (E)	HR (95% CI)†
All patients	574 (91)	576 (201)	0.39 (0.30 to 0.50)
Age < 65 years	148 (21)	152 (58)	0.29 (0.17 to 0.47)
Age ≥ 65 years	426 (70)	424 (143)	0.44 (0.33 to 0.58)
Geographic region – Europe	341 (55)	344 (122)	0.42 (0.31 to 0.58)
Geographic region – North America	86 (14)	77 (29)	0.30 (0.16 to 0.57)
Geographic region – rest of the world	147 (22)	155 (50)	0.40 (0.24 to 0.66)
ECOG status 0 at baseline	448 (67)	443 (146)	0.38 (0.29 to 0.51)
ECOG status 1 at baseline	125 (24)	133 (55)	0.43 (0.27 to 0.70)
Gleason score at initial diagnosis < 8	171 (21)	187 (47)	0.42 (0.25 to 0.70)
Gleason score at initial diagnosis ≥ 8	386 (65)	373 (151)	0.36 (0.27 to 0.48)
Disease localization at baseline – bone only	268 (35)	245 (82)	0.33 (0.22 to 0.49)
Disease localization at baseline – soft tissue only	51 (5)	45 (12)	0.42 (0.15 to 1.20)
Disease localization at baseline – bone and soft tissue	217 (50)	241 (104)	0.42 (0.30 to 0.60)
Baseline PSA value at or below overall median	293 (41)	305 (96)	0.38 (0.26 to 0.54)
Baseline PSA value above overall median	279 (50)	269 (104)	0.41 (0.30 to 0.58)
Low volume of disease	220 (14)	203 (47)	0.25 (0.14 to 0.46)
High volume of disease	354 (77)	373 (154)	0.43 (0.33 to 0.57)
No prior docetaxel therapy	471 (70)	474 (166)	0.37 (0.28 to 0.49)
Prior docetaxel therapy	103 (21)	102 (35)	0.52 (0.30 to 0.89)
Previous use of ADT or orchiectomy	535 (88)	515 (179)	0.41 (0.32 to 0.53)
No previous use of ADT or orchiectomy	39 (3)	61 (22)	0.19 (0.06 to 0.62)



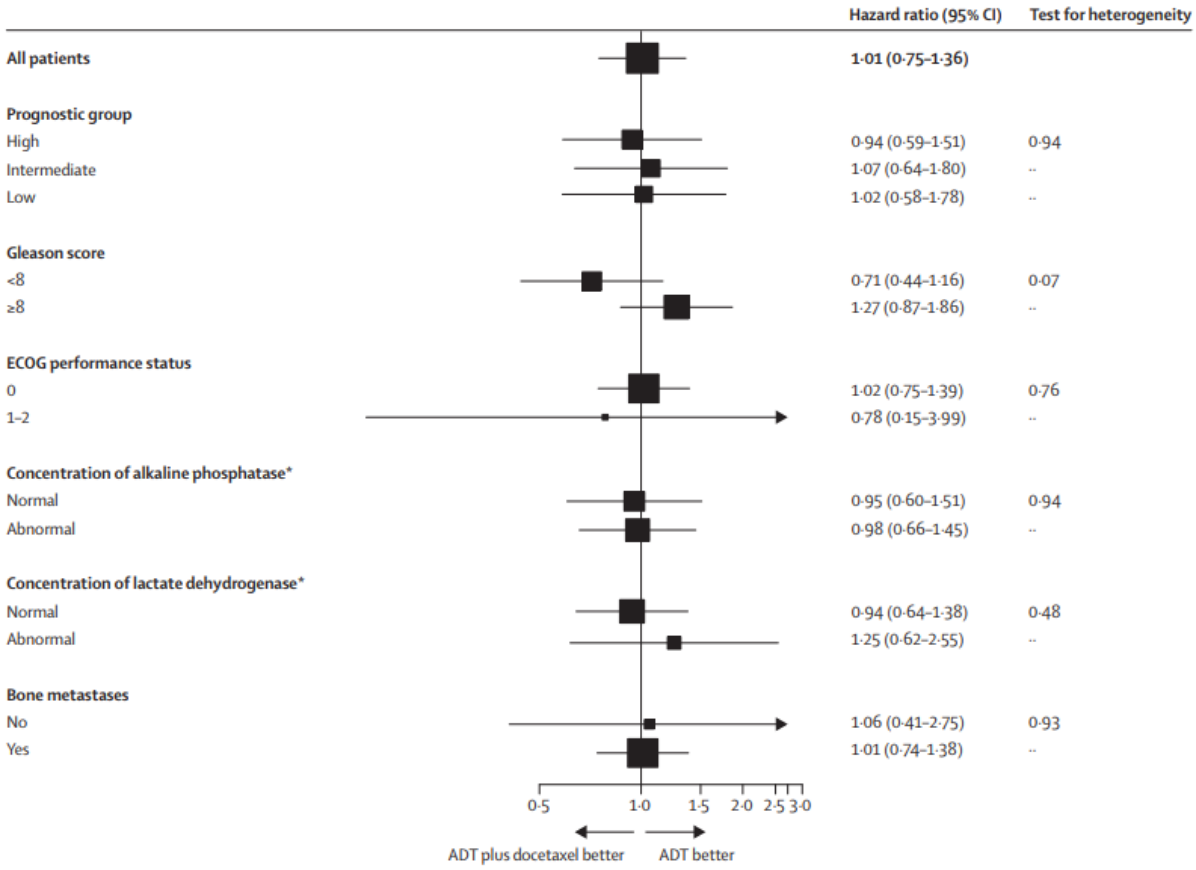
Notes: Taken from Armstrong et al 2019(1)

Figure 6: CHAARTED trial forest plot of OS for subgroups



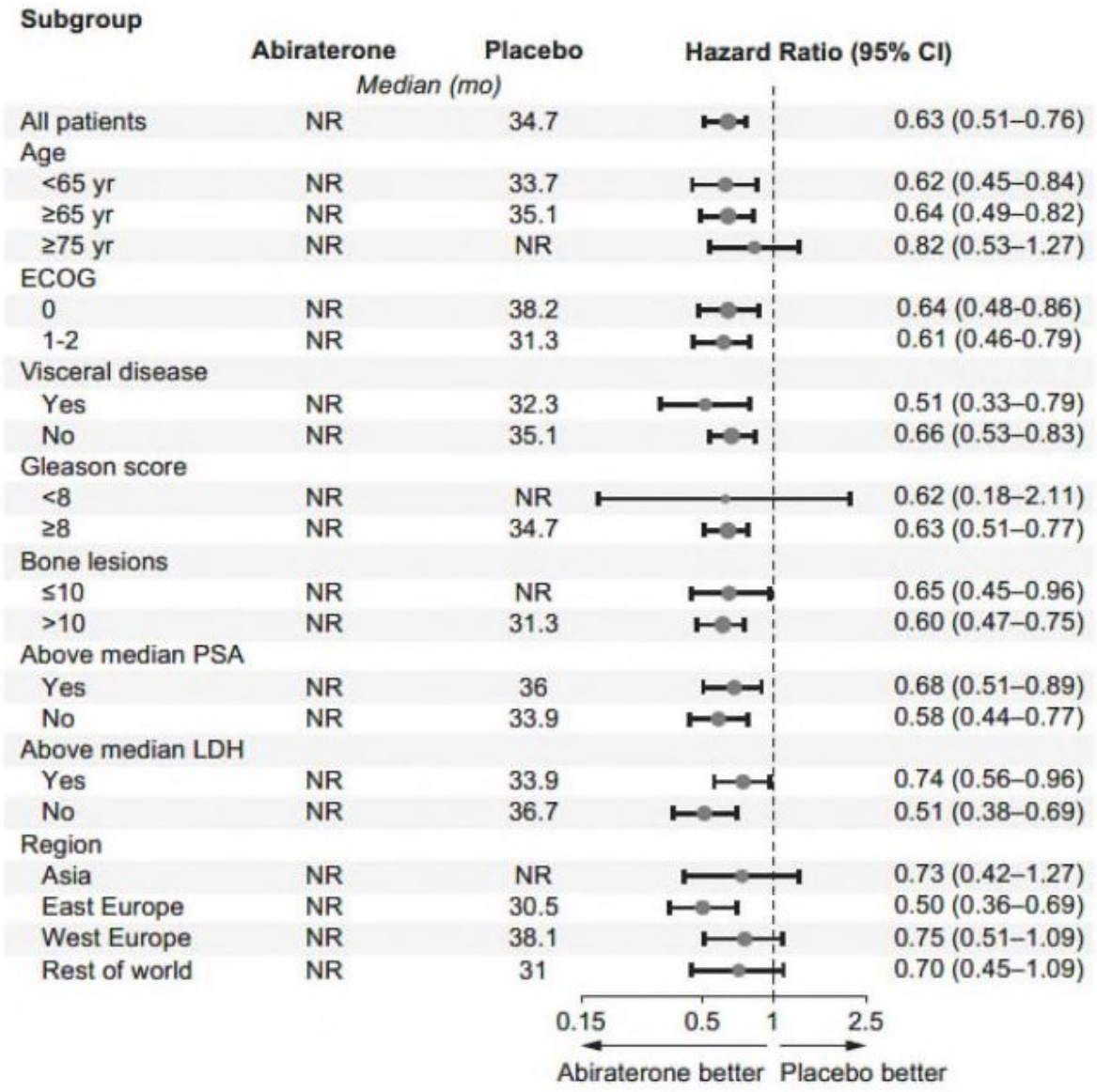
Note: Figure taken from Sweeney et al 2015 (2)

Figure 7: GETUG-AFU 15 forest plot of OS for subgroups



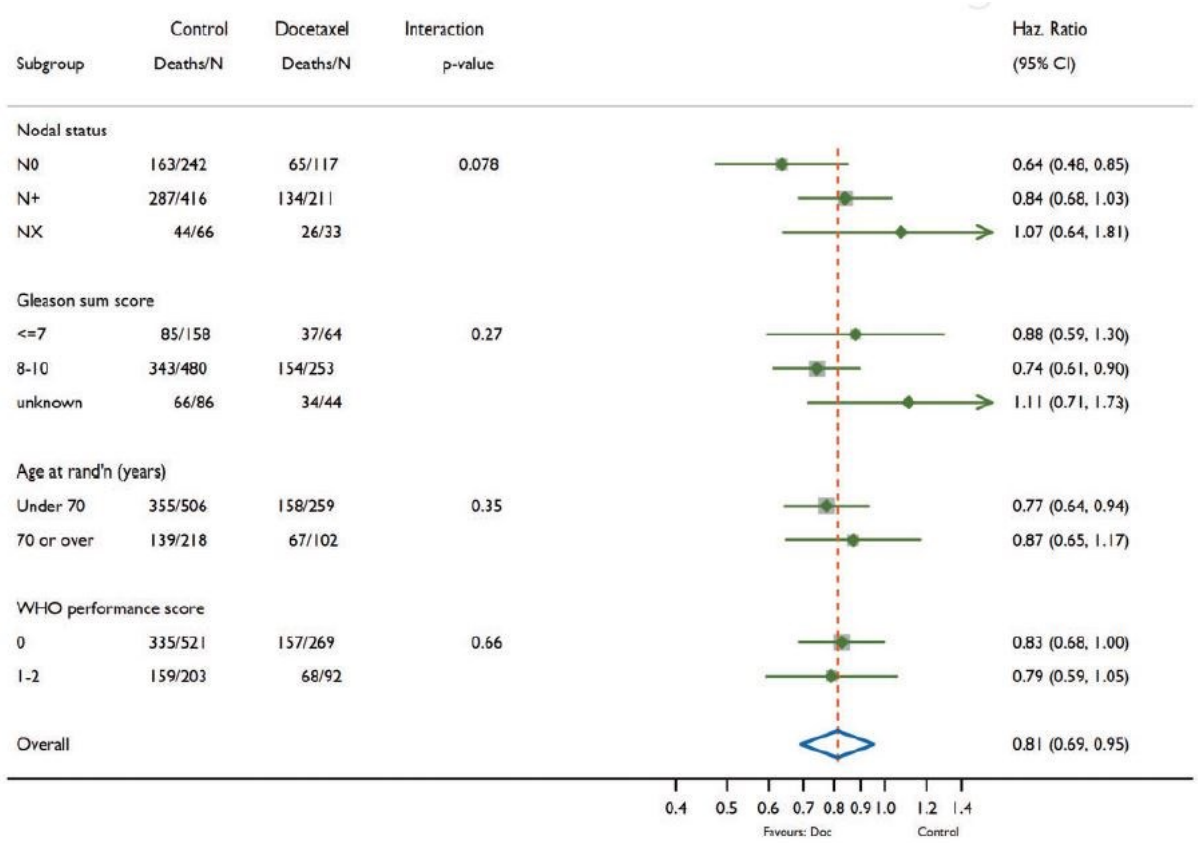
Note: Figure taken from Gravis 2013(3)

Figure 8: LATITUDE forest plot of OS for subgroups



Note: Figure taken from Fizazi 2017(4) supplementary appendix

Figure 9: STAMPEDE-3 forest plot of OS for subgroups



Note: Figure taken from Clarke 2019(5)

We compared the similarities between the trials used in the base case NMA (Appendix D Figures 2-6). The baseline characteristics compared were not identified as treatment effect modifiers, in addition, the proportions associated with these characteristics were considered to be relatively comparable across trials in the evidence base (where data was available). From the assessment, no systematic differences were detected in study population that would result in changing the relative treatment effects.

A3. CS page 66 notes that the exploratory analysis of ARASENS identified no evidence of treatment effect modification and that “This was confirmed by HTA and clinical expert input.”. Please could you elaborate on the input received?

Bayer response

Figure 16 Appendix E from ARASENS CSR was presented in HTA expert interviews to gain input on if they were aware of any other treatment effect modifiers in this disease area or if there are other resources available to assess treatment effect

modifiers in this disease area, and to assess whether they consider any of the variables explored in the subgroups analyses to indicate effect modifying properties. It was noted in HTA expert interview that from the ARASENS trial data, "*nothing looks like treatment effect modifiers*". Additionally, in the advisory board report: "*In subgroups, clinicians were not able to point to any definitive evidence proving any treatment effect modifiers and requested to see the interaction effects for the subgroups in ARASENS to confirm their understanding that no treatment effects were identified in the key trial*." That is, they did not highlight any specific clinical justification for a certain characteristic being a treatment effect modifier and no treatment effect modifiers were identified in the ARASENS trial patient level data.

Clinical study reports

A4. The ARASENS Clinical Study Report does not include section 14 'Tables, Figures and Graphs' as listed in the table of contents. Cross references within the CSR text to tables figures and graphs in section 14 are therefore not accessible to the EAG. Please can these be provided.

Bayer response

CSR section 14 'Tables, Figures and Graphs' has been attached to this response. Please note the full content of these files is confidential.

A5. The ARASENS Clinical Study Report lists '16. Appendices' in the table of contents but no appendices are included in the report itself. Please can the appendices be made available to the EAG (except for the study protocol and statistical analysis plan which have already been provided as separate documents). If any of the appendices are currently unavailable please can you list their title(s), for transparency.

CSR section 16 'Appendices' have been attached to this response. Please note the full content of these files is confidential.

Section B: Clarification on cost-effectiveness data

Discrepancies between model and submission

B1. Priority question. The visiting and testing frequencies for patients receiving cabazitaxel + ADT or radium 223 + ADT reported in CS Table 57 differ from the values used in the model in the HCRU spreadsheet. Please comment on whether the values in the model or the table are correct.

Bayer response

Our apologies, after inspection we can confirm there is an error in Table 57. Incorrect HCRU rates were copied into Table 57 for cabazitaxel + ADT or radium 223 + ADT from the cost-effectiveness model. We have updated the visiting and testing frequencies for patients receiving cabazitaxel + ADT or radium 223 + ADT in mHRPC with the correct values from the HCRU model spreadsheet in Table 1 below.

Table 1: Visits and testing frequencies included as HRU for patients receiving cabazitaxel+ADT or radium-223+ADT in mHRPC in the model while on treatment

Service mHRPC (PD1–3)	mHRPC cabazitaxel+ADT or radium-223+ADT			Reference
	% of patients	No. of visits	Every x weeks	
Outpatient visit oncologist	100%	1.00	3.00	TA712(10)
CT scan	5%	1.00	6.00	
Radiographic or MRI scan	5%	1.00	6.00	
ECG	5%	1.00	6.00	
Ultrasound	5%	1.00	6.00	
Bone scan	5%	1.00	6.00	
Full blood count	100%	1.00	3.00	
Liver function test	100%	1.00	3.00	
Kidney function test	100%	1.00	3.00	
PSA test	100%	1.00	3.00	

Key: CT, computed tomography, ERG, Evidence Review Group, HRU, health-care resource use, mHRPC, metastatic hormone-relapsed prostate cancer, no., number, MRI, magnetic resonance imaging, PSA, prostate-specific antigen, TA, technology appraisal.

B2. Priority question. The subsequent treatment distribution reported in CS Table 58 differs to the values used in the model. In the model those patients receiving subsequent treatment of no treatment / best supportive care are reported as receiving ADT only in CS Table 58. Please comment on whether the values in the model or the table are correct. Please also explain why the subsequent treatment costs for patients receiving ADT are zero in the model.

Bayer response

Thank you for your question. If we understand correctly, the difference you are referring to is that the % of patients that is reported to receive 'ADT' in CS Table 58 are modelled to receive 'No treatment/BSC' in the cost-effectiveness model workbook. In this instance the description in CS Table 58 is more accurate, as 'No treatment/BSC' still receive ADT. However, both categories are functionally the same in the model, as explained below, so moving all 'No treatment/BSC' mHRPC patients to 'ADT' will not change any of the model outcomes.

In the model, we assume that background treatment with ADT is continued indefinitely, regardless of the mHSPC or post-progression treatment status of a patient. In addition, the ADT costs per cycle are assumed to be the same across all health states. This approach of modelling is in line with previous prostate cancer TAs (TA712(10), TA721(11), and TA741(12)) and was validated by UK clinical experts.

Because the ADT costs are constant and applied equally for all patients across all health states, the ADT background therapy costs are tracked separately from all other costs in the model, to simplify the calculations. Consequently, the subsequent treatment cost for ADT alone are modelled as £0, as ADT costs are already accounted for in the ADT background therapy cost calculations. The 'No treatment/BSC' and 'ADT' categories in the Subseq_Trt sheet are therefore functionally the same, as both rely on the same input and have £0 additional costs.

B3. Priority question. The subsequent treatment durations reported in CS table 59 differ from those values used in the model for docetaxel, radium 223 and

cabazitaxel. Please comment on whether the values in the model or the table are correct.

Bayer response

We appreciate the EAG's question. In this instance the model is correct. We are happy to provide further clarification for the discrepancies in subsequent treatment durations between the economic model and the CS table 59.

As described in Doc B, the model uses mean PFS and treatment durations to model the subsequent treatment costs. However, for several subsequent treatments, only median values were reported. We therefore estimated the mean values by adjusted reported medians by /LN(2). This correction was initially applied for all subsequent treatments. However, because docetaxel, radium 223 and cabazitaxel have a fixed treatment duration, such a correction would overestimate treatment use. We therefore updated the model and assumed that mean and median duration would be the same for these treatments, but accidentally omitted to also update CS Table 59. Please find the corrected CS Table 59 below to align our assumptions in the economic model:

Table 2: Subsequent treatment durations and PFS used for the subsequent treatment calculations

Subsequent treatment	Mean* PFS (weeks)	Mean* treatment duration (weeks)	Source
ADT	24.5	28.9	Estimated using median ToT and PFS from PREVAIL(13)
Abiraterone	103.5	86.6	Estimated using median time on treatment of clinical trial, TA387 (Table 67 pg 150 of manufacturer's submission(14) and median rPFS TA387 page 79 of 308(14))
Enzalutamide	123.6	111.1	Estimated using median time to treatment discontinuation TA377 (page 16 of NICE pre-meeting briefing) and median rPFS TA377 (Table A1, page 26 of NICE company submission)(15)
Docetaxel	73.4	28.5**	Median ToT 9.5 cycles of 21 days, TAX 327, Table 2(16) and estimated using median PFS, Bajranada et al. (2016).(17)
Radium 223	89.0	20.3**	ToT Bayer internal data [Data on file] PFS estimated from median PFS, TA412 slide 28.(18)

Cabazitaxel	55.2	18.0**	Estimated using median TTP: TA391 (pg 71 of ACD).(19) Median ToT: TROPPIC 6 cycles of 21 days (as stated in TA712, Table 48)(20)
Key: ADT, androgen deprivation therapy, PFS, progression-free survival, pg., page, rPFS, radiographic progression-free survival, TA, technology appraisal, ToT, time-on-treatment *When no mean duration was reported, means were estimated by adjusting the reported median with /LN(2). ** *Mean and median treatment duration assumed equal, due to predefined max treatment duration			

B4. Priority question. The Marie Curie nursing service cost component of the terminal care costs in the model (£550) differ from the figure give in the source document (£500; page 3 Georghiou and Bardsley 2014). Please comment on which is the correct value**.**

Bayer response

Our apologies, after inspection we can confirm that the cost in the model should have been £500, in line with the source. We have updated terminal care costs in the model and this change has only a very limited impact on the ICERs. Please see Table 3 below for the updated company base case results.

Table 3: Reported and updated model outcomes with terminal care cost updated

Treatment	Reported model results (Doc B)			Updated model results		
	Cost	QALYs	ICER	Cost	QALYs	ICER
Darolutamide + docetaxel + ADT	£92,740	5.32	-	£92,697	5.32	
Docetaxel + ADT	£68,395	3.69	£14,950	£68,348	3.69	£14,953
Enzalutamide + ADT	£163,259	4.42	Darolutamide dominant	£163,214	4.42	Darolutamide dominant
ADT alone	£71,263	2.99	£9,216	£71,213	2.99	£9,218
Key: ADT, androgen deprivation therapy, ICER, incremental cost-effectiveness ratio, QALYs, quality-adjusted life years.						

B5. Priority question. The source for the calculation for the AE unit cost for diarrhoea is NHS reference costs 2020-2021; NES: weighted average of PF26A, PF26B, PF26C. This gives a cost of £877.67, not £952.61 as given in the CS and

model. £952.61 is the weighted average of PF26A and PF26B only. Please comment on which is the correct unit cost.

Bayer response

Our apologies, in the CS, the description PF26C was included by mistake. In the economic model, the cost was calculated by the weighted average of PF26A and PF26B only, in line with the input used in previous oncology models in past TAs.(21, 22)

Model input parameters

B6. Please comment on why paediatric costs (PF26A, PF26B, PF26C) for diarrhoea have been used for an adult condition (CS Table 62).

Bayer response

To our knowledge, no specific HRG code is available for diarrhoea in the latest NHS National Cost Collection. We therefore conducted a targeted search in the previous oncology TAs to identify costs for diarrhoea. TA712 used a weighted average of NEL PF28A, PF28B, PF28C, PF28D, PF28E from NHS reference costs 2016-2017. However, this resulted in a cost of £2,689.81, which we considered to be an over-estimate to treat diarrhoea. We therefore used the cost code used in TA405, in which the ERG stated a preference to use a weighted average of the paediatric codes PF26A&B to inform diarrhoea costs, in line with the costs used in TA370, despite both being adult conditions.(21, 22)

In addition, the diarrhoea cost used only have a very minor impact on the model outcomes, with the ICERs vs docetaxel + ADT and ADT alone only increasing to £14,951 (+£1) and £9,221 (+£6) respectively when a diarrhoea cost of £2,689.81 is used (as in TA712) and enzalutamide dominated in both scenarios.

So, considering the small impact on the model results, face validity of the resulting aggregate costs, and precedence set in TA405, we considered it would be appropriate to use PF26A&B to inform diarrhoea costs, despite being paediatric cost-codes.

B7. Please confirm the source for the enzalutamide rPFS (CS Table 59). Page 16 of the TA377 NICE pre-meeting briefing only mentions the median time to treatment discontinuation.

Bayer response

Our apologies, upon closer inspection of TA377 we indeed realized that rPFS was not reported in the pre-meeting briefing, but only in the manufacturer's submission document (for example in Table A1, on page 26). We have updated the reference in Table 2 above.

B8. Please can you confirm the reference for the Papaioannou et al. checklist (Appendix H.4.3, page 120). This publication does not appear to have been cited in the CS documents.

Bayer response

Our apologies, this reference was omitted in the CS documents. Please see below for the reference for Papaioannou et al. checklist:

- Papaioannou D, Brazier J and Paisley S. Systematic searching and selection of health state utility values from the literature. Value Health. 2013; 16(4):686-95.

Section C: Textual clarification and additional points

Presentation of the studies included in the SLR and NMA

C1. The presentation of the studies included in the SLR and the NMA in Appendix D is inconsistent, ambiguous and, therefore, difficult to follow. This is particularly the case when comparing between tables. Please could clarification be provided in respect of the following:

C1a. Table 5 'Summary of the clinical evidence base' lists 27 included studies by primary publication author *and* trial name (where applicable). We propose no change to the presentation of this table (but see below).

C1b. Table 6: 'Quality assessment of included RCT studies using NICE checklist' lists 27 included studies by primary publication author *only* (no trial

name, where applicable). It would be helpful if primary publication author *and* trial name (where applicable) were included, as per Table 5.

Bayer response

Please find below Table 6 ‘Quality assessment of included RCT studies using NICE checklist’ updated to include author and trial name (where applicable).

Study	Randomization appropriate?	Allocation concealment adequate?	Groups similar at the outset of the study in terms of prognostic factors?	Blinding to treatment allocation?	Unexpected imbalances in drop-outs between groups?	Authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis?
Boccon-Gibod 1997	Yes	Yes	Yes	No	No	No	Yes
Eisenberger 1998 (SWOG study-S8894)	Yes	No	Yes	Yes	No	No	Yes
Klijn 1993 (EORTC-TRIAL 30843)	No	No	No	No	No	No	No
Fizazi 2021 (PEACE-1)	Unclear	No	Unclear	No	Unclear	No	Unclear
Agarwal 2021(SWOG S1216)	No	No	No	No	No	No	Yes
Gravis 2013 (GETUG-AFU 15)	Yes	No	Yes	No	No	No	Yes
Chang 1996	Yes	No	Yes	Yes	No	No	No
Kulkarni 2003	No	No	Yes	Yes	No	No	Yes
Kaisary 1995	No	No	Yes	No	No	No	No
Davis 2019 (ENZAMET)	Yes	Yes	Yes	No	No	No	Yes
Zalcberg 1996	No	No	Yes	Yes	No	No	Yes
Schröder 2004 (EORTC-30892)	No	No	Yes	No	No	No	Yes
Armstrong 2019 (ARCHES)	Yes	Yes	Yes	Yes	No	No	Yes
Chi 2019 TITAN	Yes	Yes	Yes	Yes	No	No	Yes

Study	Randomization appropriate?	Allocation concealment adequate?	Groups similar at the outset of the study in terms of prognostic factors?	Blinding to treatment allocation?	Unexpected imbalances in drop-outs between groups?	Authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis?
Kirby 1999	No	No	Yes	Yes	No	No	Yes
Saltzstein 2021 (HERO Study)	Unclear	No	Yes	No	No	No	Yes
Iversen 1996	No	No	Yes	No	No	No	No
Bruun 1996	Yes	No	Yes	No	No	No	No
Ferrari 1996	No	No	Yes	No	No	No	No
Thorpe 1996	Yes	No	Yes	No	Yes	No	Yes
Vaishampayan 2021	Yes	No	Yes	No	Yes	No	Yes
Vogelzang 1995	No	No	No	No	No	No	Yes
Chodak 1995	No	No	Yes	No	No	No	Yes
Fizazi 2017 (LATITUDE)	Yes	Yes	Yes	Yes	No	No	Yes
James 2016 (STAMPEDE)	Yes	No	Yes	No	No	No	Yes
Sweeney 2015 (CHAARTED)	Yes	No	Yes	No	No	No	Yes
CSR 2022 (ARASENS)	Yes	Yes	Yes	Yes	No	No	Yes

Key: CSR, clinical study report; NICE, National Institute for Health and Care Excellence; RCT, randomized controlled trial.
Notes: Full citation details for each study can be found in the SLR report.(23)

C1c. ‘Table 7 Summary of treatments’ lists 35 trials, by *either* trial name *or* primary publication author. It would be helpful if primary publication author *and* trial name (where applicable) were included, as per Table 5.

Bayer response

Please find below Table 7 ‘Summary of treatments’ updated to include author and trial name (where applicable).

Study	Treatment	Treatment class	Sample size	Dose	Frequency	Delivery	Treatment cycle	Number of cycles of treatment received
CSR 2022 (ARASENS)	Darolutamide + ADT + docetaxel	Anti-androgen + ADT + chemotherapy	651	Darolutamide: 600mg	Darolutamide: BID	Darolutamide: Oral	Docetaxel: 3 weeks	1127 patients received 6 cycles 38 patients received 5 cycles 29 patients received 4 cycles 21 patients received 3 cycles 28 patients received 2 cycles 36 patients received 1 cycle
	Placebo + ADT + docetaxel	ADT + chemotherapy	654	Docetaxel: 75 mg/m^2	Docetaxel: every 21 days	Docetaxel: IV	Docetaxel: 3 weeks	23 patients received 0 cycles
Sweeney 2015 (CHAARTED)	ADT	ADT	393	ADT: LHRH analogues	NR	NR	3 weeks	NR
	Docetaxel + ADT	ADT + chemotherapy	397	Docetaxel: 75 mg/m^2 ADT: LHRH analogues	3 weeks	NR	3 weeks	6 cycles

Study	Treatment	Treatment class	Sample size	Dose	Frequency	Delivery	Treatment cycle	Number of cycles of treatment received
Davis 2019 (ENZAMET)	Enzalutamide + ADT ± Docetaxel	Anti-androgen + ADT ±chemotherapy	563	Enzalutamide: 160 mg Docetaxel: 75 mg/m^2	Once daily	Oral	Docetaxel: 3 weeks	6 cycles
	SNA + ADT ± Docetaxel	SNA + ADT ± chemotherapy	562	Bicalutamide 50mg/ nilutamide 150mg/ flutamide 250mg	NR	Oral	Docetaxel: 3 weeks	6 cycles
Gravis 2013 (GETUG-AFU 15)	ADT	ADT	193	LHRH analogues alone or combined with non-steroidal antiandrogens.	Varies	NR	NR	ADT given continuously until unacceptable toxic effects or discontinuation on the patients' request
	Docetaxel + ADT	ADT + chemotherapy	192	ADT: Varies Docetaxel: 75 mg/m^2	ADT: Varies Docetaxel: every 21 days	IV	Docetaxel: 3 weeks ADT: continuously until unacceptable toxic effects	Up to 9 cycles

Study	Treatment	Treatment class	Sample size	Dose	Frequency	Delivery	Treatment cycle	Number of cycles of treatment received
							or discontinuation on the patients' request	
Fizazi 2021 (PEACE-1)	Abiraterone + Docetaxel + ADT	Anti-androgen + chemotherapy + ADT	NR (710 patients in total)	Abiraterone: 1000mg/day Docetaxel: 75 mg/m^2 ADT :agonist, LHRH antagonist or orchiectomy	Abiraterone: BID	NR	Docetaxel: 3 weeks	6 cycles
	Docetaxel + ADT	Chemotherapy + ADT	NR (710 patients in total)	Docetaxel: 75 mg/m^2 ADT :agonist, LHRH antagonist or orchiectomy	NR	NR	Docetaxel: 3 weeks	6 cycles
James 2016 (STAMPEDE -1)	ADT	ADT	1184	gonadotropin-releasing hormone agonists or antagonists	NR	NR	NR	NR
	Docetaxel + ADT	Chemotherapy +ADT	592	Docetaxel: 75 mg/m^2	NR	NR	Docetaxel: 3 weeks	6 cycles

Study	Treatment	Treatment class	Sample size	Dose	Frequency	Delivery	Treatment cycle	Number of cycles of treatment received
				ADT: gonadotropin-releasing hormone agonists or antagonists				
	Docetaxel + Zoledronic acid + ADT	Chemotherapy +ADT	593	Zoledronic acid: 4 mg Docetaxel: 75 mg/m^2. ADT: gonadotropin-releasing hormone agonists or antagonists	NR	NR	Docetaxel: 3 weeks	Zoledronic acid: 6 cycles then 4-weekly until 2 years Docetaxel: 6 cycles
	Zoledronic acid + ADT	ADT	593	Zoledronic acid: 4 mg ADT: gonadotropin-releasing hormone agonists or antagonists	NR	NR	Docetaxel: 3 weeks	6 cycles then 4-weekly until 2 years
	Docetaxel + ADT	Chemotherapy + ADT	362	Docetaxel: 75 mg/m^2	NR	NR	Docetaxel: 3 weeks	6 cycles

Study	Treatment	Treatment class	Sample size	Dose	Frequency	Delivery	Treatment cycle	Number of cycles of treatment received
Clarke 2019 (STAMPEDE -3)	ADT	ADT	724	NR	NR	NR	NR	NR
Sydes 2018 (STAMPEDE -4)	Abiraterone acetate + ADT	Antiandrogen + ADT	377	Abiraterone: 1000mg/day	NR	NR	NR	NR
	Docetaxel + ADT	Chemotherapy + ADT	189	Docetaxel: 75 mg/m^2	NR	NR	Docetaxel: 3 weeks	6 cycles
Ferrari 1996	Leuprolide	ADT	76	NR	Every 28 days	IM	NR	NR
	Leuprolide + Flutamide	ADT + SNA	74	Leuprolide: NR	Leuprolide: every 28 days	Leuprolide: IM	NR	NR
				Flutamide: 250mg	Flutamide: TID	Flutamide: NR	NR	NR
Kulkarni 2003	Bilateral orchiectomy	Orchiectomy	50	NR	NR	Placebo: Oral	NR	NR
	Bilateral orchiectomy + Flutamide	Orchiectomy + SNA	50	250 mg	TID	Flutamide: Oral	NR	NR
Eisenberger 1998 (SWOG study-S8894)	Bilateral orchiectomy	Orchiectomy	687	NR	NR	Placebo: Oral	NR	NR
	Bilateral orchiectomy + Flutamide	Orchiectomy + SNA	700	250 mg	TID	Flutamide: Oral	NR	NR
Vaishampayan 2021	Bicalutamide + ADT	SNA + ADT	35	Bicalutamide: 50 mg	Once daily	Oral	NR	NR

Study	Treatment	Treatment class	Sample size	Dose	Frequency	Delivery	Treatment cycle	Number of cycles of treatment received
				ADT: Orchiectomy/LHRH analogue Leuprolide or goserelin			NR	NR
	Enzalutamide + ADT	Antiandrogen + ADT	36	Enzalutamide 160 my (4 x 40mg)	Four times daily	Oral	NR	NR
				ADT- Orchiectomy/LHRH analogue Leuprolide or Goserelin			NR	NR
Zalcberg 1996	Bilateral orchiectomy	Orchiectomy	110	NR	TID	Oral	NR	NR
	Bilateral orchiectomy + Flutamide	Orchiectomy + SNA	112	Flutamide: 250 mg	TID	Flutamide: Oral	NR	NR
Boccon-Gibod 1997	Flutamide	SNA	54	250 mg	TID	Oral	NR	NR
	Orchiectomy	ADT	50	formal/subcapsular orchidectomy	NR	NR	NR	NR
Chang 1996	Diethylstilbestrol	ADT	48	1 mg	TID	Oral	NR	NR
	Flutamide	SNA	44	250 mg	TID	Oral	NR	NR
Chodak 1995	Bicalutamide	SNA	259	50 mg	Once daily	NR	NR	NR
		Orchiectomy	257	NR		NR	NR	NR

Study	Treatment	Treatment class	Sample size	Dose	Frequency	Delivery	Treatment cycle	Number of cycles of treatment received
	Castration (Medical or surgical)				Goserelin acetate: every 28 days	Note: Castration done either as bilateral orchiectomy or a depot injection of LHRH analogue, Goserelin acetate	NR	NR
Schröder 2004 (EORTC-30892)	Cyproterone acetate	Antiandrogen	156	100 mg	TID	Oral	NR	NR
	Flutamide	SNA	154	250 mg	TID	Oral	NR	NR
Iversen 1996	Bicalutamide	SNA	186	50 mg	once daily	NR	NR	NR
	Bilateral orchiectomy	Orchiectomy	190	NR	NR	NR	NR	NR
Kaisary 1995	Bicalutamide	SNA	119	50 mg	Once daily	Oral	NR	NR
	Castration (Medical or surgical)	Orchiectomy	126	Zoladex (goserelin 3.6 mg s.c. every 28 days), or	Goserelin acetate: every 28 days	SC for medical castration	NR	NR
Kirby 1999	Finasteride + Flutamide	Antiandrogen + SNA	35	Finasteride:10.0 mg Flutamide: 250 mg	Flutamide: TID	Finasteride/flutamide: NR	NR	NR
	Goserelin + Finasteride	ADT + antiandrogen	36	Goserelin: 3.6 mg Finasteride:10mg	Goserelin: Monthly Finasteride: Daily	Goserelin: SC	NR	NR
						Finasteride: NR	NR	NR
		ADT + SNA	35			Goserelin: SC	NR	NR

Study	Treatment	Treatment class	Sample size	Dose	Frequency	Delivery	Treatment cycle	Number of cycles of treatment received
	Goserelin + Flutamide			Goserelin:3.6 mg + Flutamide, 250 mg	Goserelin: Monthly Flutamide: TID	Flutamide: NR	NR	NR
Armstrong 2019 (ARCHES)	ADT	ADT	576	bilateral orchiectomy or LHRH agonist/antagonist.	Daily	Oral	NR	NR
	Enzalutamide + ADT	Antiandrogen + ADT	574	Enzalutamide:160 mg/day	Daily	Oral	NR	NR
				ADT: bilateral orchiectomy or LHRH agonist/antagonist.			NR	NR
Bruun 1996	Buserelin	ADT	72	Buserelin: 0.5 mg for the first week and then intranasally at a dose of 0.4 mg t.i.d.	TID	Subcutaneously and Intranasally	NR	NR
Bruun 1996	Conventional Antiandrogenic Treatment (Oestrogens or Bilateral orchiectomy)	Orchiectomy	68	Oestrogen: Comprised of different dosage schedules:	Oestrogen: Comprised of different dosage schedules:	NR	NR	NR
				• Polyestradiol phosphate: 160 mg 80 mg.	• Polyestradiol phosphate: monthly		NR	NR

Study	Treatment	Treatment class	Sample size	Dose	Frequency	Delivery	Treatment cycle	Number of cycles of treatment received
				• Polyestradiol phosphate + ethinylestradiol: Polyestradiol phosphate 160 and then ethinylestradiol 50 µg and then as maintenance dose ethinylestradiol 50 µg.	• Polyestradiol phosphate + ethinylestradiol: monthly for 3 months and then ethinylestradiol 50 µg TID. for 3 months and then as maintenance dose ethinylestradiol given BID.		NR	NR
				• Polyestradiol phosphate + estradiol: Polyestradiol phosphate 160 mg and then estradiol 10 mg and then 5 mg daily.	• Polyestradiol phosphate + estradiol: Polyestradiol phosphate monthly for 3 months and then estradiol BID a fortnight initially and then daily.		NR	NR
				• Diethylstilbestrol: initial high-dose of 5 mg and then 1 mg as a maintenance dose.	• Diethylstilbestrol: TID		NR	NR

Study	Treatment	Treatment class	Sample size	Dose	Frequency	Delivery	Treatment cycle	Number of cycles of treatment received
				• Estramustine phosphate: two capsules b.i.d.	• Estramustine phosphate: BID		NR	NR
					Bilateral orchiectomy: NR		NR	NR
				Bilateral orchiectomy: NR			NR	NR
Klijn 1993 (EORTC-TRIAL 30843)	Buserelin + Cyproterone acetate	ADT + antiandrogen	NR	Buserelin: 0.5 mg followed by 400µg	Buserelin: TID	Buserelin: subcutaneously, intranasally	NR	NR
				Cyproterone acetate: 50mg	Cyproterone acetate: TID		NR	NR
						Cyproterone acetate: NR	NR	NR
	Buserelin + Cyproterone acetate 2wk	ADT + antiandrogen	NR	Buserelin: 0.5 mg followed by 400µg	Buserelin: TID	Buserelin: subcutaneously, intranasally	NR	NR
				Cyproterone acetate: 50mg	Cyproterone acetate: TID		NR	NR
						Cyproterone acetate: NR	NR	NR
	Orchiectomy	ADT	NR	NR	NR	NR	NR	NR
Saltzstein 2021 (HERO Study)	Leuprolide	ADT	70	22.5 mg (or 11.25 mg in Japan and Taiwan based on local labels)	3 months	Subcutaneous injection	NR	NR

Study	Treatment	Treatment class	Sample size	Dose	Frequency	Delivery	Treatment cycle	Number of cycles of treatment received
	Relugolix	ADT	141	120 mg once daily after a single oral loading dose of 360 mg).	Daily	Oral	NR	NR
Fizazi 2017 (LATITUDE)	Abiraterone acetate + Prednisone + ADT	Antiandrogen + ADT	597	Abiraterone acetate : 1000g	Daily	Oral	NR	NR
				Prednisone: 5 mg			NR	NR
	ADT	ADT	602	LHRH agonists or surgical castration	Daily	Oral	NR	NR
James 2016 (STAMPEDE -2)	Abiraterone acetate + Prednisone + ADT	Antiandrogen + ADT	960	Abiraterone:1000 mg prednisolone:5 mg. ADT: gonadotropin-releasing hormone agonists or antagonists	Abiraterone: Daily	NR	NR	NR
	ADT	ADT	957	ADT: gonadotropin-releasing hormone agonists or antagonists	Daily	NR	NR	NR

Study	Treatment	Treatment class	Sample size	Dose	Frequency	Delivery	Treatment cycle	Number of cycles of treatment received
Parker 2018 (STAMPEDE -5)	Radiotherapy + ADT	Radiotherapy + ADT	1032	36 Gy - 55 Gy	Weekly fractions for 6 weeks or 20 daily fractions for 4 weeks	NR	NR	NR
	ADT	ADT	1029	NR	NR	NR	NR	NR
Clark 2013 (STAMPEDE -6)	ADT	ADT	630	NR	NR	NR	NR	NR
James 2016 (STAMPEDE -7)	Celecoxib + ADT	ADT	291	400 mg	Twice daily	Oral	NR	NR
	ADT	ADT	584	NR	NR	NR	NR	NR
Thorpe 1996	Cyproterone acetate	Antiandrogen	175	100 mg	TID	NR	NR	NR
	Goserelin	ADT	175	3.6 mg	Every 28 days	S.C.	NR	NR
	Goserelin + Cyproterone acetate	ADT + antiandrogen	175	Goserelin acetate: 3.6 mg	CPA:TID goserelin acetate: every 28 days	Goserelin: S.C.	NR	NR
						Cyproterone acetate: NR	NR	NR
				CPA: 100mg			NR	NR
Chi 2019 (TITAN)	ADT	ADT	527	GnRHa (agonist or antagonist)	Daily	Oral	NR	NR
	Apalutamide + ADT	Antiandrogen + ADT	525	Apalutamide: 240 mg (4 x 60 mg)	Daily	Oral	NR	NR
				ADT: GnRHa (agonist or antagonist)			NR	NR

Study	Treatment	Treatment class	Sample size	Dose	Frequency	Delivery	Treatment cycle	Number of cycles of treatment received
Vogelzang 1995	Goserelin	ADT	138	3.6 mg	Every 28 days	S.C.	NR	NR
	Orchiectomy	ADT	145	NR	NR	NR	NR	NR

Key: ADT, androgen deprived therapy; BID, twice a day; Gy, gamma rays; IV, intravenous; LHRH, luteinising hormone-releasing hormone; NR, not reported, S.C., subcutaneous, SNA, nonsteroidal antiandrogen; TID, three times a day;
Note: SOC as it was either ADT or docetaxel + ADT. Full citation details for each study can be found in the SLR report.[23]

C1d. The Table 7 caption does not refer to any particular set of studies, but the in-text reference to Table 7 refers to "..the studies in the evidence base". It would be helpful if, respectively, the Table caption and the in-text reference to Table 7 could be worded more specifically and are consistent. Also, please provide an explanation in the text and in a table footnote as to why 35 studies and not 27 are listed.

Bayer response

Apologies for the lack of clarity with regards to the number of studies which were considered in the NMA. A total of 27 studies were identified in the SLR and were presented in Table 5. In Table 5, the STAMPEDE study is classified as one study, however, in Table 7 which present studies considered for the NMA the STAMPEDE trial was counted as seven distinct studies due to the multi-arm multi-stage platform design of STAMPEDE, this results in the 33 studies presented in Table 7. We also noted after inspection Agarwal 2021 (SWOG S1216) was missing from Table 7 and that a total of 36 treatments were identified across 33 studies in the evidence base. Please find the corrected text which is now worded more specifically and an updated Table 7 below to align. The figure below shows a summary of the study exclusions at each stage for clarity.

Summary of study exclusions for NMA

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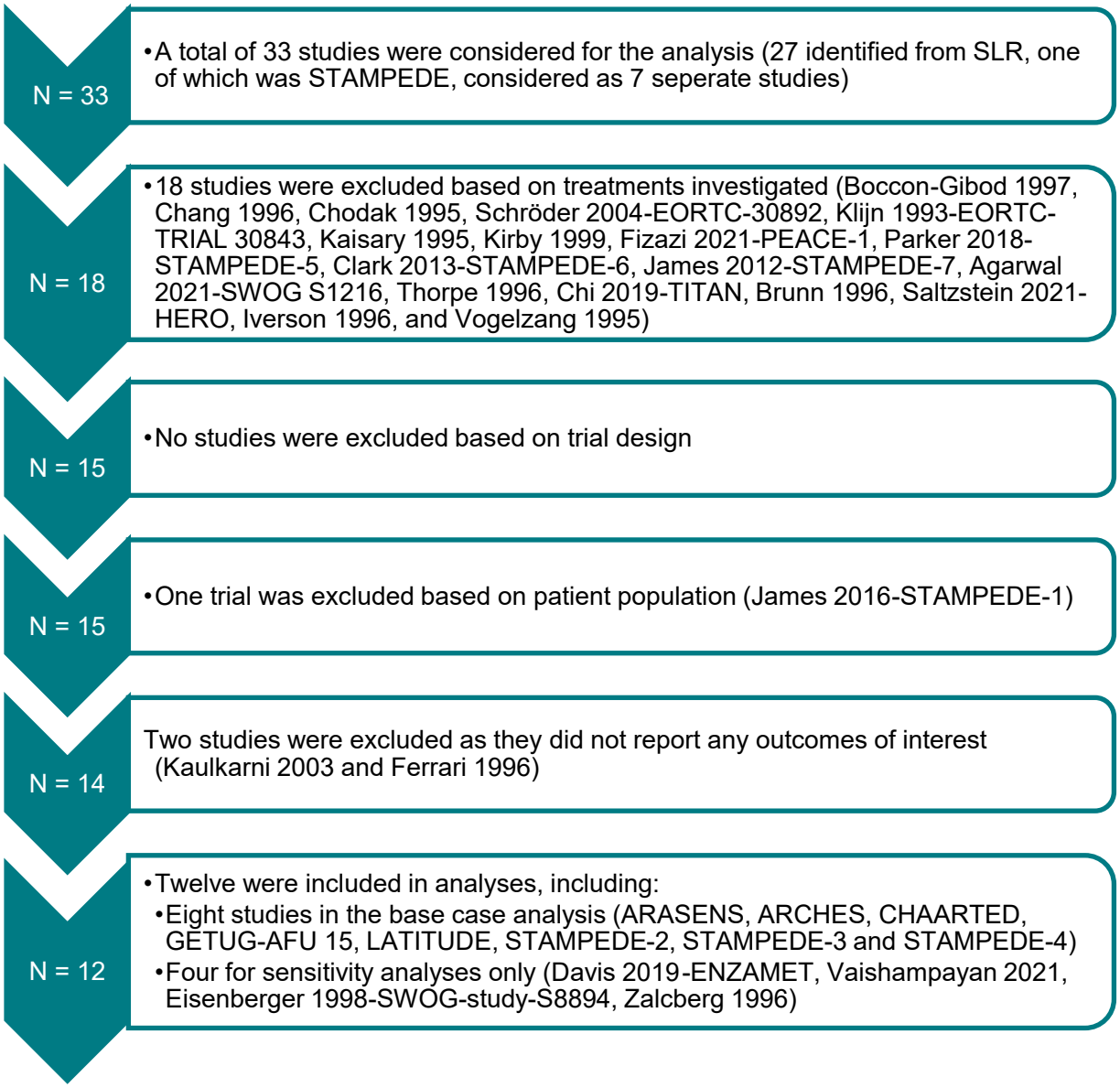

Updated text and Section B.2.9.1.2 Treatments

A total of 27 studies were identified in the SLR, however, the STAMPEDE trial is split into seven distinct studies due to the multi-arm multistage platform design of STAMPEDE, therefore this results in 33 studies. To assess trial comparability of the 33 studies identified, the differences and similarities between treatments of interest, treatment dosing, frequency, delivery, and treatment cycle were investigated (tables summarizing treatments are included in Table 7 Appendix D). The relevant

comparators for darolutamide+docetaxel+ADT are enzalutamide+ADT, docetaxel+ADT and ADT alone. Abiraterone+ADT is not considered a relevant comparator, but, as it has been a treatment studied in STAMPEDE against both docetaxel+ADT and ADT alone (two of the comparators in this appraisal), studies that investigated abiraterone were considered if they provided indirect evidence to enrich the network through the formation of loops.

36 treatments were identified across 33 trials in the evidence base.

Updated text and table 7 for Section D.1.6.2.

Treatments

Table 7 presents the dose, frequency of dose, delivery methods of treatment and treatment cycles (for docetaxel-treated patients) for the studies identified from the SLR. A total of 27 studies were identified in the SLR, however, the STAMPEDE trial is split into seven distinct studies in Table 7 due to the multi-arm multi-stage platform design of STAMPEDE. Details of study exclusions are discussed in Table 8.

The seven trials identified which include docetaxel are presented in Table 7.

Fourteen studies in the evidence base include SNAs and are presented in Table 7. Three different SNA treatments were identified; bicalutamide, nilutamide, and flutamide and dosing for these treatments were consistent. These have been assumed to be similar and combined into one node in the network; this also follows what was done in the enzalutamide submission (TA712)(10). In the enzalutamide submission (TA712)(10), orchiectomy and ADT were grouped into one node in the network. In Vaishampayan 2021, orchiectomy/LHRH analogue leuprolide or goserelin were given as ADT treatments, therefore, we have grouped orchiectomy and ADT into one node in the network.

Twelve trials in the evidence base compared other treatments of interest, summarised in Table 7. Patients in Brunn 1996 were treated with either oestrogen orchiectomy or bilateral orchiectomy; whereas, patients in the HERO study were treated with leuprolide and relugolix. Vogelzang 1995 compares goserelin and

orchiectomy. These are all ADT treatments. Other studies in the evidence base did not specify which ADT was used in their trial. In the enzalutamide NICE submission(10) and Vaishampayan 2021, ADT treatments include, orchiectomy or LHRH analogues, such as goserelin, buserelin and leuprorelin. These were grouped into one node in the network, therefore, Brunn 1996, HERO study and Vogelzang 1995 were excluded as they collapse down to a single arm trial when treatments were grouped.

Nine trials were excluded as they do not investigate comparators of interest for this appraisal. Cyproterone acetate was not a comparator of interest, therefore we have excluded EORTC-TRIAL 30843 and Thorpe 1996 from the analysis. Radiotherapy and celecoxib were not relevant comparators of darolutamide + docetaxel + ADT. Therefore, STAMPEDE-5 and STAMPEDE-7 have not been included in the analysis. Apalutamide + ADT is only recommended for patients where docetaxel is not suitable, therefore, TITAN has been excluded from the analysis.

Table 7: Summary of treatments from clinical evidence base identified in the SLR

Study details	Treatment	Treatment class	Sample size	Dose	Frequency	Delivery	Treatment cycle	Number of cycles of treatment received
CSR 2022 ARASENS	Darolutamide + ADT + docetaxel	Anti-androgen + ADT + chemotherapy	651	Darolutamide: 600mg	Darolutamide: BID	Darolutamide: Oral	Docetaxel: 3 weeks	1127 patients received 6 cycles 38 patients received 5 cycles 29 patients received 4 cycles 21 patients received 3 cycles 28 patients received 2 cycles 36 patients received 1 cycle
	Placebo + ADT + docetaxel	ADT + chemotherapy	654	Docetaxel: 75 mg/m^2	Docetaxel: every 21 days	Docetaxel: IV	Docetaxel: 3 weeks	23 patients received 0 cycles
Sweeney 2015 CHAARTED	ADT	ADT	393	ADT: LHRH analogues	NR	NR	3 weeks	NR
	Docetaxel + ADT	ADT + chemotherapy	397	Docetaxel: 75 mg/m^2	3 weeks	NR	3 weeks	6 cycles

Study details	Treatment	Treatment class	Sample size	Dose	Frequency	Delivery	Treatment cycle	Number of cycles of treatment received
				ADT: LHRH analogues				
Davis 2019 ENZAMET	Enzalutamide + ADT ± Docetaxel	Anti-androgen + ADT ±chemotherapy	563	Enzalutamide: 160 mg Docetaxel: 75 mg/m^2	Once daily	Oral	Docetaxel: 3 weeks	6 cycles
	SNA + ADT ± Docetaxel	SNA + ADT ± chemotherapy	562	Bicalutamide 50mg/ nilutamide 150mg/ flutamide 250mg	NR	Oral	Docetaxel: 3 weeks	6 cycles
Gravis 2013 GETUG-AFU 15	ADT	ADT	193	LHRH analogues alone or combined with non-steroidal antiandrogens.	Varies	NR	NR	ADT given continuously until unacceptable toxic effects or discontinuation on the patients' request
	Docetaxel + ADT	ADT + chemotherapy	192	ADT: Varies Docetaxel: 75 mg/m^2	ADT: Varies Docetaxel: every 21 days	IV	Docetaxel: 3 weeks ADT: continuously until unacceptable toxic effects	Up to 9 cycles

Study details	Treatment	Treatment class	Sample size	Dose	Frequency	Delivery	Treatment cycle	Number of cycles of treatment received
							or discontinuation on the patients' request	
Fizazi 2021 PEACE-1	Abiraterone + Docetaxel + ADT	Anti-androgen + chemotherapy + ADT	NR (710 patients in total)	Abiraterone: 1000mg/day Docetaxel: 75 mg/m^2 ADT :agonist, LHRH antagonist or orchiectomy	Abiraterone: BID	NR	Docetaxel: 3 weeks	6 cycles
	Docetaxel + ADT	Chemotherapy + ADT	NR (710 patients in total)	Docetaxel: 75 mg/m^2 ADT :agonist, LHRH antagonist or orchiectomy	NR	NR	Docetaxel: 3 weeks	6 cycles
James 2016 STAMPEDE-1*	ADT	ADT	1184	gonadotropin-releasing hormone agonists or antagonists	NR	NR	NR	NR
	Docetaxel + ADT	Chemotherapy +ADT	592	Docetaxel: 75 mg/m^2 ADT: gonadotropin-releasing hormone agonists or antagonists	NR	NR	Docetaxel: 3 weeks	6 cycles

Study details	Treatment	Treatment class	Sample size	Dose	Frequency	Delivery	Treatment cycle	Number of cycles of treatment received
	Docetaxel + Zoledronic acid + ADT	Chemotherapy +ADT	593	Zoledronic acid: 4 mg Docetaxel: 75 mg/m^2. ADT: gonadotropin-releasing hormone agonists or antagonists	NR	NR	Docetaxel: 3 weeks	Zoledronic acid: 6 cycles then 4-weekly until 2 years Docetaxel: 6 cycles
	Zoledronic acid + ADT	ADT	593	Zoledronic acid: 4 mg ADT: gonadotropin-releasing hormone agonists or antagonists	NR	NR	Docetaxel: 3 weeks	6 cycles then 4-weekly until 2 years
Clarke 2019 STAMPEDE-3*	Docetaxel + ADT	Chemotherapy + ADT	362	Docetaxel: 75 mg/m^2	NR	NR	Docetaxel: 3 weeks	6 cycles
	ADT	ADT	724	NR	NR	NR	NR	NR
Sydes 2018 STAMPEDE-4*	Abiraterone acetate + ADT	Antiandrogen + ADT	377	Abiraterone: 1000mg/day	NR	NR	NR	NR
	Docetaxel + ADT	Chemotherapy + ADT	189	Docetaxel: 75 mg/m^2	NR	NR	Docetaxel: 3 weeks	6 cycles
Ferrari 1996	Leuprolide	ADT	76	NR	Every 28 days	IM	NR	NR
	Leuprolide + Flutamide	ADT + SNA	74	Leuprolide: NR	Leuprolide: every 28 days	Leuprolide: IM	NR	NR
				Flutamide: 250mg	Flutamide: TID	Flutamide: NR	NR	NR

Study details	Treatment	Treatment class	Sample size	Dose	Frequency	Delivery	Treatment cycle	Number of cycles of treatment received
Kulkarni 2003	Bilateral orchiectomy	Orchiectomy	50	NR	NR	Placebo: Oral	NR	NR
	Bilateral orchiectomy + Flutamide	Orchiectomy + SNA	50	250 mg	TID	Flutamide: Oral	NR	NR
Eisenberger 1998 SWOG study-S8894	Bilateral orchiectomy	Orchiectomy	687	NR	NR	Placebo: Oral	NR	NR
	Bilateral orchiectomy + Flutamide	Orchiectomy + SNA	700	250 mg	TID	Flutamide: Oral	NR	NR
Vaishampayan 2021	Bicalutamide + ADT	SNA + ADT	35	Bicalutamide: 50 mg	Once daily	Oral	NR	NR
				ADT: Orchiectomy/LHRH analogue Leuprolide or goserelin			NR	NR
	Enzalutamide + ADT	Antiandrogen + ADT	36	Enzalutamide 160 my (4 x 40mg)	Four times daily	Oral	NR	NR
				ADT- Orchiectomy/LHRH analogue Leuprolide or Goserelin			NR	NR
Zalcberg 1996	Bilateral orchiectomy	Orchiectomy	110	NR	TID	Oral	NR	NR
	Bilateral orchiectomy + Flutamide	Orchiectomy + SNA	112	Flutamide: 250 mg	TID	Flutamide: Oral	NR	NR
	Flutamide	SNA	54	250 mg	TID	Oral	NR	NR

Study details	Treatment	Treatment class	Sample size	Dose	Frequency	Delivery	Treatment cycle	Number of cycles of treatment received
Boccon-Gibod 1997	Orchiectomy	ADT	50	formal/subcapsular orchidectomy	NR	NR	NR	NR
Chang 1996	Diethylstilbestrol	ADT	48	1 mg	TID	Oral	NR	NR
	Flutamide	SNA	44	250 mg	TID	Oral	NR	NR
Chodak 1995	Bicalutamide	SNA	259	50 mg	Once daily	NR	NR	NR
	Castration (Medical or surgical)	Orchiectomy	257	NR	Goserelin acetate: every 28 days	NR	NR	NR
						Note: Castration done either as bilateral orchiectomy or a depot injection of LHRH analogue, Goserelin acetate	NR	NR
Schröder 2004 EORTC-30892	Cyproterone acetate	Antiandrogen	156	100 mg	TID	Oral	NR	NR
	Flutamide	SNA	154	250 mg	TID	Oral	NR	NR
Iversen 1996	Bicalutamide	SNA	186	50 mg	once daily	NR	NR	NR
	Bilateral orchiectomy	Orchiectomy	190	NR	NR	NR	NR	NR
Kaisary 1995	Bicalutamide	SNA	119	50 mg	Once daily	Oral	NR	NR
	Castration (Medical or surgical)	Orchiectomy	126	Zoladex (goserelin 3.6 mg s.c. every 28 days), or	Goserelin acetate: every 28 days	SC for medical castration	NR	NR
Kirby 1999	Finasteride + Flutamide	Antiandrogen + SNA	35	Finasteride:10.0 mg Flutamide: 250 mg	Flutamide: TID	Finasteride/flutamide: NR	NR	NR

Study details	Treatment	Treatment class	Sample size	Dose	Frequency	Delivery	Treatment cycle	Number of cycles of treatment received
	Goserelin + Finasteride	ADT + antiandrogen	36	Goserelin: 3.6 mg Finasteride:10mg	Goserelin: Monthly Finasteride: Daily	Goserelin: SC	NR	NR
						Finasteride: NR	NR	NR
	Goserelin + Flutamide	ADT + SNA	35	Goserelin:3.6 mg + Flutamide, 250 mg	Goserelin: Monthly Flutamide: TID	Goserelin: SC	NR	NR
						Flutamide: NR	NR	NR
Armstrong 2019 ARCHES	ADT	ADT	576	bilateral orchiectomy or LHRH agonist/antagonist.	Daily	Oral	NR	NR
	Enzalutamide + ADT	Antiandrogen + ADT	574	Enzalutamide:160 mg/day	Daily	Oral	NR	NR
				ADT: bilateral orchiectomy or LHRH agonist/antagonist.			NR	NR
Bruun 1996	Buserelin	ADT	72	Buserelin: 0.5 mg for the first week and then intranasally at a dose of 0.4 mg t.i.d.	TID	Subcutaneously and Intranasally	NR	NR
	Conventional Antiandrogenic Treatment (Oestrogens or Bilateral orchiectomy)	Orchiectomy	68	Oestrogen: Comprised of different dosage schedules:	Oestrogen: Comprised of different dosage schedules:	NR	NR	NR
				• Polyestradiol phosphate: 160 mg 80 mg.	• Polyestradiol phosphate: monthly		NR	NR

Study details	Treatment	Treatment class	Sample size	Dose	Frequency	Delivery	Treatment cycle	Number of cycles of treatment received
				• Polyestradiol phosphate + ethinylestradiol: Polyestradiol phosphate 160 and then ethinylestradiol 50 µg and then as maintenance dose ethinylestradiol 50 µg.	• Polyestradiol phosphate + ethinylestradiol: monthly for 3 months and then ethinylestradiol 50 µg TID. for 3 months and then as maintenance dose ethinylestradiol given BID.		NR	NR
				• Polyestradiol phosphate + estradiol: Polyestradiol phosphate 160 mg and then estradiol 10 mg and then 5 mg daily.	• Polyestradiol phosphate + estradiol: Polyestradiol phosphate monthly for 3 months and then estradiol BID a fortnight initially and then daily.		NR	NR
				• Diethylstilbestrol: initial high-dose of 5 mg and then 1 mg as a maintenance dose.	• Diethylstilbestrol: TID		NR	NR
				• Estramustine phosphate: two capsules b.i.d.	• Estramustine phosphate: BID		NR	NR
					Bilateral orchiectomy: NR		NR	NR

Study details	Treatment	Treatment class	Sample size	Dose	Frequency	Delivery	Treatment cycle	Number of cycles of treatment received
				Bilateral orchiectomy: NR			NR	NR
Klijn 1993 EORTC-TRIAL 30843	Buserelin + Cyproterone acetate 2wk	ADT + antiandrogen	NR	Buserelin: 0.5 mg followed by 400µg	Buserelin: TID	Buserelin: subcutaneously, intranasally	NR	NR
				Cyproterone acetate: 50mg	Cyproterone acetate: TID		NR	NR
						Cyproterone acetate: NR	NR	NR
	Orchiectomy	ADT	NR	NR	NR	NR	NR	NR
Saltzstein 2021 HERO Study	Leuprolide	ADT	70	22.5 mg (or 11.25 mg in Japan and Taiwan based on local labels)	3 months	Subcutaneous injection	NR	NR
	Relugolix	ADT	141	120 mg once daily after a single oral loading dose of 360 mg).	Daily	Oral	NR	NR
Fizazi 2017 LATITUDE	Abiraterone acetate + Prednisone + ADT	Antiandrogen + ADT	597	Abiraterone acetate : 1000g	Daily	Oral	NR	NR
				Prednisone: 5 mg			NR	NR
	ADT	ADT	602	LHRH agonists or surgical castration	Daily	Oral	NR	NR
James 2017 STAMPEDE-2*	Abiraterone acetate + Prednisone + ADT	Antiandrogen + ADT	960	Abiraterone:1000 mg prednisolone:5 mg. ADT: gonadotropin-	Abiraterone: Daily	NR	NR	NR

Study details	Treatment	Treatment class	Sample size	Dose	Frequency	Delivery	Treatment cycle	Number of cycles of treatment received
				releasing hormone agonists or antagonists				
	ADT	ADT	957	ADT: gonadotropin-releasing hormone agonists or antagonists	Daily	NR	NR	NR
Parker 2018 STAMPEDE-5*	Radiotherapy + ADT	Radiotherapy + ADT	1032	36 Gy - 55 Gy	Weekly fractions for 6 weeks or 20 daily fractions for 4 weeks	NR	NR	NR
	ADT	ADT	1029	NR	NR	NR	NR	NR
Clark 2013 STAMPEDE-6*	ADT	ADT	630	NR	NR	NR	NR	NR
James 2012 STAMPEDE-7*	Celecoxib + ADT	ADT	291	400 mg	Twice daily	Oral	NR	NR
	ADT	ADT	584	NR	NR	NR	NR	NR
Thorpe 1996	Cyproterone acetate	Antiandrogen	175	100 mg	TID	NR	NR	NR
	Goserelin	ADT	175	3.6 mg	Every 28 days	S.C.	NR	NR
	Goserelin + Cyproterone acetate	ADT + antiandrogen	175	Goserelin acetate: 3.6 mg	CPA:TID goserelin acetate: every 28 days	Goserelin: S.C.	NR	NR
						Cyproterone acetate: NR	NR	NR
				CPA: 100mg			NR	NR

Study details	Treatment	Treatment class	Sample size	Dose	Frequency	Delivery	Treatment cycle	Number of cycles of treatment received
Chi 2019 TITAN	ADT	ADT	527	GnRHa (agonist or antagonist)	Daily	Oral	NR	NR
	Apalutamide + ADT	Antiandrogen + ADT	525	Apalutamide: 240 mg (4 x 60 mg)	Daily	Oral	NR	NR
				ADT: GnRHa (agonist or antagonist)			NR	NR
Vogelzang 1995	Goserelin	ADT	138	3.6 mg	Every 28 days	S.C.	NR	NR
	Orchiectomy	ADT	145	NR	NR	NR	NR	NR
Agarwal 2021 SWOG S1216	Bicalutamide + ADT	SNA + ADT	641	ADT : LHRH agonist	NR	Oral	NR	NR
				Bicalutamide: 50 mg	Bicalutamide: Daily			
	Orteronel (TAK-700) + ADT	ADT	638	ADT: LHRH agonist	NR	Oral	NR	NR
				TAK-700: 300mg	TAK-700: Twice daily			

Key: ADT, androgen deprived therapy; BID, twice a day; Gy, gamma rays; IV, intravenous; LHRH, luteinising hormone-releasing hormone; NR, not reported, S.C., subcutaneous, SNA, nonsteroidal antiandrogen; TID, three times a day;
Note: SOC as it was either ADT or docetaxel + ADT. Full citation details for each study can be found in the SLR report.[23]
*The STAMPEDE study is split into 7 distinct studies here due to the multi-arm multistage platform design of STAMPEDE.

C1e. Table 8 ‘Study inclusion and exclusion from NMA evidence base and rationale for excluding’ lists 33 trials by primary publication author *and* trial name (where applicable). This is fine, though please clarify why 33 trials and not 27 are listed.

Bayer response

Please see response above response to C1d for detailed response. A total of 27 studies were identified in the SLR with the STAMPEDE study classified as one study, however, for consideration in the NMA the STAMPEDE trial is split into seven distinct studies, this results in 33 studies included in Table 7.

C1f. Table 9: ‘Table of inclusion/exclusion criteria’. We deduce that the criteria in the table caption are those employed by the individual trials included in the (base case) NMA, as opposed to inclusion/exclusion criteria for the NMA itself. We also note that 6 studies are included in this table rather than 8 studies, and that this discrepancy is due to STAMPEDE studies 2, 3 and 4 counted as one study. Please confirm if we are correct.

Bayer response

Table 9 presents the inclusion/exclusion criteria of individual trials included in the base case NMA. It is also correct as to why there are six studies in Table 9, due to the multi-arm multi-stage platform design of STAMPEDE only the inclusion/exclusion for STAMPEDE studies 2, 3 and 4 are the same, therefore, only a single row for STAMPEDE is provided in Table 9.

C2. A footnote to Appendix D Table 8: ‘Study inclusion and exclusion from NMA evidence base and rationale for excluding’ states “Orange highlighted cells denote studies excluded from the base case NMA but included in sensitivity analyses”. There is no such orange highlighting in the table, just grey and white shading. Please can you clarify this discrepancy.

Bayer response

Apologies for this omission. Please see updated table below with these cells now highlighted orange.

Table 8: Study inclusion and exclusion from NMA evidence base and rationale for excluding

Study details	NMA (Y/N)		Rationale for excluding from base case NMA
	Base case	Sensitivity	
CSR 2022 ARASENS	Y	Y	NA
Armstrong 2019 ARCHES	Y	Y	NA
Boccon-Gibod 1997	N	N	SNA alone is not a relevant comparator
Bruun 1996	N	N	ADT vs ADT study. ADT is a relevant comparator however all ADT treatments were grouped into one node. Therefore, studies that investigate two ADT treatments do not provide any evidence for the network
Sweeney 2015 CHAARTED	Y	Y	NA
Chang 1996	N	N	SNA alone is not a relevant comparator
Chodak 1995	N	N	SNA alone is not a relevant comparator
Davis 2019 ENZAMET	N	Y	Patients were stratified by docetaxel use, trial included both patients treated with enzalutamide + ADT + docetaxel (not a comparator of interest) or SNA + ADT + docetaxel whilst the rest received enzalutamide + ADT (comparator of interest) or SNA + ADT. Baseline characteristics not reported for each stratification group therefore not possible to assess the presence of heterogeneity. Excluded from base case network but included in sensitivity analysis.
Schröder 2004 EORTC-30892	N	N	SNA alone is not a relevant comparator
Klijn 1993 EORTC-TRIAL 30843	N	N	Cyproterone acetate is not a relevant comparator of darolutamide + docetaxel + ADT
Ferrari 1996	N	N*	SNA + ADT is not a relevant comparator of darolutamide + docetaxel + ADT
Gravis 2013 GETUG-AFU 15	Y	Y	NA
Saltzstein 2021 HERO	N	N	ADT vs ADT study. ADT is a relevant comparator and all ADT treatments have been grouped into one node. Therefore, studies that investigate two ADT treatments do not provide any evidence for the network

Study details	NMA (Y/N)		Rationale for excluding from base case NMA
	Base case	Sensitivity	
Iversen 1996	N	N	ADT vs ADT study. ADT is a relevant comparator and all ADT treatments have been grouped into one node. Therefore, studies that investigate two ADT treatments do not provide any evidence for the network
Kaisary 1995	N	N	SNA alone is not a relevant comparator
Kirby 1999	N	N	Finasteride is not a relevant comparator of darolutamide + docetaxel + ADT
Kulkarni 2003	N	N*	SNA + ADT is not a relevant comparator of darolutamide + docetaxel + ADT
Fizazi 2017 LATITUDE	Y	Y	NA
Fizazi 2021 PEACE-1	N	N	Abiraterone + docetaxel + ADT is not a relevant comparator of darolutamide + docetaxel + ADT
James 2016 STAMPEDE-1	N	N	Includes M0 and M1 patients
James 2017 STAMPEDE-2	Y	Y	NA
Clarke 2019 STAMPEDE-3	Y	Y	NA
Sydes 2018 STAMPEDE-4	Y	Y	NA
Parker 2018 STAMPEDE-5	N	N	Radiotherapy is not relevant comparator
Clark 2013 STAMPEDE-6	N	N	Single arm ADT study. This study only investigates one treatment and therefore provides no evidence in the network
James 2012 STAMPEDE-7	N	N	Celecoxib is not relevant comparator
Agarwal 2021 SWOG S1216	N	N	Orteronel (TAK-700) is not a relevant comparator of darolutamide + docetaxel + ADT

Study details	NMA (Y/N)		Rationale for excluding from base case NMA
	Base case	Sensitivity	
Eisenberger 1998 SWOG study-S8894	N	Y	SNA + ADT is not a relevant comparator of darolutamide + docetaxel + ADT. Included in sensitivity analysis as provides indirect link between ENZAMET trial and ADT.
Thorpe 1996	N	N	Cyproterone acetate is not a relevant comparator of darolutamide + docetaxel + ADT
Chi 2019 TITAN	N	N	Apalutamide + ADT is not a relevant comparator of darolutamide + docetaxel + ADT
Vaishampayan 2021	N	Y	Low power phase II open-label study with patient accrual stopped prematurely (82 patients target sample size for power calculation as per study design; 71 patients actually enrolled), high risk of bias (Table 6), disproportionately short follow-up and immature data, and overrepresentation of black ethnicity (41%). Excluded from base case network but included in sensitivity analysis.
Vogelzang 1995	N	N	ADT vs ADT study. ADT is a relevant comparator and all ADT treatments have been grouped into one node. Therefore, studies that investigate two ADT treatment do not provide any evidence for the network
Zalcberg 1996	N	Y	SNA + ADT is not a relevant comparator of darolutamide + docetaxel + ADT. Included in sensitivity analysis as provides indirect link between ENZAMET trial and ADT.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Darolutamide with androgen deprivation therapy and docetaxel for treating hormone-sensitive metastatic prostate cancer [ID3971]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Prostate Cancer UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Prostate Cancer UK is a voluntary organisation based in London. It is a registered charity in England and Wales (1005541) and in Scotland (SC039332). Registered company number 02653887.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	£10k has been received from Bayer for our improvement programmes, £24k from Bayer has been verbally agreed in the last 2 weeks for match funding.
4c. Do you have any direct or indirect links	no

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	Via our clinical nurse specialists and talking directly with patients who have experience of having darolutamide or chemotherapy.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Although prostate cancer affects each patient differently we know that a diagnosis of metastatic prostate cancer initially causes fear, distress and anxiety for the patients and their families. Many will live for some years with advanced prostate cancer but the incurable nature of advanced disease can, for some, be very difficult to manage psychologically. Some patients will initially be asymptomatic whilst others may experience or develop symptoms, often bone pain. Whilst the prostate cancer is responding to first line hormone therapy, as patients in this cohort will be either de novo metastatic or will have progressed but still be responding to hormone therapy, many patients and their families can establish a fulfilling lifestyle as this treatment can result in prolonged control. However, anxiety is often reported during this stage as a patient will be anxious when their next (often 3 monthly) PSA blood test is due. This is because an elevated PSA level can indicate the response to the hormone therapy they are receiving is decreasing. Each time a treatment is no longer controlling their disease, fear and uncertainty about the future can return with the subsequent impact on quality of life. As advanced prostate cancer progresses, men may experience different symptoms (depending on where their cancer is) from their prostate cancer including those below: Pain may develop and for some men this can be significant. Clearly this is distressing for both men and their families as well as having an impact on quality of life. Men with advanced prostate cancer who have bone metastasis, including in the spine, may develop spinal cord compression. These men require urgent treatment to prevent permanent nerve damage and potential paralysis. This can be a debilitating and life-changing problem. Bone metastasis can also result in spontaneous fractures, without trauma and increased risk of fracture associated with trauma. For men whose prostate cancer affects their bone marrow, they may become anaemic (so be more tired or become breathless) requiring blood transfusion, thrombocytopenic (be more prone to bruising and bleeding) and low white blood cell counts (making them more susceptible to infection). Visceral metastases most commonly involve the liver and the lungs, causing considerable and intractable morbidity; Brain metastases commonly result in significant and distressing neurological deficits. Weight loss and reduced appetite can often be a particular concern for carers. If prostate cancer advances in the region around the prostate, men may experience urinary tract problems and renal problems.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Currently patients who have become metastatic but are still responding to hormone therapy, or those who are newly diagnosed metastatic have a few treatment options available to them. These include ADT alone, or docetaxel plus prednisolone or prednisone plus ADT or lastly, enzalutamide plus ADT. Those patients who have metastatic prostate cancer and are responding to hormone therapy but who are unable to have docetaxel can have Apalutamide plus ADT. These treatments provide a number of options to those who are hormone sensitive metastatic where curative treatment is not a possibility.
8. Is there an unmet need for patients with this condition?	Currently patients are missing out on the survival benefit of additional months of life of this combined treatment which creates an unmet need amongst the population of potential patients who would be eligible.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	One of the main fears a patient has in this indication is worrying when their prostate cancer may become hormone resistant. Patients have said to us that this is the point where they believe that “their cancer is progressing and they will be running out of options”. The ARASENS trial showed that compared to patients who received the placebo, patients who received darolutamide had a delay in their cancer becoming castration-resistant. Also, there was a delay in worsening pain, cancer-related bone fractures, or related symptoms needing additional therapies. In summary, patients have the benefit of increased survival from darolutamide plus docetaxel compared to docetaxel alone. It also provides another choice for patients at this stage of disease providing a greater sense of control which can help ease anxiety.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Although there is a clear benefit from combining darolutamide with docetaxel (the ARASENS trial showed that combining darolutamide with ADT and docetaxel increased the chance of survival and lowered the risk of death by 32.5% compared to combining ADT and docetaxel with the placebo) the disadvantage of this treatment regimen is that it would only be suitable for those who are deemed eligible to tolerate chemotherapy. Another disadvantage this treatment combination has is its administration. Chemotherapy requires delivery via a drip into the arm which needs to be undertaken in a hospital. This requires the patient to be able to travel to and from hospital and take considerable time out of their daily lives, perhaps even time off work, to be able to have this treatment. The side effect profile of this combined treatment was shown to be consistent with that of the known listed side effects for docetaxel alone, for example alopecia, neutropenia and fatigue. Many patients consider these and other associated side effects with chemotherapy as a disadvantage to this technology as the side effects are often considered incredibly debilitating and can affect a patient's quality of life considerably. Patients have directly told us that fatigue is a life changing side effect, hindering daily activities which can then impact their family and carers. Others have also reported breast pain and breast development as a side effect of darolutamide and hormone therapy.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients who are physically able to tolerate chemotherapy, for example those without comorbidities or who are less frail, will benefit from this technology. This technology will give another treatment choice to those who have recurrent or de novo prostate cancer who are responsive to hormone therapy. Patients who have a history of seizures are more likely to be able to have darolutamide, where they may not be able to have enzalutamide or apalutamide. Patients who are too frail to have docetaxel will not be able to benefit from this treatment combination. Prostate Cancer UK has previously undertaken analysis of data from 'Get Data Out', published by PHE. 63.6% of men with a new diagnosis of metastatic prostate cancer aged under 70 receive chemotherapy. This starkly decreases to 21.9% for men aged over 70 and drops further to 5.7% for men aged 80 and above. These data reveal a cohort of men who are unable to take chemotherapy, strongly correlated with their increasing age.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	n/a

Other issues

13. Are there any other issues that you would like the committee to consider?	n/a

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• The incurable nature of advanced disease can, for some, be very difficult to manage psychologically so it is imperative that patients have a greater treatment choice in this indication. • One of the main fears a patient has in this indication is worrying when their prostate cancer may become hormone resistant. Patients have said to us that this is the point where they believe that "their cancer is progressing and they will be running out of options". • The ARASENS trial showed that compared to patients who received the placebo, patients who received darolutamide had a delay in their cancer becoming castration-resistant. Also, there was a delay in worsening pain, cancer-related bone fractures, or related symptoms needing additional therapies. • Although the negative aspects of this treatment combination hinges mostly on that of the addition of docetaxel and the associated negative aspects of the administration and side effects of this chemotherapy, we believe through talking with patients that this combination would still be a popular and needed treatment option for many patients who would be eligible due to the compelling evidence from the ARASENS trial. •

Thank you for your time.

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Single Technology Appraisal

Darolutamide with androgen deprivation therapy and docetaxel for treating hormone-sensitive metastatic prostate cancer [ID3971]

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- Your response should not be longer than 10 pages.

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About you

1.Your name	[redacted]
2. Name of organisation	Tackle Prostate Cancer
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Tackle is a patient centred charitable organisation whose aims are to support men and their families whose lives are affected by prostate cancer. In addition we aim to represent the opinions of patients on any subject which is relevant to the diagnosis and treatment of prostate cancer. We represent around 90 support groups in England and Wales and through them have several thousand individual members - men and their families whose lives have been affected by prostate cancer. Tackle is a registered Charity. Income is from bequests/gifts and fundraising by members. We receive unrestricted grants from various companies in the pharmaceutical industry. Tackle are currently in receipt of funding from the National Lottery for some specific purposes.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in	NO

the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	NO
5. How did you gather information about the experiences of patients and carers to include in your submission?	Tackle gain regular feedback from our members via face to face contact at local and national meetings, from direct contact by telephone from individuals and from the questions and queries of patients on our patient helpline. We have a medical advisory board who advise when and where necessary. I do not have personal experience of being treated with Darolutamide. Tackle have not had direct contact with any patient currently receiving the triple combination therapy under discussion. However, I have spoken with patients who continue to be treated with a combination of Darolutamide and ADT and patients who have had been treated with chemotherapy and ADT.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Metastatic hormone-sensitive prostate cancer may occur for two main reasons: • Known hormone-sensitive disease may progress to a metastatic phase whilst remaining still hormone sensitive • A patient may present with mHSPC at the time of initial diagnosis. This is the more common clinical scenario with which Tackle have experience. This group is mirrored by the overall patient profile of the ARASENS trial. A man diagnosed with mHSPC is given a total 'bombshell' of a diagnosis. Not only is he told he has a cancer which has spread but also the possibility that he now only has a limited life span. Prostate cancer is the most common cancer in men across the UK. The National Prostate Cancer Audit 2019 stated that 17% of newly diagnosed men in England and Wales had metastatic disease at diagnosis. Although in numerical terms this can be a relatively small group of patients, the impact on those individual patients cannot be under-stated. It will devastate the lives of not only the patient but of those around him – particularly his family and those who care for him. Whilst there may tend to be an overall majority of older men in this group of patients, experience of talking with men from support groups suggests that an increasing number of younger men are being diagnosed with mHSPC at the time of first diagnosis as men become more aware of the need for PSA testing at an earlier age. Younger men may have less co-morbidities than an older age group and may thus be more suitable for the triple therapy under appraisal. It is a time of deep emotional and psychological distress for all of these men, their families and carers. This is particularly true for those men who are newly diagnosed. Many will have had no symptoms and have often been diagnosed on a routine medical examination. They find not only do they have a cancer but one that has already spread and will have serious life-changing consequences. A significant number of these men will be relatively young and with young families. Once the shock has passed, they will realise they have a vast number of decisions to make such as: Decisions about possible treatments available and their relative merits, efficacy and side effects. Decisions about future employment and financial implications of his diagnosis. Decisions about future life in general and planning for his potential early death. The diagnosis will undoubtedly take over the life of the patient not only immediately but often for the whole of the life he has remaining. What he will expect are swift and definitive treatment options. His future life will be significantly changed by not only the symptoms of his disease and its potential for progression but also by the potential side effects of his treatments. He will know he has an expected limited life-span and will wish to have the best quality of life during that period, and the possibility of extending life and increasing the time before hormone therapy becomes ineffective.

	There will be practical implications depending on the regime of treatment given. This will inevitably require visits to hospital for consultations, potentially for a series of chemotherapy infusions. This may influence decisions about treatment options. Side effects of treatment such as chemotherapy can be not only reflected physiologically in blood tests etc but also in effects on quality of life. General feelings of tiredness, lack of concentration, slowing of thought, fatigue etc are often reported. This is frequently referred to by patients as 'Chemo-Fog'.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Historically the initial choice of treatment would have been standard ADT - normally intermittent injectable hormone therapy as stand alone treatment. This has now been extended to include chemotherapy with docetaxel where appropriate. Chemotherapy may be substituted with novel hormonal agents (NHAs) in patients who are unsuitable for chemotherapy. ADT alone would now be considered as potentially being substandard therapy. Whilst current dual therapy is now considered to be the best standard of care, it is not always offered to patients or acceptable to them. ADT with an additional Novel Hormonal Agent may be offered as an alternative.
8. Is there an unmet need for patients with this condition?	All patients will wish for (and not unreasonably expect) the most effective treatment regime to be available and offered to them. Many patients, particularly those in a younger age group and with no co-morbidities, would be willing to consider triple therapy rather than the currently available dual therapy providing that the increased effectiveness could be matched by an acceptable increase in side effects. Whilst it will be understood that this treatment cannot have 'curative intent', such treatment would be seriously considered by many patients – particularly those that are in a relatively young age group and have few co-moribidities. The drugs being used in the triple therapy under appraisal are already established drugs for use in the treatment of prostate cancer. What is innovative here is the use of three drugs together. Whilst triple therapy is not uncommon in the initial treatment of some other cancers, the treatment under appraisal is indeed innovative in the initial therapy of prostate cancer.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Darolutamide is a molecule which binds to the androgen receptor to a greater degree than apalutamide or enzalutamide. It also appears to cross the blood brain barrier to a lesser degree than other novel hormonal agents. This is reflected in 'real life' terms in patients as an effective medication with an acceptable side effect profile. Discussions with patients with prostate cancer already taking darolutamide for other clinical indications have confirmed this acceptability. All patients with mHSPC eventually progress to become hormone resistant when further treatment will be needed. Slowing the progression of the cancer, slowing the onset of side effects of the cancer and the extension of survival are certainly huge increases in quality of life. The advantages of this new technology, in particular increased overall survival time and increased time to onset of hormone resistance, would be highly acceptable to patients who are deemed appropriate for triple therapy. The patient that is coping well with all aspects of their disease and its treatment, one who is not too fatigued and one who has an overall improvement in quality of life is one that is easier to live with. Any therapy that increases the well-being of the patient either physiologically or psychologically will undoubtedly have a positive benefit for those around them. It can be very tough seeing a loved one not only have a cancer but also someone who is not coping well with it or the onset of unpleasant side effects or both. Benefits can be felt not only by the patients themselves but all of those closely involved in their lives.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The ultimate aim for patient is that any new or additional therapy should have the maximum therapeutic benefits but with minimal additional side effects. As has been already stated, patients prescribed darolutamide for other clinical indications report an acceptable side effect profile. The requirement of taking 2 extra doses of oral medication per day is not a huge disadvantage. The cost of additional therapy may be an issue and will have an additional financial burden on healthcare providers. This, however, is not the responsibility or the concern of the patient. It is the responsibility of patient organisations to ensure that every individual patient get the best and most appropriate therapy. Recommendations / guidelines produced by NICE should be instituted within three months of that approval. However there is no mechanism to ensure this occurs and a treatment may not be always available locally to every patient on the cost grounds. A potential disadvantage of this new technology will be that, when the cancer progresses, treatment options will not be able to include a further novel hormonal agent under current NHS England funding rules, although a further course of chemotherapy may be allowed. However progress in the treatment of advanced prostate cancer is undoubtedly improving. Patients who have had this triple therapy may well be suitable for other treatments such as Radium^{223} (which is already approved by NICE) or potentially Lutetium^{177} treatment in the future if it gains similar approval.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	By definition this triple therapy will only be available to patients who are suitable for chemotherapy. NICE have already recognised a group of patients who are chemotherapy unsuitable and this group of patients will be unable to take advantage of this innovative advance in therapy. There is however no solution to this problem. Patients unsuitable for chemotherapy in combination with ADT as ideal therapy may have a novel hormonal agent instead of chemotherapy This cannot occur during triple therapy as there is no evidence that taking two novel hormonal agents at the same time is of any great benefit than taking one alone.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	The major equality issues that could arise will be cost related and whether prescribers and those bodies providing healthcare will actually fund the treatment if approved. There are no gender equality issues. The problem of chemotherapy unsuitable patients has been considered at Q11

Other issues

13. Are there any other issues that you would like the committee to consider?	Historically the approach to the treatment of prostate cancer has been one which is best described as reactive rather than proactive. Treatment pathways have been based on serial monotherapy rather than early multi modal therapy as is common with other cancers. This new innovative approach with triple therapy marks a significant step change in treatment strategies. Men with prostate cancer are now aware of such treatment strategies in other cancers and will undoubtedly be reassured that progress is being made in the treatment of their own cancer.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• 17% of newly diagnosed men will have mHSPC. To be told that not only do you have cancer but also that it has already spread is a 'bombshell' of a moment. There are long term life changing consequences to both the diagnosis and the potential treatment. Newly diagnosed men comprise the largest group of patients eligible for the new treatment regime under appraisal. • Patients will wish for (and not unreasonably expect) an effective treatment regime to be available and to be offered to them. The combination therapy regime under appraisal has the ability to provide an increased standard of care for those patients for whom it is appropriate. • The addition of Darolutamide to the existing standard of care for mHSPC (ADT + chemotherapy) may give a longer time to the onset of hormone resistance and overall survival time. Both of these outcomes would be highly desirable for patients given this triple therapy. • The addition of Darolutamide to ADT and chemotherapy does not significantly increase the incidence of side effects. Data presented strongly suggests that most side effects maybe from the chemotherapy component and indeed the worst degree of side effects occurs during the period of chemotherapy. Improved treatment outcomes from additional therapy without a significant increase in side effects is highly desirable. • The introduction of triple therapy for the treatment of prostate cancer is truly innovative and a potential step-change in the treatment pathway. It mirrors the principles of multi-modal therapy already used in other cancers. It uses established drugs for which there exists good clinical experience.

Thank you for your time.

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External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Darolutamide with androgen deprivation therapy and docetaxel for treating hormone-sensitive metastatic prostate cancer [ID3971]

Post factual accuracy check version

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Declared competing interests of the authors and advisors

The authors report none. Dr Deborah Enting reports the following financial relationships with companies associated with this appraisal in the previous 12 months: speaker's fee for AstraZeneca relating to Olaparib; advisory board member to Bayer relating to Ra223; and, educational meeting and speaker's fee for Astellas relating to Enforumab Vedotin.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Lorna Hazell critically appraised the clinical effectiveness systematic review and the company's network meta-analysis, and drafted the report; Keith Cooper critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Fay Chinnery critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Karen Pickett critically appraised the clinical effectiveness systematic review, contributed to project management of the review and drafted the report; David Scott critically appraised the company's network meta-analysis and drafted the report; Jonathan Shepherd critically appraised the clinical effectiveness systematic review, wrote the report, project managed the review and is the project guarantor.

Commercial in confidence information in blue

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LIST OF ABBREVIATIONS

ADT	Androgen deprivation therapy
AIC	Akaike information criterion
ALP	Alkaline phosphatase
ARTA	Androgen receptor targeted agent
BIC	Bayesian information criterion
BPI-SF	Brief Pain Inventory – Short Form
CI	Confidence interval
CROD	CRPC or death
CRPC	Castration-resistant prostate cancer
CS	Company submission
CSR	Clinical study report
DSU	Decision Support Unit
EAG	External Assessment Group
ECOG	Eastern Cooperative Oncology Group
EQ-5D	European Quality of Life Working Group Health Status Measure 5 Dimensions
FAS	Full analysis set
HR	Hazard ratio
HRGs	Healthcare Resource Groups
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
iNMB	Incremental net monetary benefit
ITT	Intent to treat
LYG	Life years gained
mCRPC	Metastatic castration-resistant prostate cancer
mHRPC	metastatic hormone-relapsed prostate cancer
mHSPC	Metastatic hormone-sensitive prostate cancer
NCCN-FACT-FPSI-17	National Comprehensive Cancer Network Functional Assessment of Cancer Therapy Prostate Symptom Index (17 Item Version)
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
nmCRPC	Non-metastatic castration-resistant prostate cancer
OS	Overall survival

OWSA	One-way sensitivity analysis
PAS	Patient Access Scheme
PFS	Progression-free survival
PSA	Prostate-specific antigen
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
rPFS	Radiological progression-free survival
SD	Standard deviation
SNA	Standard nonsteroidal antiandrogen
SLR	Systematic literature review
SmPC	Summary of product characteristics
SSE	Symptomatic skeletal event
SSE-FS	Symptomatic skeletal event-free survival
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TSD	Technical Support Document
TTCROD	Time to CRPC or death
ULN	Upper limit of normal
UK	United Kingdom
US	United States

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 0 to 1.6 explain the key issues in more detail. Background information on the condition, health technology, evidence and information on the issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1 List of EAG's key issues

ID	Summary of issue	Report sections
1	Cost-effectiveness results are not provided for the subgroups listed in the NICE scope	2.3, 3.2.5.4 and 3.3.3
2	Reasons for censoring in the ARASENS trial not reported	3.2.4
3	Loss to follow up in the ARASENS trial not fully explained	3.2.2
4	Use of unadjusted hazard ratios in the network meta-analysis (NMA) for trials that allowed crossover	3.4.1
5	Out of date PFS hazard ratio from ARCHES trial used in the NMA	3.4.1

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are described in section 1.7.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

The company's base case deterministic cost-effectiveness results (darolutamide + docetaxel + androgen deprivation therapy (ADT) versus each comparator) are shown in Table 2. Darolutamide + docetaxel + ADT provides an increase of [redacted] QALYs at an additional cost of [redacted] compared with docetaxel + ADT. The ICER for darolutamide + docetaxel + ADT compared with docetaxel + ADT is £14,950 per QALY. ADT is dominated by docetaxel + ADT as it is more expensive and less effective.

Enzalutamide + ADT is dominated by darolutamide + docetaxel + ADT, i.e. it is a more expensive and less effective treatment. The EAG have provided results using the Patient Access Scheme (PAS) discounts for all treatments in a separate confidential addendum.

Table 2 **Incremental base case results (company)**

Treatments	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER (£/ICER)
Doc + ADT	[redacted]	[redacted]	[redacted]	-	-	-	-
ADT alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Daro + Doc + ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,950
Enza + ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Key: ADT, androgen deprivation therapy, Daro, darolutamide; Doc, docetaxel, ICER, incremental cost-effectiveness ratio, Incr., incremental; LYs, life years, PAS, Patient Access Scheme; QALYs, quality-adjusted life years.

Source: Base case model results CS Table 69

1.3 The decision problem: summary of the EAG's key issues

Issue 1 Cost-effectiveness results are not provided for the subgroups listed in the NICE scope

Report section	2.3, 3.2.5.4 and 3.3.3
Description of issue and why the EAG has identified it as important	The NICE scope specifies people with 'high-risk' and 'newly diagnosed' metastatic hormone-sensitive prostate cancer (mHSPC) as subgroups of interest. The company have not provided cost effectiveness results for these subgroups (we describe the clinical effectiveness results provided in the second paragraph of this key issue below). The company explain that these terms are not used consistently across the evidence base in mHSPC. The clinical expert advising the EAG confirmed that there is variation between trials with respect to definitions of high-risk disease in mHSPC, but noted that disease volume tends to be more commonly used for risk stratification than the term 'high-risk disease'.

	The ARASENS trial did not include subgroup analysis by disease volume or for patients explicitly defined as high- versus low- risk. The company have, however, presented subgroup analyses for patients with and without metastasis at diagnosis. The HR for patients with metastasis at diagnosis was similar to that of the whole trial population, which is not unexpected given that approximately 86% of patients in the trial had de novo metastatic disease. The treatment effect in patients without metastasis at initial diagnosis is less certain, due to smaller numbers of patients in this subgroup.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	The EAG acknowledges that the ability to explore this issue further is limited due to lack of relevant subgroup data in ARASENS and across the mHSPC comparator trials in the NM. Therefore, the cost-effectiveness of darolutamide + docetaxel + ADT for these patient subgroups remains uncertain.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 2 Reasons for censoring in the ARASENS trial not reported

Report section	3.2.4
Description of issue and why the EAG has identified it as important	The company did not provide the number and proportion of participants in each of the ARASENS trial arms who were censored, and reasons for censoring, from the time to castration-resistant prostate cancer (CRPC) outcome analysis. In particular, it is unclear if there is a difference between trial arms in censoring of participants who received subsequent systemic antineoplastic therapy without meeting the criteria for CRPC and who were without a post prostate-specific antigen (PSA) progression event. The EAG therefore cannot determine if this is informative censoring, which could mean time to CRPC is potentially biased.
What alternative approach has the EAG suggested?	A breakdown of the number and proportion of participants censored, with reasons for censoring, in each trial arm could have been provided for the time to CRPC outcome.
What is the expected effect on the cost-effectiveness estimates?	Cancer progression in the company's economic model base case was based on time to CRPC or death (CROD), an outcome measure which combines time to CRPC and pre-progression overall survival (OS) from the ARASENS trial. If censoring is informative, then the time to CRPC outcome would be biased. The impact on cost-effectiveness is currently uncertain.
What additional evidence or analyses	We suggest that the company provide a breakdown of the number and proportion of participants censored for each reason in each

might help to resolve this key issue?	trial arm for time to CRPC. In the case of the censoring of participants who had subsequent systemic antineoplastic therapy without meeting the criteria for CRPC and who were without a post PSA progression, we suggest that the company provides details about the reasons why participants switched treatments (such as due to toxicity) and the number and proportion of participants switching treatments for each reason. We also suggest the company provide an accompanying narrative summary of whether or not there were any important differences between the trial arms in censoring reasons and how any differences may potentially impact on the time to CRPC efficacy and cost-effectiveness estimates.

Issue 3 Loss to follow up in the ARASENS trial not fully explained

Report section	3.2.2
Description of issue and why the EAG has identified it as important	We judged that there was an unexpected imbalance between the ARASENS trial arms in loss to follow-up among participants who had discontinued study treatment and who had then entered a planned 'Active follow-up' trial phase. The reasons why some patients who discontinued therapy did not enter the active follow-up as planned is not apparent to the EAG from the information provided in the company submission (CS). It is therefore unknown if this imbalance might potentially bias the results of the trial.
What alternative approach has the EAG suggested?	The company provided a breakdown of the flow of the trial participants through the study in CS Appendix D.3, Table 20. However, these data do not appear to explain the discrepancy identified by the EAG. We suggest a clearer outline of the participants' flow through the trial could have been provided.
What is the expected effect on the cost-effectiveness estimates?	The OS and time to CRPC outcomes are used in the company's economic model base case (time to CRPC is used through its combination with OS in the CROD outcome). It is unclear if there is a risk of attrition bias that may affect these efficacy estimates and thus the cost-effectiveness results.
What additional evidence or analyses might help to resolve this key issue?	We suggest that the company provide a full and clear breakdown of the reasons why participants did not enter active follow-up in each arm, presenting the number and proportion of the randomised participants who did not enter this stage of the trial for each reason. The risk of attrition bias in the trial and any resulting impact on cost effectiveness estimates can then be assessed.

Issue 4 Use of unadjusted hazard ratios in the network meta-analysis (NMA) for trials that allowed crossover

Report section	3.4.1
Description of issue and why the EAG has identified it as important	The company have used the unadjusted hazard ratios (HR) for OS from the ARCHES and LATITUDE trials in their NMA. Notably, ARCHES was the only trial connecting darolutamide + docetaxel + ADT to enzalutamide + ADT in the company base case so

	would have a marked impact on the results comparing these two treatments. Both trials allowed crossover from placebo to the active treatment arm at unblinding of the study after the primary analysis. The company argue that using the unadjusted HR is appropriate since this aligns with the approach used when the clinical effectiveness evidence was appraised for apalutamide in technology appraisal (TA) 741. The NICE Committee in TA741 considered that not adjusting for crossover may be reasonable since, in practice, patients who receive ADT alone are likely be offered enzalutamide or abiraterone on disease progression and these treatments would be expected to offer a similar survival benefit to apalutamide. However, we note that the NICE Committee preferred to consider both unadjusted and adjusted estimates for OS in their decision making in TA741 because there are uncertainties about a) the methods used in adjustment and b) whether it is appropriate to adjust or not in this setting. Furthermore, in TA741 not adjusting for crossover in the pivotal trial was considered conservative as this may underestimate the treatment effect for apalutamide. In contrast, for the current appraisal, the crossover occurs in the comparator trials and so using unadjusted estimates in the NMA may underestimate the treatment effect for the comparators which, in turn, may overestimate the clinical and cost-effectiveness of darolutamide.
What alternative approach has the EAG suggested?	We have performed a scenario analysis using the crossover-adjusted OS estimates for ARCHES and LATITUDE. This results in a less favourable treatment effect for darolutamide + docetaxel + ADT compared to enzalutamide + ADT.
What is the expected effect on the cost-effectiveness estimates?	Accounting for crossover in the ARCHES and LATITUDE studies used in the NMA increases the ICER vs docetaxel + ADT to [redacted] per QALY and reduces the incremental net monetary benefit (iNMB) vs enzalutamide + ADT from [redacted] to [redacted] in the company's base case (using the company base case assumptions). The expected effect on the cost effectiveness estimates including all comparator PAS discounts is shown in the EAG confidential addendum (Table 7).
What additional evidence or analyses might help to resolve this key issue?	Further discussion as to the appropriateness of adjusting for crossover in comparator trials.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

The EAG has not identified any cost-effectiveness key issues. We have identified several minor issues and these are listed in section 1.7.

1.6 Other issues: summary of the EAG's view

Issue 5 Out of date PFS hazard ratio from ARCHES trial used in the NMA

Report section	3.4.1
Description of issue and why the EAG has identified it as important	The company have used the most mature hazard ratios (HRs) from comparator trials as inputs to their NMA for OS and progression-free survival (PFS). However: • For the ARCHES study (enzalutamide + ADT), the company have used the most recent estimate for OS from Armstrong 2022[1] but have not used the updated PFS estimate (measured as radiological progression-free survival (rPFS)) from the same publication. The Armstrong 2022 publication was not available at the time of the company's systematic literature review. The updated rPFS (HR:0.63; 95% confidence interval (CI): 0.52, 0.76) from ARCHES is notably less favourable to that reported in the primary analysis[2] (HR:0.39; 95% CI:0.30, 0.50). The reasons for this difference are uncertain. We also note that: o while the more recent publication for the ARCHES trial (Armstrong et al. 2022) suggests a more favourable effect of enzalutamide + ADT versus ADT on OS, the effect of this treatment combination on PFS is attenuated. o the ARCHES trial allowed crossover from placebo to the active treatment arm following unblinding after the primary analysis. A crossover-adjusted estimate for rPFS has also been provided in Armstrong 2022 (HR: 0.55; 95% CI: 0.44, 0.67). o In addition, the primary analysis measured rPFS using centralised independent review whereas the updated results state the term 'investigator-assessed' which may explain the differences in effects. • The choice of HR for rPFS in ARCHES changes the NMA results and may therefore impact the cost-effectiveness results.
What alternative approach has the EAG suggested?	We have performed scenario analyses using the more recent PFS estimates for ARCHES, resulting in a more favourable treatment effect for darolutamide + docetaxel + ADT compared to enzalutamide + ADT.
What is the expected effect on the cost-effectiveness estimates?	Without applying the PAS discounts for the other treatments, the iNMB vs enzalutamide + ADT is reduced from [redacted] to [redacted] (using the company base case assumptions).
What additional evidence or analyses might help to resolve this key issue?	No further evidence or analyses are required. We have presented results of our scenarios with and without the updated PFS estimates for completeness.

The following issues identified by the EAG in the cost effectiveness evidence are not considered as key issues as they only have a small impact on the model results:

- **Disutility for docetaxel treatment** (EAG report section 4.2.7.4)**:** based on advice from our clinical expert, we assume that patients treated with docetaxel have an associated lower quality of life for six months from starting treatment.
- **Subsequent treatment distributions** (EAG report section 4.2.8.5): NHS patients with prostate cancer are only eligible to receive one androgen receptor targeted agent (ARTA). However, some patients in the model who initially receive enzalutamide subsequently receive abiraterone. We change the subsequent treatment distributions so that no patients receive more than one ARTA.
- **Diarrhoea adverse event costs** (EAG section 4.2.8.6): We use Healthcare Resource Groups (HRGs) costs relating to adult patients, rather than paediatric patients.
- **End of life costs** (EAG section 4.2.8.7): We use end-of-life costs that relate specifically to cancer patients rather than the general population.
- **Extrapolation of OS, PFS and time on treatment** (EAG section 4.2.6)**:** Our clinical expert considered that the long-term extrapolation for OS (30 years) and time on treatment (10 years) were optimistic. We therefore chose alternative survival curves.

1.7 Summary of EAG's preferred assumptions and resulting ICER

Based on the EAG critique of the company's model (discussed in section 4.2), we have identified several aspects of the company base case with which we disagree. Our preferred model assumptions are:

- **Disutility for docetaxel** (EAG report section 4.2.7.4): This disutility is applied for the first 6 months of treatment, rather than while patients receive docetaxel (approximately 4.5 months).
- **Subsequent treatment distributions** (EAG report section 4.2.8.5): The treatment distributions for metastatic hormone-relapsed prostate cancer (mHRPC) enzalutamide + ADT follow those reported in TA712 (Table 35), rather than the distributions presented in the CS, because patients in the United Kingdom (UK) will not receive a second ARTA following treatment with enzalutamide. We used the TA712 subsequent treatment distributions for mHRPC for docetaxel + ADT, enzalutamide + ADT, and for ADT alone in a scenario.
- **Diarrhoea adverse event costs** (EAG report section 4.2.8.6): Using Healthcare Resource Groups (HRGs) relating to adult patients, rather than paediatric patients. We used a weighted average of FD10J, FD10K, FD10L and FD10M (Non-malignant

gastrointestinal tract disorders without interventions, Day Case). The cost for treating diarrhoea is estimated to be £576.27, rather than £952.61.

- **End-of-life costs** (EAG report section 4.2.8.7): Using costs in the report by Georghiou and Bardsley[3] specific to the population who have had a cancer diagnosis, rather than figures for the general population. The estimate for end-of-life costs is £9,719, rather than £8,000.
- **Alternative distributions for OS, PFS and time on treatment:**
    - log-logistic distribution for OS
    - log-normal distribution for PFS
    - generalized gamma distribution for time on treatment.

The EAG's preferred assumptions decreased the ICER for darolutamide + docetaxel + ADT compared with docetaxel + ADT to £9,125 per QALY (Table 3).

Table 3 Cumulative change from the company base case with the EAG's preferred model assumptions for darolutamide + docetaxel + ADT vs docetaxel + ADT

Assumption	Incremental costs	Incremental QALYs	ICER (£/QALY)
Company base case	[redacted]	[redacted]	£14,950
+ Applying the disutility for docetaxel for 6 months	[redacted]	[redacted]	[redacted]
+ Using the TA712[4] subsequent treatment distribution for enzalutamide	[redacted]	[redacted]	[redacted]
+ Applying the corrected diarrhoea costs	[redacted]	[redacted]	[redacted]
+ Using end-of-life costs for people with a cancer diagnosis	[redacted]	[redacted]	[redacted]
+ Use log-logistic distribution for OS	[redacted]	[redacted]	[redacted]
+ Use log-normal distribution for PFS	[redacted]	[redacted]	[redacted]
+ Use generalized gamma distribution ToT	[redacted]	[redacted]	[redacted]
EAG base case	[redacted]	[redacted]	£9,125

The EAG did not identify any modelling errors in the company economic model. For further details of the exploratory and sensitivity analyses performed by the EAG, see section 6.2.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report is a critique of the company's submission (CS) to NICE from Bayer on the clinical effectiveness and cost effectiveness of darolutamide + docetaxel + androgen deprivation therapy (ADT) for treating metastatic hormone-sensitive prostate cancer (mHSPC). It identifies the strengths and weakness of the CS. A clinical expert was consulted to advise the external assessment group (EAG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the EAG via NICE on 4th October 2022. A response from the company was received by the EAG via NICE on 18th October 2022 and this can be seen in the NICE committee papers for this appraisal.

2.2 Background

2.2.1 Background information on metastatic hormone-sensitive prostate cancer

The company provide a comprehensive overview of the different stages of prostate cancer, its epidemiology, treatment and disease burden in CS section B.1.3.

CS Figure 2 provides an overview of the different stages of prostate cancer. The scope of the current technology appraisal focuses on the group of patients with mHSPC. These patients have prostate cancer that has spread from the prostate to more distant body sites (e.g., bone, non-regional lymph nodes, the lung, the liver and the brain). Patients with mHSPC may have hormone-naïve or hormone-sensitive disease depending on whether they have been exposed to hormonal therapies such as ADT, and whether their disease is controlled by this therapy.

Clinical expert advice to the EAG suggests that up to around 55% of patients with mHSPC present with metastasis at diagnosis (de novo disease/synchronous disease). The remaining 45% patients present with mHSPC after progression from localised prostate cancer (progressive/metasynchronous disease). Patients with de novo disease, particularly with high-volume disease have a poorer prognosis.[5] The company note that other factors associated with poorer prognosis include a Gleason score ≥8 (a grading score based on microscopic assessment with a higher score indicating more aggressive disease), measurable visceral metastases and ≥3 bone metastasis. Our clinical expert also noted the following: Eastern Cooperative Oncology Group (ECOG) performance score >1, prostate specific antigen (PSA) level and pattern of metastases (e.g., liver involvement vs no liver involvement) are additional prognostic factors; some blood parameters e.g. haemoglobin

and neutrophil count may also be considered but these are less well-defined; and the role of age and ethnicity is less certain.

Patients with mHSPC who progress despite hormone deprivation therapy develop hormone-relapsed prostate cancer (mHRPC, also known castration-resistant prostate cancer (mCRPC)). The company report that prognosis for mCRPC is poor with estimated median survival from 9-30 months. Our clinical expert considered that survival for mCRPC is around 2-3 years.

2.2.2 Background information on darolutamide + docetaxel + ADT

Darolutamide is recommended by NICE (TA660) for use in men with non-metastatic castration-resistant prostate cancer (nmCRPC) at high risk of developing metastatic disease.[6,7] However, the current technology appraisal assesses the clinical and cost-effectiveness of darolutamide in the context of a proposed extension to its product licence for patients with mHSPC.

CS section B.1.2 describes the mechanism of action of darolutamide in detail. Briefly, darolutamide is a non-steroidal androgen receptor inhibitor. The recommended dose is 600mg orally, twice daily with dose reductions advised for patients with severe renal impairment. For mHSPC, it is intended for use in combination with docetaxel chemotherapy and in patients who continue to receive ADT (namely, gonadotrophin-releasing hormone analogues) or who have had a bilateral orchidectomy. The company report that this 'triplet' combination therapy provides a multimodal approach with docetaxel targeting the androgen-insensitive component of the tumour, ADT targeting the androgen receptor axis centrally and darolutamide acting as an androgen receptor antagonist.

2.2.3 The position of darolutamide + docetaxel + ADT in the treatment pathway

Currently recommended treatments for patients with mHSPC include ADT, docetaxel chemotherapy (in combination with ADT) or androgen receptor targeted agents (ARTAs) such as enzalutamide (TA712[4]) or apalutamide (TA741[8]), again in combination with ADT (Figure 1).[9]

Docetaxel chemotherapy was originally used off-label for mHSPC and has only recently gained a marketing authorisation for use in this indication.[10] Docetaxel treatment involves intravenous infusion in hospital and is not suitable for all patients (e.g., patients with poor performance score, comorbidities). During the COVID-19 pandemic, patients were instead offered enzalutamide + ADT to avoid the risks associated with chemotherapy and hospital

visits. This temporary guidance was superseded when enzalutamide + ADT was recommended by NICE in July 2021 (TA712). Docetaxel and enzalutamide have not been directly compared but have both been shown to improve overall survival compared to ADT alone.[1,11-13]

Apalutamide + ADT is only recommended by NICE for patients for whom docetaxel is not suitable (TA741[8]) and thus is not included as a relevant comparator in the current appraisal since darolutamide is intended for use only in combination with docetaxel for patients with mHSPC.

Due to National Health Service (NHS) restrictions, a patient can only receive one ARTA-based therapy during the course of their treatment pathway for prostate cancer. This means that patients prescribed darolutamide for mHSPC would not be eligible to receive a second ARTA (enzalutamide, abiraterone, apalutamide) when they develop mCRPC.

Our clinical expert advised that the majority of patients with mHSPC receive ADT monotherapy despite evidence to escalate treatment (by addition of docetaxel or an ARTA). This expert also considered that most clinicians would prescribe enzalutamide or apalutamide + ADT and that there is a lack of evidence available to identify which patients are likely to benefit from docetaxel chemotherapy.

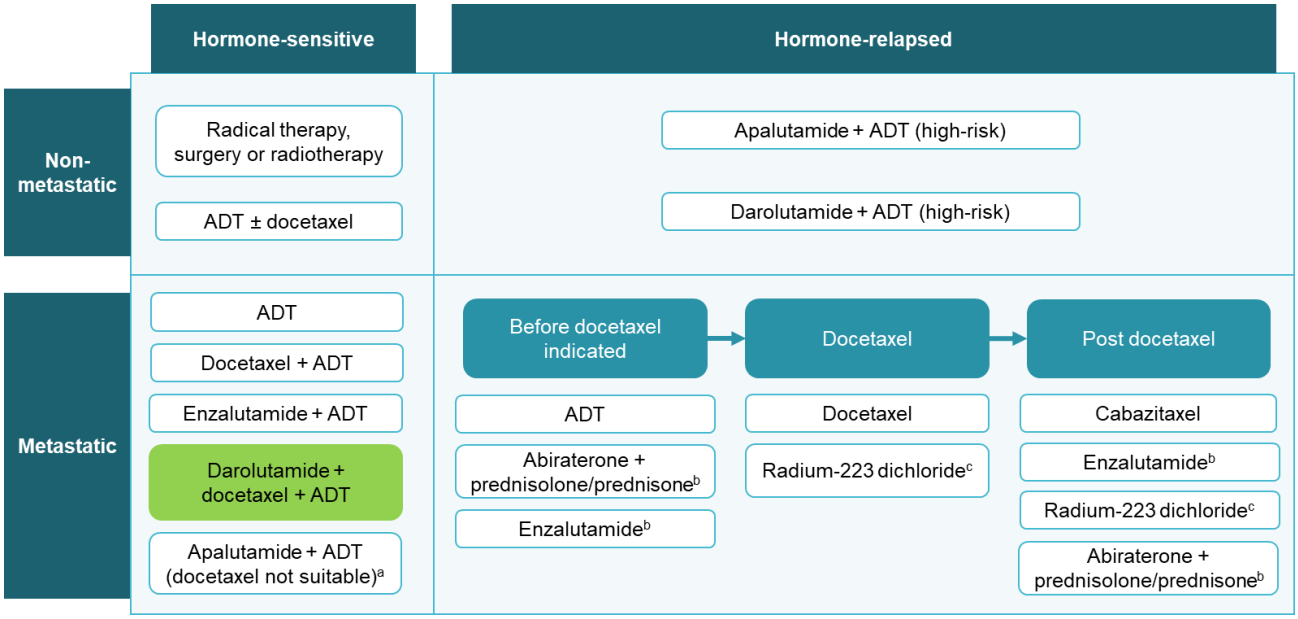

Figure 1: Clinical pathway of care for prostate cancer and proposed darolutamide plus docetaxel and ADT positioning

Key: ADT, androgen deprivation therapy.
Notes: [a] Recommended only if docetaxel is not suitable; [b] only if a novel anti-hormonal agent (i.e. darolutamide, enzalutamide, apalutamide or abiraterone) has not been used before; [c] only if patients have already had docetaxel, or if docetaxel is contraindicated or is not suitable. Green refers to the proposed positioning of darolutamide plus docetaxel and ADT.
Source: Adapted from NICE prostate cancer: diagnosis and management (NG131);[9] NHS England commissioning policy statement for docetaxel;[14] BNF treatment summary for prostate cancer.[15]
Source CS Figure 3

EAG comment

The background information provided by the company accurately describes the disease epidemiology and treatment pathway for patients with mHSPC.

2.3 Critique of the company's definition of the decision problem

Table 4 summarises the decision problem addressed by the company in the CS in relation to the final scope issued by NICE and the EAG's comments on this.

Table 4 Summary of the decision problem

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
Population	People with hormone-sensitive metastatic prostate cancer	As per final scope	Not applicable	As per final scope
Intervention	Darolutamide with androgen deprivation therapy and docetaxel	As per final scope	Not applicable	As per final scope
Comparators	• Androgen deprivation therapy alone (including orchidectomy, luteinising hormone-releasing hormone agonist therapy, degarelix, monotherapy with bicalutamide) • Docetaxel with androgen deprivation therapy • Enzalutamide with androgen deprivation therapy	As per final scope	Not applicable	As per final scope except for monotherapy with bicalutamide which is not considered a relevant comparator by the company (CS Appendix D 1.6.2 Table 8). Our clinical expert agreed as bicalutamide monotherapy is considered inferior and is not standard of care.
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rate • Prostate-specific antigen response	The outcome measures to be considered include: • Overall survival • Time to castration-resistant prostate cancer (CRPC)	Time to CRPC is a secondary endpoint in the ARASENS study and is composed of biochemical progression and radiological progression. Imaging was to be performed on a yearly basis after the end of	The outcomes measured in the ARASENS trial match the final scope. The company have used time to CRPC or death (CROD) to capture progression-free survival in the partitioned survival economic model. Clinical

	• Time to prostate-specific antigen progression • Adverse effects of treatment • Health-related quality of life	• Prostate-specific antigen (PSA) response • Time to pain progression • Symptomatic skeletal event-free survival (SSE-FS) • Time to first symptomatic skeletal event (SSE) • Time to initiation of subsequent systemic antineoplastic therapy • Time to worsening of disease-related physical symptoms • Time to initiation of opioid use for ≥ 7 consecutive days • Time to PSA progression • Adverse effects of treatment • Health-related quality of life	docetaxel treatment and in case of signs of clinical progression at the investigator's discretion. Therefore, imaging could be performed at any time in case of PSA progression, symptomatic progressive disease or change of antineoplastic therapy. The rationale for this schedule was to mimic a real-world setting where imaging is driven by clinical signs and symptoms or biochemical progression, compared to rPFS which is based on a fixed assessment schedule every few months. Time to CRPC is therefore more aligned with clinical practice and is the progression-free survival outcome measure that was collected in ARASENS and will be used in the appraisal.	expert advice to the EAG confirmed that the CRPC definition of progression is more sensitive and reflective of clinical practice than radiological PFS (rPFS). Use of the composite outcome time to CROD is appropriate for the partitioned survival model.

Subgroups	If the evidence allows, the following subgroups of people will be considered: • People with newly diagnosed metastatic prostate cancer • People with high-risk metastatic prostate cancer	The following prespecified subgroups were analysed in ARASENS: • Extent of disease • Alkaline phosphatase (ALP) at baseline • Age category • Race • Geographical region • Prostate-specific antigen (PSA) values • Eastern Cooperative Oncology Group (ECOG) performance status • Gleason score • Metastasis at initial diagnosis	There is inconsistent use of 'newly diagnosed' and 'high risk' subgroups across all mHSPC trials. These sub-populations would be most relevant to abiraterone, which is specifically licensed for the newly diagnosed, high risk population. However, abiraterone is not a relevant comparator in this appraisal and it has not been approved for use in NHS practice. In the ARASENS study: 1. Both patients with M1 (synchronous) and M0 (metachronous) disease at initial diagnosis have been included. The majority of patients (86%) were de novo and the results in ARASENS have been consistent across these subgroups 2. Patients were stratified by extent of disease (i.e. non-regional lymph node metastasis, bone metastasis, and visceral metastasis). The efficacy observed in ARASENS was consistent across	Clinical expert advice to the EAG confirmed that there is variation between trials with respect to definitions of high-risk disease in mHSPC and that the terms high-risk and high-volume are both used. Our expert considered disease volume to be more commonly used for risk stratification. We note that the company have presented subgroup analyses for a range of prognostic factors but, in contrast to some of the comparator trials in mHSPC, the ARASENS trial does not explicitly provide subgroup data for patients with high and low volume disease. The company have provided subgroup analyses from the ARASENS trial for patients with and without metastasis at initial diagnosis. Our expert noted that the proportion of patients with de novo disease in ARASENS was higher than would typically be seen in practice (86% versus 55%).

			these three subgroups. There was no classification by 'high-risk' disease in ARASENS The appraisal is focused on the ITT population on which the ARASENS study was designed and powered to detect an effect, and not on subgroups for which the study was not powered.	The company have not presented any subgroup analyses for cost-effectiveness.
Key: ADT, androgen deprivation therapy; ALP, alkaline phosphatase; CRPC, castration-resistant prostate cancer; ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; PSA, prostate-specific antigen; SSE, symptomatic skeletal event; SSE-FS, symptomatic skeletal event-free survival. Source: CS Table 1				

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company carried out a broad clinical effectiveness systematic literature review (SLR), to identify evidence on the efficacy, safety and tolerability of treatments approved or forthcoming for mHSPC (CS section B.2.1 and CS Appendix D.1). This broad review was carried out to meet the needs of international health technology assessment bodies, but only studies including treatments relevant to the comparisons of interest in this appraisal were included in the CS (CS section B.2.9.1). Appendix 9.1 of this EAG report provides a summary of the EAG's critical appraisal of the company's review.

Overall, the EAG considers that the review was appropriately carried out, but that the searches are out-of-date, having been conducted from database inception to 18th October 2021. There is a risk therefore that if relevant studies have been published recently, they will have been missed. The EAG updated the company's searches but found only two relevant publications that were not listed among the company's search results.[1 16] These two studies provided updated results for two of the trials that are included in the company's network meta-analysis (NMA). We note, however, that not all of the updated results from these publications have been used in the company's NMA. The company cite results from the Armstrong 2022 publication in the background section of the CS (CS section B.1.3.2) but this paper was not available at the time of the company's SLR. This issue is further discussed in section 3.4.1.

3.2 Critique of studies of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included studies

The company's systematic literature review identified 27 studies, reported in 222 publications, that met the systematic review's eligibility criteria (CS Appendix D.1.3). The review's eligibility criteria were broader than the NICE scope to capture all existing evidence on approved and upcoming treatments for mHSPC. The review included one randomised controlled trial (RCT) comparing darolutamide + docetaxel + ADT against placebo + docetaxel + ADT: the ARASENS trial[17] in people with mHSPC (NCT02799602).

The remaining 26 identified studies, along with ARASENS, were considered for inclusion in the company's NMA (CS Appendix D.1.6). They assessed a range of treatments, including

ADT alone, docetaxel + ADT and enzalutamide + ADT (CS Appendix D.1.6, Table 7). The studies considered for inclusion in and that informed the NMA are discussed further in section 3.3.2. We focus on describing the ARASENS trial here.

The company also report results from one other study in the CS, as additional information: Appukkutan et al. (2021)[18] (CS sections B.2.2 and B.2.6.4.1). The company does not detail how this study was identified. It is a study of potential drug-drug interactions to novel androgen receptor antagonists, including darolutamide and enzalutamide, among non-metastatic castration-resistant prostate cancer patients. The company acknowledges that the indication differs to the focus of the appraisal but state that they provide details of this study for information as potential drug-drug interactions are important considerations in clinical practice in elderly populations with multiple morbidities (CS section B.2.6.4.1). As this is not an outcome specified to be of interest in the NICE scope and the data were not used in the company's NMA or economic model, we do not discuss the study further in this report.

The ARASENS trial was funded by Bayer and Orion Pharma.[19] The primary document reporting results from the trial was the clinical study report (CSR)[17] (CS Appendix D.1.4), which the company included in their submission (some CSR tables and figures and all appendices were missing from the company's original submission but provided in response to clarification questions A4 and A5). Four clinical outcomes from the trial are used in the company's economic model: overall survival (OS), time to CRPC or death (CROD), adverse events from treatment and time on treatment for darolutamide. The trial outcomes and how they were defined are discussed further in section 3.2.3.

3.2.1.1 Study characteristics

The CS details the characteristics and methodology of the ARASENS trial in CS Tables 3 and 4, CS Figure 4, and in CS sections B.2.2 and B.2.3. We have summarised key aspects of the study in Table 5 below. ARASENS was a phase III, double-blind RCT in people with mHSPC, comparing darolutamide + docetaxel + ADT against placebo + docetaxel + ADT. The key participant eligibility criteria for the trial are provided in CS Table 4, with selected criteria summarised in Table 5 here. The clinical expert advising the EAG stated that the eligibility criteria are reflective of the patients treated in clinical practice. We note that the trial only included people with a performance status of 0 or 1, and the expert advising us indicated that this was justified in the context of receiving chemotherapy. The expert also noted that an appropriate definition of documented and confirmed metastatic disease (see CS Table 4 for the definition) had been used in the trial as part of the eligibility criteria.

We note that the dosing regimen of darolutamide used in the ARASENS trial [redacted]. Additionally, the docetaxel dosing regimen, used in both trial arms, matches the docetaxel SmPC.[20] The clinical expert advising the EAG confirmed that the docetaxel dosing regimen and the ADTs used in the trial (LHRH agonist/antagonist started ≤ 12 weeks before randomisation or orchiectomy) are reflective of treatment in clinical practice.

After randomisation, there were three stages to the trial (as described in CS Figure 4, CS section B.2.3 and the study protocol[21]):

1. Treatment period – in which participants received the study treatment and were assessed every 12 weeks, until symptomatic disease progression, death, non-adherence, change in antineoplastic therapy, unacceptable toxicity or patient or physician choice to discontinue.
2. Active follow-up period – in which participants who had discontinued treatment were assessed approximately every 12 weeks for a year. Outcomes assessed included [redacted].[21]
3. Long-term (survival) follow-up – which participants entered after 'Active follow-up' and were assessed for outcomes [redacted].[21]

The trial's primary outcome was OS. The CS includes results from the final efficacy analysis, with a data cut-off of 25th October 2021 (CS section B.2.4).

The company provide details of the numbers and proportions of participants who entered active or survival follow-up in the ARASENS trial who received subsequent life-prolonging systematic antineoplastic therapy in CS Appendix M, Table 44. We note, based on clinical expert advice, that many of the participants in the darolutamide + docetaxel + ADT trial arm who entered these stages of the trial (as shown in CS Appendix M, Table 44) received therapies that patients who will receive darolutamide within the NHS, should it be recommended for use, will not be able to access in practice in England (abiraterone, enzalutamide and apalutamide) (other than by receiving these drugs within a clinical trial). We discuss this issue further in section 3.2.5.1.

The EAG has no concerns about the design or methodology of the trial, but as stated above, note that the subsequent treatments received by participants in the darolutamide + docetaxel + ADT arm are not reflective of those received in NHS practice in England.

Table 5 ARASENS RCT study characteristics

Study characteristics	Intervention: Darolutamide + docetaxel + ADT	Comparator: Placebo + docetaxel + ADT
Design: Phase III, international, double-blind RCT (23 countries, with 29 participants randomised from 8 UK centres). **Population:** People with mHSPC. **Stratification criteria:** • Extent of disease [a] • ALP level [b] **Key eligibility criteria:** • Males aged ≥18 years • Documented and confirmed metastatic disease (defined in CS Table 4) • ECOG performance status of 0 or 1 **Number randomised:** N=[redacted] (Darolutamide: [redacted]; Placebo: [redacted]; plus [redacted] participant excluded due to a GCP violation) **Median length of follow up:** OS (primary endpoint): darolutamide, 43.7 months; placebo, 42.4 months.	**Darolutamide:** 600 mg (2 tablets of 300 mg) taken twice a day with food, resulting in a total daily dose of 1,200 mg. **Docetaxel:** 6 cycles were received, with a dose of 75 mg/m^2 on day 1 and every 3 weeks. Investigators could choose to also administer prednisone or prednisolone. **ADT:** All participants received ADT (LHRH agonist/antagonist started ≤ 12 weeks before randomisation or orchiectomy) as standard therapy prior to randomisation. Investigators chose the ADT received. If participants received LHRH agonists, it was recommended that they were treated for at least 4 weeks before randomisation with a first generation anti-androgen.	**Placebo:** matching placebo, with the same dosing as darolutamide. **Docetaxel:** 6 cycles were received, with a dose of 75 mg/m^2 on day 1 and every 3 weeks. Investigators could choose to also administer prednisone or prednisolone. **ADT:** All participants received ADT (LHRH agonist/antagonist started ≤ 12 weeks before randomisation or orchiectomy) as standard therapy prior to randomisation. Investigators chose the ADT received. If participants received LHRH agonists, it was recommended that they were treated for at least 4 weeks before randomisation with a first generation anti-androgen.

Source: partly reproduced from CS Tables 3 and 4, CS Figure 4, CS Appendix D.3 Figure 15, CS Appendix M Table 44 and CS sections B.2.3 and B.2.6.1.1.
ADT, androgen deprivation therapy; ALP, alkaline phosphatase; CS, company submission; ECOG, Eastern Cooperative Oncology Group; GCP, good clinical practice; LHRH, luteinizing hormone releasing hormone; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival; RCT, randomised controlled trial.
[a] non-regional lymph nodes metastases only equivalent to tumour, node, metastasis (TNM) category M1a; bone metastases with or without lymph node metastases equivalent to TNM M1b; and visceral metastases with or without lymph node metastases or with or without bone metastases equivalent to TNM M1c.
[b] ALP < upper limit of normal [ULN] and ALP ≥ ULN.

3.2.1.2 Patients' baseline characteristics

Participants' baseline characteristics were well-balanced between the ARASENS trial arms (see Table 6 below). In terms of the participants' representativeness of the patients seen in clinical practice, the clinical expert advising the EAG noted that the trial participants' age was reflective of practice. The expert noted, though, that the participants in the ARASENS trial generally have a better ECOG performance status than those in clinical practice. She stated that given the majority of the participants in the trial had metastatic prostate cancer at initial diagnosis, rather than a relapse after initial localised prostate cancer, the proportion of participants with a performance status score of 0 seems higher than usual in practice (these patients would be expected to have a performance status of 1 at least). The expert stated that a worse performance status score generally results in poorer treatment outcomes and prognosis. The participants in the trial may therefore have been more well than those treated in practice. The clinical expert advising the EAG also noted that patient ethnicity may be slightly different to clinical practice, with Black people not well represented in the trial. The expert noted that, overall, Black men have worse outcomes. Further, fewer patients with de novo disease would be seen in clinical practice compared to the ARASENS trial (around 55% versus 86% respectively). The expert stated that people with de novo disease have worse outcomes than those with relapsed disease.

Table 6 Patient baseline characteristics in the ARASENS RCT (Full analysis set)

Characteristic	Darolutamide+ docetaxel N = 651	Placebo+ docetaxel N = 654
Age, years		
Mean (SD)	[redacted]	[redacted]
Median	67.0	67.0
Min, max	41, 89	42, 86
Age group in years, n (%)		
< 65	243 (37.3)	234 (35.8)
65–74	303 (46.5)	306 (46.8)
75–84	102 (15.7)	110 (16.8)
≥ 85	3 (0.5)	4 (0.6)
Race, n (%)		
White	345 (53.0)	333 (50.9)
Black or African American	26 (4.0)	28 (4.3)
Asian	230 (35.3)	245 (37.5)
Other[a]	7 (1.1)	2 (0.3)
Not reported	43 (6.6)	46 (7.0)
Geographical region, n (%)		

Characteristic	Darolutamide+ docetaxel N = 651	Placebo+ docetaxel N = 654
North America	125 (19.2)	119 (18.2)
Asia Pacific	229 (35.2)	244 (37.3)
Rest of the world	297 (45.6)	291 (44.5)
Body mass index group in kg/m^2, n (%)		
< 20	[redacted]	[redacted]
20–< 25	[redacted]	[redacted]
25–< 30	[redacted]	[redacted]
≥ 30	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Extent of metastatic disease at study entry using eCRF, n (%)		
M1a	23 (3.5)	16 (2.4)
M1b	517 (79.4)	520 (79.5)
M1c	111 (17.1)	118 (18.0)
ALP at baseline – central laboratory using eCRF, n (%)		
ALP < ULN	290 (44.5)	291 (44.5)
ALP ≥ ULN	361 (55.5)	363 (55.5)
Stage of prostate cancer at initial diagnosis using TNM classification, n (%)		
Stage I	[redacted]	[redacted]
Stage IIA	[redacted]	[redacted]
Stage IIB	[redacted]	[redacted]
Stage III	[redacted]	[redacted]
Stage IV	[redacted]	[redacted]
Stage IV M0	[redacted]	[redacted]
Stage IV M1	558 (85.7)	566 (86.5)
Missing	7 (1.1)	6 (0.9)
Gleason score at initial diagnosis of prostate cancer, n (%)		
< 8	122 (18.7)	118 (18.0)
≥ 8	505 (77.6)	516 (78.9)
Missing	24 (3.7)	20 (3.1)
PSA at baseline – central laboratory, ng/mL		
Mean (SD)	[redacted]	[redacted]
Median	30.30	24.20
Min, max	0.0, 9,219.0	0.0, 11,947.0
Missing, n	[redacted]	[redacted]
ECOG Performance Status, n (%)		
0	466 (71.6)	462 (70.6)
1	185 (28.4)	190 (29.1)
Missing	[redacted]	[redacted]

Characteristic	Darolutamide+ docetaxel N = 651	Placebo+ docetaxel N = 654
Source: reproduced from CS Table 5.		
ADT, androgen deprivation therapy; ALP, alkaline phosphatase; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; PSA: Prostate-specific antigen; SD, standard deviation; TNM, tumour, node, metastasis; ULN, upper limit of normal. [a] Race 'Other' includes "American Indian or Alaska Native", "Native Hawaiian or other Pacific Islander", and "Multiple".		

EAG comment on included studies

The company included one RCT (ARASENS) comparing darolutamide + docetaxel + ADT against placebo + docetaxel + ADT in people with mHSPC in the CS. The EAG identified no concerns about the design or methodology of the trial. We note, however, that the included participants were not fully representative of the patients seen in practice, with a higher proportion having an ECOG performance status score of 0 than expected in practice and proportionally more having de novo disease than seen in practice. Black people were not well-represented in the trial.

3.2.2 Risk of bias assessment

The company critically appraised the ARASENS trial using the criteria recommended by NICE[22] (CS section B.2.5, CS Appendix D.1.5 and CS Appendix D.4). Appendix 9.2 of this EAG report (Table 40) shows a comparison of the company's and the EAG's assessments of the trial. The company did not report a rationale for their judgements. The EAG agreed with all of the company's risk of bias judgements, except that we judged there was an unexpected imbalance between the trial arms in the proportion of participants who had discontinued study treatment and who had then entered a planned 'Active follow-up' trial phase ([redacted] of those who discontinued treatment in the darolutamide + docetaxel + ADT arm versus [redacted] who discontinued in the placebo + docetaxel + ADT trial arm entered active follow-up; see Table 7 and Appendix 9.2). [redacted].[21] The reasons why some patients who discontinued therapy did not enter the active follow-up as planned is not apparent to the EAG from CS Appendix D.3, Table 20. It is therefore unknown if this might potentially bias the results of the trial.

Overall, the EAG considers that the ARASENS trial was well conducted and is at a low risk of selection, detection, performance and reporting bias. However, there is a potential risk of attrition bias, in an unknown direction, due to an imbalance between the treatment arms in unexplained reasons for why some patients who discontinued study treatment did not enter the active follow-up period as planned.

Table 7 EAG summary of participant disposition in the ARASENS trial at the 25 October 2021 data-cut

Participant disposition	Darolutamide + docetaxel + ADT arm, n / N (%)	Placebo + docetaxel + ADT arm, n / N (%)
Randomised	[redacted]	[redacted]
Discontinued study treatment (% of those randomised)	[redacted]	[redacted]
Those discontinuing who entered 'Active follow-up' [a] (% of those discontinuing)	[redacted] [b]	[redacted] [b]

Source: partly reproduced from CS Appendix D.3, Table 20.
ADT, androgen deprivation therapy.
[a] CS section B.2.3 states that after participants discontinue treatment, they will enter the Active Follow-up period, which includes assessments of survival status and study drug-related serious adverse events.
[b] Percentages calculated by EAG.

3.2.3 Outcome assessment

The outcomes measured in the ARASENS trial are described in CS section B.2.3 and CS Table 4. As stated in section 3.2.1 above, the clinical outcomes from the trial that were used in the company's economic model were OS, time to CROD, adverse events from treatment and time on treatment for darolutamide. We describe and critique these outcomes here, and provide a brief description of how health-related quality of life (HRQoL) was measured in the trial.

3.2.3.1 Efficacy outcomes

OS was defined as time (in days) to death from any cause from the date of randomisation (section B.2.3). This is a standard outcome used in trials of cancer drugs and the definition is appropriate.

Time to CRPC was defined as the time to occurrence of one of the following events from randomisation: PSA progression (according to PCWG3 criteria[23]), radiological progression by soft tissue and visceral lesions (measured according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1[24]), or radiological progression by bone lesions (defined according to PCWG3 criteria). Please see CS Table 4 for a detailed description of how each of these elements was measured. The company argue in CS Table 1 that time to CRPC better reflects how disease progression is measured in UK clinical practice than

rPFS. One reason for this is that imaging is done at the investigator's discretion when they judge there are signs of clinical progression, rather than assessment being based on a set schedule as it is when measuring rPFS. Clinical expert advice to the EAG confirms that the time to CRPC outcome reflects clinical practice. The expert stated that it is a more practical outcome measure than rPFS. In practice, symptoms and PSA progression guide imaging and treatment decisions. This means that clinicians may call progression earlier than if they were scanning patients at fixed intervals. The expert had no concerns about the use of this outcome measure in the trial.

Time to CROD, defined as the time from randomisation to a CRPC event (radiological or PSA progression) or death (see CS B.2.6.2.1.1), was used in the company's partitioned survival economic model (CS B.3.2.2). This is a composite outcome, combining data on OS and CRPC. The EAG assumes this is a post-hoc analysis as this outcome [redacted].[21]

3.2.3.2 HRQoL outcomes

HRQoL was measured in the ARASENS trial using the National Comprehensive Cancer Network Functional Assessment of Cancer Therapy Prostate Symptom Index (17 Item Version) (NCCN-FACT-FPSI-17)[25] and Brief Pain Inventory – Short Form (BPI-SF)[26] questionnaires (CS section B.2.6.3.3). These measures were not used to determine the health state utilities in the company's economic model (CS section B.3.4.6), so we do not describe or critique them further here.

3.2.3.3 Safety outcomes

Safety data is presented in the CS up to the 25th October 2021 data cut-off. The company provides a range of adverse event results in the CS, including treatment emergent and treatment-related adverse events and adverse events of special interest. Adverse events with grade ≥ 3 were included in the economic model for both arms of the ARASENS trial, if they had an incidence of ≥5% (see section 4.2.6.4).

EAG comment on outcomes assessment

The EAG has not identified any concerns with the OS, time to CRPC/CROD and adverse event outcomes measured in the ARASENS trial.

3.2.4 Statistical methods of the included studies

The company report the statistical methods used in the ARASENS trial in CS section B.2.4 and we summarise these in Table 8 below. As stated in section 3.2.1.1 above, the final

efficacy analysis is presented in the CS which comes from the 25th October 2021 data-cut (CS section B.2.4). The trial appears to be adequately powered and used an intention-to-treat population (Full analysis set (FAS) population) for analyses. The only concern the EAG has about the statistical methods is that the company did not provide a breakdown of the number and proportion of participants censored for each censoring reason in the time to CRPC analysis. In particular, it is unclear if censoring participants who had received subsequent systemic antineoplastic therapy without meeting the criteria for CRPC, and who were without a post PSA progression event, differed between trial arms and could potentially bias the CRPC efficacy estimate (and, in turn, the time to CROD efficacy estimate used in the company's economic model). The EAG therefore cannot determine if censoring was informative and, as a consequence, whether or not the survival estimates may be biased.

Table 8 Statistical methods used in the ARASENS trial

Statistical element	ARASENS trial
Analysis populations	
Brief description: The analysis populations are defined as follows in CS Table 6: **Full analysis set (FAS)**: all randomised participants, except for those with critical 'good clinical practice' violations (n = [redacted], as reported in CS Appendix D.3 Figure 15). Participants were analysed according to the group to which they were randomised. **Safety Analysis Set (SAS)**: all randomised participants who received at least one dose of darolutamide or placebo, except for [redacted] with a 'good clinical practice' violation. Participants were analysed according to actual treatment received; if any dose of darolutamide had been received, they were included in the darolutamide arm.	
EAG comment: The analysis populations are appropriate. Although excluding participants with critical 'good clinical practice' violations is a technical violation of ITT, as only [redacted] /1305 participants were excluded on this basis the EAG believes the FAS population can be considered as an intention-to-treat population.	

Sample size calculations
Brief description: The power calculation is reported in CS section B.2.4 and was calculated based on the primary outcome, OS. It was planned that 1,300 participants needed to be randomised to reach a 90% power and to be sensitive to a 25% decrease in death risk with darolutamide compared with placebo, using a one-sided test with a Type 1 error of 0.025. Data were considered mature when approximately 509 deaths occurred.
EAG comment: 1,305 participants were randomised into the trial (CS Appendix D.3, Figure 15). At the 25th October 2021 database cut-off, there had been 533 OS events (CS section B.2.6.1.1). The trial therefore appears to have been adequately powered.
Methods to account for multiplicity
Brief description: The company managed multiplicity (analysis of multiple outcomes) by testing secondary outcomes hierarchically, so that if a prior outcome analysis was statistically significant, then the next outcome in the ordered list of outcomes would be tested for statistical significance. The order of the outcomes tested is described in CS section B.2.4 and included time to CRPC as the first secondary outcome to be tested.
EAG comment: The company's approach to handling multiple testing of outcomes is appropriate.
Analysis of outcomes
Brief description: How time-to-event outcomes were statistically analysed is reported in CS Table 6. Briefly, stratified log-rank tests were used, using the randomisation stratification factors (extent of disease and ALP level). Kaplan-Meier estimates and curves were presented. The CS does not detail how the other measured outcomes of PSA response and HRQoL were analysed.
EAG comment: Time to event outcomes are appropriately analysed, but details are lacking about the statistical methods used to analyse other outcomes. These outcomes are not used in the economic model, so do not influence cost-effectiveness results.
Handling of missing data
Brief description: Participant censoring rules for when participants were missing event details are reported in CS Table 6. CS section B.2.4 states that an algorithm was used to estimate missing or partially missing event dates, but no further information is given about this in the CS. The statistical analysis plan[27] states that [redacted]
EAG comment: The CS does not provide a breakdown of the reasons why participants were censored in each trial arm and the number and proportion of participants censored for each reason. It is therefore unclear if censoring may be informative and, as a consequence, whether the time to CRPC results may be biased.[28,29] Of particular note, it is unclear if censoring participants who had received subsequent systemic antineoplastic therapy without meeting the criteria for CRPC and who were without a post PSA progression event differed between trial arms and could potentially bias the CRPC efficacy estimate. The algorithm used to impute missing date data appears to be appropriate.

Sensitivity & post-hoc analyses
Brief description: Sensitivity analyses are described in CS Table 6. With respect to outcomes used in the economic model, three sensitivity analyses of OS were conducted, using different assumptions about stratification (1. no stratification, 2. stratification using factors collected from the eCRF, and 3. stratification based on extent of disease stratification factors from the central imaging review). A sensitivity analysis of time to CRPC used central and local laboratory PSA data.
EAG comment: The EAG does not have any concerns about the sensitivity analyses conducted. As previously noted, we assume the time to CROD analysis is a post-hoc analysis.
Source: CS section B.2.4, CS Appendix D.3 Figure 15, and CS section B.2.6.1.1. ADT, androgen deprivation therapy; ALP, alkaline phosphatase; CRPC, castration-resistant prostate cancer; CS, company submission; eCRF, electronic case report form; FAS, full analysis set; HRQoL, health-related quality of life; ITT, intention to treat; OS, overall survival; PSA, prostate-specific antigen; SAS, safety analysis set.

EAG comment on study statistical methods

The EAG does not have concerns about the statistical methods used in the ARASENS trial, except that a breakdown of the number and proportion of participants in each trial arm who were censored for each censoring reason from the time to CRPC analysis is not provided. Therefore, the EAG has not been able to assess if censoring reasons differed between arms and thus could potentially bias the results.

3.2.5 Efficacy results of the intervention studies

The company provide a summary of results from ARASENS for primary and secondary outcomes in CS Table 7 and describe individual outcomes in more depth in CS sections B.2.6.1 and B.2.6.2. Exploratory outcomes are shown in CS section B.2.6.3. In this section of the EAG report we focus on the three outcomes included in the company's economic model.

3.2.5.1 Overall survival (Primary outcome)

Figure 2 below shows the Kaplan-Meier curves for overall survival. A statistically significant reduction in the hazard rate of death was observed for the darolutamide + docetaxel group compared to docetaxel + placebo (HR for OS: 0.68; 95% CI: 0.57, 0.80; p value <0.001). Median survival was not reached in the darolutamide + docetaxel group versus 48.9 months (95% CI: 44.4, NE) in the docetaxel + placebo group. The primary analysis used the randomisation stratification factors (extent of disease and ALP level). Sensitivity analyses using no stratification or stratification by different factors produced similar results (CS Appendix M.1 Table 45).

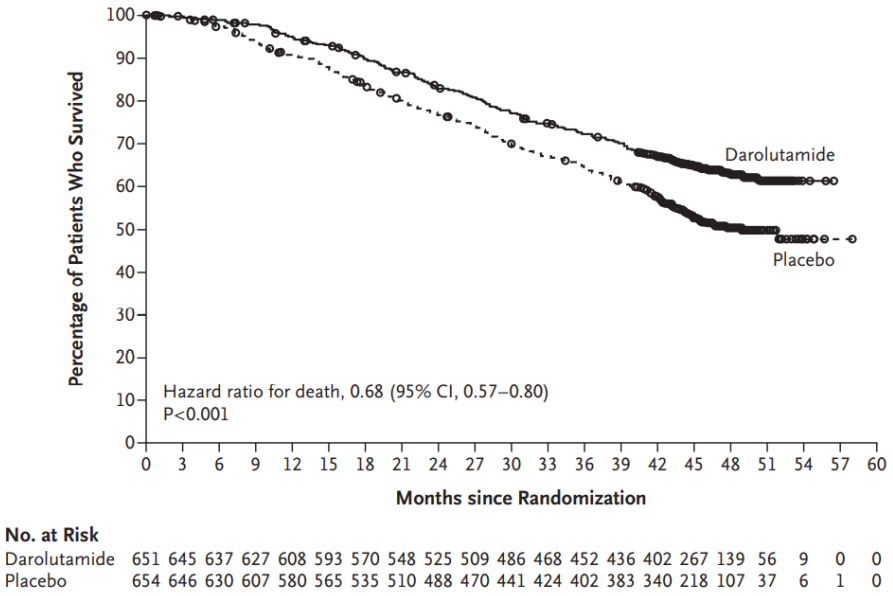

Figure 2 Kaplan–Meier curves of overall survival (FAS)

Source: CS Figure 5

Patients in the darolutamide arm of the ARASENS trial were permitted to receive a second ARTA-based treatment post-progression. This does not reflect NHS practice as a patient can only receive one ARTA during their treatment for prostate cancer. The company did not adjust their OS estimates for subsequent therapy on the assumption that any survival benefit gained is minimal. This is a reasonable assumption as our clinical expert advised that the currently available ARTA-based therapies are considered to have a similar mechanism of action. Therefore, the expectation is that patients who progressed after treatment with one ARTA would be unlikely to respond to a second ARTA post-progression. This is further supported by the company's post-hoc analysis of post-progression survival, stratified per subsequent treatment (CS Figure 20 and 21) which suggests no evidence of benefit was gained from these second ARTA therapies for the darolutamide + docetaxel arm whereas some benefit was observed for the placebo + docetaxel arm. The company did not adjust for the subsequent therapies used in the placebo arm which is reasonable as such an adjustment would be non-conservative and tend to favour darolutamide. The company point out that the overall survival benefit was observed despite a higher proportion of patients in the placebo arm receiving subsequent life-prolonging therapies (75.6% of patients who discontinued study treatment and entered active or survival follow up) compared to the active arm (56.8%) (CS Section B.2.6.1.1 and Appendix M.1 Table 44).

3.2.5.2 Time to CRPC or death (CROD) exploratory outcome

The company used the exploratory outcome 'time to CROD' from ARASENS (Figure 3) as the base case PFS outcome in the company's partitioned survival model. Time to CROD is defined as time to CRPC (radiological or PSA progression) or death if a patient has no CRPC event. The company assert that time to CRPC is a better measure of progression than radiological progression alone (rPFS), which was not measured in ARASENS and does not reflect clinical practice. Time to CROD includes both CRPC and death which ensures that the event measures all pre-progression risks (CS section B.3.2.2). A statistically significant reduction in the hazard rate of CROD was observed for the darolutamide + docetaxel group compared to docetaxel + placebo alone (HR for time to CROD: [redacted]

Figure 3 Kaplan–Meier curves of time to CROD

Source: CS Figure 7

3.2.5.3 Time to CPRC (Secondary outcome)

A statistically significant reduction in the hazard rate of progression measured as CRPC was observed for the darolutamide + docetaxel group compared to docetaxel + placebo alone (HR for CRPC:0.36; 95% CI: 0.30, 0.42; p value <0.001) (Figure 4). This outcome measure was used as an alternative definition for PFS in the company's NMA (see section 3.3.3) and was therefore used only in a scenario analysis in the company model. Sensitivity analyses using central and local laboratory PSA and testosterone data produce similar results (CS section B.2.6.2.1).

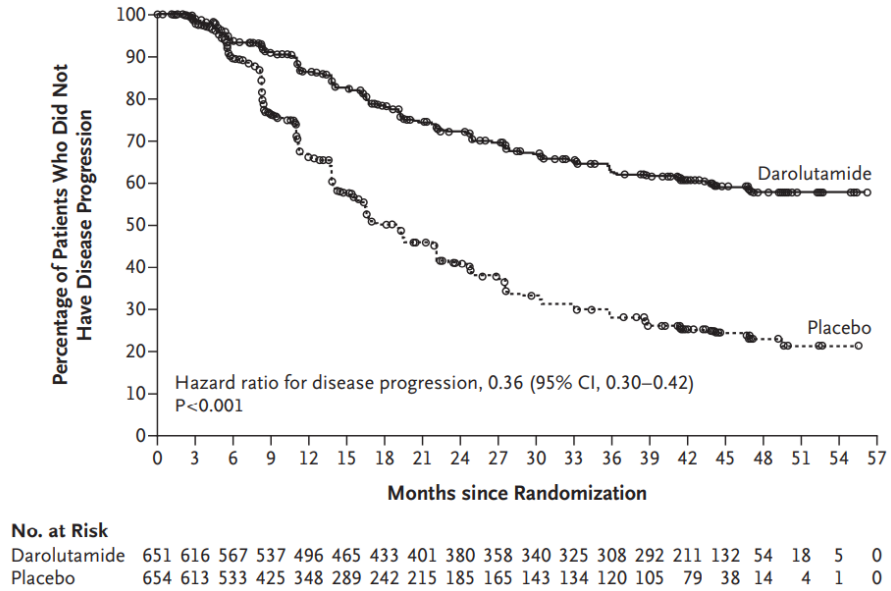

Figure 4 Kaplan–Meier curves of time to CRPC

Source: CS Figure 8

3.2.5.4 Subgroup analyses

Pre-specified subgroup analyses from the ARASENS trial are presented for the OS outcome in CS Appendix E, Figure 16. HRs remained favourable for the darolutamide + docetaxel trial arm for all of the subgroups analysed, although the treatment effect became statistically non-significant in some subgroups; however, this is most likely due to the smaller sample size in these groups. The company consider that no treatment effect modifiers were identified from the ARASENS subgroup analyses, however, the EAG notes that these analyses are unlikely to have been powered to detect differences between subgroups. Further discussion of potential treatment effects modifiers is provided in section 3.3.3.

The NICE scope mentions two subgroups of interest: people with high-risk metastatic prostate cancer and patients with newly diagnosed metastatic prostate cancer. The company note that definitions of both of these subgroups are inconsistent across mHSPC trials. Our clinical expert explained some clinical trials of treatments in mHSPC have defined high- versus low- risk disease based on the number of bone metastases and/or presence of visceral metastases (e.g. the LATITUDE trial),[30] whereas other trials have used high- versus low-volume disease. The latter risk stratification measure is used more commonly and is referred to in guidelines and consensus reports such as the Advanced Prostate Cancer Consensus Conference (APCCC).[31] De novo vs relapsed mHSPC is also important. In patients treated with ADT alone, the group with the poorest prognosis are those with de novo, high volume disease.[5] In ARASENS, patients with metastatic disease at diagnosis

comprised 86% of patients. The HR for OS in this group was [redacted] compared to [redacted] in patients with no metastasis at diagnosis. The HR for patients with metastasis at diagnosis was similar to that of the whole trial population (HR: 0.69; 95% CI:0.58, 0.82) which is not unexpected given that approximately 86% of patients in the trial had de novo disease. The treatment effect in patients without metastasis at initial diagnosis is less certain due to smaller numbers of patients in this subgroup. ARASENS did not stratify results by disease volume or explicitly by high- versus low- risk subgroups. The company assert, however, that the survival outcomes were comparable across subgroups with different extent of disease (non-regional lymph nodes, bone and visceral metastases).

3.2.6 HRQoL outcomes

HRQoL outcomes are presented in CS section B.2.6.3.3 and CS Appendix M.11. No clinically or statistically significant differences between treatment arms in ARASENS were observed in changes from baseline in mean values for:

- disease-related physical symptoms, emotional symptoms, treatment side effects or total score (measured using the NCCN-FACT-FPSI-17 questionnaire), or
- pain interference and pain severity scores (measured using the BPI-SF questionnaire).

These HRQoL scores were generally stable during treatment but became less favourable at or close to the end of treatment. Estimates of HRQoL were more uncertain in the active follow up period after discontinuation of treatment as the questionnaire response [redacted].

The European Quality of Life Working Group Health Status Measure 5 Dimensions (EQ-5D) HRQoL measure preferred by NICE was not used in the ARASENS trial.

3.2.7 Safety outcomes

Adverse event frequencies reported in ARASENS are presented in CS section B.2.10 Tables 21-25 and in CS Appendix F. The EAG note the following:

- Treatment-emergent adverse events (TEAE) were experienced by most patients in both trial arms.
- Approximately half of patients in each trial arm experienced a TEAE that was related to study drug ([redacted]% darolutamide versus [redacted] % placebo) while almost [redacted]% of patients in each trial arm experienced an adverse event that was related to docetaxel ([redacted]% darolutamide versus [redacted]% placebo) .

- The overall proportions of patients experiencing TEAE of severity grade ≥ 3 were similar between trial arms but the proportions of people experiencing grade ≥ 3 TEAEs related to the study drugs ([redacted]% in darolutamide arm and [redacted]% in placebo arm) were low compared with those related to docetaxel ([redacted] in both arms).
- Similar proportions of patients in each trial arm experienced TEAEs of severity grade 5 (4.1% versus 4.0%) or serious TEAEs (44.8% versus 42.3%).
- Similar proportions of patients experienced TEAEs leading to docetaxel dose modifications ([redacted]% in both trial arms) while a higher proportion of patients experienced a study drug dose modification in the darolutamide arm than in the placebo arm [redacted] (for further details, see CS section B.2.10.2.3).
- Patients in the darolutamide arm remained on the study treatment for longer (median duration 41 months) than in the placebo arm (16.7 months). Similar proportions of patients in each trial arm (>85%) received the full 6 cycles of docetaxel. Further details of study drug and docetaxel exposure are provided in CS section B.2.10. 3.1 and CS section B.2.10.3.2 respectively.
- TEAE frequencies were higher in the first 6 months of treatment which may reflect the period in which patients received docetaxel. Most patients in both groups received the full six cycles of docetaxel chemotherapy.

The most frequently reported TEAEs (CS section B.2.10.3) occurring in 25% or more of patients were alopecia, fatigue, anaemia, arthralgia, peripheral oedema, decreased neutrophil count, and diarrhoea. These were reported at similar frequencies in both trial arms but had a higher exposure-adjusted incidence rate (EAIR) in the placebo arm. Severity grade 3 or 4 TEAEs reported in more than 5% of patients include decreased neutrophil count, decreased white blood cell count, hypertension, and neutropenia. These were reported at comparable frequencies in both trial arms with the exception of grade 3 hypertension ([redacted]). The incidence rates of these grade 3 or 4 TEAEs were, however, higher in the placebo arm after adjusting for exposure with the exception of hypertension which was reported at a similar incidence rate in both trial arms (EAIR: 4.9 events per 100 person-years).

Adverse events of special interest representing potential risks known to be associated with ADT or with anti-androgen therapy are discussed in detail in CS section B.2.10.6. The company report that most of these events were comparable between trial arms and that most were assigned Grade 1 or 2 severity. Exceptions include hypertension, breast

disorders, rash, coronary artery disorders, cerebral haemorrhage and seizures. The company report exposure-adjusted incidence rate ratios (CS Table 25) but do not provide 95% confidence intervals and as such the precision of these estimates and any differences between trial arms cannot be fully assessed.

Overall, the company have provided a comprehensive review of the safety information from the ARASENS trial. Darolutamide was considered to have an acceptable safety profile in the target population and did not show an increase in the expected adverse events associated with docetaxel.

3.2.8 Pairwise meta-analysis of intervention studies

No pairwise meta-analysis was performed as only one RCT was identified for darolutamide.

3.3 Critique of studies included in the network meta-analysis

3.3.1 Rationale for NMA

The ARASENS RCT provides a direct comparison of the clinical effectiveness between darolutamide + docetaxel + ADT (triplet therapy) and docetaxel + ADT. No direct head-to-head trials are available to compare this triplet combination with the other comparators listed in the NICE scope. The company therefore performed an NMA to provide an indirect comparison with enzalutamide + ADT and with ADT alone. The EAG agree that there is clear rationale for an NMA to be performed.

3.3.2 Identification, selection and feasibility assessment of studies for NMA

The company conducted an SLR to inform the evidence base for the NMA (CS section B.2.9 and CS Appendix D.1.). This SLR identified 27 studies as potentially relevant to the current decision problem. CS Appendix D.1.4 Table 5 lists these 27 studies and their associated publications. One of the 27 studies (STAMPEDE) is a multi-arm trial platform from which 7 RCTs were eligible for inclusion and considered as separate RCTs for the purposes of the NMA. Therefore, a total of 33 separate studies were initially assessed for inclusion in the NMA. The company corrected some minor inconsistencies/omissions in presentation of information on the trials included in the NMA in response to clarification question C1. The treatments studied in these trials are summarised in CS Table 11. (We note this table excludes the ARASENS trial and appears to have omitted one of the treatments in the Zalcberg 1996 trial which compared bilateral orchidectomy with or without flutamide.)

CS Appendix D.1.2 Table 8 provides reasons for inclusion/exclusion of the 33 studies in the base-case and sensitivity NMAs. Twenty-one of the 33 studies were excluded from the NMA due to the studies including no relevant comparator (n=14) or only including comparisons between different types of ADT (n=4), lack of outcome data (n=2) or due to the study population including patients without metastatic disease (n=1). We consider these exclusions to be appropriate.

Of the remaining 12 studies, 8 RCTs were included in the company's base-case NMA: ARASENS, STAMPEDE-2, STAMPEDE-3, STAMPEDE-4, ARCHES, LATITUDE, CHAARTED and GETUG (Figure 5 below). These trials include the treatments and comparators relevant to the current decision problem. Orchiectomy and/or luteinising hormone releasing hormone (LHRH) analogues were combined in a single treatment node (ADT in the NMA). We consider this appropriate. Our clinical expert considered that the different ADT options may have slight differences in toxicity but have similar effectiveness.

An additional node for abiraterone + ADT (not in itself a relevant comparator) is included as this provides a connected loop to provide additional data for indirect comparison. This additional node makes use of results from the STAMPEDE trial. As mentioned above, the company have treated the three STAMPEDE comparisons in this loop as three separate trials. However, we consider that these comparisons are not necessarily independent. For example, some of the patients in the docetaxel + ADT arm of STAMPEDE-4 may also be included in the docetaxel + ADT arm of STAMPEDE-3 and the abiraterone +ADT arm of STAMPEDE-4 may be a subset of STAMPEDE-2. It would therefore be more appropriate to consider this one multi-arm trial to avoid double-counting, however, this requires individual patient data (IPD) in order to identify the degree of overlap and correct for correlation. In the absence of IPD we have performed a scenario analysis assuming STAMPEDE-4 is comprised of a subset of STAMPEDE-2 and STAMPEDE-3, thereby excluding the abiraterone node (see section 3.6 below).

The final four RCTs (Enzamet, Vaishapayan 2021, Zalcberg 1996 and SWOG-study-S8894) were included in the company's sensitivity NMA only (Figure 5 below) which included an additional node for nonsteroidal antiandrogens with ADT (standard nonsteroidal antiandrogen (SNA) + ADT). This is not a relevant comparator but provides a further connected loop in the network to facilitate indirect comparisons with enzalutamide + ADT. The ENZAMET trial was considered problematic because this trial included patients who did not receive docetaxel which contrasts with the population relevant to this decision problem where all patients are assumed to be eligible for docetaxel. The company used the HRs for

the subgroup of patients who did not receive docetaxel in the sensitivity analysis that included ENZAMET noting that enzalutamide +docetaxel + ADT is not a relevant comparator for this appraisal (CS section B.2.9.1). The patients who did not receive docetaxel in ENZAMET had better survival outcomes, but it is unclear whether any or all of these patients were fit to receive chemotherapy. While it is reasonable to include this subgroup data for ENZAMET, neither subgroup (i.e., those who did or did not receive docetaxel) is strictly relevant to the current decision problem. The company also note that the study by Vaishapayan et al had a number of methodological issues, namely lack of blinding, short follow up and over-representation of black ethnicity. We agree that it is reasonable to exclude these two studies (and therefore this loop of evidence) from the base case NMA. We also considered that it may be appropriate to combine the SNA + ADT node and ADT node. Our clinical expert advised that there may be a small difference in efficacy between SNA + ADT and ADT alone but no survival difference. We provide scenario analyses for this modification to the NMA in section 3.6 below.

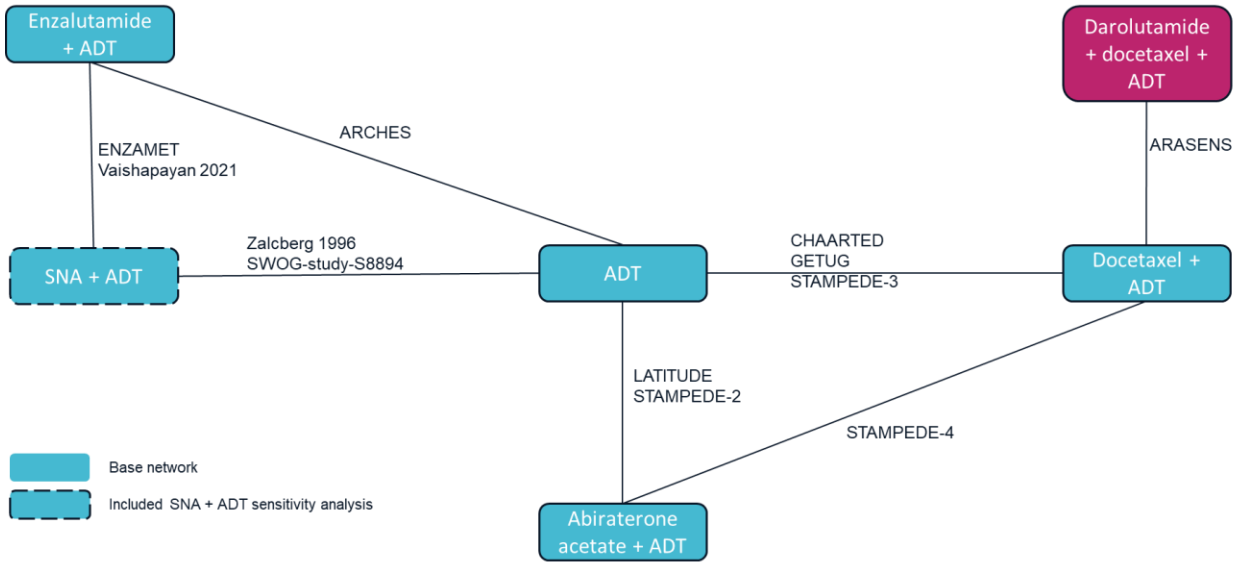

Figure 5 Evidence network for company NMA

Key: ADT, androgen deprivation therapy; NMA, network meta-analysis; SNA, nonsteroidal antiandrogen

Source: Reproduced from CS Figure 15

3.3.3 Clinical heterogeneity assessment

The company assessed potential sources of heterogeneity across the studies as follows:

Patient population

The company did not exclude any of the eight base case studies on the basis of differences in inclusion/exclusion criteria between trials. Eligibility criteria with respect to for age, ECOG status and method of diagnosis were similar across trials (CS Appendix D.1.6.5, Table 9). The company note some variation between trials with respect to receipt of prior cancer treatment and its duration but considered that most trials in the base case NMA were similar to ARASENS with respect to prior treatments received by patients. One exception was that prior docetaxel therapy was permitted in the ARCHES trial (17.8% of patients). The company acknowledge this as a potential source of heterogeneity stating that patients offered docetaxel may have a worse prognosis. The EAG note, however, that patients who are eligible for docetaxel (and deemed fit enough to receive chemotherapy) may represent patients who could be considered to have a better response. Despite this uncertainty, we note that the HR for the subgroup in ARCHES who received prior docetaxel is similar to that of the whole trial population.

Similarly, the company did not exclude any studies on the basis of any observed differences in selected baseline characteristics, namely the prognostic factors age, ECOG status, Gleason score, PSA levels and prostate cancer stage (CS Appendix D.1.65.45 Figures 2-6). The company reason that they did not expect these prognostic factors to be treatment effect modifiers since no differences in treatment effect were detected between these subgroups in the ARASENS trial. In response to clarification question A1, the company explain that they chose to assess these prognostic factors as they were most often presented for the other trials in the NMA (and therefore facilitated comparison between these trials). The company reported that clinical expert advice did not identify any specific treatment effect modifiers. The company also present subgroup analyses from the other trials in the NMA, where available. Like those in ARASENS, these generally show no evidence of a difference in respective treatment effects between the subgroups assessed. However, both the company and the EAG note that conclusions from subgroup analyses alone may be unreliable due to lack of statistical power.

The company did not explore differences between trials with respect to other prognostic factors such as low/high volume disease and synchronous/metasynchronous disease. The EAG note that differences between trials have been highlighted in previously published

NMAs.[32-37] Menges et al recently published a similar NMA of RCT in mHSPC noting that the LATITUDE trial included only patients with de novo disease. [37] However, like Menges et al, we found that excluding this trial did not have a material impact on the OS HRs generated by the NMA. Menges et al also conducted subgroup analyses based on low/high volume disease, de novo/progressive mHSPC and ECOG score 0/≥1. Whilst no evidence of effect modification was found in these analyses, the results are somewhat inconclusive since the relevant subgroup data were not available for all trials. In particular, no data were available for disease volume subgroups in the ARASENS or ARCHES studies (for enzalutamide, some data were available from ENZAMET only). No subgroup data were available for de novo/progressed mHSPC for enzalutamide.

Median overall survival in the docetaxel arms of GETUG, CHAARTED and STAMPEDE-3 ranged from 57.6 to 62.1 months (not reported for mHSPC patients in STAMPEDE-4). For studies with an ADT arm, median survival ranged from 36.5 months (LATITUDE trial) to not estimable at 5 years of follow up in the ARCHES trial. Reasons for these differences are uncertain but may relate to differences in patient population in these trials or in changes in patient care over time.

Treatments

Seven of the 8 trials in the base-case NMA included docetaxel treatment. In 6 of these 7 trials the same dosing regime was used. The other study (GETUG) included 9 cycles whereas the other 7 studies included only 6 cycles (CS Appendix D.1.6.2 Table 7). The company therefore performed a sensitivity analysis excluding GETUG from their base-case NMA (CS Appendix D.1.6.9.1 Table 15).

The company did not assess the comparability across the trials in the NMA with respect to the proportions of patients who received life-prolonging subsequent treatment following progression. The EAG note that the proportions of patients receiving a subsequent ARTA-based treatment varies across the trials in mHSPC [37] but this is not unexpected since the availability of these treatments has increased over time. We also note that some patients in the active arm of trials ARTA-based therapies (ARASENS, LATITUDE, ARCHES, STAMPEDE-2 and STAMPEDE-4) received a second ARTA which does not reflect NHS practice. Patients in the placebo arms of the NMA trials may have received more than one ARTA-based therapy following progression. The potential impact of these differences between trials and between the trials and NHS practice is uncertain. We acknowledge, however, that the company would not be able to explore this (e.g., by using methods to adjust for subsequent therapies) without individual patient data.

Outcomes

While overall survival was similarly defined across the trials, the definition of PFS varied. CS Appendix D.1.6.6 Table 10 provides further details of the outcome definitions used for each trial.

The company formed two different PFS outcomes for the purposes of the NMA. For their base case NMA, the company use time to CROD from ARASENS and the closest matching progression outcome for the other trials that incorporated death within the outcome definition. For the other trials the outcome measure chosen was either

- rPFS,
- time to clinical progression,
- clinical PFS or
- failure-free survival (FFS) defined as radiologic, clinical, or PSA progression or death from prostate cancer.

The company also performed an alternative PFS NMA that used time to CRPC from ARASENS and the closest matching outcomes from the other trials (i.e., not necessarily including death). For this alternative PFS NMA, the outcome measures deemed closest to time to CRPC from the comparator trials included

- time to biochemical PFS,
- time to subsequent therapy,
- FFS and PSA progression-free survival.

Clinical advice to the EAG is that the company's choice of proxy outcomes for their base case time to CROD and alternative time to CRPC outcomes from the comparator trials are reasonable and match closely.

HRs for the individual trial endpoints were assessed for violation of proportional hazards where data were available using log-cumulative hazards plots, Schoenfeld residual plots and Schoenfeld's global test. In one trial, CHAARTED, the OS outcome was deemed borderline non-proportional, therefore the company performed a sensitivity analysis to assess any potential impact by excluding this trial form their base case NMA (CS Appendix D.1.6.6, Tables 12 and 13). Whilst the Company deemed proportional hazards plausible for PFS, the EAG considered this reasonable.

3.3.4 Risk of bias assessment for studies included in the NMA

The company performed a risk of bias assessment for all 33 comparisons (27 studies) included in the SLR using the criteria recommended by NICE.[38] The full assessment is shown in CS Appendix D.1.4. One collective assessment was undertaken for the seven STAMPEDE trials. Appendix 9.3 (Table 41) of this EAG report summarises these company assessments for the subset of RCTs that were included in the company's base case NMA (n=8) and sensitivity analysis (n=12). We note that most of the trials were open-label by design. This is unlikely to bias estimates of overall survival but could impact PFS estimates if outcome assessment was based on more subjective clinical assessments and by assessors with knowledge of treatment allocation. Exclusion of these studies, however, would have meant the NMA was not feasible.

We agreed with the company's assessments with the exception that in some cases we judged the criteria to be of unclear risk of bias as we were unable to locate the necessary detail in the main source publication for the trial (NB we did not check study protocols or supplementary material):

- We could not determine whether the methods of randomisation were appropriate in three studies. [39-41] We also found that concealment of treatment allocation (prior to randomisation, as opposed to blinding after randomisation) was unclear for all studies except ARASENS.
- It was unclear whether the treatment groups were balanced at baseline for two studies because these data were only available for the whole trial population and not the subgroup used in the NMA [42,43]
- We could not assess drop-out rates in one trial as this information was not fully elaborated [30]. Potential attrition bias for ARASENS trial is further discussed in section 3.2.2.

In addition to the assessments above, the EAG note that crossover from placebo to active arm was permitted after unblinding in the ARCHES and LATITUDE studies. This is a potential source of bias in these studies since crossover of this nature may lead to an under-estimate of the treatment effect for the respective active treatment. We discuss this further in section 3.4.1

3.4 Critique of the network meta-analysis

3.4.1 Data inputs to the NMA

The data inputs for the NMAs are presented in CS Table 16. The EAG have checked these against the source data and the extracted HRs are mostly correct with some possible qualifications as described below.

Crossover in ARCHES and LATITUDE trials

- Both the ARCHES and LATITUDE studies allowed crossover from placebo to intervention arm at unblinding. The results of these two studies have been published adjusting for this crossover using methods such as rank preserving structure failure time modelling and/or inverse probability of censoring weights.[1,44] The adjusted HRs for OS are more favourable for enzalutamide + ADT versus ADT alone in ARCHES and for abiraterone + ADT versus ADT alone in LATITUDE (Table 9).
- The company have used the unadjusted HRs for their NMA arguing that crossover adjustment is not necessarily required in this setting. The appropriateness of adjusting for crossover was previously discussed in TA741 in respect of the TITAN trial (apalutamide + ADT versus ADT alone). The committee in TA741 considered it reasonable not to adjust for crossover in survival estimates since doing so may bias in favour of the active treatment. The adjustment assumes no patients in the control arm would subsequently receive treatment with an ARTA which is unlikely to reflect clinical practice. On the other hand, not adjusting could mean that patients in these trials received an ARTA treatment earlier than they would do in practice since crossover occurred after unblinding not due to progression. We note that the committee in TA741 considered both unadjusted and adjusted approaches in their decision-making. In light of these uncertainties, the EAG have conducted a scenario analysis using the cross-over adjusted HR estimates for OS in ARCHES and LATITUDE (see section 3.6).

Use of update PFS HRs from ARCHES and STAMPEDE-2

- Updated longer-term results are available for ARCHES[1] and STAMPEDE-2. [16] The company have used the updated results for OS for ARCHES in their NMA as these results were available from conference papers at the time of company's SLR.{Armstrong, 2021 #164} The updated result for PFS in Armstrong 2022 has not been used in the company's NMA as this paper had not been published at the time of the company's SLR. The EAG note that the updated ARCHES results suggest a less favourable effect of enzalutamide + ADT versus ADT on rPFS (HR:0.63; 95%CI: 0.52, 0.76) compared to that reported in the primary analysis (HR:0.39; 95% CI:0.30,

0.50). The reasons for this difference are uncertain. We note that the ARCHES trial allowed crossover from placebo to active arm following unblinding after the primary analysis. A crossover-adjusted estimate for rPFS has also been provided in Armstrong 2022 (HR: 0.55; 95%CI: 0.44, 0.67). In addition, the primary analysis measured rPFS using centralised independent review whereas the updated results mention the term 'investigator-assessed'. To explore this uncertainty, the EAG have performed scenario analysis using the updated HRs for these studies (see section 3.6).

HRs used in company's sensitivity NMA

- We assume the company used the Guyot methods to derive the HRs for the two older trials in the SNA+ADT loop as only Kaplan-Meier plots are available in these publications.[40,41] The EAG have not validated these HR estimates.

Table 9 Unadjusted and cross-over adjusted estimates for ARCHES and LATITUDE

Trial/Outcome	% of patients randomised to control arm who crossed over and received active treatment	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)
ARCHES (enzalutamide +ADT versus ADT)			
OS	31.3%	0.66 (0.53, 0.81)	0.57 (0.45, 0.70)
PFS		0.63 (0.52, 0.76)[b]	0.55 (0.44, 0.67**)**
LATITUDE (abiraterone +ADT)			
OS	12.0%	0.66 (0.56,0.78)	0.63 (0.53, 0.76)

[a] adjusted using rank preserving structure failure time modelling
[b] this PFS estimate is not used in company base case NMA; estimate is calculated after unblinding at time of updated OS analysis.
Source: Armstrong 2022[1]; Feyerabend 2019[44]

3.4.2 Statistical methods for the NMA

The company has used a Bayesian approach for all NMAs, with non-informative priors, in line with the recommended NICE Decision Support Unit (DSU) methodology (CS section B.2.9.2 and Appendix D.1.6.7). Trial-level data were available as treatment differences (logHRs), therefore an appropriate normal likelihood function with identity link was used. The company used the 'gemtc' package in R software to derive posterior distributions for model parameters for the NMAs. The EAG have validated the results of the NMAs in WinBUGS software using DSU template code: TSD2-7a (Random effect) and TSD-7b (Fixed effects).

No adjustment for correlation was made since all trials were treated as having only two arms (see also section 3.3.2.).

A summary of the different NMAs conducted by the company is given in CS Table 17. Three clinical effectiveness outcomes were considered: base-case OS, base-case PFS (CROD) and an alternative PFS definition (CRPC) (see section 3.3.3 above). Sensitivity analyses were also conducted to explore the impact of potential sources of heterogeneity detailed in section 3.3.3, namely, variations in PFS outcome definition, potential non-proportionality of hazards and different numbers of docetaxel cycles. The additional loop for SNA+ADT was used to strengthen the network in sensitivity analyses only, as the studies in this loop were considered a-priori to be a source of potential heterogeneity. HRs from these sensitivity analyses were broadly similar to the base case NMAs albeit with wider credible intervals for the PFS NMAs that excluded the GETUG trial (CS Appendix Tables 15, 17 & 19).

Homogeneity of treatment effects for pairwise comparisons were assessed in general terms for each NMA by comparing model fit statistics (deviance information criterion (DIC)) for fixed effect (FE) and random effect (RE) models.

- For the base case OS, a FE NMA was preferred by the company. We consider this a reasonable choice as both the RE and FE models generated similar results (CS Table 18) and no strong evidence of improved model fit was observed for the RE NMAs compared to the FE NMA (CS Appendix Table 14).
- For the PFS NMAs, a RE NMA was preferred by the company due to the anticipated heterogeneity arising from differences in outcome definitions across studies. Results were similar from both FE and RE models with model fit favouring RE (CS Appendix Table 16 and 18). The EAG agree RE an appropriate choice for PFS.

Consistency of treatment effects between direct and indirect evidence was assessed using a node splitting method i.e., comparison of direct and indirect evidence for connected loops in the network. For the base case this was performed for the loop formed with abiraterone + ADT (CS Appendices Figures 10, 12 & 14). No evidence of inconsistency was observed however, the reliability of these assessments may be limited by the small number of trials included in this loop. The CS does not provide the results of the assessment of inconsistency for the sensitivity analyses which included the additional SNA + ADT node.

3.4.3 Summary of EAG critique of the NMA

EAG comment on the studies included in the NMA

- The search methods and selection criteria for the NMA are appropriate. We consider that all relevant studies have been identified and included in the company's NMA.
- The company's search was out of date, however. We performed an updated search and identified longer-term data providing updated HRs for two of the trials included in the NMA. We include scenario analyses based on these updated trial results.
- We agree with the choice of base-case NMA and the company's exclusion of studies comparing enzalutamide + ADT and SNA + ADT alone from their base case NMA due to issues highlighted with respect to patient characteristics and/or methodological weaknesses. We provide a scenario analysis combining the SNA + ADT and ADT nodes.
- The company acknowledge differences between studies with respect to study and patient characteristics but did not consider these factors to be effect modifiers based on trial level subgroup analyses and expert advice. The company did not explore all potential sources of heterogeneity, in particular, important prognostic factors such as disease volume and whether patients had de novo or progressed mHSPC were not examined. We note, however, that the ability to assess all potential effect modifiers is limited by the lack of relevant subgroup data in key trials in the NMA. Thus, there remains some uncertainty as to the extent of heterogeneity and its impact on the NMA results.
- The company have chosen an appropriate outcome measure for PFS in their base case NMA (time to CROD). The company acknowledges that this outcome is not measured in the comparator trials but, given the data available, we consider that the company have selected an appropriate PFS outcome measure from each comparator trial to match as closely as possible to that of the ARASENS trial in their NMA.
- The company's statistical approach is appropriate.

3.5 Results from the network meta-analysis

NMA results for base case overall survival and PFS are presented in CS Tables 18 to 20 and summarised below in Table 10. HRs represent the relative effect of darolutamide +

docetaxel + ADT compared to each of the other treatments in the NMA. NB abiraterone + ADT is included in these tables but is not considered a relevant comparator for this appraisal.

Key NMA results:

- [redacted]., the highest probability of being ranked most effective. This was seen for all three clinical outcomes.
- [redacted] (CS Tables 19 and 20).
- The company's sensitivity analyses including the SNA + ADT node, excluding the GETUG trial and excluding the CHAARTED trial showed similar results to the base case NMA results (CS Appendix D.1.6.9).

Table 10 Relative effect of darolutamide + docetaxel + ADT compared to all other treatments (company's base-case)

Treatment	OS	PFS
	FE HR (95% CrI)	RE, Unif(0,5) HR (95% CrI)
Darolutamide + docetaxel + ADT		
Enzalutamide + ADT	[redacted]	[redacted]
Abiraterone acetate + ADT*	[redacted]	[redacted]
Docetaxel + ADT	[redacted]	[redacted]
ADT	[redacted]	[redacted]

Key: ADT, androgen deprivation therapy; CrI, credible interval; FE, fixed effect; HR, hazard ratio; OS, overall survival; PFS: progression-free survival; RE, random effect

[redacted]

3.6 Additional work on clinical effectiveness undertaken by the EAG

The following additional NMAs were performed:

- Company base case OS NMA using cross-over adjusted HRs for ARCHES and LATITUDE: this resulted in a less favourable treatment effect for darolutamide + docetaxel + ADT compared to enzalutamide + ADT (Table 11).
- Company base case for OS excluding abiraterone node to address double counting STAMPEDE patients: this did not have a major impact on NMA results but did reduce precision (Table 11).
- Scenario analysis for OS in which the SNA + ADT were combined into one node with ADT: this resulted in a less favourable treatment effect for darolutamide + docetaxel + ADT compared to enzalutamide + ADT (Table 11).
- Company base case PFS NMA using updated rPFS data from ARCHES and FFS data from STAMPEDE-2: this results in a much more favourable treatment effect for darolutamide + docetaxel + ADT compared to enzalutamide + ADT (Table 12).

Table 11 Results of EAG scenario analyses for OS

Treatment	Company base case OS	EAG scenario for OS using crossover-adjusted estimates for ARCHES and LATITUDE)	EAG scenario removing abiraterone node	EAG scenario combining SNA+ADT with ADT into one node
	FE HR (95% CrI)	FE HR (95% CrI)	FE HR (95% CrI)	FE HR (95% CrI)
Darolutamide + docetaxel + ADT				
Enzalutamide + ADT	[redacted]	[redacted]	[redacted]	[redacted]
Abiraterone acetate + ADT*	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + ADT	[redacted]	[redacted]	[redacted]	[redacted]
ADT	[redacted]	[redacted]	[redacted]	[redacted]

Key: ADT, androgen deprivation therapy; CrI, credible interval; FE, fixed effect; HR, hazard ratio; OS, overall survival

[redacted]

Source: CS Table 18

Table 12 Results of EAG scenario analyses for company base PFS

Treatment	Company NMA results	EAG Scenario analyses RE HR (95% CrI)		
		Using updated HRs for ARCHES and STAMPEDE- 2	Excluding abiraterone loop	Combining SNA + ADT and ADT node
Darolutamide + docetaxel + ADT				
Enzalutamide + ADT	[redacted]	[redacted]	[redacted]	[redacted]
Abiraterone acetate + ADT*	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + ADT	[redacted]	[redacted]	[redacted]	[redacted]
ADT	[redacted]	[redacted]	[redacted]	[redacted]

Key: ADT, androgen deprivation therapy; CrI, credible interval; HR, hazard ratio; OS, overall survival; PFS: progression-free survival; RE, random effect

[redacted]

3.7 Conclusions on the clinical effectiveness evidence

The company identified one RCT directly comparing darolutamide + docetaxel + ADT against placebo + docetaxel + ADT in people with mHSPC: the ARASENS trial. The trial adequately reflects the population, intervention, docetaxel with ADT comparator and outcomes specified in the company's decision problem and the NICE scope. The company did not, however, provide a subgroup analysis for patients with high-risk pancreatic cancer, which was a subgroup specified of interest in the NICE scope. The EAG judged that the trial was generally well conducted but noted a concern about an unclear risk of attrition bias (see below). We also note (based on advice from our clinical expert) that the participants were not fully representative of the patients seen in practice in terms of ECOG performance status, the proportion with de novo disease and ethnicity. The trial found statistically significant reductions in the hazard rate of death, CROD and time to CRPC for the darolutamide + docetaxel + ADT group compared to the docetaxel + placebo + ADT group. Adverse events were generally similar between treatment arms.

The EAG has identified the following uncertainties associated with the clinical effectiveness evidence presented in the CS from the ARASENS trial:

- There is an unclear risk of attrition bias due to unexplained, unequal loss to follow-up in the proportion of participants in each trial arm discontinuing study treatment who entered the Active follow-up phase of the trial.
- It is not possible to determine if the time to CRPC (used in combination with OS in the CROD outcome used in the company's economic model) may be biased, as the company did not provide information about how many and what proportion of participants were censored from this analysis for each censoring reason.

The company conducted an NMA to indirectly compare darolutamide + docetaxel + ADT with enzalutamide + ADT and with ADT alone. We assessed that the company's approach to the NMA was generally appropriate, but we note the following concerns:

- OS and PFS HRs adjusted for crossover in LATITUDE and ARCHES trials are different to the unadjusted HRs for these outcomes, but there is uncertainty over whether or not adjustment is needed, as NICE have previously (i.e., in TA741) considered that crossover adjustment may not be required in this setting.
- The NMA does not use all of the most up-to-date HR estimates from the key trials. However, there is some uncertainty as to whether the updated rPFS estimate for ARCHES uses the same outcome definition as the primary analysis estimate used in the company's NMA.
- The company use results of subgroup analyses to justify their assertion that there is no evidence of effect modification, but these analyses may not be powered to detect such effects. In addition, the company does not discuss all potential sources of heterogeneity, such as disease volume and de novo disease. We note, however, that the ability to assess all potential effect modifiers is limited by the lack of relevant subgroup data in key trials in the NMA. Therefore, uncertainty remains as to the extent of heterogeneity and its impact on the NMA results.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The company conducted an SLR to identify cost-effectiveness studies in mHSPC published between October 2011 and 18 November 2021, and relevant conference abstracts published in the previous two years (2019-2021). Relevant electronic databases, conference proceedings and UK Health Technology Assessment (HTA) databases were searched, and bibliographic searches of key systematic reviews published in the past three years were conducted (CS Appendix G 1.1). Eligibility criteria for cost and resource use studies are given in CS Appendix G Tables 30 and 31. There were no restrictions in terms of interventions and comparators.

Twenty-three unique studies were identified and included in the company's review. The company focussed on studies conducted in Europe, Canada and the United States (US), giving 16 studies, listed in CS Appendix G Table 32. The CS summarises details from the three UK studies identified: SMC Abiraterone (2021),[45] Lu et al. (2012),[46] and Woods et al. (2018)[47] in CS Section 3.1 Table 26, as well as three previous NICE STAs for adults with mHSPC (in CS Section 3.1 Table 27):

- TA712 - Enzalutamide for treating hormone-sensitive metastatic prostate cancer[4]
- TA741 - Apalutamide with androgen deprivation therapy for treating hormone-sensitive metastatic prostate cancer[8]
- TA721 - Abiraterone for treating newly diagnosed high-risk hormone-sensitive metastatic prostate cancer[48].

The company did not find any economic studies that investigated the cost-effectiveness of darolutamide + docetaxel + ADT in adult men with mHSPC.

EAG conclusion

The company searched relevant databases and conference proceedings and their assessment of the economic evaluation evidence was thorough. The EAG has no major concerns regarding the company's approach. However, the searches are almost 11 months old. The EAG updated the searches using EMBASE and MEDLINE and identified five additional relevant economic evaluations by Saad et al. (2022),[49] Wang et al. (2022),[50] Clarke et al. (2022),[51] Pelloux-Payer et al. (2021), [52] and Parmar et al. (2022).[53]

- Saad et al. conducted a network meta-analysis and cost-effectiveness analysis of enzalutamide + ADT versus apalutamide + ADT versus ADT alone for the treatment of mHSPC in Canada.

- Wang et al. compared ADT monotherapy with docetaxel, abiraterone acetate, enzalutamide, and apalutamide, added to ADT, respectively from the US healthcare sector perspective for patients with mHSPC.
- Clarke et al. conducted a cost-utility analysis of abiraterone acetate + prednisolone + standard of care compared with standard of care in patients with newly diagnosed advanced prostate cancer in England, based on the STAMPEDE trial data.
- Pelloux-Prayer et al. compared the cost-effectiveness of various sequential treatment strategies, from the start of first-line treatment in mHSPC to the death of the patients. The analysis was performed from the French public health care system perspective.
- Parmar et al. performed a cost-utility analysis of apalutamide + ADT compared with ADT alone for treatment of mHSPC, from the Canadian healthcare perspective.

The EAG also found two recent reviews of cost effectiveness studies in by Pelloux-Prayer et al. (2022)[54] and Yanev et al. (2022)[55] that identified similar studies in mHSPC to the company's searches.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

The company's economic model fulfils the requirements of NICE's reference case (Table 13).

Table 13 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on the CS
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes

Synthesis of evidence on health effects	Based on systematic review	Yes. Evidence from ARASENS trial and NMA based on SLR.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes
PSS, Personal Social Services		

4.2.2 Model structure

4.2.2.1 Overview of the model structure

The company developed a partitioned survival model in Microsoft Excel consisting of three health states (pre-progression, post-progression and death). The CS states that this approach is widely used in oncology modelling and is consistent with previous TAs for mHSPC (TA712 and TA741)[4 8] and the darolutamide model in nmCRPC (TA660).[6] The model structure is illustrated in CS Figure 16, reproduced below in Figure 6.

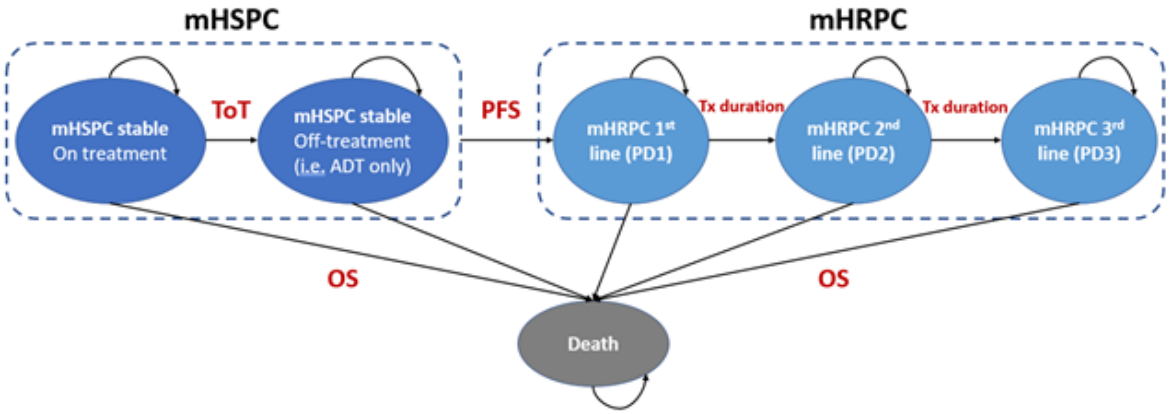

Figure 6 Company model structure

Reproduced from CS Figure 16

Key: mHRPC, metastatic hormone-relapsed prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival; PD1, progressed disease – first line; PD2, progressed disease – second line; PD3, progressed disease – third line; PFS, progression-free survival; ToT, time on treatment; Tx, treatment.

Patients enter the model in the mHSPC health state (progression-free). At disease progression, patients transition to the mHRPC health state (progressed disease), which is irreversible, so patients are not able to return to the mHSPC health state. Patients in the mHSPC and mHRPC states may die from cancer or other causes.

The original PFS (time to CRPC) analysis in the ARASENS trial did not include death as an event. The company conducted a new analysis of the ARASENS data to include death as an outcome, defined as time to CROD (CRPC or death). Time to CROD is discussed in more detail in section 3.2.5.2 and 4.2.6.2. The transitions between health states are estimated from the OS and PFS (time to CROD) curves in the ARASENS trial,

- mHSPC = time to CROD
- mHRPC = OS – time to CROD
- Dead = 1 - OS

The model estimates the proportion of patients within the mHSPC health state who remain on active treatment based on data from ARASENS trial and the NMA. Patients in the mHRPC health state, receive subsequent treatments (up to three lines of treatment). Subsequent treatment costs are applied as a single weighted lump-sum cost upon progression to the mHRPC health state. The CS comments that there is no direct trial data

to inform progression between the different lines of post-progression treatment, so they based the estimate of the duration of subsequent treatments on data from the literature.

The model uses a 28-day cycle length. A half-cycle correction is applied throughout the model to both costs and health outcomes.

The features of the company's economic analysis are tabulated and compared with previous appraisals for mHSPC (TA712, TA741 and TA721) in CS Table 28 with justification for the company's approach. The features listed in Table 28 are similar between appraisals, with the exception of the cycle length which is for different durations in the appraisals. The CS states that the 28-day cycle aligns well with the darolutamide dosing schedule.

4.2.2.2 EAG critique of model assumptions

4.2.2.2.1 Assumption 1

All the modelled OS extrapolations were adjusted to ensure that the probability of death would not be lower than that of the UK age and gender-matched general population.

4.2.2.2.2 Assumption 2

The PFS extrapolations were adjusted to ensure that the probability of progression was not greater than the probability of death in each cycle.

4.2.2.2.3 Assumption 3

The ToT extrapolations were adjusted to ensure that the probability of treatment discontinuation was not greater than the probability of progression in each cycle.

EAG comment on model structure

The three-state partitioned survival model used in the company's economic evaluation is a standard modelling approach and has been applied in previous NICE appraisals for mHSPC and is commonly used in models for oncology. We consider that the model structure and partitioned survival approach is appropriate.

4.2.3 Population

The population considered in the company model is adult patients with mHSPC who are eligible for chemotherapy. The population is aligned with the baseline characteristics of the ARASENS trial (see CS section 2.3.2), i.e. intent to treat (ITT) population. As shown in CS

Table 5, the majority of patients had stage IV metastatic prostate cancer (87%). The mean age of the population was 66.8 years, mean body weight was 77.5 kg and body surface area 1.79 m^2. The CS states that clinical experts' advice to the company confirmed that the ARASENS trial population was reflective of the patients who would be considered suitable for chemotherapy in UK clinical practice.

EAG comment on model population

Clinical expert advice to the EAG suggested that patients in the ARASENS trial generally have a better ECOG status than those in UK clinical practice so may be in better health, and patient ethnicity may be slightly different to clinical practice with black patients not well represented. Further, fewer patients with de novo disease would be seen in clinical practice compared to the ARASENS trial (55% versus 86% respectively). The population used in the economic model aligns with the NICE scope and the expected marketing authorisation for darolutamide (anticipated date of publication [redacted]).

The NICE scope further specifies two potential subgroups to be analysed if evidence allows for people with newly diagnosed metastatic prostate cancer and people with high-risk metastatic prostate cancer. The CS states that the appraisal is focussed on the ITT population and that the clinical trial was not powered for the specified subgroups. Further the company notes that the definitions of subgroups are inconsistent across mHSPC trials. Clinical advice to the EAG noted there is no consensus on marker(s) of high-risk disease (see section 3.2.5.4 for more discussion on this issue).

4.2.4 Interventions and comparators

The economic model compares darolutamide + docetaxel + ADT with ADT alone, docetaxel + ADT and enzalutamide + ADT.

Darolutamide is taken orally, with a recommended dose of 600mg twice daily (total daily dose of 1200mg). Darolutamide is administrated until disease progression or unacceptable toxicity. Docetaxel is administered as an intravenous infusion every three weeks for six cycles. Patients may also receive prednisolone or prednisone 5mg orally twice daily. ADT comprises HRH agonists and antagonists. ADT is a background therapy and is continued indefinitely for all patients. More details of the ADT therapies used in the model are given in section 4.2.8.1 below. Enzalutamide is taken orally, with a recommended dose of

160mg/day. Enzalutamide is administrated until disease progression or unacceptable toxicity.

EAG comment on intervention and comparators

The intervention and comparators in the economic model are consistent with the NICE scope.

4.2.5 Perspective, time horizon and discounting

The perspective of the analysis is that of the NHS and Personal Social Services (PSS). Costs and QALYs are discounted at 3.5% per year in the base case, as per the NICE reference case.[22] In the base case, the model has a lifetime horizon of 34 years. The CS comments that the lifetime horizon is sufficient to capture the plausible maximum life expectancy for the ARASENS ITT population (mean age 66.8 years).

EAG comment on perspective, time horizon and discounting

The company adopted the recommended perspective and discounting rates and an appropriate time horizon, which are all in line with NICE guidelines[22] and previous NICE appraisals for mHSPC.

4.2.6 Treatment effectiveness and extrapolation

The treatment effectiveness estimates for OS and PFS for docetaxel + ADT were fitted to the ARASENS data. The other treatment arms for darolutamide + docetaxel + ADT, ADT alone and enzalutamide were modelled by applying the NMA HRs to the extrapolated docetaxel data. The NMA HRs are shown in Table 14. These HRs are the same as those presented in Table 10, but are reported against a different comparator. The validity of using proportional hazards was considered by using log-cumulative plots and Schoenfeld residuals. The company fitted seven standard parametric models (i.e. exponential, log-normal, log-logistic, Weibull, generalized gamma, Gompertz and gamma) to the ARASENS data. The best fitting curve was determined, as recommended in NICE DSU Technical Support Document (TSD) 14, by considering the statistical fit using the Akaike information criterion (AIC) / Bayesian Information Criterion (BIC) and visual inspection of the of the extrapolated PFS and OS curves alongside the KM data and external data.

Table 14 NMA HR estimates versus docetaxel + ADT for OS and PFS and versus darolutamide for time on treatment

	OS	PFS	ToT
Darolutamide + Doc + ADT	[redacted]	[redacted]	-
Docetaxel + ADT	-	-	-
Enzalutamide + ADT	[redacted]	[redacted]	[redacted]
ADT alone	[redacted]	[redacted]	-

Source: CS Table 32, 35, 38

Reference treatment for OS and PFS is docetaxel + ADT; reference treatment for ToT is Darolutamide + Doc + ADT

4.2.6.1 Docetaxel OS extrapolation

The company assessed whether the proportional hazards (PH) assumption is supported using the log-cumulative hazard and Schoenfeld residuals plots (CS Appendix N). They concluded that the PH assumption holds for OS and therefore it is reasonable to assume constant hazards.

Standard parametric models were fitted to the docetaxel arm of the ARASENS trial. The statistical fits using the AIC/BIC are shown in CS Table 30 and the OS extrapolations are shown compared to the observed survival in ARASENS in CS Figure 17. The CS comments that all curves had comparable statistical fit to the ARASENS data, except the exponential and Gompertz curves. The extrapolations were also compared to the STAMPEDE-3 and CHAARTED trials,[56 57] which provide long-term survival estimates for docetaxel. The company chose the log-normal as this aligned most closely to the long-term STAMPEDE-3 data. The log-logistic was explored in a scenario analysis. A comparison of the docetaxel OS extrapolation for all parametric distributions is shown in CS Table 31 and for the log-normal and log-logistic distributions in Table 15.

Table 15 Comparison of docetaxel OS extrapolations and published data

Docetaxel+ADT	Predicted % alive at					
	1 year	**2 years**	**3 years**	**5 years**	**7 years**	**9 years**
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHAARTED	*94.9%*	*83.6%*	*71.7%*	*46.5%*	*23.9%*	*23.9%*
STAMPEDE	*91.7%*	*76.9%*	*65.4%*	*48.8%*	*35.2%*	*21.4%*
ARASENS	*90.3%*	*76.8%*	*63.8%*	*N/A*	*N/A*	*N/A*

Key: ADT, androgen deprivation therapy; N/A, not available; OS, overall survival.

Source: CS Table 31.

The comparator OS curves were calculated by applying NMA HRs to the docetaxel arm (Table 14). The OS estimates for the comparator curves are shown in CS Table 32 and in Figure 7.

Figure 7 OS curves for the modelled treatments

The EAG agrees with the company's assessment of the PH assessment. Furthermore, the EAG considers that the log-normal and log-logistic are reasonable distributions for OS, based on the fit to the observed OS data from ARASENS and STAMPEDE. Clinical advice to the EAG was that the STAMPEDE trial provides the most representative long-term survival estimates to UK clinical practice. Further, they commented that 30-year OS estimates for darolutamide (CS Table 32) appeared optimistic. On this basis, we preferred the log-logistic distribution to the lognormal as it provided less optimistic long-term extrapolation. The EAG also notes that the cost effectiveness results are robust to the choice

of OS curve and the log-normal and the log-logistic are the two most conservative OS curves (i.e. produced the lowest ICERs).

4.2.6.1.1 Adjustment of OS due to subsequent treatments

ARASENS was a multi-national trial and some participants received abiraterone and enzalutamide after treatment with darolutamide, which is not permitted in UK clinical practice. However, the company did not adjust OS within the model for this, based on advice from their advisory board clinicians and health economic experts. The experts thought no modification was needed, because the OS benefit seen in ARASENS was not driven by additional ARTAs. There was no difference in post-progression survival between patients receiving an ARTA, or another subsequent treatment in the ARASENS darolutamide + docetaxel + ADT arm (CS Section B.3.5.3 Figure 20). However, a post-progression survival benefit was seen for patients in the docetaxel + ADT arm who subsequently received either abiraterone or enzalutamide (CS Section B.3.5.3 Figure 21). The EAG's clinical expert concurred with the company's clinical advisory board and did not consider there were significant differences in the efficacy of the ARTAs (only in their side effect profiles) and there would be unlikely to be any further benefit from a second ARTA therapy (see section 3.2.5.1 for more discussion on this issue).

4.2.6.2 Docetaxel time to CROD extrapolation

Progression in the model was based on time to CROD which combines time to CRPC and pre-progression OS from ARASENS. The CS states that this CRPC is likely to be more representative of UK clinical practice than rPFS, because it combines both rPFS and PSA progression and does not rely on a set scanning frequency. This is discussed in more detail in sections 3.2.3.1 and 3.2.5.2 above. Time to CROD is a more appropriate measure of progression for use in the partitioned survival model because it accounts for the competing risks prior to progression.

The company checked whether the proportional hazards (PH) assumption is supported by visual inspection of the log-cumulative hazard plots and Schoenfeld residual plots (CS Appendix J). They concluded that the PH assumption does hold and so, as with OS, HRs were applied to the docetaxel data to inform PFS for all other treatments.

The fitted parametric distributions compared to the observed data are shown in CS Figure18. The best fitting models for time to CROD for the ARASENS trial, by AIC/BIC statistics, were the generalised gamma and the log-normal (CS Table 33). The clinical experts to the

company noted that most docetaxel progression predictions were lower than what they observed in clinical practice and on this basis the company chose the generalized gamma for their base case and the log-logistic as the second choice (used in scenario analyses) as these proved the highest progression estimates.

The CS compares the time to CROD estimates with those reported for STAMPEDE and CHAARTED at different time points in CS Table 34. The CS comments that both the CHAARTED and STAMPEDE trials predicted a higher percentage of PFS patients at all assessed timepoints. This is likely to be due to differences in definition of clinical progression, as discussed above.

The comparator PFS curves were calculated by applying NMA HRs to the docetaxel arm (Table 14). The PFS estimates for the comparator curves are shown in CS Table 32 and in Figure 8.

Figure 8 PFS for the modelled treatments

The EAG agrees with the company's assessment of the PH assessment. Furthermore, the EAG considers that the generalisable gamma provides a reasonable distribution for PFS, based on the fit to the observed PFS data from ARASENS trial. As mentioned above, the clinical expert considered the long-term estimates for darolutamide were likely to be optimistic for long-term survival and the proportion of patients remaining on treatment,

therefore we preferred the lognormal distribution. The lognormal also has a reasonable fit to the ARASENS trial data.

4.2.6.3 Time on treatment

Time on treatment (ToT) was modelled using the darolutamide + docetaxel + ADT arm as the anchor and the NMA HRs were applied to obtain the comparator ToT curves. Treatment with docetaxel was for a maximum of six cycles. Treatment with ADT was assumed to continue irrespective of disease progression.

The extrapolation of ToT for darolutamide + docetaxel + ADT was informed by a post-hoc analysis of the ARASENS trial data. The company checked whether the proportional hazards (PH) assumption is supported by visual inspection of the log-cumulative hazard plots and Schoenfeld residual plots (CS Appendix N). They concluded that the PH assumption does hold and so HRs were applied to the darolutamide data to inform ToT for the enzalutamide arm.

The fitted parametric distributions compared to the observed data are shown in CS Figure19. The best fitting models for ToT for the ARASENS trial, by AIC/BIC statistics, were the log-logistic and the Gompertz distributions (CS Table 36). The clinical experts to the company suggested there would not be a large gap between ToT and progression. On this basis and the statistical fit, the log-logistic was chosen as the most suitable with the Gompertz explored in scenarios analysis. The extrapolations for ToT are shown in CS Table 37 and the ICERs using alternative parametric distributions are shown in section 6.1.

The EAG agrees that the company's choice of parametric distribution provides a good fit to the ARASENS data. As advised by our clinical expert, we also agree with the assumption that ToT should be similar to the time to CRPC or death (TTCROD). The clinical expert to the EAG considered that after ten years there would be unlikely to be more than 10% of patients remaining on treatment and therefore the proportion of patients remaining on treatment with darolutamide ([redacted]) is likely to be optimistic. Therefore, we preferred the generalized gamma distribution. The generalised gamma also has a reasonable fit to the ARASENS trial data.

EAG comment on treatment effectiveness and extrapolation

The methods used to extrapolate OS and PFS for the economic model are reasonable and consistent with NICE's recommended methodology. The ARASENS

trial data is fairly mature with a median follow-up of more than 40 months. In addition, the company compared OS and PFS fitted curves against long-term historical trial data from the STAMPEDE and CHAARTED trials. The EAG agrees that the company's choice of parametric distributions for OS, PFS and ToT are reasonable and plausible. However, on advice from our clinical expert we prefer distributions that provide less optimistic survival. On this basis, we prefer the log-logistic for OS, lognormal for PFS and the generalized gamma distribution for time on treatment. We note that the model results are not sensitive to changes in the parametric curves chosen (section 6.1). The ARASENS trial provides head-to-head data for darolutamide + docetaxel + ADT vs docetaxel + ADT. Comparison with ADT alone and enzalutamide + ADT are modelled using HRs from the company's NMA. The uncertainties and issues related to the NMA HR estimates are discussed in more detail in section 3.4.3. We note that the modelled survival estimates for ADT and enzalutamide + ADT are not similar to those from the ARCHES study (section 5.3.2.1).

4.2.6.4 Adverse events

Adverse events with grade ≥ 3 were included in the economic model for both arms of the ARASENS trial, if they had an incidence of ≥5%. For enzalutamide and ADT alone adverse event incidence was informed by the ARCHES trial.[2] Adverse event incidences and durations for subsequent treatments in the mHRPC were taken from TA712. The average adverse event rate per treatment across the different trials was calculated by combining the observed number of adverse events and the number of patients per arm for the different trials and is presented in CS Table 40 for mHSPC and Table 41 for nmHRPC. In addition, symptomatic skeletal event rates (CS Table 42) were included in a scenario analysis.

4.2.7 Health related quality of life

4.2.7.1 Systematic literature review for utilities

The company used the methodology described in CS Appendix G1.1 to conduct a systematic literature review for HRQoL studies. The searches were completed on 18 November 2021; eligibility criteria are given in CS Appendix H Table 35.

Twenty studies, including two previous NICE TAs, met the inclusion criteria. The company prioritised studies reporting primary utility studies, giving results from eight studies (listed in CS Appendix H Table 36). The remaining 12 studies reported secondary utility studies and these data were not extracted.

Three studies reported utilities that were calculated using a UK tariff. Hall et al. (2019)[58] was a vignette study, which the company considered unreliable and did not use. Instead they have used the utilities derived from patient-reported outcomes from the clinical trials discussed in TA712 (ARCHES[2] and AFFIRM[59]) and TA741 (SPARTAN[60] and TITAN[61]). The company highlights that utility values from TA721 (Abiraterone for treating newly diagnosed high-risk hormone-sensitive metastatic prostate cancer)[48] may have been relevant to the current appraisal, but, these values were unobtainable as they were redacted throughout the Committee papers. The utility values used in TA712 and TA741 are summarized in CS Section B.3.4.3 Table 39 and shown below in Table 16.

4.2.7.2 Study-based health related quality of life

The ARASENS trial did not collect EQ-5D data. Disease-specific HRQoL measurements from ARASENS included the NCCN-FACT-FPSI-17 and BPI-SF. The company conducted a targeted literature review looking for any mapping algorithms from NCCN-FACT-FPSI-17 and BPI-SF to EQ-5D, but none were found. The search covered publications from 01 Jan 2020 to 01 June 2022 and the company searched appropriate sources. Full details are given in CS Appendix O Table 62. The EAG searched for relevant publications in PubMed without limiting the search period, but did not find any relevant studies.

The company considered these disease-specific HRQoL measures from ARASENS unsuitable for use in the cost-effectiveness model, and has therefore used other external data for the health state utility values.

4.2.7.3 Utility values applied in the model

The model uses the ERG-preferred utilities from TA712 (obtained from the EQ-5D-5L data in the key enzalutamide clinical trials: ARCHES and AFFIRM) as the base case health state utilities (Table 16).

Table 16 Health state utilities used in the model base case

Health state	Utility value	Source
mHSPC	0.806	NICE TA712 (Technical response form, page 26)[4]
mHRPC 1L	0.723	
mHRPC 2L	0.630	
mHRPC 3L+	0.530	
Key: 1L, first line, 2L, second line, 3L, third line, mHRPC, metastatic hormone-relapsed prostate cancer, NICE, National Institute for Health and Care Excellence, TA, technology appraisal.		

Health state	Utility value	Source
Source: CS Section 3.4.6 Table 45		

The company also considered utility values from TA741, but felt these were less relevant because apalutamide is restricted to patients for whom docetaxel is not suitable. Furthermore, TA712 evaluated three treatments that are comparators in the current CS (enzalutamide + ADT, docetaxel + ADT, and ADT alone). All utilities used in the model have been appropriately adjusted for age using current UK general population utility values.[62]

4.2.7.4 Disutility for docetaxel

In the TA741 appraisal, the company chose to implement an on-treatment disutility for docetaxel. In the current appraisal, the company does not include this disutility for docetaxel in their base case explaining that, based on results from the ARASENS trial, clinical experts did not see any clinical grounds for applying a specific docetaxel disutility. The CS states that any negative impacts of docetaxel therapy due to tolerability are captured in the adverse event disutilities (CS Section B.3.4.5).

4.2.7.5 Adverse event disutilities

Adverse event rates for darolutamide + docetaxel + ADT and for docetaxel + ADT were taken from the ARASENS trial. The ARCHES trial provided adverse event rates for enzalutamide + ADT, and for ADT alone. Post-progression, adverse event rates for subsequent treatments were taken from relevant RCTs (CS Section B.3.4.4 Tables 40 and 41 for mHSPC and mHRPC, respectively).

The adverse event disutilities and their duration and source are shown in Table 17. The disutility for each adverse event was combined with its expected duration to estimate the average QALY loss per treatment, which was applied as a one-off decrement in the first model cycle. The CS explains that adverse events are expected to occur in the short term after initial treatment.

Table 17 Adverse event disutilities

Adverse event	Disutility	Duration	Source
Alanine aminotransferase increased	0.000	28.0	Assumed to be 0
Anaemia	-0.119	10.5	Swinburn 2010[63]
Bone pain	-0.069	10.5	Doyle 2008[64]

Decreased neutrophil count	-0.090	10.5	Nafees 2008[65]
Decreased white blood cell count	-0.090	10.5	Assumed equal to neutropenia
Diarrhoea	-0.137	10.5	Nafees 2008,[65] Swinburn 2010,[63] and Lloyd 2006[66] (as reported in TA712)
Febrile neutropenia	-0.120	10.5	Lloyd 2006[66] and Nafees 2008[65]
Hypertension	-0.153	10.5	Swinburn 2010[63]
Hypokalaemia	0.000	28.0	Assumed to be 0[a]
Hepatotoxicity	-0.131	91.3	Assumed equal to fatigue in Lloyd 2006,[66] Nafees 2008[65] and Swinburn 2010[63] (as reported in NICE TA712)
Neutropenia	-0.090	10.5	Nafees 2008[65]
Thrombocytopaenia	-0.09	10.5	Assumed the same as neutropenia: Nafees 2008[65] (as reported in TA712)

Key: N/A, not applicable, NICE, National Institute for Health and Care Excellence, TA, technology appraisal.

[a] No disutilities were available for hypokalaemia

Source: Adapted from CS Section B.3.4.5 Table 43

4.2.7.6 Symptomatic skeletal event disutilities

Symptomatic skeletal event (SSE) data were only available from the ARASENS trial, so the company does not include the effect of these events in their base case. They explore the impact of SSEs for darolutamide + docetaxel + ADT, compared with docetaxel + ADT, using the ARASENS SSE rates (CS Section B.3.4.4 Table 42) and SSE disutilities previously reported in TA377 and TA712.

EAG comment on HRQoL

The EAG has no concerns with the company's HRQoL searches, other than they are 11 months old. The EAG updated the searches and did not find any other articles reporting utility values for patients with mHSPC.

The company uses the utility values from TA712 that were suggested by the EAG for that appraisal and were previously accepted by the NICE Committee. Enzalutamide + ADT is a comparator in this appraisal. The EAG agrees these utility values are appropriate.

The EAG does not consider that all the adverse effects of treatment with docetaxel have been captured in their base case analysis. In TA741 (apalutamide for mHSPC), a disutility for docetaxel of 0.02 was applied for one year. Clinical experts at the NICE committee meeting explained that the adverse effects of docetaxel were likely to last for six to 12 months. Our clinical experts explained that patients with mHSPC taking docetaxel would generally have a lower health-related quality of life compared with patients treated with enzalutamide + ADT, and ADT alone. The company assumes no disutility from being on docetaxel independent of adverse events, but based on the clinical advice, the EAG considers that the disutility for docetaxel should be included for 6 months and this is included in the EAG preferred assumptions in section 6.2.

4.2.8 Resources and costs

The costs in the model have the perspective of the NHS and PSS, using NHS reference costs,[67] Personal Social Services Research Unit (PSSRU) costs[68] and information from previous prostate cancer technology appraisals. All costs were appropriately inflated to 2021–2022 costs, using the 2021 PSSRU inflation indices.[68] The model costs consist of:

- Drug acquisition and administration costs
- Monitoring costs
- Subsequent treatment costs
- Costs associated with the management of adverse events
- End-of-life care costs

4.2.8.1 Drug acquisition

Table 18 presents the drug acquisition costs for darolutamide and its comparators included in the economic model (CS Table 46). The licenced daily dose of darolutamide used in the model is 1200mg (two 300mg tablets taken twice a day). The list price of the drug is £4,040 for a pack of 112 x 300mg tablets, giving a cost per daily dose of £114.28,[69] which is reduced to [redacted] after applying the Patient Access Scheme (PAS) price discount of [redacted]%. The CS states that the model base case assumes full vial(s) would be used for any drugs administered intravenously, with no vial sharing, and the optimum vial size would be used to minimise wastage.

Table 18 Drug acquisition costs

Treatment	Pack size x formulation	Unit cost (£)	Source
Darolutamide	112 x 300 mg	£4,040.00	MIMS, accessed 11 Feb 2022[69]
Docetaxel	1 x 20 mg	£3.56	eMIT, January 2021, accessed 11 Feb 2022[70]
	4 x 20 mg	£8.90	
	8 x 20 mg	£17.38	
Enzalutamide	112 x 40 mg	£2,734.67	MIMS, accessed 11 Feb 2022[69]
Abiraterone (mHRPC)	56 x 500 mg	£2,735.00	MIMS, accessed 11 Feb 2022[69]
Radium-223 (mHRPC)	6.0 ml (6000 kBq)	£4,040.00	NICE TA412[71]
Cabazitaxel (mHRPC)	60 mg / 1.5 mL	£3,696.00	MIMS, accessed 11 Feb 2022[69]
ADT treatments			
Leuprorelin	1 x 3.75 mg	£75.24	MIMS, accessed 11 Feb 2022[69]
Goserelin	1 x 3.6 mg	£70.00	MIMS, accessed 11 Feb 2022[69]
Triptorelin (Decapeptyl)*	1 x 3 mg	£69.00	MIMS, accessed 11 Feb 2022[69]

Key: ADT, androgen deprivation therapy, eMIT, electronic market information tool, mHRPC, metastatic hormone-relapsed prostate cancer; MIMS, Monthly Index of Medical Specialities, TA, technology appraisal.
Note: * Assumed Decapeptyl as cheaper than Gonapeptyl
Source: CS Section B.3.5.1.1. Table 46

The CS states that the relative dose intensity (RDI) for all treatments was high, with patients receiving 97% of their planned darolutamide dose and 96% of their planned docetaxel dose in ARASENS. For comparison, the RDI of enzalutamide is 99% of the label dose (CS Section B.3.5.1.1.3). The company's base case adjusts the darolutamide and enzalutamide treatment costs by the relative dose intensity.

4.2.8.2 Drug administration

Drug administration costs include the cost of intravenous infusions (£258.56; NHS 2020–2021 reference costs[70]) and subcutaneous injections (£32.00; PSSRU 2021 costs[68]), applied over the treatment duration for each appropriate therapy. The model assumes that oral treatments do not have an administration cost.

4.2.8.3 Resource use

The company conducted a systematic literature review to identify sources of costs and resource use (CS Appendix I), using the same methodology as described in CS Appendix G1.1. The searches were completed on 18 November 2021; eligibility criteria are given in CS Appendix G.2 Table 30). The company identified 38 studies, including three technology appraisals in mHSPC,[4,8,48] from 49 publications. The company prioritised studies from Europe, Canada and the US, resulting in 26 studies from 37 reports. The company did not extract data from the remaining 12 studies.

The company focussed on the healthcare resource use reported in the three technology appraisals for mHSPC (TA712 (enzalutamide),[4] TA721 (abiraterone),[48] TA741 (apalutamide),[8] considering that these studies are most similar to the population and decision problem of the current CS. The company concludes that TA712 is the most appropriate source for healthcare resource use rates, because it evaluated three comparators in the scope for this appraisal (enzalutamide + ADT, docetaxel + ADT and ADT alone). The company also considers resource use data from TA741 less relevant, as apalutamide is restricted to patients for whom docetaxel is not suitable.

4.2.8.4 Monitoring costs

CS Section B.3.5.2 Table 50 details the direct medical costs included in the model: cost of outpatient visits, monitoring costs, and costs for community nursing care. Resource use frequencies and distributions for each treatment arm are given in CS Section B.3.5.2 Tables 51-53. Similarly, CS Section B.3.5.2 Tables 54-57 report healthcare resource use rates for subsequent treatment options once patients progress to mHRPC. The EAG notes the resource use costs for mHRPC cabazitaxel and radium-223 in the model do not match those in the CS, but do match the figures from TA712. The company provided a corrected table in their response to the EAG's clarification questions, which confirms the figures from TA712 and those used in the model are correct (Company clarification response, Question B1 Table 1).

The company's clinical advisory board suggested changes to the resource use described in TA712:

1. Patients receiving docetaxel should alternate outpatient oncologist and nurse visits on a 50/50 basis (rather than 67% oncologist visits and 33% nurse visits)
2. At least 50% of patients who are treated with docetaxel would receive one MRI scan per year

3. Patients taking darolutamide would likely require fewer outpatient oncologist or nurse visits than patients taking enzalutamide, as less toxicity and fewer drug-drug interactions were expected than for enzalutamide. The clinicians recommended one visit every 12 weeks visits for darolutamide after the final docetaxel cycle, in contrast to one visit every 8 weeks recommended in TA712.

Our clinical expert considers that these changes were reasonable. Monitoring costs per cycle are shown in Table 19 for each of the mHSPC treatments.

Table 19 mHSPC monitoring cost per model cycle

mHSPC treatment	Monitoring cost per cycle
Darolutamide (on docetaxel)	£305.11
Darolutamide (off docetaxel)	£97.65
Docetaxel	£305.11
Enzalutamide	£114.23
ADT	£114.23
Key: ADT, androgen deprivation therapy, mHSPC, metastatic hormone-sensitive prostate cancer,	

4.2.8.5 Subsequent treatment costs

The model includes costs for post-progression treatment, allowing for up to three lines of subsequent treatment. The company consulted their clinical advisory board to determine the post-progression treatment options. Their experts' consensus for subsequent treatment distribution is presented in Table 20.

Table 20 Subsequent treatment distribution according to initial mHSPC treatment

Treatment	Darolutamide + docetaxel + ADT in mHSPC			Docetaxel + ADT in mHSPC			Enzalutamide + ADT in mHSPC			ADT alone in mHSPC		
	1L	2L	3L	1L	2L	3L	1L	2L	3L	1L	2L	3L
ADT	[redacted]											
Abiraterone	[redacted]											
Enzalutamide	[redacted]											
Docetaxel	[redacted]											
Radium-223	[redacted]											
Cabazitaxel	[redacted]											

Key: 1L, first line, 2L, second line, 3L, third line, ADT, androgen deprivation therapy, mHSPC, metastatic hormone-sensitive prostate cancer, N/A, not available.

Source: CS Section B.3.5.3 Table 58

The EAG were advised by a clinical expert that ADT should be given 100% throughout, as it is the backbone of treatment for mHSPC. The company assumes that background treatment with ADT is continued indefinitely, regardless of the mHSPC or post-progression treatment status of a patient. The model includes ADT drug and administration costs for every cycle for all treatments arms. Patients described as receiving 'No treatment/BSC' in the model still receive ADT and so are included in the group receiving ADT in CS Section B.3.5.3 Table 58.

The company assumes that 2.5% to 5% of patients in the enzalutamide + ADT arm would go on to receive abiraterone. However, in the UK, patients are only eligible to one androgen receptor-targeted agent (ARTA) (i.e. darolutamide, abiraterone, apalutamide or enzalutamide) as part of their prostate cancer treatment pathway.

The proportions of patients who receive each subsequent treatment, according to their initial treatment, in Table 20 are similar to those reported in TA712. However,

- Patients receiving enzalutamide did not go on to receive abiraterone in TA712, instead either receiving best supportive care, radium-233 or cabazitaxel
- The company's base case assumes that more patients initially receiving docetaxel + ADT, go on to receive enzalutamide (45%) and abiraterone (45%) on progressing, compared with 35% (enzalutamide) and 30% (abiraterone) of patients in TA712.
- In TA712, a higher proportion of patients initially receiving ADT alone continue with best supportive care/ADT alone (1L=20%, 2L=30%, 3L=85%)

The durations for each of the subsequent treatments is shown in Table 21 (CS Table 59). TA712 reported median treatment durations, whereas the company estimated mean values by adjusting reported medians by dividing the median value by LN(2) (the formula is derived from rearranging the exponential survival function). The company initially applied this conversion for all subsequent treatments. However, because docetaxel, radium-223 and cabazitaxel have fixed treatment durations, the model assumes that mean and median durations are the same for these treatments. The company provided a corrected version of CS Table 59 as part of their clarification response to question B3, the numbers now align with the economic model.

Using the subsequent treatment distributions with their associated treatment durations (Table 20 and Table 21), acquisition costs and administration costs (CS Section B.3.5.1 Tables 46 and 49), the CS calculates a one-off lump-sum post-progression treatment costs used in the model, shown in Table 22 (CS Table 60).

Table 21 Subsequent treatment durations and PFS used for the subsequent treatment calculations

Subsequent treatment	Mean* PFS (weeks)	Mean* treatment duration (weeks)
ADT	24.5	28.9
Abiraterone	103.5	86.6
Enzalutamide	123.6	111.1
Docetaxel	73.4	28.5**
Radium-223	89.0	20.3**
Cabazitaxel	55.2	18.0**

Key: ADT, androgen deprivation therapy, PFS, progression-free survival
*When no mean duration was reported, means were estimated by adjusting the reported median with /LN(2).
**Mean and median treatment duration assumed equal, due to predefined max treatment duration.
Source: Company clarification response, Question B3, Table 2

Table 22 One-off lump-sum subsequent treatment and administration costs per mHSPC treatment, applied upon progression

mHSPC treatment	One-off lump-sum subsequent treatment costs	One-off lump-sum subsequent admin costs
Darolutamide + Docetaxel + ADT	[redacted]	[redacted]
Docetaxel + ADT	[redacted]	[redacted]
Enzalutamide + ADT	[redacted]	[redacted]
ADT alone	[redacted]	[redacted]

Key: ADT, androgen deprivation therapy; mHSPC, metastatic hormone-sensitive prostate cancer.
Source: CS Section B.3.5.3 Table 60

4.2.8.6 Costs associated with adverse events

The CS presents costs related to managing adverse events (CS Section B.3.5.4 Table 63), which are modelled according to the proportion of adverse events per treatment arm. The company uses two NHS reference cost codes[67] for their weighted average for diarrhoea in the model (PF26A and PF26B), but the CS also includes a third (PF26C). The EAG also notes that PF26A, PF26B and PF26C are codes for a paediatric condition (Paediatric Other Gastrointestinal Disorders, Non-elective Short Stay).

In their response to the EAG's clarification question B6, the company explains that there is no specific Healthcare Resource Group code for diarrhoea in the latest NHS National Cost Collection. The company looked at previous technology appraisals and used the cost codes

in line with TA405[72] and TA370;[73] the description PF26C was included in the CS by mistake. The EAG prefers to use a weighted average of FD10J, FD10K, FD10L and FD10M (Non-Malignant Gastrointestinal Tract Disorders without Interventions, Day Case),[67] to calculate the cost of diarrhoea as an adverse event, resulting in a unit cost of £576.27.

Costs for symptomatic skeletal events are the same as those submitted and accepted by the NICE committee as part of the TA712 appraisal for enzalutamide.

4.2.8.7 End-of-life care costs

The model includes End-of-life costs. The EAG notes the modelled end-of-life costs from the report by Georghiou and Bardsley (2014)[3] are for the general population, rather than for people with a cancer diagnosis. In addition, the company's base case does not account for the cost of GP visits, which is a component of Georghiou and Bardsley's calculations. The report also expects cancer patients to use more hospital resources and less nursing and residential care in comparison to the general population. Full terminal care costs for cancer patients from the report, after adjusting for inflation, are £9,720 (Table 23). The effect of this on the company's base case ICER is minimal, decreasing it to [redacted] per QALY for docetaxel + ADT, and [redacted] per QALY for ADT alone.

Table 23 Terminal care costs (one-off costs based on the last 3 months of life), inflated to 2021/22 prices

Cost	Company base case	Patients with a cancer diagnosis[3]
GP visits	Not included	£423
District nurse visits	£322	£681
Nursing and residential care	£1,193	£530
Hospital care – inpatient (hospice)	£637	£637
Hospital care – final 3 months of life	£5,211	£6,821
Marie Curie nursing service	£637	£628
Total	**£8,000**	**£9,719**

4.2.8.8 Concomitant medication costs

The CS states that the model does not include costs for use of concomitant medications, based on expert clinical advice received by the company. In keeping with the TA712 appraisal, the company ran a scenario in which granulocyte-colony stimulating factor (G-

CSF) is used prophylactically for 7 days in 8.1% of the total number of patients who receive docetaxel, cabazitaxel or radium-223 (CS Section B.3.5.5).

EAG comment on resources and costs

Drug costs and administration costs used in the model are correctly implemented, dosage calculations are appropriate, drug administration assumptions match UK clinical practice and are in line with past mHSPC appraisals. Darolutamide and enzalutamide treatment costs in mHSPC were appropriately adjusted by the reported relative dose intensity (RDI) in the modelled base case. The company provides an option to not include RDI, which increases the ICER to [redacted] per QALY compared with docetaxel + ADT, and to [redacted] per QALY versus ADT alone.

The EAG concurs that the healthcare resource use frequencies and costs from TA712 are suitable for the current appraisal and costs have been inflated appropriately.

The EAG notes that patients in the UK would not receive abiraterone following treatment with enzalutamide (Table 20). Using the TA712 subsequent treatment distributions increases the ICER for darolutamide + docetaxel + ADT to [redacted] per QALY compared with docetaxel + ADT (6.2).

The lump-sum post-progression treatment and administration costs are appropriate for a partitioned survival analysis model. This approach was used in TA660 (Darolutamide with androgen deprivation therapy for treating hormone-relapsed non-metastatic prostate cancer),[6] and accepted by the committee for that appraisal.

The EAG notes minor discrepancies in the modelled adverse event cost for diarrhoea (see 4.2.8.6) and end of life care costs (see 4.2.8.7), which we have corrected.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company reports their base case cost-effectiveness analysis results for darolutamide + docetaxel + ADT versus ADT, docetaxel + ADT and enzalutamide + ADT in CS section B.3.10.1 Table 69, using the PAS discount price for darolutamide, but no discounts for any of the comparators or subsequent treatments. Table 24 shows the base case incremental

analyses. Results using the PAS discounts for all treatments have been produced by the EAG in a separate confidential addendum.

Table 24 Company base case results using PAS price for darolutamide, incremental analyses

Treatments	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£ per QALY)
Docetaxel + ADT	[redacted]	[redacted]	-	-	
ADT alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Darolutamide + docetaxel + ADT	[redacted]	[redacted]	[redacted]	[redacted]	£14,950
Enzalutamide + ADT	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Key: ADT, androgen deprivation therapy; ICER; incremental cost effectiveness ratio; QALY, quality-adjusted life-year
Source: Base case model results CS Table 69

The company's base case results show that darolutamide + docetaxel + ADT offers a QALY gain of [redacted] for an additional cost of [redacted] versus docetaxel + ADT, with an ICER of £14,950 per QALY. ADT alone and enzalutamide + ADT are dominated treatments, i.e. they are more expensive and less effective, compared with docetaxel + ADT and darolutamide + docetaxel + ADT respectively.

5.2 Company's sensitivity analyses

5.2.1 Deterministic sensitivity analyses

The company initially considers 92 parameters in their one-way sensitivity analyses (OWSA), applying the PAS discount for darolutamide. The company excludes parameters with no associated uncertainty (e.g. drug costs) and parameters that cannot be varied individually (e.g. efficacy extrapolation parameters). Broadly, the parameters covered by the scenarios are:

- Altering PFS and OS hazard ratios for the treatments
- Time on treatment durations
- Subsequent treatment durations
- Utilities for different health states
- An on-treatment disutility for docetaxel
- Disutilities for adverse events and symptomatic skeletal events
- Healthcare resource use for treatments in mHSPC and mHRPC

Variations in input parameters were based on the 95% confidence intervals. If no confidence interval and/or standard deviation or error was available, the company varies the parameter using an assumed standard error of 10% of the mean.

As the ARASENS trial evaluated darolutamide + docetaxel + ADT versus docetaxel + ADT, we focus on this comparison and reproduce the sensitivity analyses for these two comparators, listing the most influential parameters by ICER (Figure 9). The company reports the top 10 parameters with the greatest impact on incremental net monetary benefit (iNMB) for darolutamide + docetaxel + ADT versus enzalutamide + ADT, and ADT alone in CS Section 3.11.2 Tables 73-74 and Figures 27-28.

[redacted]

The mHSPC health state utility has the most effect on the ICER for docetaxel + ADT, increasing it to [redacted] per QALY. The model is also sensitive to the PFS and OS hazard ratios from the NMA, and subsequent treatment durations of enzalutamide and abiraterone. The company explores uncertainty regarding utility and NMA inputs in their scenario analyses (discussed in section 5.2.2).

Figure 9 Top 10 most influential parameters for darolutamide + docetaxel + ADT versus docetaxel + ADT, by ICER

Key: 1L, first-line, 3L, third line, ADT, androgen deprivation therapy, HRU, healthcare resource use, ICER, incremental cost effectiveness ratio, mHRPC, metastatic hormone-relapsed prostate cancer, mHSPC, metastatic hormone-sensitive prostate cancer, OS, overall survival, PFS, progression-free survival, Tx, treatment.

Source: Adapted from CS Section 3.11.2 Figure 26

5.2.2 Deterministic scenario analysis

The CS includes 17 scenario analyses, described in CS Section B.3.11.3 Table 75. The scenarios include:

- Using darolutamide data from ARASENS as the anchor curve for all treatments
- Using docetaxel OS and time to CROD data from ARASENS extrapolated using dependent extrapolations (i.e. treatment effect models)
- Using different extrapolation curves for OS, PFS and time on treatment
- Excluding individual studies when calculating hazard ratios from the NMA
- Excluding relative dose intensity
- Using health state utilities reported in TA741
- Including an on-treatment docetaxel disutility
- Altering the time horizon of the model

The CS presents the deterministic scenario analysis results for the cost-effectiveness of darolutamide + docetaxel + ADT versus docetaxel + ADT, enzalutamide + ADT and ADT alone in CS Section B.3.11.3 Tables 76, 78 and 80, ranked by difference in iNMB.

For the comparison with docetaxel + ADT, running the base case analysis using the Gompertz time on treatment curve to model treatment use (scenario 5) had the greatest effect on the ICER, reducing it to [redacted] per QALY (Table 25). In the remaining scenarios, the ICERs ranged from [redacted] per QALY when using the log-logistic parametric distribution for PFS (scenario 4), to [redacted] per QALY when excluding the relative dose intensity in the model (scenario 11).

Table 25 Deterministic scenario results for darolutamide + docetaxel + ADT versus docetaxel + ADT

No.	Scenario description	ICER (£/QALY)
Base case		£14,950
1	Run the base case analysis using darolutamide data from ARASENS to extrapolate OS, TTCROD and ToT as an anchor for all treatments	[redacted]
2	Run the base case analysis using docetaxel OS and TTCROD data from ARASENS extrapolated using dependent extrapolations (i.e. treatment effect models)	[redacted]
3	Run the base case analysis using the log-logistic ARASENS OS curve to model survival	[redacted]
4	Run the base case analysis using the log-logistic ARASENS TTCROD curve to model progression	[redacted]
5	Run the base case analysis using the Gompertz ARASENS ToT curve to model treatment use	[redacted]
6	Assume enzalutamide ToT is equal to PFS, rather than applying the PFS HR to the ToT data	[redacted]
7	Use the resulting hazard from the NMA when GETUG-AFU 15 trial is excluded.	[redacted]

No.	Scenario description	ICER (£/QALY)
8	Include studies using SNA which may have indirectly contributed to the NMA	[redacted]
9	Exclude CHAARTED from the NMA, as it did not show proportional hazards for OS.	[redacted]
10	Use the alternative PFS network NMA hazards to model progression for indirect comparators	[redacted]
11	Exclude RDI	[redacted]
12	Use health state utilities for pre-progression, 1L, 2L and 3L+ from those reported in TA741.	[redacted]
13	Include an on-treatment disutility for patients treated with docetaxel.	[redacted]
14	Include prophylactic G-CSF costs as concomitant treatment for patients receiving docetaxel, cabazitaxel or radium-223	[redacted]
15*	Include SSE costs and disutilities for darolutamide and docetaxel only	[redacted]
16	A time horizon of 20 years is used instead of the lifetime time horizon	[redacted]
17	A time horizon of 25 years is used instead of the lifetime time horizon	[redacted]

Key: ADT, androgen deprivation therapy; alt. alternative; G-CSF, granulocyte-colony stimulating factor; HR; hazard ratio; ICER, incremental cost-effectiveness ratio; iNMB, incremental net monetary benefit; mHRPC, metastatic hormone-relapsed prostate cancer; NMA, network meta-analysis; OS, overall survival; PH, proportional hazards; PFS, progression-free survival; RDI, relative dose intensity; SNA; nonsteroidal antiandrogen; ToT, time on treatment; TTCROD, time to CRPC or death
Note: *Scenario only performed versus docetaxel + ADT, as SSE data were only available for docetaxel.

Source: Adapted from CS Section B.3.11.3 Table 75

5.2.3 Probabilistic sensitivity analysis

CS Section B.3.11.1 describes the company's probabilistic sensitivity analysis using a Monte Carlo simulation with 2,000 simulations. The uncertainties in the individual parameters for treatment effect, costs and utilities were characterized using probability distributions, and are described in CS Section B.3.9.1 Table 67. The individual inputs for the parametric survival extrapolations were varied using the variance-covariance matrices, to preserve the functional relations between the individual survival inputs. The results are given in Table 26, with less than £1,200 per QALY difference in the deterministic and probabilistic ICERs for all three treatment comparisons. The EAG confirms that the probabilistic results are similar to the deterministic results.

Table 26 Comparison of deterministic and probabilistic ICERs (£/QALY) vs darolutamide + docetaxel + ADT

Analysis	Docetaxel + ADT	Enzalutamide + ADT	ADT alone
Deterministic ICER	£14,950	Dominated (-£78,321)	£9,216
Probabilistic ICER	£13,763	Dominated (-£77,749)	£8,560
Difference (%)	£1,187 (7.9%)	£572 (7.3%)	£656 (7.1%)
Source: Adapted from CS Section 3.11.1 Table 71			

CS Section B.3.11.1 Figures 22-24 show the cost-effectiveness scatterplot for each treatment and CS Figure 25 presents the cost-effectiveness acceptability curve. Darolutamide has an [redacted] and [redacted] probability of being cost-effective versus all comparators when considering a £20,000 and £30,000 willingness to pay (WTP) threshold, respectively.

5.2.4 Probabilistic scenario analyses

The company also performed probabilistic sensitivity analyses for the 17 scenarios described in CS Section B.3.11.3 Table 75. The company presents the scenario results in CS Section B.3.11.3 Tables 77, 79 and 81, ranked by difference in iNMB.

Results for the ICERs for docetaxel + ADT are shown in Table 26. Using darolutamide as the anchor curve for all treatments (scenario 1), had the most effect, increasing the ICER to [redacted] per QALY. The remaining ICERs ranged from [redacted] per QALY when running the base case analysis using the Gompertz time on treatment curve to model treatment use (scenario 5), to [redacted] per QALY when excluding the relative dose intensity in the model (scenario 11).

The EAG re-ran the probabilistic scenario results for all comparators. Concentrating on the comparators in ARASENS, all of the EAG's ICERs for docetaxel + ADT are within £500 per QALY of the company's respective initial probabilistic analyses.

5.3 Model validation and face validity check

5.3.1 Company's model validation

The company describes their approach to model validation in CS section B.3.14. The CS states that the economic model was extensively quality checked by an independent health economist, not involved in the model's construction. The model was reviewed for coding

errors, inconsistencies and the plausibility of inputs. It was also checked by testing using an internal checklist which included checks listed in TECH-VER.[74]

The model was checked against clinical expert opinion (nine clinical UK oncologists). The clinical experts verified the clinical validity of model assumptions and the long-term survival estimates, the NMA approach and the studies chosen for the NMA. Health economic experts also reviewed the model; they confirmed the suitability and robustness of the NMA approach, the suitability of the NMA studies, the model structure, and the survival modelling approach.

The long-term survival data from STAMPEDE-3 and CHAARTED were used to validate the docetaxel survival curves (CS Table 31 and 34). Median docetaxel OS from the model was compared against the available median OS from ARASENS, STAMPEDE-3 and CHAARTED (CS Table 82). The modelled median ([redacted] months) falls between the medians of the ARASENS (48.9 months) and STAMPEDE (59.1 months) trials.

The CS comments that there are limited results available from past technology appraisals to further validate the model results and the only available results were from TA741. They have compared modelled life years for docetaxel + ADT and ADT alone against TA741 (CS Table 83) and comment that the results were well aligned, with both models reporting comparable total life years gained.

EAG conclusions

The company conducted a full and comprehensive internal and external validity check and have reported these in detail. The EAG are satisfied with the validation completed by the company.

5.3.2 EAG model validation

The EAG checked the economic model for transparency and validity. We conducted a range of tests to verify model inputs, calculations and outputs:

- Cross-checking all parameter inputs against values reported in the CS and cited sources
- Checking all model outputs against results cited in the CS, including the base case, deterministic sensitivity analyses, scenario analyses and probabilistic sensitivity analyses
- Checking the individual equations within the model

- Manually running scenarios and checking model outputs against results reported in the CS for the deterministic sensitivity analyses and scenario analyses
- Applying a range of extreme value and logic tests to check the plausibility of changes in results when parameters are changed ('black box' checks)

The model is generally well-implemented and we have not identified any modelling errors.

5.3.2.1 External validity checks

The EAG compared results for docetaxel + ADT and ADT alone against those produced by Woods et al.[47] Woods et al. conducted an economic evaluation of mHSPC patients in the STAMPEDE trial from a UK perspective. The results for undiscounted life years and QALYs are shown in Table 27 and are comparable between the company model and Woods et al.

Table 27 Comparison of modelled life years and QALYs with study by Woods et al.

	Modelled LYG (undiscounted)			**Total modelled QALYs**		
	Company estimate	EAG estimate	Woods et al.	Company estimate	EAG estimate	Woods et al.
Docetaxel + ADT	[redacted]	[redacted]	5.79	[redacted]	[redacted]	3.51
ADT alone	[redacted]	[redacted]	4.90	[redacted]	[redacted]	3.01

ADT, androgen deprivation therapy; LYG, life years gained; QALY, quality-adjusted life-years

We also compared the modelled results against those given in Wang et al.[50] Wang et al. conducted a partitioned survival model from the US healthcare perspective that compared docetaxel, abiraterone acetate, enzalutamide, and apalutamide. The results for the life years and QALYs are shown in Table 28 with a discount rate of 3% and a life-time horizon of 30 years (as used in Wang et al). The results are reasonably similar for ADT and docetaxel. For enzalutamide, the modelled results are more favourable than those from Wang et al. This is likely to be because Wang et al. did not use the latest trial evidence from the ARCHES trial, which shows more favourable results for enzalutamide.

Table 28 Comparison of modelled life years and QALYs with study by Wang et al.

	Modelled LYG			**Total modelled QALYs**		
	Company estimate	EAG estimate	Wang et al.	Company estimate	EAG estimate	Wang et al.
Enzalutamide + ADT	[redacted]	[redacted]	4.96	[redacted]	[redacted]	3.92

Docetaxel + ADT	[redacted]	[redacted]	5.11	[redacted]	[redacted]	3.92
ADT alone	[redacted]	[redacted]	4.42	[redacted]	[redacted]	3.38

ADT, androgen deprivation therapy; LYG, life years gained; QALY, quality-adjusted life-years

ARCHES has published long-term survival results for enzalutamide + ADT versus ADT (Armstrong et al.2022).[1] We compare these results with the modelled results in Table 29. The modelled survival is lower than those in the ARCHES trial for enzalutamide + ADT and ADT alone and this is because the survival of patients with ADT alone was higher in the ARCHES trial than the STAMPEDE and CHAARTED trials.

Table 29 Comparison of the modelled survival of enzalutamide + ADT and ADT alone estimates with the ARCHES trial results

	Enzalutamide + ADT, ARCHES	Enzalutamide + ADT, company model	ADT, ARCHES	ADT, company model
2 years	86%	[redacted]	82%	[redacted]
3 years	78%	[redacted]	69%	[redacted]
4 years	71%	[redacted]	57%	[redacted]

ADT, androgen deprivation therapy

5.3.3 EAG corrections to the company model

The EAG did not find any technical errors in the company's economic model.

5.3.4 EAG summary of key issues and additional analyses

A full summary of EAG observations on key aspects of the company's economic model is presented in Table 30. We investigate uncertainties through additional scenario analysis in section 6.2.

Table 30 EAG observations of the key aspects of the company's economic model

Parameter	Company base case	EAG comment	EAG base case
Progression free survival (PFS)	Generalised gamma	Reasonable fit to ARASENS data but may be optimistic for long-term extrapolation.	Lognormal
Overall survival (OS)	Lognormal		Loglogistic
Treatment duration	Log-logistic		Generalised gamma
Utilities			

Health state utilities		From TA712	We agree	No change
AE disutility	Docetaxel	Not included	We disagree, we do not think the base case captures the disutility of docetaxel treatment sufficiently.	Disutility for docetaxel of 0.02 applied for six months.
	SSE disutilities	From TA377 and TA712	We agree	No change
Age-related disutility		Indirectly modelled by adjusting for the general population utility	We agree	No change
Resource use and costs				
Administration costs		CS Section B.3.5.1.2 and Table 49	We agree	No change
Subsequent therapy		CS Section B.3.5.3 and Table 58	We disagree, our clinical experts advised that patients taking enzalutamide for mHSPC would not receive a second ARTA in their treatment pathway.	We use the subsequent treatment distributions for enzalutamide + ADT from TA712.
AE costs		CS Section B.3.5.4 and Table 63	We disagree, the base case uses a weighted average of the paediatric codes PF26A and PF26B (Paediatric Other Gastrointestinal Disorders, Non-elective Short Stay).	We use a weighted average of FD10J, FD10K, FD10L and FD10M (Non-Malignant Gastrointestinal Tract Disorders without Interventions, Day Case).
Resource use		CS Section B.3.5	We disagree, the end-of-life costs used in the base case are for the general population.	We use costs specific to the population who have had a cancer diagnosis.
Treatment costs		CS Section B.3.5.1.1 and Table 46	We agree	No change

6 EAG'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

The EAG conducted additional scenario analyses for:

- alternative parametric distributions for OS, PFS and ToT,
- using crossover adjusted hazard ratios for overall survival,
- proportions of patients who receive each subsequent treatment according to TA712.

The EAG conducted scenario analyses with all alternative parametric distributions for overall survival, progression-free survival and time on treatment for darolutamide + docetaxel + ADT compared with docetaxel + ADT. The company's choice of parametric distributions for OS and PFS are conservative, i.e. produce the highest ICER. Using any of the other curves for PFS decreases the ICER below the company's base case figure (Table 31). Using the log-logistic distribution for OS increases the ICER to [redacted] per QALY and using the log-normal distribution for ToT increases the ICER to [redacted] per QALY. All other options decrease the ICER below the company's base case (Table 31).

Table 31 Scenario analyses results for varying parametric distributions for OS, PFS and ToT for darolutamide + docetaxel + ADT versus docetaxel + ADT

Distribution	ICER (£/QALY)		
	OS	PFS	ToT
Exponential	[redacted]	[redacted]	[redacted]
Log-normal	£14,950 (company base case)	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	£14,950 (company base case)
Gompertz	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Generalized Gamma	[redacted]	£14,950 (company base case)	[redacted]
Gamma	[redacted]	[redacted]	[redacted]

Key: ADT, androgen deprivation therapy; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; ToT, time on treatment

Two trials in the NMA (ARCHES and LATITUDE) permitted patients to crossover from the comparator treatment into the experimental arm. The company does not adjust for this in their base case, explaining that this aligns with the committee recommendations from the TA741 appraisal for apalutamide. We used the alternative OS hazard ratios (Table 32) for

the comparators versus docetaxel + ADT, which account for crossover in the ARCHES and LATITUDE studies (see section 3.4.1 for more details on this issue).

Table 32 Crossover adjusted hazard ratios for overall survival versus docetaxel + ADT

Comparators	OS Hazard Ratio
Darolutamide + docetaxel + ADT	0.68
Enzalutamide + ADT	0.74
ADT alone	1.30
Key: ADT, androgen deprivation therapy; Doc, docetaxel; Daro, darolutamide; Enza, enzalutamide; OS, overall survival; PFS, progression-free survival;	

The ICER for darolutamide + docetaxel + ADT versus docetaxel + ADT increased to [redacted] per QALY, and the ICER versus ADT alone increased to [redacted] per QALY.

[redacted]

The proportions of patients who receive each subsequent treatment, according to their initial treatment, in the company's base case are similar to those reported in TA712 (Table 33). However,

- Patients receiving enzalutamide did not subsequently receive abiraterone in TA712, instead either receiving best supportive care, radium-233 or cabazitaxel
- The company's base case assumes more patients initially receiving docetaxel + ADT subsequently receive enzalutamide (45%) and abiraterone (45%) on progressing, compared with 35% (enzalutamide) and 30% (abiraterone) of patients in TA712
- In TA712, a higher proportion of patients initially receiving ADT alone continue with best supportive care/ADT alone (1L=20%, 2L=30%, 3L=85%)

Table 33 Subsequent treatment distribution according to initial mHSPC treatment, data from TA712 vs darolutamide + docetaxel + ADT

Treatment	Docetaxel + ADT in mHSPC			Enzalutamide + ADT in mHSPC			ADT alone in mHSPC		
	1L	2L	3L	1L	2L	3L	1L	2L	3L
ADT	10%	25%	80%	20%	25%	80%	20%	30%	85%
Abiraterone	30%	5%	-	-	-	-	35%	5%	-
Enzalutamide	35%	5%	-	-	-	-	35%	10%	-
Docetaxel	25%	-	-	60%	15%	-	10%	30%	-
Radium-223	-	30%	10%	20%	30%	10%	-	20%	10%
Cabazitaxel	-	35%	10%	-	30%	10%	-	5%	5%

Key: 1L, first line, 2L, second line, 3L, third line, ADT, androgen deprivation therapy, mHSPC, metastatic hormone-sensitive prostate cancer, N/A, not available.
Source: Adapted from TA712;[4] and CS Table 58

The EAG used the TA712 subsequent treatment distribution for enzalutamide + ADT. This change did not affect the ICER versus docetaxel + ADT, and without applying the PAS for enzalutamide, darolutamide + docetaxel + ADT dominates enzalutamide + ADT (Table 34).

We also ran a scenario using the TA712 treatment distributions for enzalutamide + ADT, docetaxel + ADT and ADT alone, which increased the ICER versus docetaxel + ADT to [redacted] per QALY (Table 34).

Our clinical expert thought that having 2% of patients alive after 30 years (if the median age at diagnosis is 67), and more than 10% of patients on treatment after 10 years was optimistic. We used the log-logistic distribution for OS; the log-normal distribution for PFS and the generalized gamma distribution for time on treatment so simulate a more pessimistic scenario. This decreased the ICER versus docetaxel + ADT to [redacted] per QALY (Table 34).

Table 34 Additional EAG scenario results, using the company base case model vs darolutamide + docetaxel + ADT

No.	Scenario description	ICER (£/QALY) versus docetaxel + ADT	ICER (£/QALY) versus enzalutamide + ADT	iNMB (£) versus enzalutamide + ADT
Company base case		£14,950	Daro dominant	[redacted]
1	Using the subsequent treatment distributions	[redacted]	[redacted]	[redacted]

No.	Scenario description	ICER (£/QALY) versus docetaxel + ADT	ICER (£/QALY) versus enzalutamide + ADT	iNMB (£) versus enzalutamide + ADT
	for mHRPC for enzalutamide + ADT from TA712			
2	Using the subsequent treatment distributions for mHRPC for docetaxel + ADT, enzalutamide + ADT, and ADT alone from TA712	[redacted]	[redacted]	[redacted]
3	Log-logistic distribution for OS; log-normal distribution for PFS and the generalized gamma ToT	[redacted]	[redacted]	[redacted]

Key: ADT, androgen deprivation therapy; Daro, darolutamide; HR; hazard ratio; ICER, incremental cost-effectiveness ratio; iNMB, incremental net monetary benefit; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year; ToT, time on treatment

6.2 EAG's preferred assumptions

Based on the EAG critique of the company's model (discussed in section 4.2) and the scenarios we ran in section 6.1, we have identified several aspects of the company base case with which we disagree. Our preferred model assumptions are:

- **Disutility for docetaxel** (EAG report section 4.2.7.4): This disutility is applied for the first 6 months after starting treatment.
- **Subsequent treatment distributions** (EAG report section 4.2.8.5): The treatment distributions for mHRPC enzalutamide + ADT follow those reported in TA712 (Table 33), rather than the distributions presented in the CS, because patients in the UK will not receive a second ARTA following treatment with enzalutamide. We used the TA712 subsequent treatment distributions for mHRPC for docetaxel + ADT, enzalutamide + ADT, and for ADT alone in a scenario.
- **Diarrhoea adverse event costs** (EAG report section 4.2.8.6): Using HRGs relating to adult patients, rather than paediatric patients. We used a weighted average of FD10J, FD10K, FD10L and FD10M (Non-malignant gastrointestinal tract disorders without interventions, Day Case). The cost for treating diarrhoea is estimated to be £576.27, rather than £952.61.
- **End-of-life costs** (EAG report section 4.2.8.7): Using costs in the report by Georghiou and Bardsley[3] specific to the population who have had a cancer

diagnosis, rather than figures for the general population. The estimate for end-of-life costs is £9,719, rather than £8,000.

- **Alternative distributions for OS, PFS and time on treatment:**
  - log-logistic distribution for OS
  - log-normal distribution for PFS
  - generalized gamma distribution for time on treatment.

Table 35 shows the cumulative effect of each of these changes. The EAG's preferred assumptions reduced the ICER for darolutamide + docetaxel + ADT compared with docetaxel + ADT to £9,125 per QALY.

Table 35 Cumulative change from the company base case with the EAG's preferred model assumptions

Assumption	Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Company base case	Doc + ADT	[redacted]	[redacted]	-	-	£14,950
	Daro + doc + ADT	[redacted]	[redacted]	[redacted]	[redacted]	
Applying the disutility for docetaxel for 6 months	Doc + ADT	[redacted]	[redacted]	-	-	[redacted]
	Daro + doc + ADT	[redacted]	[redacted]	[redacted]	[redacted]	
Using the subsequent treatment distribution for enzalutamide from TA712[4]	Doc + ADT	[redacted]	[redacted]	-	-	[redacted]
	Daro + doc + ADT	[redacted]	[redacted]	[redacted]	[redacted]	
Diarrhoea adverse event costs	Doc + ADT	[redacted]	[redacted]	-	-	[redacted]
	Daro + doc + ADT	[redacted]	[redacted]	[redacted]	[redacted]	
Using end-of-life costs for people with a cancer diagnosis	Doc + ADT	[redacted]	[redacted]	-	-	[redacted]
	Daro + doc + ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Use log-logistic distribution for OS	Doc + ADT	[redacted]	[redacted]	-	-	[redacted]
	Daro + doc + ADT	[redacted]	[redacted]	[redacted]	[redacted]	
Use log-normal distribution for PFS	Doc + ADT	[redacted]	[redacted]	-	-	[redacted]
	Daro + doc + ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Use generalized gamma distribution ToT	Doc + ADT	[redacted]	[redacted]	-	-	
	Daro + doc + ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case	Doc + ADT	[redacted]	[redacted]	-	-	£9,125
	Daro + doc + ADT	[redacted]	[redacted]	[redacted]	[redacted]	
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; OS, overall survival; PFS, progression-free survival; ToT, time on treatment						

The EAG re-ran a selection of the company's deterministic scenario analyses using our base case assumptions (Table 36). In scenarios 3, 4 and 5 we ran the EAG base case, but used the company's chosen distributions for OS, PFS and time on treatment, respectively. In scenario 7 we switched off the disutility for docetaxel.

Using the log-logistic distribution to model time on treatment (scenario 5) had the greatest effect, increasing the ICER to [redacted] per QALY. The remaining ICERs ranged from [redacted] per QALY (using health state utilities from TA741 - scenario 6) to [redacted] per QALY (using treatment effect models – scenario 2) (Table 36).

Table 36 Deterministic scenario results for darolutamide + docetaxel + ADT vs docetaxel + ADT, using the EAG base case model

No.	Scenario description	ICER (£/QALY)
EAG base case		£9,125
1	Run the base case analysis using darolutamide data from ARASENS to extrapolate OS, TTCROD and ToT as an anchor for all treatments	[redacted]
2	Run the base case analysis using docetaxel OS and TTCROD data from ARASENS extrapolated using dependent extrapolations (i.e. treatment effect models)	[redacted]
3	Run the base case analysis using the log-normal ARASENS OS curve to model survival	[redacted]
4	Run the base case analysis using the generalized gamma ARASENS TTCROD curve to model progression	[redacted]
5	Run the base case analysis using the log-logistic ARASENS ToT curve to model treatment use	[redacted]
6	Use health state utilities for pre-progression, 1L, 2L and 3L+ from those reported in TA741.	[redacted]
7	Do not include an on-treatment disutility for patients treated with docetaxel.	[redacted]
Key: ADT, androgen deprivation therapy; HR; hazard ratio; ICER, incremental cost-effectiveness ratio; mHRPC, metastatic hormone-relapsed prostate cancer; OS, overall survival; ToT, time on treatment; TTCROD, time to CRPC or death Source: Adapted from CS Section B.3.11.3 Table 76		

Table 38 describes the results of the additional scenarios the EAG ran using our base case model:

1. Using the TA712 subsequent treatment distributions for enzalutamide + ADT, docetaxel + ADT and ADT alone (Table 33)
2. Using the alternative OS hazard ratios that account for crossover in the ARCHES and LATITUDE studies (Table 32)
3. Removing the abiraterone loop from the NMA (Table 37)
4. Combining the SNA+ADT studies with ADT as one node in the NMA (Table 37)
5. Using updated rPFS data from ARCHES[1] and FFS data from STAMPEDE-2[16] (Table 37)
6. Using alternative distributions to give less optimistic long-term (30 year) overall survival estimates: OS: generalized gamma; PFS: exponential; ToT: gamma

Table 37 Alternative hazard ratios versus docetaxel + ADT used in the EAG scenario analyses

Comparators	Abiraterone loop removed from the NMA		SNA+ADT studies combined with ADT as one node in the NMA		Most recent ARCHES and STAMPEDE-2 PFS HRs
	OS	PFS	OS	PFS	
Daro + doc + ADT	0.68	0.42	0.68	0.42	0.42
Enza + ADT	0.83	0.59	0.78	0.55	0.95
ADT alone	1.26	1.52	1.29	1.52	1.51

Key: ADT, androgen deprivation therapy; Doc, docetaxel; Daro, darolutamide; Enza, enzalutamide; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; SNA, nonsteroidal antiandrogen

Table 38 Additional EAG scenario results, using the EAG base case model

No.	Scenario description	ICER (£/QALY) versus docetaxel + ADT	ICER (£/QALY) versus enzalutamide + ADT	iNMB (£) versus enzalutamide + ADT
EAG base case		£9,125	Daro dominant	[redacted]
1	Using the subsequent treatment distributions for mHRPC for docetaxel + ADT, enzalutamide + ADT, and ADT alone from TA712	[redacted]	[redacted]	[redacted]
2	Using the alternative OS hazard ratios that account for crossover in the ARCHES and LATITUDE studies	[redacted]	[redacted]	[redacted]

No.	Scenario description	ICER (£/QALY) versus docetaxel + ADT	ICER (£/QALY) versus enzalutamide + ADT	iNMB (£) versus enzalutamide + ADT
3	Removing the abiraterone loop from the NMA	[redacted]	[redacted]	[redacted]
4	Combining the SNA+ADT studies with ADT as one node in the NMA	[redacted]	[redacted]	[redacted]
5	Using updated rPFS data from ARCHES and FFS data from STAMPEDE-2	[redacted]	[redacted]	[redacted]
6	Using alternative distributions for less optimistic long-term survival • PFS: exponential • OS: generalized gamma • ToT: gamma	[redacted]	[redacted]	[redacted]

Key: ADT, androgen deprivation therapy; Daro, darolutamide; ICER, incremental cost-effectiveness ratio; iNMB, incremental net monetary benefit; mHPRC, metastatic hormone-refractory prostate cancer; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year; SNA, nonsteroidal antiandrogen; ToT, time on treatment

6.3 Conclusions on the cost effectiveness evidence

The company's de novo partitioned survival model generated a base case ICER of £14,950 per QALY for darolutamide + docetaxel + ADT versus docetaxel + ADT, using the PAS discount for darolutamide. ADT alone and enzalutamide + ADT are dominated treatments although this analysis does not include the confidential PAS discount for enzalutamide and other subsequent treatments. The results are robust to changes in assumptions, including the use of alternative parametric distributions.

The EAG has not identified any significant errors or issues with the company economic model. Generally, the model is well documented and implemented and is consistent with NICE scope and previous NICE appraisals for mHSPC. The EAG suggest several minor changes but these have minimal effect on the ICER. The EAG base case assumptions produce an ICER of £9,125 per QALY for darolutamide + docetaxel + ADT versus docetaxel + ADT.

7 SEVERITY

The company estimates QALYs for the general population using appropriate sources, and the sex distribution and starting age from the ARASENS trial population and patient population described in CS Section B.3.2.1. The expected discounted QALYs for people living with mHSPC on current treatment are based on the company base case results.

The absolute QALY shortfalls for all treatments are below 12 and the proportional QALY shortfalls are all less than 85%, so the company did not apply a multiplier for disease severity for any of the comparisons.[22]

EAG comment on severity

The EAG agrees with the company's evaluation; a greater QALY weighting is not appropriate, because none of these treatment comparisons meet the criteria for severity.

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9 Appendices

Appendix 9.1 EAG assessment of company's methods of review

Table 39 EAG appraisal of systematic review methods

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
Was the review question clearly defined using the PICOD framework or an alternative?	No	The CS does not explicitly define the review question. CS section B.2.1 and CS Appendix D.1 state that the purpose of the review was to identify all evidence on the efficacy, safety and tolerability treatments approved or forthcoming for mHSPC.
Were appropriate sources of literature searched?	Yes	An adequate range of sources were searched, including core medical literature databases (MEDLINE In Process (PubMed), Embase and MEDLINE, and The Cochrane Library) (CS Appendix D.1.1). Appropriate conferences were also searched, as well as the reference lists of key systematic reviews and meta-analyses that had been published in the preceding three years (CS Appendix D.1.1).
What time period did the searches span and was this appropriate?	No – searches around one year out-of-date	The database searches were conducted from database inception (date coverage not reported) to 18th October 2021 but

		time limits were applied (RCTs from 1995 onwards, systematic reviews 2018 onwards). The EAG believes these time limits are reasonable; clinical expert advice to the EAG indicates that searching for RCTs published from 1995 onwards is sufficient for identifying relevant evidence. No update searches are reported. The searches are therefore around a year out-of-date. If any relevant studies have been published in the past year, these will not have been identified. The EAG conducted update searches to check if any studies had potentially been missed. Two additional relevant publications with updated trial results for two studies in the NMA were identified (see section 3.3.2). The company also searched conferences between 2019 to 2021, which the EAG considers an adequate timescale, although, again, the searches are not up-to-date.
Were appropriate search terms used and combined correctly?	Yes	The company report the search strategies used in CS Appendix D.1.1, Tables 1 to 3. The EAG have no major concerns about the terms used. A minor point is that there is a lack of transparency about whether MeSH or Emtree headings were used and if and how they were mapped, but we do not believe that it is likely studies would have been missed because of this.
Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and	Yes	The study selection criteria are reported in CS Appendix D.1.2, Table 4, and

relevant to the decision problem?		appropriately match the company's decision problem.
Were study selection criteria applied by two or more reviewers independently?	Yes	CS Appendix D.1.2 states that two independent reviewers screened references, with a third, independent reviewer resolving discrepancies.
Was data extraction performed by two or more reviewers independently?	Unclear	CS Appendix D.1.3 states that one reviewer carried out data extraction and another independent reviewer quality checked the data against the original source. It is unclear to the EAG if this means that data extraction was carried out in duplicate (i.e. independently) or if the second reviewer had sight of the first reviewer's data extraction. Nonetheless, the EAG considers the approach used is acceptable.
Was a risk of bias assessment or a quality assessment of the included studies undertaken? If so, which tool was used?	Yes	A risk of bias assessment of the 27 studies included in the systematic review was carried out using the NICE methodology checklist[38] (CS Appendix D.1.5 and CS Appendix D.4).
Was risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently?	Unclear	The CS does not report the process used for the risk of bias assessments.
Is sufficient detail on the individual studies presented?	Yes	Sufficient details about the design, methodology and results of the pivotal trial of darolutamide (ARASENS) is provided in CS sections B.2.2 to B.2.6. Details of the studies included in the company's NMA are also reported in sufficient detail in CS section B.2.9.1 and CS Appendix D.1.6 and in response to clarification question C1.

If statistical evidence synthesis (e.g. pairwise meta-analysis, NMA) was undertaken, were appropriate methods used?	Yes	The company have used appropriate methods for the NMA. We believe all relevant trials have been included but there is some uncertainty over the most appropriate choice of effect estimates to use from these trials. We discuss this in section 3.4.1.
CS, company submission; EAG, evidence assessment group; NMA, network meta-analysis.		

Appendix 9.2 Company and EAG risk of bias assessments for the ARASENS trial

Table 40 Company and EAG risk of bias assessments for the ARASENS trial

Criterion	Company judgement	EAG judgement
Was randomisation carried out appropriately?	Yes	Yes – [redacted].[21]
Was the concealment of treatment allocation adequate?	Yes	Yes – [redacted]
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes – all baseline characteristics were well-balanced between study arms (see CS Table 5).
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes – [redacted].[17] Although not explicitly stated the EAG presumes outcome assessors were blinded [redacted]
Were there any unexpected imbalances in drop-outs between groups?	No	Yes – CS section B.2.3 states that after treatment discontinuation, participants were to enter an 'Active follow-up period'. We note from CS Appendix D.3, Table 20, that [redacted] of the participants who discontinued study treatment in the darolutamide + docetaxel + ADT [redacted] than placebo + docetaxel + ADT [redacted] arms entered the follow-up period (percentages calculated by the EAG) and the reasons for this are not explained nor discernible to the EAG from the information provided (e.g. such as from the number of people discontinuing treatment due to death or patient withdrawal). See Table 7 in the main body of this report, section 3.2.2, for a summary of the flow of the participants through the trial up to entering the Active follow-up stage.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No – the EAG has not found any evidence that the company measured more outcomes than they reported.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods	Yes	Yes - all randomised participants [a] were included in the primary endpoint analysis (overall survival),[19] and were analysed according to treatment assignment rather than

used to account for missing data?		actual treatment received (referred to as the 'full analysis set' (FAS) in the CS; CS Table 6). Thus, the analysis follows the intention-to-treat principle. From the number of participants reported to be included in the time to CRPC results (CS section B.2.6.2.1), this analysis also appears to have been based on the FAS. Partial or missing event dates were imputed using an algorithm (CS section B.2.4).
Source: partly reproduced from CS Appendix D.4, Table 21. CRPC, castration-resistant prostate cancer; CS, company submission; EAG, Evidence Assessment Group; FAS, full analysis set; vs, versus. [a] Except for those with critical 'good clinical practice' violations (n = [redacted], as reported in CS Appendix D.3 Figure 15).		

Appendix 9.3 Quality assessment of RCTs included in NMA using the NICE checklist

Table 41 Company quality assessment of RCTs included in NMA using the NICE checklist

Study details	Trial name	Randomization appropriate?	Allocation concealment adequate?	Groups similar at the outset of the study in terms of prognostic factors?	Blinding to treatment allocation?	Unexpected imbalances in drop-outs between groups?	Authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis?
Base-case network								
Armstrong 2019	ARCHES	Yes	Yes	Yes	Yes	No	No	Yes
CSR 2022	ARASENS	Yes	Yes	Yes	Yes	No	No	Yes
Gravis 2013	GETUG-AFU 15	Yes	No	Yes	No	No	No	Yes
Fizazi 2017	LATITUDE	Yes	Yes	Yes	Yes	No	No	Yes
James 2016	STAMPEDE 2 STAMPEDE 3 STAMPEDE 4	Yes	No	Yes	No	No	No	Yes
Sweeney 2015	CHAARTED	Yes	No	Yes	No	No	No	Yes
Sensitivity analysis								
Davis 2019	ENZAMET	Yes	Yes	Yes	No	No	No	Yes
Eisenberger 1998	SWOG study-S8894	Yes	No	Yes	Yes	No	No	Yes
Vaisham-payan 2021	NA	Yes	No	Yes	No	Yes	No	Yes
Zalcberg 1996	NA	No	No	Yes	Yes	No	No	Yes

Key: CSR, clinical study report; NA, not applicable; NICE, National Institute for Health and Care Excellence; RCT, randomized controlled trial.
Notes: Full citation details for each study can be found in the SLR report. [75]
Source: Adapted from CS Appendix D.1.4, Table 5

Single Technology Appraisal

Darolutamide with androgen deprivation therapy and docetaxel for treating hormone-sensitive metastatic prostate cancer [ID3971]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by the end of **23 November 2022** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Clinical effectiveness

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report Section 1.6, page 15 states "For the ARCHES study (enzalutamide + ADT), the company have used the most recent estimate for OS from Armstrong 2022[1] but have not used the updated PFS estimate (measured as radiological progression-free survival (rPFS)) from the same publication."	We suggest this sentence be amended to "For the ARCHES study (enzalutamide + ADT), the company have used the most recent estimate for OS reported in both Armstrong 2021 (and again in Armstrong 2022[1]). However, have not used the updated PFS estimate (measured as radiological progression-free survival (rPFS)) as they were unavailable at the time of the company's SLR."	Factual inaccuracy. The amendment will avoid any misinterpretation of the evidence used in the NMA. All data used in NMA was identified through the SLR conducted by Bayer. We completed the SLR and identified the ARCHES OS HR from Armstrong, et al. 2021. ESMO abstract (LBA25 Final overall survival (OS) analysis from ARCHES: A phase III, randomized, double-blind, placebo (PBO)-controlled study of enzalutamide (ENZA)+ androgen deprivation therapy (ADT) in men with metastatic hormone-sensitive prostate cancer (mHSPC). Annals of Oncology, 32, S1300-S1301). This data was included in the NMA, no rPFS was reported in Armstrong, et al. 2021.	We have edited the text to indicate that the Armstrong 2022 paper was not available at the time of the SLR.

		The updated Armstrong 2022 paper was identified through a targeted non-systematic approach as part of the development of the background section of the submission document. EAG have updated the searches and identified updated data for ARCHES (including rPFS) and STAMPEDE-2 and included this in a scenario NMA.	
EAG report Section 3.1, page 26 states "We note, however, that not all of the updated results from these publications have been used in the company's NMA despite the results from the Armstrong 2022 publication being cited by the company in CS section B.1.3.2. This issue is further discussed in section 3.4.1."	We suggest this sentence be amended to "We note, however, that the updated results from these publications were not used in the company's NMA as they were not identified in the company's SLR. This issue is further discussed in section 3.4.1."	Factual inaccuracy, the amendment will avoid any misinterpretation of the evidence used in NMA. See linked response above.	We have edited the text to indicate that the Armstrong 2022 paper was not available at the time of the SLR.

EAG report Section 2.4.1, page 50 sentence would benefit from clarity as all data used in the NMA was identified from the CS SLR. EAG states "Updated longer-term results are available for ARCHES.[1] and STAMPEDE-2. [16] The company have used the updated results for OS in their NMA but not for PFS despite reporting the updated rPFS results for ARCHES in the CS section B.1.3.2."	We suggest this sentence be amended to "Updated longer-term results are available for ARCHES.[1] and STAMPEDE-2. [16] The ARCHES updated results for OS were available at the time of the company's SLR in Armstrong et al. 2021 abstract at the ESMO Congress 2021 and used in the NMA. Updated rPFS results for ARCHES were unavailable at the time of the CS SLR and thus not used in the NMA."	Factual inaccuracy, the amendment will avoid any misinterpretation of the evidence used in NMA. Data used in the NMA was identified from the company's SLR. See linked response above.	We assume this refers to section 3.4.1 of the EAG report. We have edited the text to indicate that the Armstrong 2022 paper was not available at the time of the SLR.
EAG report Section 3.4.2, page 52 states: "It is not clear if inconsistency was also formally assessed for the sensitivity analyses which included the additional SNA + ADT node."	We propose that this sentence should be removed.	Inconsistency was assessed for all endpoints for the NMAs including the additional SNA + ADT node. For brevity of the document these were only presented for the base case. No evidence of statistically significant inconsistency was found for these analyses.	Not a factual error. We have changed to "The CS does not provide the results of the assessment of inconsistency for the sensitivity analyses which included the additional SNA + ADT node."

EAG report Section 3.3.2, page 44 states "The company used the HRs for the subgroup of patients who did not receive docetaxel in the sensitivity analysis that included ENZAMET but do not fully explain why they chose this subgroup."	We propose that this sentence be reworded to "The company used the HRs for the subgroup of patients who did not receive docetaxel in the sensitivity analysis that included ENZAMET as enzalutamide+ADT+docetaxel was not a comparator of interest."	The amendment will clarify that enzalutamide+ADT+docetaxel was not a comparator of interest thus why the subgroup of patients who did not receive docetaxel were used in the scenario including ENZAMET. This was reported in CS Section B.2.9.1 page 62 "ENZAMET compared enzalutamide+ADT±docetaxel or standard nonsteroidal antiandrogen (SNA)+ADT±docetaxel, and the administration of docetaxel was applied as a stratification factor. About 45% of patients received enzalutamide+ADT+docetaxel (not a comparator of interest) or SNA+ADT+docetaxel, and the remaining patients received enzalutamide+ADT (comparator of interest) or SNA+ADT."	Text edited to reflect company's comment that enzalutamide+ADT+docetaxel not a comparator of interest.
EAG report Section 3.3.4, p. 49 would benefit from clarity to avoid misinterpretation. EAG	Suggest changing the sentence to "It was unclear whether the treatment groups were balanced at baseline for two studies used because the data were available for the whole	To clarify that these data were not necessarily available for the subgroup used in the NMA and ENZAMET was included in scenario NMAs. Additionally,	Not a factual error. We have changed the word 'presented' to 'available' to clarify that the issue is due to lack of

states: “It was unclear whether the treatment groups were balanced at baseline for two studies because these data were only presented for the whole trial population and not the subgroup used in the NMA.[42, 43]”	trial population and not the subgroup used in the NMA.[42, 43] However, one of these studies was used only in the scenario NMA (ENZAMET) and none of the baselines were identified as treatment effect modifiers.”	none of the baselines were identified as treatment effect modifiers in either ARASENS or comparator trials used in the NMA (where data was available).	availability of information from the source publications.

Issue 2 AE reporting errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report – Section 3.2.7 page 41 The percentage of patients who experience an AE that was related to docetaxel is incorrect	Please could you change the sentence from: “Approximately half of patients in each trial arm experienced a TEAE that was related to study drug ([redacted]% darolutamide versus [redacted]% placebo) while [redacted]% of patients in each trial arm experienced an adverse event that was related to docetaxel” To “Approximately half of patients in each trial arm experienced a TEAE that was	The amendment will correct the percentage of patients who experienced an AE that was related to docetaxel	Text updated as suggested.

	related to study drug ([redacted]% darolutamide versus [redacted]% placebo) while almost [redacted]% of patients in each trial arm experienced an adverse event that was related to docetaxel ([redacted]% darolutamide versus [redacted]% placebo)"		
EAG report – Section 3.2.7 page 42 The percentage of patients who experience dose modifications due to TEAEs with docetaxel is incorrect	Please could you change the sentence from: "Similar proportions of patients experienced dose modifications due to TEAEs with docetaxel ([redacted]% in both trial arms)" To "Similar proportions of patients experienced dose modifications due to TEAEs with docetaxel ([redacted]% in both trial arms)"	The amendment will correct the percentage of patients who experience dose modifications due to TEAEs with docetaxel	Not a factual error. Text amended for clarity to match CS Table 21.
EAG report – Section 3.2.7 page 42 The exposure-adjusted incidence rates for Grade 3 or 4 TEAEs was not mentioned	Please could you change the sentence from: "These were reported at comparable frequencies in both trial arms with the exception of grade 3 hypertension ([redacted]% in darolutamide arm versus [redacted]% in placebo arm)." To	The amendment gives further information about the Grade 3 or 4 TEAEs exposure-adjusted incidence rates	Additional text added in line with suggested.

	"These were reported at comparable frequencies in both trial arms with the exception of grade 3 hypertension ([redacted]% in darolutamide arm versus [redacted]% in placebo arm). Grade 3 or 4 TEAEs reported in more than 5% of patients had a higher exposure-adjusted incidence rate in the placebo arm with the exception of grade 3 hypertension which had the same value in each arm."		

Issue 3 Cost-effectiveness

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report – Section 5.2.3 page 86 When describing the uncertainty in the individual parameters, the EAG mentions our selected parametric survival curves: "The company assigns a log-normal distribution to the docetaxel overall survival curve, a generalized gamma	We suggest the sentence could be replaced with: "The individual inputs for the parametric survival extrapolations were varied using the variance-covariance matrices, to preserve the functional relations between the individual survival inputs."	To aid in both the accuracy and clarity of the document.	The text has been amended as suggested.

distribution to the docetaxel time to CROD curve and a log-logistic distribution to the darolutamide time on treatment curve used in their base case." Although this sentence accurately represents what parametric models we used in our base-case, these parametric models are not related to modelling uncertainty. This sentence is therefore somewhat out of context			
EAG report – Section 5.3.4, page 91 The Company base case column for PFS and OS is incorrect. The parametric models there seem to have been accidentally swapped.	Please update the Company base case column in the table to: PFS: Generalised gamma OS: Lognormal	The amendment will align the wording with the parametric models used in our base case	Thank you for the correction, we have updated Table 30 with the correct parametric models for PFS and OS.
EAG report – Section 5.3.4, page 91	Please change 'Not included' to "Indirectly modelled by adjusting for the	The amendment will align the wording more closely with how utilities were modelled	The text has been amended as suggested.

The EAG describes that age-related disutility was 'Not included' in our model. Although it is true that we did not explicitly model any age-related disutility, it is indirectly modelled by adjusting the modelled utilities for the general population utility.	general population utility" and assess if the other cells can stay the same		

Issue 4 Minor text inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 63: Incorrect indication used within sentence "The three-state partitioned survival model used in the company's economic evaluation is a standard modelling approach and has been applied in previous NICE appraisals for DLBCL"	Update to "The three-state partitioned survival model used in the company's economic evaluation is a standard modelling approach and has been applied in previous NICE appraisals for mHSPC"	To aid in both the accuracy and clarity of the document.	The text has been amended as suggested.

EAG report – Section 1.7 page 16 The EAG report states that in their preferred scenario the docetaxel disutility 'is applied for the first 6 months of treatment, rather than 3 months.' However, in the company submission the docetaxel disutility scenario was not applied for 3 months, but rather for the full duration of docetaxel treatment (approximately 4.5 months).	Please could you change the sentence to: "This disutility is applied for the first 6 months of treatment, rather than while patients receive docetaxel (approximately 4.5 months)."	The amendment will align the wording with how the disutility was modelled	The text has been amended as suggested.
EAG report – Section 4.2 page 63 The EAG report states the subsequent treatment duration was based on expert opinion. However, only the distribution of subsequent treatments was based on expert opinion, the	Please could you update the statement to: "they based the estimate of the duration of subsequent treatments on data from the literature."	The amendment will align the wording with how the subsequent treatment duration was informed	The text has been amended as suggested.

duration was based on data from the literature.			
EAG report – Section 4.2.8.4 page 77 The EAG report states that in our model 'At least 50% of patients would receive one MRI scan per year'. Although this is indeed in line with the expert advice we received, this statement is only true for patients receiving docetaxel.	To avoid confusion, could you please change the wording to: "At least 50% of patients who are treated with docetaxel would receive one MRI scan per year"	The amendment will make the wording more specific to avoid confusion	The text has been amended as suggested.

Issue 5 Cross referencing errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report – Section 3.2.7 page 42 The section reference for details of exposure is incorrect	Please could you change the sentence from: "Further details of exposure are provided in CS section B.2.10.2.3" To "Further details of study drug and docetaxel exposure are provided in CS	The amendment will align the section numbering with that in the Company Submission	This has been corrected.

	Section B.2.10.2.1 and B.2.10.2.2, respectively”		
EAG report – Section 3.2.7 page 42 The section reference for the most frequently reported TEAEs is incorrect	Please could you change the sentence from: “The most frequently reported TEAEs (CS section B.2.10.2) occurring in 25%” To “The most frequently reported TEAEs (CS section B.2.10.3) occurring in 25%”	The amendment will align the section numbering with that in the Company Submission	This has been corrected.
EAG report – Section 1.7 and Section 6.2 pages 16 and 95 The EAG describes a subsequent treatment distribution from ‘TA712 (Table 35)’. However, Table 35 does not describe the subsequent treatment in either TA712 or the EAG report. From what we can tell, the subsequent treatment distribution in	Please could you change ‘Table 35’ to ‘Table 61’ in both instances	The amendment will align the table numbering with that in TA712	Thank you for highlighting the error. This link should be to Table 33 in the EAG report, not Table 35, and it has been corrected in both sections 1.7 and 6.2.

TA712 is reported in Table 61.			
EAG report – Section 4.2.6.2 page 68 The ERG states 'see discussion in section 4.2.2.2 above', but from what we can tell the issue is not discussed in section 4.2.2.2	Please could you remove "(see discussion in section **Error! Reference source not found.** above)"	The amendment will add to the clarity of the EAG report	The text has been amended as suggested.
EAG report – Section 4.2.6.3 page 70 The ERG start the sentence with 'As mentioned above', but this is the first time the clinical expert input is mentioned	Please could you leave out "As mentioned above,"	The amendment will add to the clarity of the EAG report	The text has been amended as suggested.

Location of incorrect marking	**Description of incorrect marking**	**Amended marking**	**EAG response**
EAG report – Section 3.2.5.1 page 37	We apologise the hazard ratio, 95% confidence intervals and p-value for overall survival was incorrectly marked as AIC in the submission. The	Please could you amend to the following:	This has been updated.

The hazard ratio, 95% confidence intervals and p-value for overall survival was incorrectly marked as AIC in the submission	sentence in the EAG report this applies to is as follows: "A statistically significant reduction in the hazard rate of death was observed for the darolutamide + docetaxel group compared to docetaxel + placebo (HR for [redacted])"	"A statistically significant reduction in the hazard rate of death was observed for the darolutamide + docetaxel group compared to docetaxel + placebo (HR for OS: 0.68; 95% CI: 0.57, 0.80; p value <0.001)"	
EAG report – Section 3.2.5.1 page 38 The percentage of patients who received subsequent life-prolonging therapies was incorrectly marked as AIC in the submission	We apologise the percentage of patients who recieved subsequent life-prolonging therapies was incorrectly marked as AIC in the submission. The sentence in the EAG report this applies to is as follows: "The company point out that the overall survival benefit was observed despite a higher proportion of patients in the placebo arm receiving subsequent life-prolonging therapies ([redacted]% of patients who discontinued study treatment and entered active or survival follow up) compared to the active arm ([redacted]%) (CS Section B.2.6.1.1 and Appendix M.1 Table 44)."	Please could you amend to the following: "The company point out that the overall survival benefit was observed despite a higher proportion of patients in the placebo arm receiving subsequent life-prolonging therapies (75.6% of patients who discontinued study treatment and entered active or survival follow up) compared to the active arm (56.8%) (CS Section B.2.6.1.1 and Appendix M.1 Table 44)."	This has been updated.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Darolutamide with androgen deprivation therapy and docetaxel for treating hormone-sensitive metastatic prostate cancer [ID3971]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **16 January 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we

received, and are not endorsed by NICE, its officers or advisory committees.

About you

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Bayer plc
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Current Situation** · Bayer does not have direct or indirect links with, or funding from, manufacturers, distributors or sellers of smoking products but Bayer provides pesticides for crops, which would therefore include tobacco crops. · Bayer is a member of the Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA) (http://www.coresta.org/) within the scope of recommendations of pesticides used for protection of tobacco plants. · It is also a member of country and EU business federations such as the Confederation of British Industry (CBI) and 'Business Europe', which include tobacco companies. **Past Situation** In 2006, Bayer and its subsidiary Icon Genetics piloted a new process for producing biotech drugs in tobacco plants. Icon Genetics was acquired by Nomad Bioscience GmbH from Bayer in 2012.

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: The cost-effectiveness results are not provided for the subgroups listed in the NICE scope	No	As noted within the submission, there is inconsistent use of 'newly diagnosed' and 'high risk' across all mHSPC trials; the subgroups highlighted within the NICE scope are of most relevance to abiraterone, which is specifically licensed for the newly diagnosed, high risk population. However, abiraterone is not a relevant comparator in this appraisal as it has not been approved for use in NHS practice, while the license granted by MHRA for darolutamide with docetaxel and ADT is not linked to any of these subgroups. Furthermore, neither of these subgroups were included in the most recent relevant appraisal TA721 for enzalutamide in mHSPC due to both inconsistency of definitions and relevance of these factors to treatment decision making (1). We have however, carried out further investigation within the ARASENS trial data to understand the likely impact on the comparative efficacy estimates of darolutamide + docetaxel + ADT versus placebo + docetaxel + ADT for the ARASENS ITT population and the de-novo and high risk[1] subgroups in ARASENS. The efficacy estimates in both subgroups for OS and CROD show that results are comparable to the ITT ARASENS population, with negligible differences in the treatment effect and its associated 95% confidence interval. Of the patients in the ARASENS trial 86.1 % were de-novo and 70% were high-risk.

[1] As per the high-risk definition in LATITUDE: patients were required to have at least two of three high-risk prognostic factors (Gleason score ≥8, three or more lesions on bone scan, and measurable visceral metastases, excluding lymph node metastasis)

Relative effect estimates of darolutamide + docetaxel versus placebo + docetaxel in ARASENS trial for ITT population, and de-novo and high-risk subgroups

Population	OS						CROD					
	n	HR (stratified)	Std. Err.	P-value	[95% Conf. Interval]		n	HR (stratified)	Std. Err.	P-value	[95% Conf. Interval]	
ITT	1,305	0.675	0.06	0.00	0.57	0.8	1,305	0.405	0.03	0.00	0.35	0.47
De-novo	[redacted]											
High-risk	[redacted]											

As described in the company submission, indirect treatment comparison estimates through the NMA play a key role in the cost effectiveness model, as they inform both the effectiveness of darolutamide and of all non-trial comparators in the model. We have not modelled the full cost-effectiveness in these subgroups due to the limited amount of data available and inconsistent use of these subgroups across the network of evidence to derive a reliable indirect effectiveness estimate in these subgroups.

Key issue 2: The reasons for censoring in the ARASENS trial are not reported	Yes	Please find below the number and proportion of participants in each of the ARASENS trial groups who were censored and reasons for censoring from the time to CRPC analysis. The majority of patients in both groups were censored due to no CRPC at the time of analysis (darolutamide: [redacted] %; placebo: [redacted] %). The efficacy of darolutamide resulted in a smaller proportion of patients who progressed to CRPC in the darolutamide group compared to the placebo (darolutamide: 35%; placebo: 60%). This explains the difference in the proportion of patients who were censored due to no CRPC between treatment groups.

Very few patients were censored due to other reasons and the proportions were balanced between the treatment groups, e.g. subsequent treatment before CRPC (darolutamide: [redacted] %; placebo: [redacted] %). Therefore, no bias was introduced and there would be no impact on the time to CRPC analysis.

Censoring reasons from the time to CRPC analysis (FAS)

	Darolutamide+ docetaxel (N = 651)	**Placebo+ Docetaxel (N = 654)**
Patients censored, n (%)	[redacted]	[redacted])
Censoring reasons, n (%)		
No CRPC at the time of analysis	[redacted]	[redacted])
No baseline or post-baseline assessment	[redacted]	[redacted])
Prohibited new anticancer therapy before CRPC		
Reason for new therapy[a]:		
PSA progression	[redacted]	[redacted])
Clinical progression	[redacted]	[redacted])
Radiological progression	[redacted]	[redacted])
Other	[redacted]	[redacted])
Unknown	[redacted]	[redacted])
PSA progression after two or more consecutive missing assessments	[redacted]	[redacted])

Key: CRPC, castration-resistant prostate cancer; FAS, full analysis set; PSA, prostate-specific antigen.
Note: [a] The reasons for new therapy were based on the investigator assessment only. The progression

		events did not meet the criteria for time to CRPC as stated in the protocol and the submission, therefore the patients were censored.
Key issue 3: The loss to follow-up in the ARASENS trial is not fully explained	Yes	The patient disposition in ARASENS from when patients discontinued study treatment is presented in the figure below. Patients who discontinued study treatment continued to be followed-up for survival and could either enter the active follow-up or survival follow-up periods: • The active follow-up period consisted of the end of treatment visit and active follow-up visits. During the end of treatment visit, the following assessments were performed: QoL, pain assessment, analgesic consumption, subsequent antineoplastic treatments for prostate cancer, SSEs, AEs and SAEs. Active follow-up visits occurred approximately every 12 weeks for up to 1 year; the same assessments were performed as per the end of treatment visit with the addition of survival status. After approximately 1 year of active follow-up, patients transitioned to survival follow-up. The active follow-up period therefore extended from the discontinuation of treatment period for up to 1 year or until the patient could no longer travel to the clinic, died, was lost to follow-up, or withdrew informed consent and actively objected to collection of further data • During the survival follow-up, patients were contacted approximately every 12 weeks by phone to capture all antineoplastic treatments for prostate cancer, study drug-related SAEs and survival status. The end of the survival follow-up was defined when the patient died, was lost to follow-up, withdrew consent or at the end of the study **Patient disposition in ARASENS from discontinued study treatment** [redacted] As the active follow-up period could be terminated if a patient could no longer travel to the clinic or if they actively objected to the collection of further data, patients were able to enter the survival follow-up directly from treatment discontinuation; in the survival follow-up patients were contacted via phone rather than in-person visits and there were fewer assessments which reduced the burden. The proportion of patients who entered the active follow-up (darolutamide: [redacted]]; placebo: [redacted] %]), survival follow-up (darolutamide: [redacted] %]; placebo: [redacted] %]) and ended the study (darolutamide: n = [redacted] %]; placebo: n = [redacted] %]) following treatment discontinuation were

		similar between groups. There were no imbalances that would bias the result and the outcome measures utilised in the model were collected in the same manner across the active and survival follow-up periods. Overall, there were 314/352 [89.2%] patients in the darolutamide arm and 495/526 [94.1%] patients in the placebo arm that entered some form of follow-up following treatment discontinuation, which points out to low attrition rates. Patients who discontinued or completed active follow-up were entered into the survival follow-up. The reasons for discontinuing treatment, active follow-up and survival follow-up were presented in Appendix D.3. Table 20 of the submission. There was a significant difference in the proportion of patients who discontinued study treatment due to 'progressive disease – clinical progression' (darolutamide: [redacted] [redacted] %]; placebo: [redacted] %]), and this can be attributed to the efficacy of darolutamide. There were no significant imbalances in the proportion of patients who discontinued either the active follow-up (darolutamide: [redacted] %; placebo: [redacted] %]), survival follow-up (darolutamide: [redacted] %]; placebo: [redacted] %]) or the reasons for discontinuation; any differences are not expected to impact or bias the results of the trial.
Key issue 4: The use of unadjusted hazard ratios in the network meta-analysis for trials that allowed crossover. The impact of adjusted estimates for OS should also be presented.	Yes	Please find below a discussion of the appropriateness of the use of the ITT results from the comparator trials and the limitations of the crossover adjusted results in comparator trials. Two trials in the NMA evidence base, ARCHES and LATITUDE, allowed for treatment switching of patients; however, ARASENS did not allow for treatment switching from control to intervention arm of the trial. Crossover typically occurs when patients on the control arm are allowed to crossover on to the experimental arm at some point during follow-up. Methods for treatment switching adjustments are associated with numerous uncertainties. ARCHES and LATITUDE both used the rank preserving structure failure time modelling (RPSFTM) and LATITUDE also presented inverse probability of censoring weights (IPCW) (results of these analyses are summarised in the table at end of this response for context). Here we reason that, in addition to the limitations of the crossover methods, using crossover adjusted HRs in the NMA would be biased against darolutamide based on the comparison of the proportions of treatment switching patients and patients receiving subsequent ARTA treatment across the studies of interest (and with UK practice) and therefore, the use of ITT HRs are more comparable for inclusion in the NMA. In both ARCHES and LATITUDE there is no evidence of adjustment for subsequent ARTA except from the traditional within-trial treatment switching from control to intervention treatment (enzalutamide and abiraterone, respectively). The treatment adjusted HRs aim to estimate the HR for OS by removing the impact of crossover from control to intervention; however, patients within the control arm of these trials also receive multiple other subsequent treatments (including other ARTAs) in the trials which are not adjusted for using these cross-over adjustment methods. We argue that considering the adjusted HRs from ARCHES and LATITUDE does not take into consideration the impact of the additional (non-intervention) subsequent treatments on patient survival outcomes and is therefore not a suitable approach within this NMA.

		As demonstrated within ARASENS, subsequent ARTA use has a greater impact on survival outcomes in the control arm compared to the darolutamide arm. Subsequent ARTA is the control arm patients' first ARTA (Document B Figures 20 and 21), therefore, patients in the control arms of ARASENS, ARCHES, and LATITUDE who receive subsequent ARTA may be expected to have improved survival outcomes. After removing treatment switching patients from subsequent ARTA use and comparing proportions, the control arm of ARASENS has the highest percentage of patients that receive subsequent ARTA (when compared to ARCHES and LATITUDE, see table below). This is anticipated to be unfavourable for darolutamide, as the subsequent ARTA use positively impacts the control arm, therefore, the relative effect between intervention and control arm in comparator trials will be increased as the impact of subsequent ARTA in the control arm is reduced in the crossover adjusted HRs. Although there is subsequent ARTA use in the intervention arms of the trials, it was not expected to drive the OS benefit demonstrated by darolutamide patients in the ARASENS trial (Document B Figures 20 and 21), both the advisory board clinicians and health economic experts who were consulted (2, 3), considered that no adjustment to OS was necessary, as the OS benefit demonstrated by darolutamide in ARASENS did not appear to be driven by additional ARTAs. Relating ARASENS to UK clinical practice, the majority of patients will receive ARTA following docetaxel + ADT or ADT alone, however, no patients would receive a second ARTA. We have provided further detail on patient subsequent therapy and the OS HRs in ARASENS, ARCHES and LATITUDE (ITT and adjusted for treatment switching where relevant) and have provided a comparison of the treatment switching proportions and subsequent ARTA treatments across the three trials. As noted above, the subsequent ARTA use is anticipated to have a greater impact on the control arm, therefore, we have focused primarily on comparisons of subsequent ARTA use in the control arms of the trials, considering: • Proportion of patients who switched from control to intervention arm • Proportion of subsequent ARTA use including these patients • Proportion of subsequent ARTA use excluding the treatment switching patients. Both ARCHES and LATITUDE included treatment switching, here we briefly summarise the switching processes: • After the primary analysis, ARCHES was unblinded to allow patients randomly assigned to placebo+ADT to cross over to enzalutamide + ADT in an open-label extension. 184 patients (31.9%) randomly assigned to placebo+ADT remained progression-free and consented to cross over, 180 (31.3%) of these patients received treatment with enzalutamide + ADT. In ARCHES, inclusive of treatment switching, 401 patients (70%) randomly assigned to placebo+ADT received subsequent life-prolonging

		therapy. With 241 (42%) receiving enzalutamide as the first subsequent life-prolonging therapy, comprised of 180 patients in treatment switching and 61 first subsequent therapy for prostate cancer after treatment discontinuation. • In LATITUDE due to significant improvement in OS after the first interim analysis, patients receiving placebo+ADT arm could switch to abiraterone acetate + prednisone + ADT (AA + P + ADT) during an open-label extension. At the first interim analysis, treatment was ongoing for 257 of 597 (43.0%) patients in the AA + P + ADT arm and 112 of 602 (18.6%) patients in the placebo+ ADT arm. Of the 112 patients still receiving placebo+ADT, 72 placebo+ADT patients switched to AA + P + ADT during the open-label extension. Comparing subsequent ARTA use between ARASENS and ARCHES and LATITUDE after excluding treatment switching patients: • Patients in the control arm of ARASENS have more first subsequent ARTA treatments than ARCHES. ○ The proportion of control arm patients with first subsequent ARTA (excluding switching to enzalutamide in ARCHES) is 44.3% versus 17.9% in ARASENS and ARCHES, respectively. This will likely impact the OS HR estimates as control patients in ARASENS are more likely to receive ARTA than control patients in ARCHES when using the treatment switching adjusted HRs. • Patients in the control arm of ARASENS have more subsequent ARTA treatments than LATITUDE. ○ There are only a small proportion of patients who switch treatments in LATITUDE therefore this has minimal impact on the adjusted analyses. ○ The proportion of control arm patients with any subsequent ARTA (excluding treatment switching to abiraterone) is 56.6% versus 30.4% in ARASENS and LATITUDE. This will likely impact the OS HR estimates as control patients in ARASENS are more likely to receive subsequent ARTA than control patients in LATITUDE when using the treatment switching adjusted HRs. There is no robust approach to consistently deal with the crossover of trial patients and variation in subsequent treatments by adjusting survival data across these studies. Based on the above investigation into the comparability of the subsequent treatments received in the control arms across the three trials and the inherent uncertainties in the adjusted HRs we recommend that the use of unadjusted ITT HRs in the NMA creates a more appropriate comparison with regards to the subsequent treatment proportions between the ARASENS, ARCHES and LATITUDE trials and compared to that expected in UK clinical practice. **Summary of patients' subsequent therapy in ARASENS, ARCHES and LATITUDE**

Subsequent treatment	Subsequent life prolonging systemic antineoplastic therapy ARASENS n (%)				First antineoplastic therapy for prostate cancer [a] ARCHES n (%)		Life extending subsequent therapy for prostate cancer LATITUDE[b] n (%)	
	Daro (n=651)		PBO (n=654)		Enza (n=574)	PBO (n=576)	Abi (n=597)	PBO (n=602)
	First	Any	First	Any				
Patients with systemic subsequent therapy	179 (27.5)		374 (57.2)		131 (22.8)	221 (38.4)	176 (29.5)	344 (55.5)
Subsequent ARTA	113 (17.4)	162 (24.9)	290 (44.3)	370 (56.6)	33 (5.7)	283 (49.1) Of which treatment switching: 180 (31.9)	75 (12.6)	255 (42.4) Of which treatment switching: 72 (12.0)[3]
Subsequent ARTA excluding treatment switching patients	113 (17.4)	162 (24.9)	290 (44.3)	370 (56.6)	33 (5.7)	103 (17.9)	57 (9.5)	183 (30.4)
Enzalutamide	29 (4.5)	48 (7.4)	97 (14.8)	136 (20.8)	7 (1.2)	241 (41.8) Of which treatment switching: 180 (31.9)	57 (9.5)	99 (16.4)
Abiraterone	83 (12.5)	112 (17.2)	193 (29.5)	232 (35.5)	26 (7.5)	42 (7.3)	18 (3.0)	156 (25.9) Of which treatment

								switching: 72 (12.0)[c]
Apalutamide	1 (0.2)	2 (0.3)	0	2 (0.3)	NA	NA	NA	NA

Notes: [a] ARCHES report first antineoplastic therapy for prostate cancer. Reported in Armstrong et al. 2022(4); [b] LATITUDE report 'subsequent therapy for prostate cancer' assumed to be any line subsequent treatment not only first subsequent treatment. Reported in Koroko et al. 2022.(5); [c] Table 2 in Koroko et al. 2022(5) reports number of patients received subsequent therapy for prostate cancer, with n=156 receiving abiraterone, this has been assumed to comprise of n=72 in treatment switching and n=84 subsequent therapy for prostate cancer.

Highlighted orange cells are the key comparisons of subsequent ARTA use drawn out in associated text for comparison.

OS HRs for ARASENS, LATITUDE and ARCHES

Study	Comparison	Method	OS HR (95% CI)	Timepoint	Median time to treatment switching
ARASENS	Darolutamide+docetaxel+ADT (n=651) vs placebo+docetaxel+ADT (n=654)	ITT unadjusted	0.675 (0.568; 0.801)	43.7- and 42.4-months median follow-up in the darolutamide and placebo group, respectively	NA
LATITUDE*	Abiraterone acetate + prednisone+ADT (n=597) vs placebo+prednisone+ADT (n=602)	ITT unadjusted	0.66 (0.56,0.78)	Median follow up of 51.8 months [IQR: 47.2-57.0 months]	40.07 months
		IPCW	0.629 (0.526, 0.753)		
		RPSFTM	0.616 (0.524, 0.724)		

ARCHES	Enzalutamide + ADT (n=574) vs PBO+ADT (n=576)	ITT unadjusted	0.66 (0.53, 0.81)	44.6 months median follow-up	21.5 months
		RPSFTM	0.57 (0.45, 0.70)		
Source: Armstrong et al. 2022(4); Feyerabend et al. 2019(6); Koroki et al. 2022.(5)					

In conclusion, we consider the use of the unadjusted ITT HR from ARCHES to more accurately reflect the expected relative effectiveness of darolutamide with docetaxel and ADT compared to enzalutamide and ADT in UK clinical practice. This is because when the unadjusted ITT HR is used, the proportions of subsequent ARTA (i.e. enzalutamide, abiraterone) use accross the comparator arms of ARCHES and ARASENS are aligned and are also reflective of the subsequent ARTA use following treatment with docetaxel + ADT or ADT alone in UK clinical practice as summarised in the Table below.

Number of patients receiving subsequent ARTA in ARASENS and ARCHES comparator arms relative to UK practice

Subsequent ARTA use (incl. treatment switching patients)	ARASENS comparator arm	ARCHES comparator arm	UK practice (2, 3)
Pre-crossover adjustment	290 (44.3% of all randomised patients; 77.5% of patients that received subsequent therapies)	283 (49.1% of all randomised patients)	~80%
Post-crossover adjustment	n/a	103 (17.9% of all randomised patients)	n/a

Key issue 5: An out-of-date progression-free survival hazard ratio from the	No	The longer term updated rPFS data from ARCHES and FFS data from STAMPEDE-2 were highlighted by the EAG using an updated SLR. These data were not available in the SLR used for the company NMA. The longer-term OS data was used from ARCHES in the NMAs, this was identified in a conference abstract and discussed in the response to EAG clarification questions. We agree that the longer term rPFS HR data from ARCHES and FFS HR data from STAMPEDE-2 that has now been published would be suitable to be used in the NMA as it provides higher maturity. This would also be consistent with the OS data used for the NMA from

ARCHES trial has been used in the network meta-analysis		ARCHES and the median follow-up for the longer-term OS and rPFS data from ARCHES more closely matches that of the ARASENS follow-up used in the NMA. In addition, clinical experts consulted recommended using the longest follow-up data available, and were not concerned about the long term rPFS being driven by local investigator decision, as this reflects clinical practice in which scans are not reviewed centrally/independently.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio, updated ICER (change from base case ICER)
Key issue 5: An out-of-date progression-free survival hazard ratio from the ARCHES trial has been used in the network meta-analysis	Using ARCHES and STAMPEDE rPFS and FFS hazard ratios from the initial SLR were used in the NMA	ARCHES and STAMPEDE rPFS and FFS hazard ratios were updated in line with the latest available data, to update the NMA HRs. Please note that in contrast to the EAG's base case, these updated HRs were also applied for both PFS and ToT, given that the PFS and ToT HRs are interdependent in the model.	**ICER vs Doc + ADT**: [redacted] **ICER vs Enza + ADT**: [redacted] **ICER vs ADT alone**: [redacted]
EAG report, paragraph 4.2.6.1: Using a Log-logistic OS extrapolation for docetaxel	Using a Log-normal OS extrapolation	The used OS extrapolation was changed to Log-logistic, in line with EAG preference	**ICER vs Doc + ADT**: [redacted] **ICER vs Enza + ADT**: [redacted] **ICER vs ADT alone**: [redacted]

EAG report, paragraph 4.2.6.2: Using a Log-normal PFS extrapolation for docetaxel	Using a Generalized gamma PFS extrapolation	The used PFS extrapolation was changed to Log-normal, in line with EAG preference	**ICER vs Doc + ADT**: [redacted] **ICER vs Enza + ADT**: [redacted] **ICER vs ADT alone**: [redacted]
EAG report, paragraph 4.2.6.3: Using a Generalized Gamma ToT extrapolation for docetaxel	Using a Log-logistic ToT extrapolation	The used ToT extrapolation was changed to Generalized gamma, in line with EAG preference gamma, in line with EAG preference	**ICER vs Doc + ADT**: [redacted] **ICER vs Enza + ADT**: [redacted] **ICER vs ADT alone**: [redacted]
EAG report, paragraph 4.2.7: Including a docetaxel disutility of 0.02 for 6 months	Excluding a docetaxel disutility, to avoid double counting with adverse event disutilities	A docetaxel disutility of 0.02 was included for a fixed duration of 6 months. This was largely in line with the EAG's approach. However, in contrast to the EAG, we adjusted this disutility to account for the proportion of patients alive during those 6 months.	**ICER vs Doc + ADT**: [redacted] **ICER vs Enza + ADT**: [redacted] **ICER vs ADT alone**: [redacted]
EAG report, paragraph 4.2.8.5: Using enzalutamide subsequent treatment distribution from TA712	Using a subsequent treatment distribution as confirmed by the advisory board for all treatments	The subsequent treatment distribution used in TA712 was used for subsequent treatment after enzalutamide + ADT, in line with EAG preference	**ICER vs Doc + ADT**: [redacted] **ICER vs Enza + ADT**: [redacted] **ICER vs ADT alone**: [redacted]
EAG report, paragraph 4.2.8.6: Updating the diarrhoea costs used	Using the same NHS reference costs for diarrhoea as the ones used in TA712 (Weighted average of PF26A, PF26B)	Diarrhoea costs were updated to the weighted average of NHS reference costs FD10J, FD10K, FD10L and FD10M, in line with EAG preference	**ICER vs Doc + ADT**: [redacted] **ICER vs Enza + ADT**: [redacted] **ICER vs ADT alone**: [redacted]

EAG report, paragraph 4.2.8.7: Using end of life costs for people with a cancer diagnosis	Using the overall population end of life costs, as described by Georghiou and Bardsley 2014, and excluding GP visits	End of life costs were updated to the end of life costs from Georghiou and Bardsley of people with a cancer diagnosis, including GP visits, in line with EAG preference	**ICER vs Doc + ADT**: [redacted] **ICER vs Enza + ADT**: [redacted] **ICER vs ADT alone**: [redacted]
	Old: Company's base case following technical engagement (or revised base case)		
	QALYs	**Costs**	**ICER**
	Total QALYs darolutamide: [redacted] **Incr. QALYs vs. Doc + ADT**: [redacted] **Incr. QALYs vs. Enza + ADT**: [redacted] **Incr. QALYs vs. ADT alone**: [redacted]	**Total £ darolutamide**: [redacted] **Incr. £ vs. Doc + ADT**: [redacted] **Incr. £ vs. Enza + ADT**: [redacted] **Incr. £ vs. ADT alone**: [redacted]	**ICER vs Doc + ADT**: £9,127 (-£5,823) **ICER vs Enza + ADT**: Darolutamide dominant (+N/A) **ICER vs ADT alone**: £6,062 (-£3,153)
New: Additional changes applied after identification of discounting error:			
Key issue(s) that the change relates to	**Company's base case before model change**	**Change(s) made**	**Impact on the company's base-case incremental cost-effectiveness ratio, updated ICER (change from base case ICER after tech. engagement)**
New: Error identified in the model	Upon reviewing the model, we noticed that the PFS monitoring costs for darolutamide+docetaxel+ADT and docetaxel+ADT were not discounted correctly. More specifically, only the monitoring costs for the period during which patients receive docetaxel were discounted, but for the long-term monitoring after docetaxel	We updated the model to ensure all costs are discounted properly. To make this change, we added '*I11' to the final element of the formula in PF_Daro AU11 and PF_Doc AQ11, and dragged the cells down. This ensured that all elements of the formula were linked to the cost discounting factor in column I.	**ICER vs Doc + ADT:** £8,251 (-£876) **ICER vs Enza + ADT:** Darolutamide dominant (+N/A) **ICER vs ADT alone:** £5,310 (-£752)

	discontinuation discounting was not taken into account.		
	New: Company's base case following technical engagement and after fixing the discounting error		
	QALYs	**Costs**	**ICER (and impact vs Tech eng. model)**
	Total QALYs darolutamide: [redacted] **Incr. QALYs vs. Doc + ADT**: [redacted] **Incr. QALYs vs. Enza + ADT**: [redacted] **Incr. QALYs vs. ADT alone**: [redacted]	**Total £ darolutamide**: [redacted] **Incr. £ vs. Doc + ADT**: [redacted] **Incr. £ vs. Enza + ADT**: [redacted] **Incr. £ vs. ADT alone**: [redacted]	**ICER vs Doc + ADT:** £8,251 (-£876) **ICER vs Enza + ADT:** Darolutamide dominant (+N/A) **ICER vs ADT alone:** £5,310 (-£752)

Sensitivity analyses around revised base case

Revised base case probabilistic sensitivity analysis results

The probabilistic sensitivity analysis was, using 2,000 simulations.

Table 1: Probabilistic sensitivity analysis results: pairwise comparison

Treatments	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
Darolutamide + Doc + ADT	[redacted]	[redacted]	[redacted]	[redacted]			
Docetaxel + ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,207
Enzalutamide + ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Darolutamide dominant
ADT alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,204

Key: ADT, androgen deprivation therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; LYs, life years; QALYs, quality-adjusted life years.

Figure 1: Cost-effectiveness plane – darolutamide+docetaxel+ADT vs docetaxel+ADT

[redacted]

Key: ADT, androgen deprivation therapy; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

Figure 2: Cost-effectiveness plane – darolutamide+docetaxel+ADT vs enzalutamide+ADT

[redacted]

Key: ADT, androgen deprivation therapy; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

Figure 3: Cost-effectiveness plane – darolutamide+docetaxel+ADT vs ADT alone

Key: ADT, androgen deprivation therapy; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

Figure 4: Cost-effectiveness acceptability curve

Revised base case deterministic sensitivity analysis results

Table 2: Top 10 most influential parameters for darolutamide+docetaxel+ADT versus docetaxel+ADT

Parameter	iNMB results vs Docetaxel + ADT		
Base case			
	Lower iNMB	Lower iNMB	Difference
Utilities: mHSPC			£26,129
OS Hazard ratio - Darolutamide			£18,264
PFS Hazard ratio - Darolutamide			£9,378
Subsequent treatment duration - Enzalutamide			£8,276
Subsequent treatment duration - Abiraterone			£6,555
Utilities: mHRPC 1L			£6,106
mHSPC HRU: Darolutamide off Tx			£2,367
mCRPC HRU: Docetaxel + ADT			£2,222
Utilities: mHRPC 3L			£1,790
Subsequent treatment duration - Enzalutamide			£1,526

Key: 1L, first-line, 3L, third line, ADT, androgen deprivation therapy, HRU, healthcare resource use, iNMB, incremental net monetary benefit, mHRPC, metastatic hormone-relapsed prostate cancer,

Parameter	iNMB results vs Docetaxel + ADT
mHSPC, metastatic hormone-sensitive prostate cancer, OS, overall survival, PFS, progression-free survival, Tx, treatment.	

Table 3: Top 10 most influential parameters for darolutamide+docetaxel+ADT versus enzalutamide+ADT

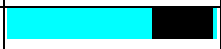
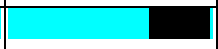
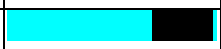
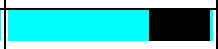
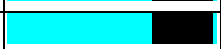
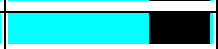
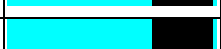
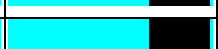
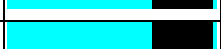
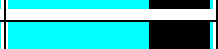
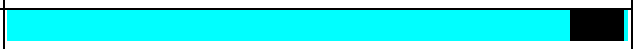
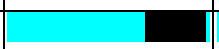
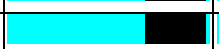
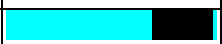
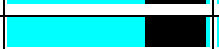
Parameter	iNMB results vs Enzalutamide + ADT		
Base case			
	Lower iNMB	Upper iNMB	Difference
Utilities: mHSPC			£25,102
OS Hazard ratio - Enzalutamide			£23,104
OS Hazard ratio - Darolutamide			£18,264
ToT Hazard ratio - Enzalutamide			£13,475
PFS Hazard ratio - Darolutamide			£9,378
Utilities: mHRPC 3L			£6,860
mCRPC HRU: Enzalutamide + ADT			£2,629
Utilities: mHRPC 1L			£2,558
mHSPC HRU: Darolutamide off Tx			£2,367
Utilities: mHRPC 2L			£2,153
Key: ADT, androgen deprivation therapy, HRU, healthcare resource use, iNMB, incremental net monetary benefit, mHSPC, metastatic hormone-sensitive prostate cancer, OS, overall survival, PFS, progression-free survival, ToT, time-on-treatment, Tx, treatment.			

Table 4: Top 10 most influential parameters for darolutamide+docetaxel+ADT versus ADT alone

Parameter	iNMB results vs ADT alone		
Base case			
	Lower iNMB	Upper iNMB	Difference
Utilities: mHSPC			£32,457
OS Hazard ratio - Darolutamide			£18,264
PFS Hazard ratio - ADT			£11,514
Subsequent treatment duration - Enzalutamide			£9,564
PFS Hazard ratio - Darolutamide			£9,378

Parameter	iNMB results vs ADT alone		
Subsequent treatment duration - Abiraterone	[redacted]	[redacted]	£7,575
Utilities: mHRPC 1L	[redacted]	[redacted]	£7,520
OS Hazard ratio - ADT	[redacted]	[redacted]	£5,922
Subsequent treatment duration - Enzalutamide	[redacted]	[redacted]	£2,383
mHSPC HRU: Darolutamide off Tx	[redacted]	[redacted]	£2,367
Key: 1L, first-line, ADT, androgen deprivation therapy, HRU, healthcare resource use, iNMB, incremental net monetary benefit, mHSPC, metastatic hormone-sensitive prostate cancer, OS, overall survival, PFS, progression-free survival, ToT, time-on-treatment, Tx, treatment.			

Figure 5: Tornado plot of most influential parameters for darolutamide+docetaxel+ADT vs docetaxel+ADT

[redacted]

Key: 1L, first-line, ADT, androgen deprivation therapy, HRU, healthcare resource use, iNMB, incremental net monetary benefit, mCRPC, metastatic castration-resistant prostate cancer, mHRPC, metastatic hormone-relapsed prostate cancer, mHSPC, metastatic hormone-sensitive prostate cancer, OS, overall survival, PFS, progression-free survival, Tx, treatment.

Figure 6: Tornado plot of most influential parameters for darolutamide+docetaxel+ADT vs enzalutamide+ADT

[redacted]

Key: ADT, androgen deprivation therapy, HRU, healthcare resource use, iNMB, incremental net monetary benefit, mHSPC, metastatic hormone-sensitive prostate cancer, OS, overall survival, PFS, progression-free survival, ToT, time-on-treatment, Tx, treatment.

Figure 7: Tornado plot of most influential parameters for darolutamide+docetaxel+ADT vs ADT alone

[redacted]

Key: 1L, first-line, ADT, androgen deprivation therapy, HRU, healthcare resource use, iNMB, incremental net monetary benefit, mHSPC, metastatic hormone-sensitive prostate cancer, OS, overall survival, PFS, progression-free survival, ToT, time-on-treatment, Tx, treatment.

Revised base case deterministic scenario analyses results

The relevant scenario analyses were rerun, using the updated base case settings. This includes all scenarios from Doc B, except for: the docetaxel disutility scenario which is already included in the updated base case, and the alternative PFS network scenario (given that no alternative PFS network was available for the updated data). In addition, the scenarios exploring the next best OS, PFS, and ToT fits, now explored the models used in the base-case instead.

Table 5: Deterministic scenario results versus docetaxel, ranked by difference in iNMB

Rank	Scenario	ICER	Δ ICER	iNMB	Δ iNMB
Deterministic base case		**£8,251**			
1	Log-logistic ToT				
2	Time horizon (20 years)				
3	Daro as anchor				
4	Treatment effect models				
5	Excluding RDI				
6	Using utilities from TA741				
7	Generalized gamma PFS				
8	Time horizon (25 years)				
9	Log-normal OS				
10	Including G-CSF costs				
11	Include SSEs*				
12	Including SNA studies				
13	Without non-PH studies				
14	Without GETUG AFU-15 trial				

Key: ADT, androgen deprivation therapy; alt. alternative; G-CSF, granulocyte-colony stimulating factor; HR; hazard ratio; ICER, incremental cost-effectiveness ratio, ITC, indirect treatment comparison; iNMB, incremental net monetary benefit, mHRPC, metastatic hormone-relapsed prostate cancer, OS, overall survival, PH, proportional hazards; PFS, progression-free survival, RDI, relative dose intensity, SNA;

Rank	Scenario	ICER	Δ ICER	iNMB	Δ iNMB
nonsteroidal antiandrogen; ToT, time on treatment; TTCRPC, time to castration-resistant prostate cancer. **Note**: *Scenario only performed versus docetaxel + ADT, as SSE data were only available for docetaxel.					

Table 6: Deterministic scenario results versus enzalutamide, ranked by difference in iNMB

Rank	Scenario	ICER	Δ ICER	iNMB	Δ iNMB
Deterministic base case		**Enz dom.**			
1	Without GETUG AFU-15 trial				
2	Including SNA studies				
3	Comparator ToT modelled with PFS*				
4	Treatment effect models				
5	Daro as anchor				
6	Log-logistic ToT				
7	Without non-PH studies				
8	Time horizon (20 years)				
9	Using utilities from TA741				
10	Generalized gamma PFS				
11	Excluding RDI				
12	Time horizon (25 years)				
13	Log-normal OS				
14	Including G-CSF costs				

Key: ADT, androgen deprivation therapy; alt. alternative; enz. dom., enzalutamide dominated by darolutamide; G-CSF, granulocyte-colony stimulating factor; HR; hazard ratio; ICER, incremental cost-effectiveness ratio, ITC, indirect treatment comparison; iNMB, incremental net monetary benefit, mHRPC, metastatic hormone-relapsed prostate cancer, OS, overall survival, PH, proportional hazards; PFS, progression-free survival, RDI, relative dose intensity, SNA; nonsteroidal antiandrogen; ToT, time on treatment; TTCRPC, time to castration-resistant prostate cancer.
Note: *Scenario only performed versus enzalutamide + ADT, as comparator ToT was not modelled for other treatments.

Table 7: Deterministic scenario results versus ADT, ranked by difference in iNMB

Rank	Scenario	ICER	Δ ICER	iNMB	Δ iNMB
Deterministic base case		**£5,310**			
1	Log-logistic ToT				
2	Time horizon (20 years)				

Rank	Scenario	ICER	Δ ICER	iNMB	Δ iNMB
3	Generalized gamma PFS				
4	Treatment effect models				
5	Without GETUG AFU-15 trial				
6	Excluding RDI				
7	Without non-PH studies				
8	Log-normal OS				
9	Time horizon (25 years)				
10	Including G-CSF costs				
11	Using utilities from TA741				
12	Daro as anchor				
13	Including SNA studies				

Key: ADT, androgen deprivation therapy; alt. alternative; G-CSF, granulocyte-colony stimulating factor; HR; hazard ratio; ICER, incremental cost-effectiveness ratio, ITC, indirect treatment comparison; iNMB, incremental net monetary benefit, mHRPC, metastatic hormone-relapsed prostate cancer, OS, overall survival, PH, proportional hazards; PFS, progression-free survival, RDI, relative dose intensity, SNA; nonsteroidal antiandrogen; ToT, time on treatment; TTCRPC, time to castration-resistant prostate cancer.

References

1. National Institute for Health and Care Excellence (NICE). Enzalutamide for treating hormone-sensitive metastatic prostate cancer [TA712] 2021 [updated 7 July 2021. Available from: https://www.nice.org.uk/guidance/ta712.
2. Bayer Healthcare. National Institute of Health and Care Excellence (NICE) submission for darolutamide +docetaxel + ADT in metastatic hormone-sensitive prostate cancer (mHSPC) advisory board [Data on file].
3. Bayer Healthcare. National Institute of Health and Care Excellence (NICE) submission for darolutamide +docetaxel + ADT in metastatic hormone-sensitive prostate cancer (mHSPC) HE validation meeting report.
4. Armstrong AJ, Azad AA, Iguchi T, Szmulewitz RZ, Petrylak DP, Holzbeierlein J, et al. Improved Survival With Enzalutamide in Patients With Metastatic Hormone-Sensitive Prostate Cancer. J Clin Oncol. 2022;40(15):1616-22.
5. Koroki Y, Taguri M, Matsubara N, Fizazi K. Estimation of Overall Survival with Subsequent Treatment Effect by Applying Inverse Probability of Censoring Weighting in the LATITUDE Study. European urology open science. 2022;36:51-8.
6. Feyerabend S, Saad F, Perualila NJ, Van Sanden S, Diels J, Ito T, et al. Adjusting Overall Survival Estimates for Treatment Switching in Metastatic, Castration-Sensitive Prostate Cancer: Results from the LATITUDE Study. Targeted oncology. 2019;14(6):681-8.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Darolutamide with androgen deprivation therapy and docetaxel for treating hormone-sensitive metastatic prostate cancer [ID3971]

Technical engagement response form

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Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **16 January 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we

received, and are not endorsed by NICE, its officers or advisory committees.

About you

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Prostate Cancer Research
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**NIL**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: The cost-effectiveness results are not provided for the subgroups listed in the NICE scope	No	From a patient perspective the subgroups of “high risk” and “newly diagnosed” appear artificial. The rationale for this sub-grouping holds good for abiraterone, since this is a treatment for advanced prostate cancer that is most commonly offered to men whose cancer has stopped responding to other types of hormone therapy. Whilst there is in any case a lack of data in the public domain relating to these two sub-groups, and a lack of consistent definitions, we are not aware of any evidence suggesting that the product might work differently these sub-groups.
Key issue 2: The reasons for censoring in the ARASENS trial are not reported	No	NIL response
Key issue 3: The loss to follow-up in the ARASENS trial is not fully explained	No	NIL response
Key issue 4: The use of unadjusted hazard ratios in the network meta-analysis for trials that allowed crossover. The impact	No	Adjusting hazard ratios in the meta-analysis for trials that allow cross-over, should not be a necessity. The comparator arm in ARASENS conforms to best practices whilst the comparator arm in ARCHES is arguably undertreated. Whilst using unadjusted estimates in the NMA may underestimate the treatment effect for the

of adjusted estimates for OS should also be presented.		comparators, adjustment may over-estimate the comparator arm in ARCHES, by boosting the relative efficacy of enzalutamide. We therefore agree with the EAG report recommendation that further discussion as to the appropriateness of adjusting for crossover in comparator trials is warranted.
Key issue 5: An out-of-date progression-free survival hazard ratio from the ARCHES trial has been used in the network meta-analysis	No	Our view is that the most up to date data should be used since this data provides for longer-term follow-up that is reflective of likely outcomes in clinical practice.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

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Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
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About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Prostate Cancer Uk
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: The cost-effectiveness results are not provided for the subgroups listed in the NICE scope	No	Prostate Cancer UK believes that it would be unnecessary and irrelevant to utilise a subgroup analysis for this particular treatment appraisal. Whilst analysis by sub-group is useful to inform clinical guidelines on use of darolutamide, given the overall survival benefit across all patients, we believe the priority and focus of the appraisal should be analysis using whole population data. It is not clear to us whether the sub-group analysis in ARASENS was sufficiently powered, but we note that the treatment effect appears to be consistent across sub-populations. We are concerned that dividing the population into subgroups may introduce uncertainty into the cost-effectiveness analysis that may result in some patients unfairly missing out on a treatment. The broader whole population indication has been approved by the MHRA for the Early Access Scheme which as a charity we fully support. From the trial, this triple therapy treatment regimen has a clear clinical benefit across the entire group. We

		would urge the committee to continue with the whole population analysis on this basis, allowing for more men to have the option of darolutamide triple therapy should it be approved.
Key issue 2: The reasons for censoring in the ARASENS trial are not reported	No	Prostate Cancer UK would be keen to understand the reasons for censoring in the ARASENS trial.
Key issue 3: The loss to follow-up in the ARASENS trial is not fully explained	No	Prostate Cancer UK would be keen to understand more detail surrounding the loss to follow up in the ARASENS trial.
Key issue 4: The use of unadjusted hazard ratios in the network meta-analysis for trials that allowed crossover. The impact of adjusted estimates for OS should also be presented.	No	We know anecdotally (from the clinicians we work with or via our own specialist nurses) that subsequent treatment with a novel hormonal agent (NHA) such as enzalutamide or abiraterone upon progression is standard practice in the UK with most (estimated at around 4 out of 5) patients taking an NHA. Prostate Cancer UK are therefore concerned that using the proposed adjusted hazard ratio as used within ARCHES would potentially underestimate the direct effectiveness of this treatment compared to enzalutamide, and also as a consequence lower the cost effectiveness in this comparison.

		Taking the above into consideration, Prostate Cancer UK would like to reiterate that subsequent treatments on progression (with abiraterone or enzalutamide) on progression is very common in practice and is the view of our CNSs and clinical experts that we regularly work with and this should be taken into consideration by the committee.
Key issue 5: An out-of-date progression-free survival hazard ratio from the ARCHES trial has been used in the network meta-analysis	Yes/No	Prostate Cancer UK would agree that an up-to-date progression-free survival hazard ratio be used within the network meta-analysis.

Additional issues

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Table 3 Additional issues from the EAR

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Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

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Sensitivity analyses around revised base case
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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Darolutamide with androgen deprivation therapy and docetaxel for treating hormone-sensitive metastatic prostate cancer [ID3971]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **16 January 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we

received, and are not endorsed by NICE, its officers or advisory committees.

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	**Tackle Prostate Cancer**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: The cost-effectiveness results are not provided for the subgroups listed in the NICE scope	Yes/No	A patient organisation such as ours does not have the scientific / statistical skills to be able to provide valid or d=credible comments on complex discussions such as this. However, we have added a comment under 'Additional Issues'
Key issue 2: The reasons for censoring in the ARASENS trial are not reported	Yes/No	N / A
Key issue 3: The loss to follow-up in the ARASENS trial is not fully explained	Yes/No	N / A
Key issue 4: The use of unadjusted hazard ratios in the network meta-analysis for trials that allowed crossover. The impact of adjusted estimates for OS should also be presented.	Yes/No	N / A

Key issue 5: An out-of-date progression-free survival hazard ratio from the ARCHES trial has been used in the network meta-analysis	Yes/No	N / A

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response

Additional issue N: Insert additional issue			As an organisation representing the views of patients, we would like to stress the uniqueness of this combination therapy. The use of triple therapy for prostate cancer has not been used so far – unlike the treatment of other cancers. Whilst the drugs being used are well known and already in established use, the combination is novel and innovative. Where a new concept of treatment is being discussed there may be no direct comparator – what is utmost to the patient is whether the new treatment being discussed can produce further benefits regarding both quality and quantity of life with minimal increase in harms. It is important is to have a wide range of therapeutic options that can be tailored to the individual patient and their needs. This triple therapy would further extend the range of treatments available to clinicians and patients. The numbers of patients eligible for this triple therapy may well not be huge. We have contact with increasing numbers of younger, relatively fit patients who have newly diagnosed metastatic prostate cancer. These patients often have young families dependent on them. Many of those would be willing and indeed able to have this more aggressive therapy if it was available.

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Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	N / A
Insert key issue number and title as described in the EAR	…	…	N / A
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	N / A

Sensitivity analyses around revised base case
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Evidence Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Darolutamide with androgen deprivation therapy and docetaxel for treating hormone-sensitive metastatic prostate cancer [ID3971]

Evidence Assessment Group's summary and critique of the company's response to technical engagement

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
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Date completed	28th February 2023

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Commercial in confidence (CIC) information in blue

Academic in confidence (AIC) information in yellow

1. Introduction

This document is the Evidence Assessment Group's (EAG) summary and critique of the response by the company, Bayer, to the key issues for technical engagement (TE) proposed in the EAG report for this appraisal (submitted to NICE on 14/11/22) (Table 1). The EAG received the company's response on 18/01/23.

The company's stakeholder response form contains the following information:

- A written response to each of the five key issues.
- A set of updated company base case cost-effectiveness results, incorporating EAG preferred assumptions

An updated version of the company's economic model accompanies the response form.

In this report we present the following:

- Our critique of the company's response to each of the five key issues for technical engagement (Section 2)
- A summary of the results of the company's updated base case cost-effectiveness analysis (Section 3)

This report is accompanied by a separate confidential addendum in which the updated base case cost-effectiveness analyses are repeated based on all available confidential patient access scheme (PAS) drug discount prices.

Table 1 Summary of key issues for technical engagement

Issue number	Summary of issue	Does this response contain new evidence, data or analyses?
1	Cost-effectiveness results are not provided for the subgroups listed in the NICE scope	No
2	Reasons for censoring in the ARASENS trial not reported	Yes
3	Loss to follow up in the ARASENS trial not fully explained	Yes
4	Use of unadjusted hazard ratios in the network meta-analysis (NMA) for trials that allowed crossover	Yes
5	Out of date PFS hazard ratio from ARCHES trial used in the NMA	No

2. Critique of the company's response to key issues for technical engagement

2.1 Issue 1 – Cost-effectiveness results are not provided for the subgroups listed in the NICE scope

Summary of the issue

The NICE scope for this appraisal specifies two subgroups of relevance: people with 'high-risk' mHSPC and people with 'newly diagnosed' mHSPC. The company didn't provide cost effectiveness results for these subgroups, stating that these terms are not used consistently across the evidence base in mHSPC.

In the ARASENS trial[1] there was no classification of patients in terms of 'high-risk' disease. Instead, the company highlights the pre-specified trial subgroup 'extent of disease' (i.e. non-regional lymph node metastasis, bone metastasis, and visceral metastasis). Expert clinical advice to the EAG confirmed that there is variation between clinical trials in definitions of high-risk disease. Some trials define high- versus low- risk disease based on the number of bone metastases and/or presence of visceral metastases (e.g. the LATITUDE trial[2]). More commonly, trials have used high- versus low-volume disease for risk stratification.

The ARASENS trial included a prespecified subgroup 'metastasis at initial diagnosis' (Yes/No). The majority of patients (86%) had stage IV metastatic disease at initial diagnosis, thus can be considered as having newly diagnosed (de novo) disease.

In both sets of subgroup analyses (i.e. 'extent of disease' and 'metastasis at initial diagnosis') the trial outcomes were consistent with the outcomes in the ITT population.

Critique of the company's response

In their response to technical engagement the company reiterate the points made in the CS (i.e. lack of consistency between trials in use of terms) as the justification for not assessing cost effectiveness in the subgroups. They also point out that the two subgroups were not included in NICE TA721 (enzalutamide in mHSPC) due to inconsistency of definitions.

Nonetheless, for technical engagement company provide clinical effectiveness subgroup analyses for the ARASENS de-novo and high-risk subgroups, for the outcomes overall survival (OS) and castration-resistant prostate cancer or death (CROD), to "understand the likely impact on the comparative efficacy estimates" (Company technical engagement response form, page 5).

- The definition of high risk disease used is as per the definition in the LATITUDE trial[2]: patients were required to have at least two of three high-risk prognostic factors (Gleason score ≥8, three or more lesions on bone scan, and measurable visceral metastases, excluding lymph node metastasis).
- The EAG notes that prespecified subgroup analyses were reported for 'metastasis at initial diagnosis' in the CS for OS. There are minor discrepancies between the CS and the current analyses in the number of patients in the subgroup and in the hazard ratios (HRs). However, these discrepancies do not alter the overall findings and conclusions.
- We assume that the subgroup analyses for de novo patients (CROD) and high-risk patients (for OS and CROD) are post-hoc.

Of the patients in the ARASENS trial, 86.1% ([redacted]) were classed as de-novo and 70% ([redacted]) were classed as high-risk. The respective subgroup analysis results are consistent with the results of the ITT population (n=1,305).

The EAG notes that the company does not provide results for the corresponding non-de novo subgroup or the non-high risk subgroups. However, the results for those subgroups would be more uncertain due to the small number of patients in each.

The company has not presented cost effectiveness analyses for these two subgroups, nor included them in their NMA. The EAG agrees with the company that this is unlikely to be feasible as not all comparator studies will have reported these subgroups, thus leaving gaps in the evidence network thereby limiting the ability to compare treatments.

EAG conclusion

We agree with the company that the assessing the cost effectiveness of the darolutamide combination in patients with high-risk mHSPC is problematic due to inconsistent definitions of risk in comparator trials. The vast majority of patients in ARASENS had newly diagnosed (de novo) mHSPC, and survival estimates in this subgroup were similar to those in the ITT population.

2.2 Issue 2 – Reasons for censoring in the ARASENS trial not reported

2.2.1 Summary of the issue

The company did not provide the number and proportion of participants in each of the ARASENS trial arms who were censored, and reasons for censoring, for the time to castration-resistant prostate cancer (CRPC) outcome analysis. In particular, it is unclear if there is a difference between trial arms in censoring of participants who received subsequent systemic antineoplastic therapy without meeting the criteria for CRPC and who were without a post prostate-specific antigen (PSA) progression event. If informative censoring is present this could bias mean time to CRPC and, in turn, the time to CROD efficacy estimate used in the company's economic model.

2.2.2 Critique of the company's response

At the EAG's request the company reported from the time to CRPC analysis the number and proportion of censored participants in the ARASENS trial arms, with reasons.

In the darolutamide arm [redacted] patients were censored, whilst the corresponding figures in the placebo arm were [redacted].

The most common reason for censoring was due to no CRPC at the time of analyses (darolutamide: [redacted]); placebo: [redacted]). The company explains that the efficacy of darolutamide resulted in a smaller proportion of patients progressing to CRPC in the darolutamide arm compared to the placebo arm (darolutamide: 35%; placebo: 60%). The EAG considers this reasonable.

The proportion of patients censored for other reasons was small [redacted] patients in the darolutamide arm; [redacted] patients in the placebo arm). The reasons given were: no baseline or post-baseline assessment; PSA progression after two or more consecutive missing assessments; and prohibited new anticancer therapy before CRPC (broken down by type of progression e.g. PSA, radiological etc). The proportion of patients in the trial arms censored for these reasons was similar (to within 1 percentage point).

EAG conclusion

For the time to CRPC analysis we have no concerns about imbalances between the trial arms in the proportion of patients censored and the reasons for censoring. We are satisfied that censoring does not bias the time to CRPC estimate and, in turn, the time to CROD estimate used in the economic model.

2.3 Issue 3 – Loss to follow up in the ARASENS trial not fully explained

2.3.1 Summary of the issue

We noted an unexplained imbalance between the ARASENS trial arms in loss to follow-up among participants who discontinued study treatment and then entered a planned 'active follow-up' trial phase (n=224/352 ([redacted]) of those who discontinued treatment in the darolutamide + docetaxel + ADT arm versus n=381/526 ([redacted]) who discontinued in the placebo + docetaxel + ADT trial arm entered active follow-up). The reasons why some patients who discontinued therapy did not enter the active follow-up as planned is not apparent to the EAG from the information provided in the CS. It is therefore unknown if this imbalance might potentially bias the results of the trial and hence the cost effectiveness analysis.

2.3.2 Critique of the company's response

In their response the company provides a figure illustrating the disposition of patients in ARASENS who discontinued study treatment, with an accompanying narrative explanation. They describe how, upon discontinuation, patients entered *either*:

- Active follow-up (whereby patients attend clinic every 12 weeks for up to 1 year for efficacy and safety assessments, including survival), *or*
- 'Survival follow-up' (patients were contacted approximately every 12 weeks by phone to assess survival, safety, use of antineoplastic treatments for prostate cancer), *or*
- Ended the study completely without follow-up.

Importantly, the company explain that the active follow-up period could be terminated if a patient could no longer travel to the clinic or if they actively objected to the collection of further data. If this applied to patients at the point of discontinuation then they could enter the survival follow-up *directly from treatment discontinuation*. Previously we assumed (based on the information in the CS) that *all* discontinuing patients were to enter active follow-up and could *only* enter survival follow up from there.

It appears that active follow-up includes a more comprehensive assessment of outcomes than survival follow-up, the latter which omitted outcomes such as QoL, pain, analgesia etc.

The company provides the proportion of patients by trial arm according to their follow up status at discontinuation:

- Entered active follow-up (darolutamide: [redacted]; placebo: [redacted]),
- Entered survival follow-up (darolutamide: [redacted]; placebo: [redacted]
- Ended the study (darolutamide: n = [redacted]; placebo: n = [redacted])

In the company's view, the trial arms are similar in the proportion of discontinuing patients entering the respective follow-ups. They state there were no imbalances that would bias the result, and the outcome measures utilised in the model were collected in the same manner across the active and survival follow-up periods.

The EAG has a slightly different interpretation to the company, noting that the proportion of patients entering active follow-up was slightly higher in the placebo arm than the darolutamide arm, by [redacted]. The clinical implications of this difference are unclear, but as follow-up outcome assessment was said to be consistent in the active follow-

up and survival follow-up analyses any difference between trial arms is unlikely to bias the economic model.

We also note that the proportion of discontinuing patients in the darolutamide arm who ended the study was almost twice that of the placebo arm, though overall this represents a small proportion of discontinuing patients (<11%)

EAG conclusion

Given the further information given by the company above (i.e. that some patients entered survival follow-up directly at treatment discontinuation) the EAG is no longer concerned about why some patients who discontinued therapy did not enter the active follow-up. There are some apparent differences between trial arms in the proportion of patients entering active follow-up, as well as in the proportion who ended the study without follow-up at discontinuation. These differences are not thought to increase the risk of bias in outcomes included in the economic model.

2.4 Issue 4 – Use of unadjusted hazard ratios in the network meta-analysis (NMA) for trials that allowed crossover

2.4.1 Summary of the issue

Crossover of patients between trial arms was not permitted in the ARASENS trial. Two comparator trials included in the company's NMA permitted patient crossover from the placebo arm to experimental treatment arm following the primary data analysis and subsequent study unblinding (the ARCHES trial of enzalutamide + ADT vs ADT alone; [3] the LATITUDE trial of Abiraterone acetate + Prednisone + ADT vs ADT alone). The company chose not to use the crossover-adjusted HRs from these trials in their NMA, stating that this aligns with the approach taken in NICE TA741 (apalutamide + ADT for mHSPC). The EAG, however, notes that in TA741 the NICE appraisal committee considered both unadjusted and adjusted OS estimates in their decision making. This was due to uncertainties about a) the methods used to adjust for the effects of patient crossover and b) whether or not it is appropriate to adjust for the effects on survival of crossover / switching to other subsequent anticancer treatments in the metastatic prostate cancer setting.

Furthermore, in TA741 it was considered that not adjusting for crossover in the pivotal trial would be conservative as it would underestimate the efficacy of apalutamide. In contrast, for the current appraisal, crossover occurs in trials of comparator treatments (e.g. enzalutamide

+ ADT vs ADT alone). Therefore, using unadjusted estimates in the NMA may underestimate the relative effects of the comparator(s), and in turn, overestimate the relative effects of darolutamide, potentially increasing its cost effectiveness.

The EAG's NMA scenario analysis using the crossover-adjusted OS estimates from ARCHES and LATITUDE reduced the treatment effect for the comparison of darolutamide + docetaxel + ADT versus enzalutamide + ADT (company unadjusted [redacted]; EAG adjusted [redacted]).

We explored the impact of using the crossover adjusted estimate on cost effectiveness in a scenario analysis using the company's original base case. The ICER for darolutamide + docetaxel + ADT versus docetaxel + ADT alone increased to [redacted] per QALY; versus ADT alone the ICER increased to [redacted] per QALY. Darolutamide + docetaxel + ADT [redacted] compared to enzalutamide + ADT. These estimates were based on the company's PAS discount price for darolutamide. Cost effectiveness estimates including all available PAS discounts are reported in a separate EAG confidential addendum.

2.4.2 Critique of the company's response

In their updated economic base case, the company did not include the crossover-adjusted effect estimates from ARCHES and LATITUDE. Instead, they maintain their view that adjustment methods for crossover in clinical trials (e.g. the rank preserving structure failure time modelling (RPSFTM) and the inverse probability of censoring weights (IPCW)) are associated with numerous uncertainties. The company does not elaborate on these uncertainties, nor do they compare the advantages and disadvantages of the various adjustment methods available with a view to identifying which, if any, could be considered 'least uncertain' and potentially explored in this appraisal (where feasible).

The company's key concern is that, after adjusting for patient crossover in ARCHES and LATITUDE, the proportion of placebo group patients who receive a subsequent ARTA is disproportionately higher in ARASENS. They go on to suggest that subsequent ARTA use has a greater impact on survival outcomes in the placebo arm of ARASENS compared to the darolutamide combination arm. (It is important to acknowledge that after crossover adjustment, any subsequent ARTA use in the placebo arm is **first ARTA use**). The presence of these two factors, in their opinion, biases against darolutamide in relative effectiveness. The company therefore favours using unadjusted, ITT population-based

survival estimates. They do not provide any counter arguments to this assumption, nor any alternative analyses.

The company emphasises the clinical relevance of their preferred approach, suggesting that the unadjusted ITT population OS HR from ARCHES more accurately reflects the expected relative effectiveness of darolutamide + docetaxel + ADT compared to enzalutamide + ADT in UK clinical practice. This is because when the unadjusted ITT HR is used, the proportions of subsequent ARTA (i.e. enzalutamide, abiraterone) used across the comparator arms of ARCHES and ARASENS are aligned, and are also reflective of subsequent ARTA use following treatment with docetaxel + ADT or ADT alone in UK clinical practice.

In Table 2 below we describe and critique aspects of the company's argument against adjusting for crossover in this appraisal.

Table 2 Description and critique the company's argument against adjusting for crossover

Company's justification	EAG comment
The treatment-adjusted HRs [from ARCHES and LATITUDE] aim to estimate the HR for OS by removing the impact of crossover from control to intervention (enzalutamide + ADT in ARCHES; abiraterone + ADT in LATITUDE). However, patients within the control arm of these trials also receive multiple other subsequent treatments (including other ARTAs) which are not adjusted for using these cross-over adjustment methods.	Because crossover occurs in trials of comparator treatments, using unadjusted HRs from ARCHES and LATITUDE in the NMA may underestimate the relative effects of the experimental treatments in these trials and, in turn, overestimate the relative effects of darolutamide. However, the company makes no mention of this possibility, and how this counteracts their argument of bias against darolutamide.
In both ARCHES and LATITUDE there is no evidence of adjustment for subsequent ARTA.	To adjust for the impact of subsequent treatments would require access to individual patient trial data in these comparator trials which, presumably, the company does not have.

	Separate adjustments for the impact of patient crossover and for subsequent treatments, if possible, would be informative. These have been considered in previous NICE appraisals (e.g. TA741).
After removing treatment switching patients from subsequent ARTA use and comparing proportions, the control arm of ARASENS has the highest percentage of patients that receive subsequent ARTA. This is anticipated to be unfavourable for darolutamide, as the subsequent ARTA use positively impacts the control arm [because this is effectively their first ARTA]. Therefore, the relative effect between intervention and control arm in comparator trials will be increased as the impact of subsequent ARTA in the control arm is reduced in the crossover-adjusted HRs.	We agree that this is plausible. Control group patients would be expected to benefit from their first exposure to an ARTA. However, we note that this assumption is partly informed by the post hoc PPS analysis of ARASENS reported in CS Figures 20 and 21. We question the company's conclusion of a "clear PPS benefit for the ARTAs in the control arm" (CS page 156) based on these data. The PPS analysis has limitations (e.g. not statistically powered, based on smaller subsets of patients) and therefore cannot be regarded as definitive. (see Appendix 4.1 below for further critique).
Although there is subsequent ARTA use in the intervention arms of the trials, it was not expected to drive the OS benefit demonstrated by darolutamide patients in the ARASENS trial. This assumption is informed by the results of the post hoc PPS analysis (CS Figures 20 and 21), and expert opinion (data on file).	We agree that this is plausible. As we comment above, however, the results of the PPS cannot be regarded as definitive. The EAG notes that this assumes that the effect of a subsequent ARTA following darolutamide would be minimal. In TA741 expert clinical opinion was that having a second newer androgen receptor inhibitor is unlikely to extend life, but might be associated with adverse effects. The company does not explicitly mention adverse effects in their response to technical engagement.

EAG conclusion

Greater clarity of the above issues may be achieved by separate adjustments for:

- crossover in the ARCHES and LATITUDE trials, to avoid overestimating the relative effects of darolutamide and
- the impact of subsequent treatments in the trials, to avoid underestimating the relative effects of darolutamide (though, as commented above, this adjustment isn't possible without access to individual patient data from these comparator trials).

The EAG believes that uncertainties arise with each of the two approaches to crossover (i.e. adjusting or not adjusting), and therefore both should be taken into account in decision making.

The company may be able to use the individual patient data from the ARASENS trial to conduct an analysis adjusting for subsequent treatments given to trial patients which would not be permitted in the NHS (i.e. a second ARTA). This analysis could provide support (or otherwise) for the company's argument that subsequent ARTA use favours the control arm and thereby reduces the relative efficacy of darolutamide. If this isn't the case, it would provide a stronger argument for the use of the crossover adjusted OS results.

In lieu of such an analysis, it may be prudent to model the trials 'as is' (i.e. without crossover adjustment – as the company has done) before considering alternative assumptions (i.e. with crossover adjustment), hence the EAG's exploratory scenario analysis. Additional expert clinical opinion may provide further clarity regarding which approach is more representative of current practice.

2.5 Issue 5 - Out of date PFS hazard ratio from ARCHES trial used in the NMA

2.5.1 Summary of the issue

The company used the most mature hazard ratios (HRs) from comparator trials as inputs to their NMA for OS and progression-free survival (PFS). However, for the ARCHES trial (enzalutamide + ADT), they used the most recent estimate for OS from Armstrong 2022[4] but not the updated PFS estimate (measured as radiological progression-free survival (rPFS)) from the same publication. The Armstrong 2022 publication was not available at the time of the company's systematic literature review.

The updated rPFS (HR:0.63; 95% confidence interval (CI): 0.52, 0.76) from ARCHES is notably less favourable for enzalutamide + ADT than the estimate in the primary analysis[3] (HR:0.39; 95% CI:0.30, 0.50). The reasons for this difference are uncertain.

We also noted that the ARCHES primary analysis measured rPFS using centralised independent review whereas the updated results state the term 'investigator-assessed', which may partly explain the differences in effects.

In the EAG report we presented NMA scenarios with and without the updated PFS estimates for completeness. The updated PFS estimates scenario showed a more favourable treatment effect for darolutamide + docetaxel + ADT compared to enzalutamide + ADT.

2.5.2 Critique of the company's response

The company agrees that the longer term rPFS HR data from ARCHES and FFS HR data from STAMPEDE-2 is suitable to be used in the NMA as it provides higher maturity. This would also be consistent with the OS data used for the NMA from ARCHES and the median follow-up for the longer-term OS and rPFS data from ARCHES more closely matches that of the ARASENS follow-up used in the NMA. The updated estimates are included in the updated company base case (see section 3.1 below).

In addition, the company reports that clinical experts consulted were not concerned about the long term rPFS being driven by local investigator decision, as in clinical practice, scans are not reviewed centrally/independently.

EAG conclusion

The company has included the updated survival estimates in their NMA and economic model, in accordance with the EAG.

3. Updated cost-effectiveness results - EAG summary and critique

3.1 Company's revised base case cost-effectiveness results

The company accepted the EAG's preferred changes to their base case and have included them in their updated model. The effect of each of these changes to the company's cost-effectiveness estimates are shown in Table 3. (NB. The updated ICERs also include a

correction made by the company to a discounting error in the PFS monitoring costs for darolutamide + docetaxel + ADT and docetaxel + ADT in the original submitted model).

Table 3 Changes made in response to technical engagement

Change	ICER (£/QALY)		
	Doc + ADT	Enza + ADT	ADT alone
Original company base case	[redacted]	[redacted]	[redacted]
Original company base case, discounting error corrected	[redacted]	[redacted]	[redacted]
Using updated ARCHES and STAMPEDE rPFS and FFS hazard ratios in line with the latest available data, to update the NMA HRs	[redacted]	[redacted]	[redacted]
Using a log-logistic OS extrapolation	[redacted]	[redacted]	[redacted]
Using a log-normal PFS extrapolation	[redacted]	[redacted]	[redacted]
Using a generalized gamma ToT extrapolation	[redacted]	[redacted]	[redacted]
Including a docetaxel disutility of 0.02 for a fixed duration of 6 months	[redacted]	[redacted]	[redacted]
Using the subsequent treatment distribution used in TA712 for subsequent treatment after enzalutamide + ADT	[redacted]	[redacted]	[redacted]
Using a weighted average of NHS reference costs FD10J, FD10K, FD10L and FD10M to calculate costs for diarrhoea adverse events	[redacted]	[redacted]	[redacted]
Updating end of life costs from Georghiou and Bardsley to those for people with a cancer diagnosis, including GP visits	[redacted]	[redacted]	[redacted]

Key: ADT, androgen deprivation therapy; FFS, failure-free survival; HR; hazard ratio; ICER, incremental cost-effectiveness ratio; mHRPC, metastatic hormone-relapsed prostate cancer; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-years; rPFS radiographic progression-free survival; ToT, time on treatment

The deterministic incremental results for the company's base case are shown in Table 4 and the pairwise results in Table 5. The EAG checked the results of the individual changes, the probabilistic sensitivity analysis (Company stakeholder TE form Table 1; Figures 1-4), the deterministic sensitivity analysis (Company stakeholder TE form Tables 2-4; Figures 5-6) and the deterministic scenario analyses (Company stakeholder TE form Tables 6-7) for the company's revised base case and consider that they are all correctly reported.

Table 4 Company's base case cost effectiveness results for mHSPC (discounted), incremental results

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Docetaxel + ADT	[redacted]	[redacted]	-	-	-
ADT alone	[redacted]	[redacted]	-	-	Dominated
Darolutamide + docetaxel + ADT	[redacted]	[redacted]	[redacted]	[redacted]	£8,251
Enzalutamide + ADT	[redacted]	[redacted]	-	-	Dominated

Key: ADT, androgen deprivation therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

Table 5 Company's base case cost effectiveness results for mHSPC (discounted), pairwise results

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Darolutamide + docetaxel + ADT	[redacted]	[redacted]			
Docetaxel + ADT	[redacted]	[redacted]	[redacted]	[redacted]	£8,251
Enzalutamide + ADT	[redacted]	[redacted]	[redacted]	[redacted]	Darolutamide dominant
ADT alone	[redacted]	[redacted]	[redacted]	[redacted]	£5,310

Key: ADT, androgen deprivation therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

3.2 EAG's preferred assumptions

Following the company's response to technical engagement, there remain two differences between the company's updated base case and the EAG base case. In the company's revised base case:

1. The updated ARCHES and STAMPEDE rPFS and FFS hazard ratios are applied for both PFS and ToT. The company explain that this is because PFS and ToT HRs are interdependent in the model.
2. The 6-month docetaxel disutility is adjusted to account for the proportion of patients alive during those 6 months.

The EAG explored using the updated rPFS data from ARCHES and FFS data from STAMPEDE-2 [5] as a scenario and noted that this resulted in a much more favourable treatment effect for darolutamide + docetaxel + ADT compared to enzalutamide + ADT (EAG report Table 12). There is also some uncertainty as to whether the updated rPFS estimate for ARCHES uses the same outcome definition as the primary analysis estimate used in the company's NMA. Consequently, we did not use the updated PFS hazard ratios in our base case. We think that the effect of adjusting the docetaxel disutility for the proportion of patients who are alive during the 6 months of treatment has a negligible effect on the ICER.

Table 6 and Table 7 show the incremental and pairwise results for the EAG base case (which also includes the company's correction for the PFS monitoring costs discounting error). The ICERs are nearly identical to the company's revised base case: £8,249 per QALY for darolutamide + docetaxel + ADT vs docetaxel + ADT, and £5,298 per QALY for darolutamide + docetaxel + ADT vs ADT alone (Table 7).

Table 6 EAG base case cost effectiveness results for mHSPC (discounted), incremental results

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Docetaxel + ADT	[redacted]	[redacted]	-	-	-
ADT alone	[redacted]	[redacted]	-	-	Dominated
Darolutamide + docetaxel + ADT	[redacted]	[redacted]	[redacted]	[redacted]	£8,249
Enzalutamide + ADT	[redacted]	[redacted]	-	-	Dominated

Key: ADT, androgen deprivation therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

Table 7 EAG base case cost effectiveness results for mHSPC (discounted), pairwise results

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Darolutamide + docetaxel + ADT	[redacted]	[redacted]			
Docetaxel + ADT	[redacted]	[redacted]	[redacted]	[redacted]	£8,249
Enzalutamide + ADT	[redacted]	[redacted]	[redacted]	[redacted]	Darolutamide dominant
ADT alone	[redacted]	[redacted]	[redacted]	[redacted]	£5,298

Key: ADT, androgen deprivation therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

3.4 Scenario analyses conducted on the company's updated model assumptions

The EAG ran some of the company's deterministic scenario analyses using the corrected company base case (Table 8). Using the log-logistic distribution to model time on treatment (scenario 5) had the greatest effect on the ICER, increasing it to [redacted] per QALY versus docetaxel + ADT (Table 8). [redacted]

Table 8 Deterministic scenario results for darolutamide + docetaxel + ADT vs comparators, using the corrected company base case model

No.	Scenario description	ICER (£/QALY) versus docetaxel + ADT	ICER (£/QALY) versus enzalutamide + ADT
Company base case		£8,251	Darolutamide dominant
1	Run the base case analysis using darolutamide data from ARASENS to extrapolate OS, TTCROD and ToT as an anchor for all treatments	[redacted]	[redacted]
2	Run the base case analysis using docetaxel OS and TTCROD data from ARASENS extrapolated using dependent extrapolations (i.e. treatment effect models)	[redacted]	[redacted]
3	Run the base case analysis using the log-normal ARASENS OS curve to model survival	[redacted]	[redacted]
4	Run the base case analysis using the generalized gamma ARASENS TTCROD curve to model progression	[redacted]	[redacted]
5	Run the base case analysis using the log-logistic ARASENS ToT curve to model treatment use	[redacted]	[redacted]
6	Use health state utilities for pre-progression, 1L, 2L and 3L+ from those reported in TA741.	[redacted]	[redacted]
7	Do not include an on-treatment disutility for patients treated with docetaxel.	[redacted]	[redacted]

Key: ADT, androgen deprivation therapy; HR; hazard ratio; ICER, incremental cost-effectiveness ratio; mHRPC, metastatic hormone-relapsed prostate cancer; OS, overall survival; ToT, time on treatment; TTCROD, time to CRPC or death
Source: Adapted from CS Section B.3.11.3 Table 76

We also ran our additional scenarios using the company's corrected base case model (Table 9). The scenario using the subsequent treatment distributions from TA712 for mHRPC (scenario 1) had the largest effect on the ICER versus docetaxel + ADT, increasing it to [redacted] per QALY. [redacted]

Table 9 EAG scenario results for darolutamide + docetaxel + ADT, using the updated company base case model

No.	Scenario description	ICER (£/QALY) versus docetaxel + ADT	ICER (£/QALY) versus enzalutamide + ADT
Updated company base case		8,251	Daro dominant
1	Using the subsequent treatment distributions for mHRPC for docetaxel + ADT, enzalutamide + ADT and ADT alone from TA712	[redacted]	[redacted]
2	Using the adjusted OS hazard ratios that account for crossover in the ARCHES and LATITUDE studies	[redacted]	[redacted]
3	Removing the abiraterone loop from the NMA	[redacted]	[redacted]
4	Combining the SNA+ADT studies with ADT as one node in the NMA	[redacted]	[redacted]
5	Using updated rPFS data from ARCHES and PFS data from STAMPEDE-2	Now included as part of the company's revised base case	
6	Using distributions for less optimistic long-term survival: • PFS: exponential • OS: generalized gamma • ToT: gamma	[redacted]	[redacted]

Key: ADT, androgen deprivation therapy; ICER, incremental cost-effectiveness ratio; iNMB, incremental net monetary benefit; mHPRC, metastatic hormone-refractory prostate cancer; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year; SNA, nonsteroidal antiandrogen; ToT, time on treatment

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4. Appendices

4.1 Additional EAG critique of company's post progression survival analysis

In the CS the company reports a post hoc analysis of post progression survival in the ARASENS trial. Survival curves for each subsequent treatment were overlaid within the same Kaplan-Meier plot, for the darolutamide combination arm (CS Figure 20) and the docetaxel + ADT arm (CS Figure 21) respectively.

For the darolutamide arm the company observe no differences in PPS between the subsequent treatments (whether an ARTA, or other subsequent treatment). The EAG notes that the confidence intervals plotted for the respective survival curves overlap, which indeed suggests no survival difference between the subsequent treatments.

For the docetaxel + ADT arm the company claims a clear PPS benefit for patients receiving subsequent ARTA compared to those receiving other non-ARTA subsequent treatments. The respective sets of survival curves (ARTA; non ARTA) themselves do not cross apart from at the very start of the period. The EAG notes that the confidence intervals for the respective survival curves overlap in the first eight months of the post progression period, followed by a period of around 16 months during which the abiraterone and enzalutamide curves separate from the (relatively shallower) non-ARTA survival curves, before confidence intervals appear to widen and converge towards the end of the post progression observation period (lasting approximately 20 months). The overlapping confidence intervals at the start and the end of the observation period represent uncertainty which is likely due to lack of events at the start, and small numbers of patients at risk towards the end. This is difficult to judge, however, as the number of patients at risk is not provided.

The EAG also notes that no summary HRs with 95% confidence intervals or other statistical test results are provided for any treatment comparisons in either Figure 20 or Figure 21. Whilst the general interpretation of these analyses appears clinically plausible, the EAG questions the validity of the company's claim that "a clear PPS benefit was observed for patients receiving either abiraterone or enzalutamide" (CS page 156) based on these data. Caution is therefore advised in the interpretation of the PPS analysis, and for the modelling assumptions informed by these data.