NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Enzalutamide for treating hormone-sensitive metastatic prostate [ID1605]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Enzalutamide for treating hormone-sensitive metastatic prostate [ID1605]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website

1. **Company submission from Astellas**
2. **Clarification questions and company responses**
3. **Patient group, professional group and NHS organisation submission from:**
   a. **Tackle Prostate Cancer**
4. **Evidence Review Group report prepared by the Aberdeen HTA Group**
5. **Evidence Review Group report – factual accuracy check**
6. **Technical report**
7. **Technical engagement response from Astellas**
8. **Technical engagement responses from experts:**
   a. Dr Sree Rodda – clinical expert, nominated by the British Uro-oncology Group
9. **Technical engagement responses from consultees and commentators**:
   a. Janssen
10. **Evidence Review Group critique of company response to technical engagement** prepared by the Aberdeen HTA Group
11. ***Company additional evidence (post April 2020 committee meeting)***
    - ***SMPC***
    - ***Final CHMP opinion***
12. **Evidence Review Group critique of company additional evidence**

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

Enzalutamide with ADT for treating metastatic hormone-sensitive prostate cancer [ID1605]

Document B

Company evidence submission

November 2019

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List of abbreviations and definitions

Abbreviation	Full name or description
$	Dollar
€	Euro
1L	First-line therapy
2L	Second-line therapy
#	Number
AA	Anti-androgen
AB	Androgen blockade
ABI	Abiraterone
ACE	Adult comorbidity evaluation
ADT	Androgen deprivation therapy
AE	Adverse events
AiC	Akaike information criterion
ALT	Alanine aminotransferase
ANZUP	Australian and New Zealand Urogenital and Prostate Cancer Trials Group
APA	Apalutamide
AR	Androgen receptor
AST	Aspartate aminotransferase
BHA	Butylated hydroxyanisole
BHT	Butylated hydroxytoluene
BiC	Bayesian information criterion
BMI	Body mass index
BNF	British National Formulary
BPI-SF	Brief Pain Inventory-Short Form
BSC	Best supportive care
BUS	Buserelin
CAB	Cabazitaxel
CAB/MAB	Combined/maximum androgen blockade
CE	Cost effectiveness
CEA	Cost-effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CI	Confidence interval
cPFS	Clinical progression-free survival
CR	Complete response
CrI	Credible interval
CRPC	Castration-resistant prostate cancer
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
Cum.	Cumulative
DAR	Darolutamide
DB	Double-blind
DCS	Dual chamber pre-filled syringe
DEG	Degarelix
DIC	Deviance information criterion

Abbreviation	Full name or description
DNA	Deoxyribonucleic acid
DOC	Docetaxel
DSMB	Data and Safety Monitoring Board
DSU	Decision Support Unit
E	Number of events
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
e.g.	For example
EMA	European Medicines Agency
eMIT	Electronic market information tool
ENZA	Enzalutamide
EORTC QLQ C30	European Organisation for Research and Treatment of Cancer Core quality of life questionnaire
EQ-5D-3L/5L	EuroQol 5 item preference-based measure of health (3 level /5 level)
ER	Emergency room
ERG	Evidence Review Group
EU	European Union
FACT-P	Functional Assessment of Cancer Therapy – Prostate
FE	Fixed effect
FFS	Failure-free survival
FLU	Flutamide
FU	Follow-up
G-CSF	Granulocyte colony-stimulating factor
GOS	Goserelin
GP	General practitioner
Hb	Haemoglobin
HCP	healthcare practitioner
HEOR	Health economics and outcomes research
HK	Hong Kong
HR	Hazard ratio
HRG	Healthcare resource group
HRk	High-risk
HRPC	Hormone-relapsed prostate cancer
HRQoL	Health-related quality of life
HRU	Health-care resource utilisation
HSPC	Hormone-sensitive prostate cancer
HTA	Health technology assessment
HVD	High volume disease
ICER	Incremental cost effectiveness ratio
ICR	Independent central review
i.e.	in other words
IEC	Independent Ethics Committee
IRB-IEC	Institutional Review Board
IRT	Interactive response technology
ITC	Indirect treatment comparison
ITT	Intent to treat
KM	Kaplan-Meier

Abbreviation	Full name or description
LA	Long acting
LCI	Lower confidence interval
LEU	Leuprorelin
LHRH	Luteinizing hormone-releasing hormone
LHRHa	Luteinizing hormone releasing hormone analogue
LOS	Length of stay
LR	Literature review
LRk	Low risk
LVD	Low volume disease
LY	Life year
LYG	Life-year gained
m	Metastatic
M0	Non-metastatic
M1	Metastatic
MAB	Maximum androgen blockade
max	Maximum
mCRPC	Metastatic castration-resistant prostate cancer
MFS	Metastasis-free survival
mHNPC	Metastatic hormone-naive prostate cancer
mHRPC	Metastatic hormone-relapsed prostate cancer
mHSPC	Metastatic hormone sensitive prostate cancer
min	Minimum
mL	Millilitre
MN	Multinational
mOS	Median overall survival
mPC	Metastatic prostate cancer
MPFS	Metastatic progression-free survival
MRI	Magnetic resonance imaging
NA	Not available / not applicable
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ND	Newly diagnosed
NDHRk	Newly diagnosed high-risk
NE	Not estimable
NEL	Non-elective long stay
ng	nanogram
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIL	Nilutamide
nm	Non-metastatic
NMA	Network meta-analysis
nmCRPC	Non-metastatic castration-resistant prostate cancer
nmHRPC	Non-metastatic hormone-relapsed prostate cancer
nmHSPC	Non-metastatic hormone-sensitive prostate cancer
NR	Not reported
NSAA	Non-steroidal anti-androgen
NYR	Not yet reached

Abbreviation	Full name or description
OL	Open label
OP	Open-label period
ORC	Orchiectomy
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PartSA	Partitioned survival analysis
PCa	Prostate cancer
PCWG2	Prostate Cancer Clinical Trials Working Group 2
PD	Progressive disease
PFS	Progression-free survival
Ph	Phase
PH	Proportionality of hazards
PICOS	Population, intervention, comparator, outcomes, study design
PLA	Placebo
PR	Partial response
PRED	Prednisone
PSA	Prostate-specific antigen
PSADecR	Rate of PSA decline to <0.2 ng/mL
PrePS	Pre-progression survival
PRO	Patient-reported outcomes
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QC	Quality control
QLQ-PR25	Quality of Life Questionnaire-Prostate 25 Module
QOL	Quality of life
RAD	Radium-223
RCT	Randomised controlled trial
RE	Random effect
REC	Recurrent
RECIST 1.1	Response Evaluation Criteria in Solid Tumours version 1.1
RMB	Renminbi
RMP	Risk management plan
rPD	Radiographic progressive disease
rPFS	Radiographic progression-free survival
RT	Radiotherapy
SA	Sensitivity analysis
SAE	Serious adverse event
SBRT	Stereotactic body radiation therapy
SE	Standard error
SF	Short Form
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SOC	Standard of care
SR	Sustained release
SSE	Symptomatic skeletal event

Abbreviation	Full name or description
SUSAR	Suspected unexpected serious adverse reaction
TCR	Time to castration resistance
TEAE	Treatment-emergent adverse event.
TINAT/TTNAnti	Time to initiation of new antineoplastic therapy
TNC	Too numerous to count
TPSA/TTPP	Time to PSA progression
TPT	Triptorelin
TSSE	Time to symptomatic skeletal event
TTD	Time to treatment discontinuation
TTO	Time trade-off
TTUri	Time to deterioration in urinary symptoms from QLQ-PR25.
Tx	Treatment
TURP	Transurethral Resection of the Prostate
UK	United Kingdom
ULN	Upper limit of normal
US	United States
VAS	Visual analogue scale
vs	Versus
WBBS	Whole-body bone scan
WTP	Willingness to pay

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

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for the intended indication which is "*the treatment of adult men with metastatic hormone-sensitive prostate cancer*"[1]. This indication includes patients who are diagnosed at the metastatic stage (i.e., newly diagnosed or *de novo* patients) and patients with a previous history of non-metastatic hormone-sensitive prostate cancer (nmHSPC) who have progressed to metastatic hormone-sensitive prostate cancer (mHSPC; i.e., recurrent). Newly diagnosed patients include patients who have not yet received androgen deprivation therapy (ADT) or any other hormonal treatment (these patients are also referred to as hormone-naive prostate cancer [HNPC]) and patients who may have already initiated ADT and are still responding to it.

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 metastatic hormone-sensitive prostate cancer (mHSPC)	As per final scope	NA
Intervention	Enzalutamide in combination with androgen deprivation therapy (ADT)	As per final scope	NA
Comparator(s)	• Androgen deprivation therapy alone (including orchidectomy, luteinising hormone-releasing hormone agonist therapy) or monotherapy with bicalutamide • Docetaxel with androgen deprivation therapy For people with newly diagnosed high-risk disease: • Abiraterone with prednisone or prednisolone and androgen deprivation therapy (subject to ongoing NICE appraisal)	• Androgen deprivation therapy alone (including orchidectomy, luteinising hormone-releasing hormone agonist therapy) or monotherapy with bicalutamide • Docetaxel with androgen deprivation therapy	At the time of this submission, NICE was still assessing the abiraterone submission in patients with newly diagnosed high-risk mHSPC. Abiraterone is not standard of care or recommended in the NICE guidance[2] in England or Wales and therefore, the Company does not consider abiraterone a relevant comparator for enzalutamide.
Outcomes	The outcome measures to be considered include: • Time to prostate-specific antigen (PSA) progression • Progression-free survival (PFS) • Overall survival (OS) • Adverse effects of treatment • Health-related quality of life (HRQoL)	The list of outcomes presented in this submission is as follows: • Time to prostate-specific antigen (PSA) progression • Progression-free survival (PFS) • Overall survival (OS) • Time to treatment discontinuation (TTD) • Time to new antineoplastic therapy (TINAT) • Adverse effects of treatment • Health-related quality of life (HRQoL)	The list of outcomes in the final scope is not exhaustive. Given the disease evolution of patients with mHSPC and proposed positioning of enzalutamide in this setting, additional outcomes such as time to treatment discontinuation or time to new antineoplastic therapy are relevant for the enzalutamide health economic model.

Abbreviations: ADT: androgen deprivation therapy; HRQoL: health-related quality of life; mHSPC: metastatic hormone-sensitive prostate cancer; NA: not applicable; OS: overall survival; PFS: progression-free survival; PSA: prostate specific antigen; TINAT: time to new antineoplastic therapy; TTD: time to treatment discontinuation.

B.1.2 Description of the technology being appraised

An overview of enzalutamide is provided in Table 2.

Table 2 Technology being appraised

UK approved name and brand name	Brand name: XTANDI®. Approved name: Enzalutamide (formerly known as MDV3100) Therapeutic class: The World Health Organisation International Working Group for Drug Statistics Methodology has assigned the following therapeutic class to enzalutamide[3]: • L: Antineoplastic and immunomodulating agents • L02: Endocrine therapy • L02B: Hormone antagonists and related agents • L02BB: Anti-androgens • L02BB04: Enzalutamide.
Mechanism of action	Androgens and androgen receptor (AR) signalling pathways are regarded as the main oncogenic drivers in prostate carcinogenesis; as such, they represent a logical target for prostate cancer therapy[4]. Prostate cancer is androgen-sensitive and responds to inhibition of AR signalling. Despite low or even undetectable levels of serum androgen, AR signalling continues to promote disease progression. Stimulation of tumour cell growth via the AR requires nuclear localisation and DNA binding[1]. Enzalutamide is an AR signalling inhibitor that targets the AR signalling pathway[5, 6]. Enzalutamide binds AR with a 5–8-fold greater relative affinity than bicalutamide (a first-generation anti-androgen)[6]. Also, in contrast to bicalutamide, enzalutamide shows no evidence of AR agonist activity[6]. Enzalutamide has a novel mechanism of action that directly and potently inhibits three stages of the AR signalling pathway[1, 5, 6]: • Blocking androgen binding • Inhibiting nuclear translocation • Impairing DNA binding, inhibiting gene transcription.
Marketing authorisation	In Europe, enzalutamide has been granted market authorisation in: • June 2013 for treatment of adult men with metastatic CRPC (mCRPC) whose disease has progressed on or after docetaxel therapy (i.e., post-chemotherapy setting) • November 2014 for treatment of adult men with mCRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated (i.e., chemotherapy naïve setting) • November 2018 for the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (nmCRPC). A Type II variation has been submitted to the European Medicines Agency (EMA) to include market authorisation for the treatment of adult men with mHSPC. Final authorisation in this

	indication is expected by June or July 2020. This is the indication of relevance for this submission. Enzalutamide has regulatory approval throughout Europe, as well as in several other countries including the US, Canada and Australia for the treatment of mCRPC patients in the post-chemotherapy and chemotherapy-naïve settings, and for nmCRPC patients.
Indications and any restriction(s) as described in the Summary of product characteristics (SmPC)	At time of submission, in Europe enzalutamide has market authorisation for the following indications[1]: • "*Treatment of adult men with mCRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated*" • "*Treatment of adult men with mCRPC whose disease has progressed on or after docetaxel therapy*" • *"Treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (nmCRPC)"* EMA authorisation for the indication of relevance here (i.e., mHSPC) is expected by June or July 2020. A risk management plan (RMP) was developed for enzalutamide in the post-chemotherapy setting and extended to include the treatment of chemotherapy-naïve mCRPC and high-risk nmCRPC patients. This RMP is expected to be further extended to include the treatment of mHSPC patients. Astellas is undertaking active pharmacovigilance for the following safety concerns: seizures, falls, non-pathological fractures and ischemic heart disease.
Method of administration and dosage	Enzalutamide is formulated as 40 mg tablets. The tablet formulation is licensed in Europe and is available in the UK. The enzalutamide dose for mHSPC in the licence applications is a single daily oral dose of 160 mg (as four × 40 mg tablets[1])
Additional tests or investigations	This indication for enzalutamide does not require any additional tests beyond what is currently done for patients with prostate cancer e.g. PSA levels and tests to determine the extent of the disease[1]. Identification of patients eligible for enzalutamide does not require any additional tests. PSA monitoring test and imaging tests are performed for staging of disease and identification of metastatic disease; they are standard within UK clinical practice[2].
List price and average cost of a course of treatment	The current UK list price is £2,734.67 per pack (112 units of 40 mg)[7]. With a daily dose of 160 mg, daily UK treatment costs are £97.64, based on the UK list price. The average cost of an entire course of enzalutamide in mHSPC based on the ARCHES median time to treatment discontinuation ([redacted]) would be £[redacted]
Patient access scheme (if applicable)	[redacted]

Abbreviations: AR: androgen receptor; CRPC: castration-resistant prostate cancer; DNA: deoxyribonucleic acid; EMA: European Medicines Agency; mCRPC: metastatic castration-resistant prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; nmCRPC: non-metastatic castration-resistant prostate cancer; PSA: prostate-specific antigen; RMP: risk management plan; UK: United Kingdom; US: United States.

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

B.1.3.1 Metastatic hormone-sensitive prostate cancer

Prostate cancer is the second most commonly diagnosed cancer (excluding non-melanoma skin cancer) and the fifth most common cancer-related cause of death in men worldwide[8]. Prostate cancer progresses through a series of characteristic and well-described clinical stages (Figure 1).

Prostate cancer is classified based on two criteria. The first one is its responsiveness to hormonal therapy (i.e., its androgen-dependent status), which forms the basis for several treatment options. Stages that are responsive to ADT or surgical castration are referred to as HSPC[9]. However, as prostate cancer progresses, further genetic mutations can affect the androgen receptors and disease progression occurs without the presence of androgen[5] or in spite of treatment related androgen receptor blockade. As a result, ADT becomes less effective, at which point serum PSA levels begin to rise again. This stage is known as hormone-relapsed (HRPC)[10] and is defined as a minimum PSA level of 1.0 ng/mL, a rising PSA that is ≥2 ng/mL higher than the nadir PSA with this rise being ≥25% over the nadir PSA and castrate levels of testosterone ≤50 ng/dL (1.7 nmol/L).

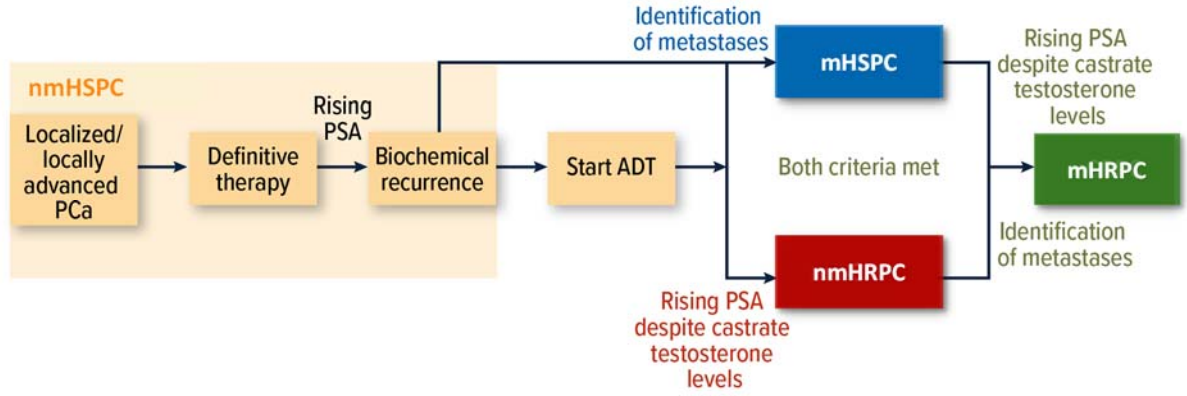
Prostate cancer is further classified based on the extent of the disease as localised, locally advanced, or metastatic. Patients with localised prostate cancer may receive radical prostatectomy or radiotherapy (definitive therapy in Figure 1). If the cancer is diagnosed at the metastatic stage, the patient is considered to have newly diagnosed or de novo mHSPC. A patient with localised or locally advanced prostate cancer is considered to have nmHSPC.

In patients with nmHSPC, the disease may progress to three different disease stages, depending on the prior treatment strategy[11, 12] (Figure 1):

- mHSPC: A patient with nmHSPC may progress to mHSPC after local therapy (i.e., prostatectomy or radiotherapy), wherein the disease spreads to other parts of the body, with a predilection for bone. At this stage, the prostate cancer is sensitive to ADT. In this document, this stage is also referred to as recurrent mHSPC.
- Non-metastatic HRPC (nmHRPC): A patient with nmHSPC who has been treated with ADT may have rising PSA (biochemical recurrent) and may progress to nmHRPC, in which the effectiveness of ADT is reduced.
- Metastatic HRPC (mHRPC): A patient with nmHSPC who has been treated with ADT may progress to mHRPC. In this stage, the ADT has become less effective, the cancer is castration resistant, and the cancer has spread to distant sites in the body.

Not all patients with prostate cancer will progress through every stage of the disease.

Figure 1. Stages of prostate cancer for those diagnosed at non-metastatic stage



Source: Adapted from Anantharaman & Small 2017[13].
Abbreviations: ADT: androgen-deprivation therapy; mHRPC: metastatic hormone-relapsed prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; nmHRPC: non-metastatic hormone-relapsed prostate cancer; nmHSPC: non-metastatic hormone-sensitive prostate cancer; PCa: prostate cancer; PSA: prostate-specific antigen. Note that patients can present with mHSPC and nmHSPC.

In a study of 1,643 patients in the UK with localised prostate cancer, 3.8% (n = 62) developed metastases within 10 years[14]. The rate of progression to metastases was 6.3 per 1,000 person-years in patients who underwent active surveillance for their disease, 3.0 per 1,000 person-years in patients who underwent radiotherapy, and 2.4 per 1,000 person-years in patients who underwent surgery[14]. Although it is not known how long patients spend in each stage, on average, within 12 months of developing mHSPC, most patients progress toward mHRPC on ADT alone[15-17].

Prostate cancer can spread to other parts of the body, with a predilection for bone, which is the most common site of distant tumour spread. Other types of metastases include visceral and non-visceral.

Development of metastases is associated with potentially serious complications for patients. Health-related quality of life (HRQoL) of patients deteriorate upon the development of metastases and the symptom burden which is initially low in these patients increases[18]. Patients with bone metastases are at high risk of skeletal-related events (SREs), including spontaneous fracture and spinal cord compression, which are a source of significant pain and decreased HRQoL[19].

In addition to bone, prostate cancer can also metastasise other sites including lymph nodes and internal organs (visceral metastases). Visceral disease, commonly including liver and lung metastases, is a negative prognostic factor[20]; visceral disease is associated with reduced survival[21]. Visceral disease is considered high volume disease (HVD).

Prognosis in mHSPC patients is dependant not only on the disease volume but also on whether the disease is newly diagnosed/de novo or recurrent. Francini *et al*[22] used the prospectively collected Dana-Farber Cancer Institute database to conduct a retrospective cohort study of consecutive patients with mHSPC treated with ADT between 1990 and 2013 and assessed overall survival (OS) based on time of metastatic disease occurrence (recurrent or newly diagnosed) and volume of disease (low volume disease [LVD] or HVD). A total of 436 patients with mHSPC were included in the analysis, 192 were recurrent (i.e.,

had had previous local therapy) and 244 were newly diagnosed at time of initiation of ADT. Of the 436 patients, 215 (49.3%) had HVD. The median OS was worse for newly diagnosed compared to recurrent patients, with newly diagnosed HVD patients having the worse OS[22].

Table 3 Overall survival in patients with recurrent or newly diagnosed mHSPC by volume of disease

Groups	N (% Events)	N = 436 (%)	5 Years OS, (%) (SE)	Median OS, Months (95% CI)	HR (95% CI)	*P* Trend	Log-Rank *P* Value
REC/LVD	125 (50)	125 (29)	74 (4.2)	92.4 (80.4-127.2)	1	< 0.0001	< 0.0001
REC/HVD	67 (75)	67 (15)	42 (6.2)	55.2 (44.4-80.4)	1.90 (1.31-2.75)		
ND/LVD	96 (70)	96 (22)	43 (5.2)	51.6 (48.0-78.0)	1.64 (1.16-2.31)		
ND/HVD	148 (84)	148 (34)	37 (4.0)	43.2 (37.2-56.4)	2.48 (1.83-3.36)		

Source: Francini *et al*[22]
P trend: 1 degree of freedom (df) Wald test P value to indicate the (trend) association. Log-rank test (score test) P value to assess the heterogeneity of the risk groups.
Abbreviations: CI: confidence interval; HR: hazard ratio; HVD: high-volume disease; LVD: low-volume disease; mHSPC: metastatic hormone-sensitive prostate cancer; ND: newly diagnosed; OS: overall survival; REC: recurrent; SE: standard error.

Depending on the number and site of metastases, mHSPC can be classified as HVD or LVD. However, the definition of HVD/LVD differs between studies, rendering comparison across studies difficult. There is no consensus regarding the extent of the disease that determines HVD vs. LVD. In the enzalutamide studies (ARCHES[23] and ENZAMET[24]), HVD was defined, using the CHAARTED criteria[17], as metastases involving the viscera or, in the absence of visceral lesions, 4 or more bone lesions, at least 1 of which was in a bony structure beyond the vertebral column and pelvis.

Metastatic HSPC can also be classified as high- or low-risk disease. High-risk factors associated with poor prognosis include a Gleason score ≥ 8 (on a scale of 2-10, with higher scores indicating more aggressive disease), at least three bone lesions, and the presence of measurable visceral metastasis[25].

B.1.3.2 Position of enzalutamide in the treatment pathway

NICE guidelines (NG131) recommend docetaxel plus ADT for people with newly diagnosed mHSPC who do not have significant comorbidities[2]. All other patients should be treated with ADT alone either surgically or with a luteinizing hormone-releasing hormone (LHRH) agonist. Treatment with docetaxel should start within 12 weeks of starting ADT.

NICE does not recommend combined/maximum androgen blockade (CAB/MAB) as a first-line treatment for people with mHSPC. However, patients should be offered monotherapy with bicalutamide (150 mg) if the patient is willing to accept the high risk of gynaecomastia with the aim of retaining sexual function[2]. Monotherapy with bicalutamide has not shown a survival benefit[2].

Enzalutamide is expected to gain marketing authorisation for the treatment of all mHSPC patients regardless of whether they are newly diagnosed or recurrent and also independent of the metastatic disease volume. Given the treatment benefit of enzalutamide over ADT alone or CAB/MAB in the two phase III enzalutamide randomised controlled trials (RCTs), the favourable results of the network meta-analysis (NMA) and the administration

advantages (oral) and better safety profile vs docetaxel, enzalutamide is expected to be administered to mHSPC patients regardless of risk level or metastatic disease volume in the UK.

B.1.4 Equality considerations

Astellas are not aware of any issues that this submission would raise regarding inequalities in NICE guidance or protocols of the treatment of patients with mHSPC.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR)[26] was conducted in May 2019 to identify clinical evidence regarding the efficacy and safety of enzalutamide and comparator drugs as outlined in the scope, and to inform an indirect treatment comparison (ITC). The SLR was conducted as part of due diligence to prepare for European HTA submissions including the NICE submission. The SLR aimed to identify all relevant efficacy and safety evidence for enzalutamide and all other treatment agents currently authorised in Europe for mHSPC patients or likely to gain market authorisation in this indication in the near future. However, only the comparators relevant to the decision problem (i.e., ADT alone and docetaxel) are presented in this submission.

The methodology used for the SLR including the search strategy, databases searched and selection criteria is detailed in appendix D. A summary of the inclusion and exclusion criteria is provided in Table 4.

In line with the above, the search strings used for the SLR were not specific for enzalutamide, ADT and docetaxel but also encompassed the following interventions: abiraterone, apalutamide, darolutamide, CAB/MAB, radiotherapy, and zoledronic acid. The scope of the SLR included both randomised and non-randomised trials, and all mHSPC patients.

Overall, 71 publications (41 studies) met the SLR selection criteria[26] (Figure 2) but only 21 publications covering 18 studies were deemed relevant for this submission. Identification of relevant studies was conducted by two experienced information specialists. Any discrepancies were discussed with a third specialist. The results for the studies with the comparator drugs relevant for this submission and the studies with CAB/MAB are presented in section B.2.9.

In addition, the databases used in the initial SLR (i.e., EMBASE and Cochrane) and the website of ESMO were searched on October 10, 2019 to identify any new relevant publications. These publications are not included in Figure 2 but are referred to when needed throughout this submission. No report was available at the time of submission for the SLR update conducted in October 2019.

Table 4 Selection criteria in the systematic literature review

PICOS	Inclusion criteria	Exclusion criteria
Population of interest	Adult patients (≥18 year) with mHSPC	Children
Interventions of interest	Enzalutamide	
Comparators of interest	ADT alone NSAA including bicalutamide, flutamide, nilutamide as monotherapy or as part of CAB/MAB Active surveillance (including placebo) Docetaxel	Therapies not standard of care or not yet at phase III setting in the mHSPC setting

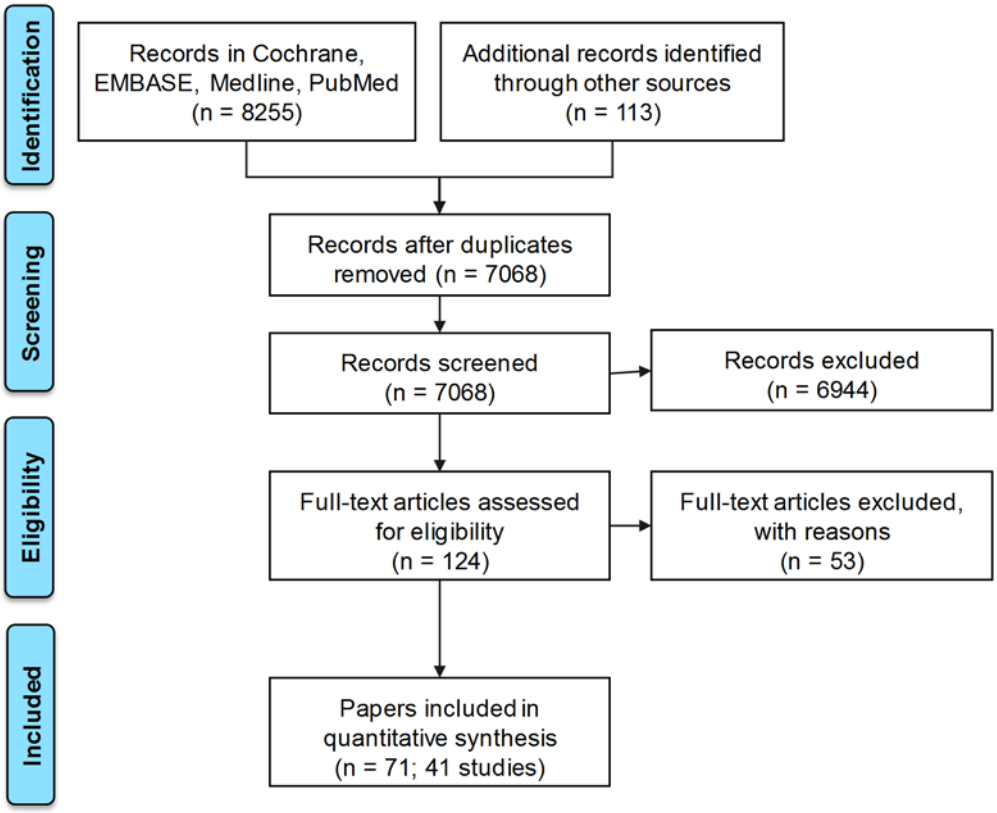
PICOS	Inclusion criteria	Exclusion criteria
	Abiraterone* Radiotherapy (for low volume disease only)* Zoledronic acid* Drugs at phase III at the time of the initial SLR: apalutamide, darolutamide (in combination with docetaxel)*	
Outcomes of interest	PFS OS Time to first SSE Time to castration resistance Time to initiation of new antineoplastic therapy Time to PSA progression (≥ 2 ng/mL) PSA undetectable rate (< 0.2 ng/mL) ORR Time to pain progression Time to treatment discontinuation Adverse events.	
Study design of interest	Meta-analyses, systematic literature reviews, RCTs, non-randomised studies, observational studies, case-cohort studies, registries	Preclinical and phase I studies, prognostic studies, case reports, reviews/ expert opinion, commentaries/letters

Source: Astellas mHSPC SLR report[26]

*Not relevant for this submission.

Abbreviations: ADT: androgen deprivation therapy; CAB/MAB: combined/maximum androgen blockade; mHSPC: non-metastatic castration resistant prostate cancer; NSAA: non-steroidal anti-androgens; ORR: overall response rate; OS: overall survival; PICOS: population, intervention, comparator, outcome, study design; PSA: prostate-specific antigen; RCT: randomised controlled trials; rPFS: radiographic progression-free survival; SOC: standard of care; SSE: symptomatic skeletal event.

Figure 2 PRISMA flow diagram with the identified studies



Source: Astellas mHSPC SLR report[26]

B.2.2 List of relevant clinical effectiveness evidence

The SLR[26] identified two randomised comparative phase III trials conducted with enzalutamide plus ADT in adults with mHSPC:

- ARCHES (NCT02677896): Multinational, double-blind, randomised, placebo-controlled, phase III trial that evaluated the efficacy and safety of enzalutamide plus ADT vs placebo plus ADT in patients with mHSPC[27]. This study enrolled 1,150 patients with either de novo or recurrent mHSPC. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients could have received up to 6 cycles of docetaxel prior to randomisation.
- ENZAMET (NCT02446405): Multinational, open-label, randomised, phase III trial that determined the effectiveness of enzalutamide plus ADT vs conventional non-steroidal anti-androgens (NSAA) plus ADT (i.e., CAB/MAB)[28]. This study enrolled 1,125 patients with mHSPC and an ECOG performance score of 0 - 2. Patients could have receive up to 2 cycles of docetaxel for metastatic disease prior to randomisation. In addition, patients were allowed to receive up to 6 cycles of concomitant docetaxel, as long as the decision to use early docetaxel was made and specified prior to randomisation and the patients had received no more than 2 cycles prior to randomisation. Given the current use of enzalutamide in clinical practice (with ADT only) and the expected label indication[1], the combination of enzalutamide plus ADT and docetaxel is not considered a relevant intervention or comparator for this

submission. Only data for patients not receiving concomitant docetaxel are provided in this submission unless stated otherwise.

ARCHES and ENZAMET data presented in this submission are drawn from both published and unpublished sources:

- ARCHES:
    - Published article: Armstrong *et al* in the Journal of Clinical Oncology[27] is the main publication. In addition, ARCHES-related data (either clinical or HRQoL) have been presented at different congresses: Armstrong *et al* presented at ASCO 2019[29], and Stenzl *et al* presented at ASCO 2019[30] and ESMO 2019[31]
    - Unpublished: ARCHES Clinical Study Report[23] and its addendum[32], and the PRO report[33].
- ENZAMET:
    - Published article: Davis *et al* in the New England Journal of Medicine[28] is the main publication. In addition, ENZAMET-related data have been presented at ASCO 2019[34] and ESMO 2019[35]
    - Unpublished: ENZAMET Clinical Study Report[24].

The SLR[26] also identified an additional randomised phase II trial (NCT02058706) assessing enzalutamide plus ADT vs bicalutamide plus ADT in adults with mHSPC. However, this study was stopped early and no efficacy results have been published[36].

The study designs of the ARCHES and ENZAMET trials are summarised in Table 5.

Table 5 ARCHES and ENZAMET trial design

Study	ARCHES		ENZAMET
Study design	Multinational, phase III, randomised, double-blind, placebo-controlled, efficacy and safety study followed by an (optional) open-label extension period.		Multinational, phase III, randomised, open-label efficacy study.
Population	Adult patients with mHSPC.		Adult patients with mHSPC.
Intervention(s)	Enzalutamide plus ADT. Enzalutamide was given orally as a daily dose of 160 mg/day in 4 capsules (40 mg each). All patients were required to receive background therapy with ADT consisting of either bilateral orchiectomy or an LHRH agonist or antagonist, which was to be maintained throughout the study.		Enzalutamide plus ADT. Enzalutamide was given orally as a daily dose of 160 mg/day in 4 capsules (40 mg each). All patients were treated with a LHRHa or surgical castration. Patients were also allowed up to 6 cycles of concomitant docetaxel (75 mg/m^2), if the decision to use early docetaxel was made and specified prior to randomisation and the patients received no more than 2 cycles prior to randomisation. ADT was to be given continuously in this study.
Comparator(s)	Enzalutamide-matching placebo plus ADT. Placebo was administered orally as 4 capsules once daily ADT consisted in the same treatment as in the intervention arm i.e., either bilateral orchiectomy or an LHRH agonist or antagonist to be maintained throughout the study.		Standard NSAA (bicalutamide 50 mg daily, nilutamide 150 mg daily or flutamide 250 mg three times a day) plus ADT. ADT consisted of an LHRH agonists or bilateral orchiectomy. ADT was to be given continuously in this study.
Indicate if trial supports application for marketing authorisation	Yes	X	X
	No		
Indicate if trial used in the economic model	Yes	X	X
	No		
Rationale for use/non-use in the model	The study provides evidence of the efficacy and safety of enzalutamide plus ADT vs placebo plus ADT in mHSPC patients.		The study provides evidence of efficacy of enzalutamide plus ADT vs standard NSAA plus ADT in mHSPC patients.

Study	ARCHES	ENZAMET
Reported outcomes specified in the decision problem	• Time to prostate-specific antigen progression • Progression free survival • Overall survival • Adverse effects of treatment • Health-related quality of life.	• Time to prostate-specific antigen progression • Progression free survival • Overall survival • Adverse effects of treatment • Health-related quality of life.
All other reported outcomes	• Time to first symptomatic skeletal event • Time to castration resistance • Time to start of new antineoplastic therapy • PSA response • Objective response rate • Time to treatment discontinuation.	• Time to treatment discontinuation.

Source: ARCHES Clinical Study Report[23], ENZAMET Clinical Study Report[24].

Abbreviations: ADT: androgen deprivation therapy; LHRH: luteinizing hormone releasing hormone; LHRHa: luteinizing hormone releasing hormone analogue; mHSPC: metastatic hormone-sensitive prostate cancer; NSAA: nonsteroidal antiandrogen; SOC: standard of care.

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

B.2.3.1 Methodology

The study design of ARCHES and ENZAMET are summarised in Table 6.

Table 6 ARCHES and ENZAMET methodology

Trial no. (acronym)	2015-003869-28 (ARCHES)	2014-003190-42 (ENZAMET)
Location	The study was conducted at a total of 204 study sites in 24 countries in North and South America, Europe, the Asia-Pacific region and Israel. Overall, 685 patients were recruited in Europe (enzalutamide: n=341; placebo: n=344) of [redacted].	The study was conducted at a total of 79 study sites in 6 countries (Australia, Canada, Ireland, New Zealand, UK and the US). Overall, 195 patients were recruited in Europe (enzalutamide: n=102; placebo: n=93) of which [redacted].
Design	ARCHES was a multinational phase III, randomised, double-blind, placebo-controlled efficacy and safety study of enzalutamide plus ADT vs placebo plus ADT in patients with mHSPC. Patients could have received up to 6 cycles of docetaxel prior to randomisation. The protocol prespecified an open-label extension period if ARCHES resulted in positive outcomes. The open-label extension phase was ongoing at the time of this submission.	ENZAMET was a multi-centre, open-label, randomised, phase III study to determine the effectiveness of enzalutamide vs a conventional NSAA, when combined with a LHRHa or surgical castration, as first line ADT. Patients could have received up to 2 cycles of docetaxel prior to randomisation and in addition, they were also allowed up to 6 cycles of concomitant docetaxel (75 mg/m^2), as long as the decision to use early docetaxel was made and specified prior to randomisation and the patients received no more than 2 cycles prior to randomisation.
Duration of study	The first subject first visit was on 21 March 2016. The data presented here corresponds to the cut-off date of 14 October 2018 when the study was read-out. However, patients are still being followed-up and data collected.	The first subject first visit was on 31 March 2014. The data presented here corresponds to the cut-off date of 28 February 2019 when the study was read-out.
Method of randomisation	Randomisation was performed via the IRT system. Patients were randomly assigned in a 1:1 ratio to receive either enzalutamide plus ADT (160 mg orally once daily as four 40-mg capsules or tablets) or matched placebo. The randomisation was stratified by volume of disease (low vs high) and prior docetaxel therapy (no prior docetaxel, 1 to 5 cycles, 6 cycles) for prostate cancer.	Randomisation was performed via a central randomisation system. Patients were randomly assigned in a 1:1 ratio to receive either enzalutamide plus ADT (160 mg orally once daily as four 40-mg capsules or tablets) or ADT with conventional NSAA (bicalutamide 50 mg daily, nilutamide 150 mg daily or flutamide 250 mg three times a day). The randomisation was stratified for volume of disease (high vs low), study site, comorbidities (ACE-27 0 to 1 vs 2 to 3), use of antiresorptive therapy (yes vs no) and planned use of docetaxel (yes vs no).
Method of blinding (care provider, patient and outcome assessor)	All patients, investigators, clinical staff and the sponsor's study management team were blinded to treatment assignment. The randomisation list and study medication blind were maintained by the IRT system. Unblinding of the study treatment assignment could be performed if the patient discontinued from	There was no blinding in this open-label study.

Trial no. (acronym)	2015-003869-28 (ARCHES)	2014-003190-42 (ENZAMET)
	the study treatment due to disease progression (must have been confirmed by central review) and, in the judgment of the investigator, this information was necessary to determine the next course of therapy. Prior to unblinding in this scenario, the investigator was to contact the sponsor's medical monitor. The sponsor could break the treatment code for patients who experienced a SUSAR, to determine if the individual case or a group of cases required expedited regulatory reporting. The Individual Emergency Code was to be provided to the limited staff responsible for breaking the codes for all SUSAR cases for reporting purposes.	
Intervention(s) (n=) and comparator(s) (n=)	ITT (n=1,150): • Enzalutamide + ADT: n=574 patients • Placebo + ADT: n=576 patients. Safety (n=1,146): • Enzalutamide: n=572 patients • Placebo: n=574 patients.	ITT (n=1,125): • Enzalutamide + ADT: n=563 patients (no concomitant DOC: n=309) • NSAA + ADT: n=562 patients (no concomitant DOC: n=313). Safety (n=1,121): • Enzalutamide + ADT: n=563 patients (no concomitant DOC: n=309) • NSAA + ADT: n=558 patients (no concomitant DOC: n=312).
Primary outcomes (including scoring methods and timings of assessments)	The primary efficacy endpoint of the study was rPFS based on central review in the ITT population and defined as objective evidence of rPD as assessed by ICR or death, as follows: Death from any cause within 24 weeks (2 scan cycles) from study drug discontinuation. rPD was defined by RECIST 1.1 for soft tissue disease or the appearance of 2 or more new bone lesions on bone scan. The date of rPD was the date the first objective evidence of rPD was documented. Unconfirmed disease progression on bone scan at week 13 was not considered as event. **Assessments:** Radiographic assessments (CT/MRI, bone scan and chest X-ray or chest CT/MRI) were performed at screening, Week 13 and	The primary endpoint was OS in the ITT population. OS was defined as the interval from the date of randomisation to the date of death from any cause. For patients without death, their last known alive date on or prior to the data cut-off date was used as a censoring date. **Assessments:** Screening/baseline visit occurred within 28 days prior to randomisation. Additional pre-specified visits occurred at Day 29 (± 7 days) and every 12 weeks (± 1 week) thereafter until clinical progression. A visit also took place at progression (PSA and/or clinical) and at end of treatment or treatment discontinuation was different from disease progression. Finally, patients were also seen at 30 to 42 days after treatment discontinuation and every 12 weeks (± 2 weeks) thereafter.

Trial no. (acronym)	2015-003869-28 (ARCHES)	2014-003190-42 (ENZAMET)
	every 12 weeks thereafter included in the long-term follow-up period.	
Secondary outcomes	The secondary endpoints were: • **OS:** defined as the time from randomisation to death from any cause. For patients who were alive at the time of the data cut-off date, OS time was censored on the last date the patient was known to be alive or the cut-off date, whichever occurred first. • **Time to first symptomatic skeletal event (SSE)*:** was defined as the time from randomisation to the occurrence of the first SSE (i.e., radiation to bone, surgery to bone, clinically apparent pathological bone fracture or spinal cord compression) prior to the data analysis cut-off date. • **Time to castration resistance:** was defined as the time from randomisation to the first castration resistance event. A castration resistance event was defined as the occurrence of rPD by ICR, PSA progression, or SSE, whichever occurred first, with castrate levels of testosterone (<50 ng/dL). • **Time to deterioration of QoL** (Functional Assessment of Cancer Therapy [FACT-P])**:** was defined as the time from the date of randomisation to the first date a decline from baseline of ≥10 points in the FACT-P total score was recorded. The FACT-P total score is the sum of all 5 subscale scores of the FACT-P questionnaire. • **Time to deterioration in urinary symptoms:** defined as the time interval between randomisation and the first deterioration in urinary symptoms at any postbaseline visit where deterioration of urinary symptoms corresponded to an increase in the urinary symptoms subscale score by ≥50% of the standard deviation observed in the urinary symptoms subscale score at baseline. • **Time to start of new antineoplastic therapy:** defined as the time from randomisation to the date of first dose administration of the first antineoplastic therapy.	The secondary endpoints were: • **PSA PFS (PCWG2 criteria):** defined as the interval from the date of randomisation to the date of first evidence of PSA progression, clinical progression, or death from any cause, whichever occurs first, or the date of last known follow-up without PSA progression. • **Clinical PFS (imaging, symptoms, signs):** defined as the interval from the date of randomisation to the date of first clinical evidence of disease progression or death from any cause, whichever occurs first, or the date of last known follow-up without clinical progression. • **Health related quality of life** (European organisation for research and treatment of cancer CORE 30 [EORTC QLQ C-30], Quality of life questionnaire-prostate 25 module [QLQ-PR-25] and EuroQoL group-5 dimensions-5 levels health questionnaire [EQ-5D-5L]) • **Health outcomes relative to costs** (incremental cost effectiveness ratio) – however, these data were not available at the time of submission

Trial no. (acronym)	2015-003869-28 (ARCHES)	2014-003190-42 (ENZAMET)
	• **Time to PSA progression (Prostate Cancer Clinical Trials Working Group 2 [PCWG2]:** calculated as the time from randomisation to the date of first observation of PSA progression where PSA progression is defined as a ≥25% increase and an absolute increase of ≥2 ng/mL above the nadir (i.e., lowest PSA value observed postbaseline or at baseline), which was confirmed by a second consecutive value at least 3 weeks later. • **PSA undetectable rate (<0.2 ng/mL):** defined as the percentage of patients with detectable (≥0.2 ng/mL) PSA at baseline, which became undetectable (<0.2 ng/mL) during study treatment. • **Objective response rate (ORR):** calculated as the percentage of ITT patients with measurable disease at baseline who achieved a complete response (CR) or partial response (PR) (unconfirmed responses) in their soft tissue disease using the RECIST 1.1 criteria, i.e., with CR or PR as best RECIST overall response. The RECIST overall time point response were assessed by the ICR from radiographic data/images provided by the investigators. ICR additionally considered image quality to perform their assessments. • **Time to pain progression:** was defined as time from randomisation to the first pain progression event, which was an increase of ≥30% from baseline in the average Brief Pain Inventory-Short Form (BPI-SF) item scores.	
Other efficacy endpoints	Other efficacy endpoints included: • Combined response (soft tissue lesions and bone lesions) • PSA reduction (≥50% or ≥90%) • Time to treatment discontinuation • EQ-5D (change from baseline, response rates, time to deterioration).	Other efficacy endpoints included: • Time to treatment discontinuation.
Safety endpoints	The safety endpoints were: • Treatment-emergent adverse events (TEAEs; frequency, severity, seriousness, and relationship to study drug)	The safety endpoint was: • Adverse events (AEs) (per national cancer institute common terminology criteria for adverse events [NCI-CTCAE] version 4.03).

Trial no. (acronym)	2015-003869-28 (ARCHES)	2014-003190-42 (ENZAMET)
	Assessments: Safety was collected at screening (after providing informed consent), at week 1, 5 and 13, and every 12 weeks thereafter until treatment discontinuation. Safety was also collected at the safety follow-up visit at 30 days after last dose of study drug.	**Assessments:** AEs and SAEs were collected and recorded from the date of randomisation to the safety follow-up visit (30-42 days after the last dose of study treatment).
Duration of follow-up	At the data cut-off date of 14 October 2018, the median follow-up period was 14.4 months.	At the data cut-off date of 28 February 2019, the median follow-up period was 33.8 months for the overall population.

Source: ARCHES Clinical Study Report[23]; ENZAMET Clinical Study Report[24]

*Symptomatic skeletal events (SSEs) are referred to as skeletal-related events (SREs)in Section B. SSEs and SREs are defined identically. However, the term SSE is maintained in Section B2 for consistency with how the endpoint was defined in ARCHES.

Abbreviations: ACE: Adult Comorbidity Evaluation; ADT: Androgen deprivation therapy; AE: Adverse events; ANZUP: Australian and New Zealand Urogenital and Prostate Cancer Trials Group; BPI-SF: Brief Pain Inventory-Short Form; CR: Complete response; CT; Computed tomography; CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; DOC: docetaxel; ECG: Electrocardiogram; EORTC QLQ C30: European Organisation for Research and Treatment of Cancer CORE 30; EQ-5D-5L: EuroQol 5 item preference-based measure of health (5L); FACT-P: Functional Assessment of Cancer Therapy – Prostate; ICR: Independent central review; IRT: Interactive Response Technology; ITT: Intent-to-treat; LHRHa: Luteinizing hormone releasing hormone analogue; mHSPC: metastatic hormone sensitive prostate cancer; MRI: Magnetic resonance imaging; NCI: National Cancer Institute; NSAA: Nonsteroidal antiandrogen; ORR: Objective response rate; OS: Overall survival; PR: Partial response; PSA: Prostate-specific antigen; QoL: quality of life; RECIST: Response Evaluation Criteria in Solid Tumours; rPD: radiographic disease progression; rPFS: radiographic progression-free survival; SSE: symptomatic skeletal event; SUSAR: suspected unexpected serious adverse reaction; TEAE: Treatment-emergent adverse events; UK: United Kingdom; US: United States.

B.2.3.1.1 ARCHES study design

The ARCHES study consisted of a double-blind treatment period followed by an open label period after study unblinding (Figure 3).

Double-blind treatment period:

After screening, patients were randomised in a 1:1 ratio to receive treatment with either enzalutamide plus ADT or, with placebo plus ADT (Figure 3A). Enzalutamide 160 mg and enzalutamide-matching placebo were administered orally as 4 capsules or tablets once daily. Treatment was continued as long as patients were tolerating enzalutamide until radiographic progression was documented or until the patients started an investigational agent or new therapy for treatment of prostate cancer or until any other discontinuation criterion was met. Patients remained on study treatment until radiographic progression was confirmed by independent central imaging review[23].

After treatment discontinuation, patients underwent long-term follow-up. Long-term follow-up assessments included monitoring for survival status, new antineoplastic therapies for prostate cancer and symptomatic skeletal events. Patients who discontinued study treatment without radiographic disease progression confirmed by central review, radiographic assessment continued every 12 weeks until radiographic progression event was confirmed by the central imaging independent reviewer or until the target number of progression events was reached, as assessed by an independent central review (ICR)[23].

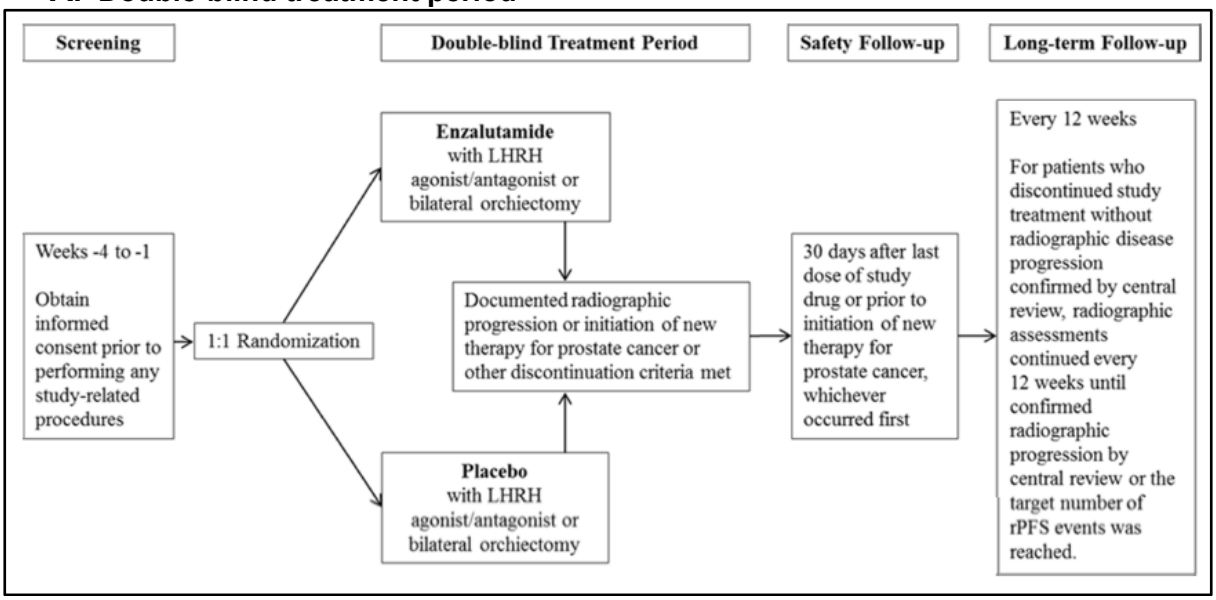
Throughout the study, safety and tolerability were assessed by the recording of adverse events (AEs), vital signs, physical examinations, 12-lead electrocardiograms (ECGs) and safety laboratory evaluations.

Open-label extension period:

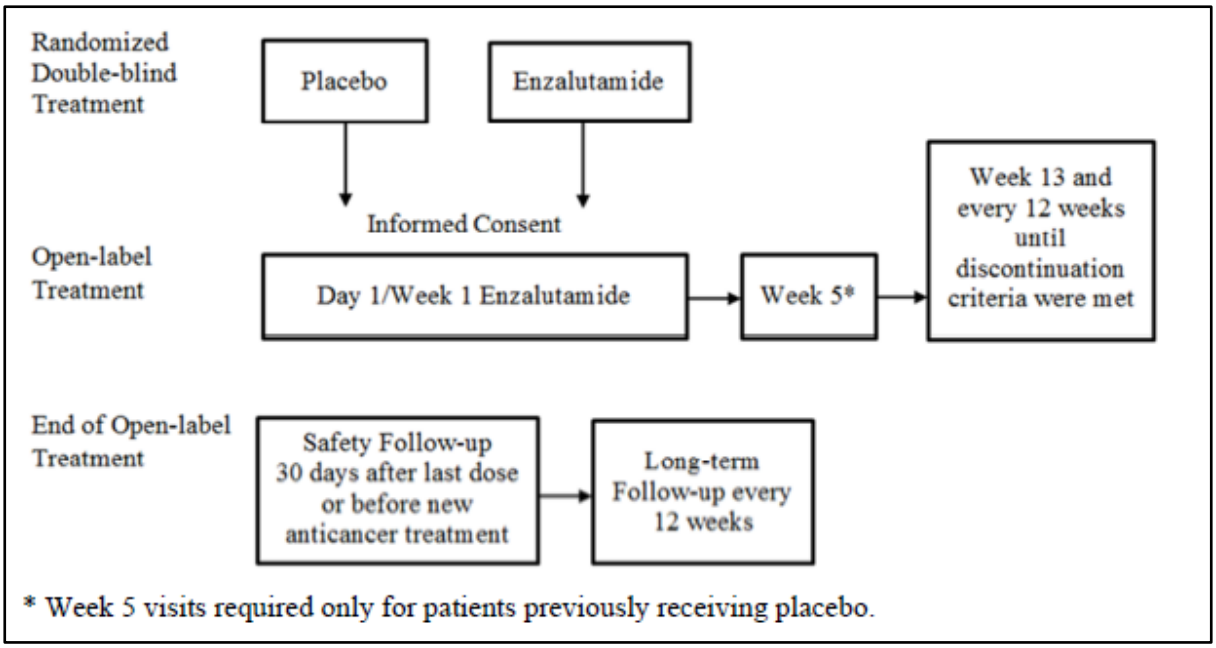
At the time of primary endpoint analysis and on the recommendation of the data safety monitoring board (DSMB) on study continuation, patients were eligible to transition to an optional open-label extension portion of the study (Figure 3B). In general, the extension study was to be performed using the same general approach as described for the double-blinded phase[23].

Figure 3 ARCHES study schematic

A. Double-blind treatment period



B. Open-label extension period



Source: ARCHES Clinical Study Report[23]
While on study drug, patients returned to the study site at weeks 5 and 13 and every 12 weeks thereafter. At week 5, general activities included brief physical examination, vital signs, clinical laboratory and PSA testing, assessment of ECOG performance status, adverse events, concomitant medications reviews and study drug dispensing. At week 13 and every 12 weeks thereafter until treatment discontinuation, general activities included radiographic assessments (including a chest x-ray or CT/MRI), testosterone testing and completion of quality of life questionnaires in addition to the activities performed at week 5.

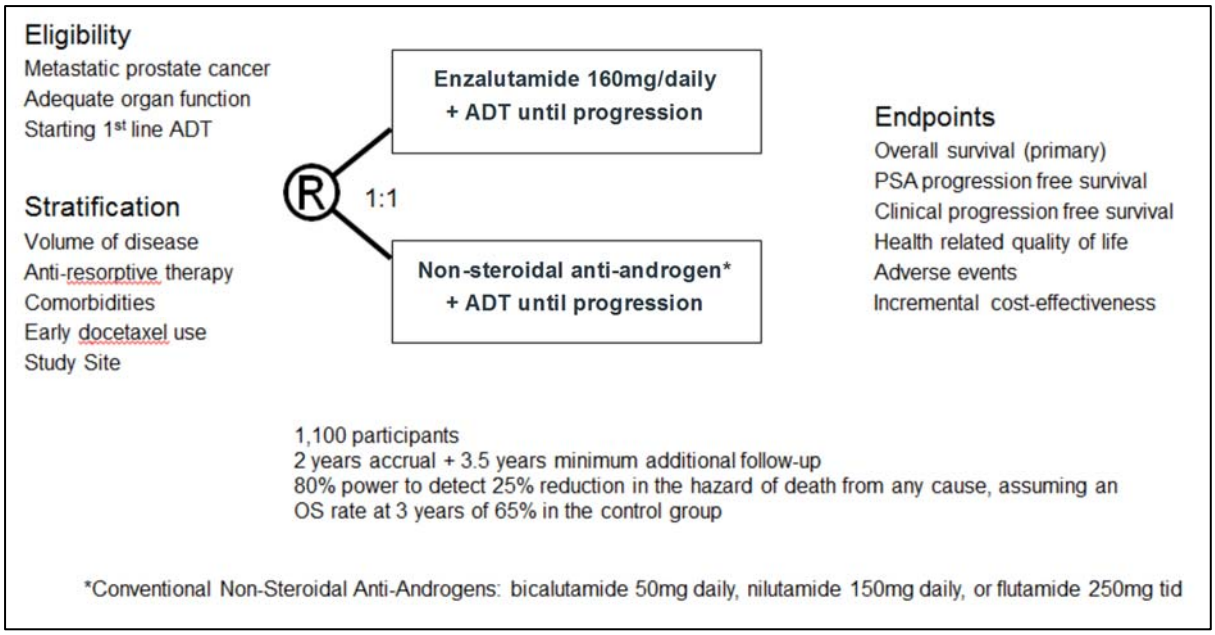
B.2.3.1.2 ENZAMET study design

The study schematic for ENZAMET is provided in Figure 4.

Patients were randomised in a 1:1 ratio to receive treatment with ADT and either enzalutamide 160 mg orally daily or conventional oral NSAA, until disease progression or prohibitive toxicity. Patients were also allowed up to 6 cycles of concomitant docetaxel (75 mg/m^2), as long as the decision to use early docetaxel was made and specified prior to randomisation and the patients received no more than 2 cycles prior to randomisation[24].

Assessments occurred at baseline, day 29, Week 12 and every 12 weeks thereafter until evidence of clinical progression. Imaging with CT or MRI and whole-body bone scan (WBBS) was conducted at baseline and at evidence of PSA or clinical progression (whichever occurred first). Blood tests for translational studies were obtained at baseline, day 29, week 24 and end of study treatment[24].

Figure 4 ENZAMET study schematic



Source: Adapted from ENZAMET Clinical Study Report[24]
Abbreviations: ADT: Androgen deprivation therapy; OS: Overall survival; PSA: Prostate-specific antigen.

B.2.3.2 Participants

Study selection criteria in ARCHES and ENZAMET are listed in Table 7.

Briefly, in ARCHES patients were eligible for enrolment if they had hormone-sensitive and metastatic prostate cancer documented by positive bone scan (for bone disease) or metastatic lesions on CT or MRI scan (for soft tissue) and had ECOG performance status of 0 or 1 at screening. Patients whose disease spread was limited to regional pelvic lymph nodes were not eligible. Patients could have received up to 6 cycles of docetaxel[23].

In ENZAMET, selection criteria were similar to those in ARCHES but patients could have an ECOG performance status 0 to 2 and could have received up to a maximum of 2 cycles of docetaxel chemotherapy for metastatic disease[24].

Table 7 Eligibility criteria in ARCHES and ENZAMET

ARCHES		ENZAMET	
Inclusion criteria	**Exclusion criteria**	**Inclusion criteria**	**Exclusion criteria**
Patients had to meet all of the following criteria: 1. IRB-/IEC-approved written informed consent and privacy language as per national regulations (e.g., Health Insurance Portability Accountability Act authorisation for United States sites) must have been obtained from the patient or legally authorised representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable). 2. Patient was considered an adult according to local regulation at the time of signing informed consent. 3. Patient was diagnosed with histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation, signet cell or small cell histology. Specific to patients enrolled in France, histological diagnosis was required. 4. Patient had metastatic prostate cancer documented by positive bone scan (for bone disease) or metastatic lesions on CT or MRI scan (for soft tissue). Patients whose disease spread was limited	Patients could not meet any of the following criteria: 1. Patient had received any prior pharmacotherapy, radiation therapy or surgery for metastatic prostate cancer (the following exceptions were permitted): • Up to 3 months of ADT with LHRH agonists or antagonists or orchiectomy with or without concurrent antiandrogens prior to day 1, with no radiographic evidence of disease progression or rising PSA levels prior to day 1; • Patient could have had 1 course of palliative radiation or surgical therapy to treat symptoms resulting from metastatic disease (M1) if it was administered at least 4 weeks prior to day 1; • Up to 6 cycles of docetaxel therapy with final treatment administration completed within 2 months of day 1 and no evidence of disease progression during or after the completion of docetaxel therapy; • Up to 6 months of ADT with LHRH agonists or antagonists or orchiectomy with or without concurrent antiandrogens prior to day 1 if patient was treated with docetaxel, with no radiographic	Patients had to meet all of the following criteria: 1. Male aged 18 or older with metastatic adenocarcinoma of the prostate defined by: • Documented histopathology or cytopathology of prostate adenocarcinoma from a biopsy of a metastatic site OR • Documented histopathology of prostate adenocarcinoma from a transrectal ultrasound guided biopsy, radical prostatectomy or transurethral resection of the prostate and metastatic disease consistent with prostate cancer OR • Metastatic disease typical of prostate cancer (i.e., involving	Patients could not meet any of the following criteria: 1. Prostate cancer with significant sarcomatoid or spindle cell or neuroendocrine small cell components. 2. History of: • Seizure or any condition that may predispose to seizure (e.g., prior cortical stroke or significant brain trauma) • Loss of consciousness or transient ischemic attack within 12 months of randomisation significant cardiovascular disease within the last 3 months including: myocardial infarction, unstable angina, congestive heart failure (New York Heart Association functional capacity class II or greater, ongoing arrhythmias of grade >2 (NCI-CTCAE, v 4.03) or thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism). Chronic stable atrial fibrillation on

ARCHES		ENZAMET	
Inclusion criteria	**Exclusion criteria**	**Inclusion criteria**	**Exclusion criteria**
to regional pelvic lymph nodes were not eligible. 5. Once randomised at day 1, patient had to maintain ADT with an LHRH agonist or antagonist during study treatment or have a history of bilateral orchiectomy. 6. Patient had an ECOG performance status of 0 or 1 at screening. 7. Patient had an estimated life expectancy of ≥12 months as assessed by the investigator. 8. Patient was able to swallow the study drug and comply with study requirements. 9. A sexually active male patient and his female partner who was of childbearing potential must have used 2 acceptable methods of birth control (1 of which must include a condom as a barrier method of contraception) from screening through 3 months after the last dose of study drug. Two acceptable methods of birth control include condom (barrier method was required) AND 1 of the following: • Consistent and correct usage of established, proper use of hormonal contraceptives that inhibit ovulation by the female partner;	evidence of disease progression or rising PSA levels prior to day 1; • Prior ADT given for <39 months in duration and >9 months before randomisation as neoadjuvant/adjuvant therapy. 2. Patient had a major surgery within 4 weeks prior to day 1. 3. Patient had received treatment with 5-α reductase inhibitors (finasteride, dutasteride) within 4 weeks prior to day 1. 4. Patient had received treatment with oestrogens, cyproterone acetate or androgens within 4 weeks prior to day 1. 5. Patient had received treatment with systemic glucocorticoids greater than the equivalent of 10 mg per day of prednisone within 4 weeks prior to day 1, intended for the treatment of prostate cancer. 6. Patient had received treatment with herbal medications that have known hormonal anti-prostate cancer activity and/or are known to decrease PSA levels within 4 weeks prior to day 1. 7. Patient had received prior aminoglutethimide, ketoconazole, abiraterone acetate or enzalutamide for the treatment of prostate cancer or participation in a clinical study of an investigational agent that inhibits the AR or androgen synthesis (e.g., TAK-700, ARN-509, ODM-201).	bone or pelvic lymph nodes or para-aortic lymph nodes) AND a serum concentration of PSA that is rising and >20ng/ml. 2. Target or nontarget lesions according to RECIST 1.1. 3. Adequate bone marrow function: Haemoglobin (Hb) ≥100 g/L and white cell count ≥4.0 x 109/L and platelets ≥100 x 109/L. 4. Adequate liver function: alanine aminotransferase (ALT) <2 x ULN and bilirubin <1.5 x ULN, (or if bilirubin is between 1.5 to 2 x ULN, patients must have had a normal conjugated bilirubin). If liver metastases were present ALT must have been <5x ULN. 5. Adequate renal function: calculated creatinine clearance >30 mL/min (Cockroft-Gault) 6. ECOG performance status of 0 to 2. Patients with performance status 2 were only eligible if the decline in performance	stable anticoagulant therapy was allowed. 3. Life expectancy of less than 12 months. 4. History of another malignancy within 5 years prior to randomisation, except for either non-melanomatous carcinoma of the skin or, adequately treated, non-muscle-invasive urothelial carcinoma of the bladder (Tis, Ta and low grade T1 tumours). 5. Concurrent illness, including severe infection that might have jeopardised the ability of the patient to undergo the procedures outlined in the protocol with reasonable safety. • HIV-infection was not an exclusion criterion if it was controlled with antiretroviral drugs that were unaffected by concomitant enzalutamide. 6. Presence of any psychological, familial, sociological or geographical condition that could have potentially hampered compliance with the study protocol and follow-up

ARCHES		ENZAMET	
Inclusion criteria	**Exclusion criteria**	**Inclusion criteria**	**Exclusion criteria**
• Established intrauterine device or intrauterine system by the female partner; • Tubal ligation in the female partner performed at least 6 months prior to patient's screening visit; • Vasectomy or other procedure resulting in infertility (e.g., bilateral orchiectomy) performed at least 6 months prior to screening; • Calendar-based contraceptive methods (Knaus-Ogino or rhythm method applicable to patients enrolled in Japan only). 10. Patient must have used a condom throughout the study if engaging in sexual intercourse with a pregnant woman. 11. Patient must have agreed not to donate sperm from first dose of study drug through 3 months after the last dose of study drug. 12. Patient agreed not to participate in another interventional study while on treatment. Waivers to the inclusion criteria were not allowed.	8. Patient received investigational agent within 4 weeks prior to day 1. 9. Patient had known or suspected brain metastasis or active leptomeningeal disease. 10. Patient had a history of another invasive cancer within 3 years of screening, with the exception of fully treated cancers with a remote probability of recurrence based on investigator assessment. 11. Patient had absolute neutrophil count <1500/μL, platelet count <100000/μL or Hb <10 g/dL (6.2 mmol/L) at screening. 12. Patient had total bilirubin ≥1.5 x the ULN (except patients with documented Gilbert's disease), or ALT or AST ≥2.5 x the ULN at screening. 13. Patient had creatinine >2 mg/dL (177 μmol/L) at screening. 14. Patient had albumin <3.0 g/dL (30 g/L) at screening. 15. Patient had a history of seizure or any condition that may predispose to seizure. 16. Patient had history of loss of consciousness or transient ischemic attack within 12 months prior to day 1. 17. Patient had clinically significant cardiovascular disease. 18. Patient had gastrointestinal disorder affecting absorption. 19. Patient had any concurrent disease, infection or comorbid condition that interfered with the ability of the patient	status was due to metastatic prostate cancer. 7. Study treatment both planned and able to start within 7 days after randomisation. 8. Willing and able to comply with all study requirements, including treatment and required assessments. 9. Had completed baseline health-related quality of life (HRQoL) questionnaires unless unable to complete because of limited literacy or vision. 10. Signed, written, informed consent.	schedule, including alcohol dependence or drug abuse. 7. Patients who were sexually active and not willing/able to use medically acceptable forms of barrier contraception. 8. Prior ADT for prostate cancer (including bilateral orchiectomy), except in the following settings: • Started less than 12 weeks prior to randomisation and PSA was stable or falling. The 12 weeks started from whichever of the following occurred earliest: first dose of oral antiandrogen, LHRHa or surgical castration. • In the adjuvant setting, where the completion of adjuvant hormonal therapy was more than 12 months prior to randomisation and the total duration of hormonal treatment did not exceed 24 months. For depot preparations, hormonal therapy was deemed to have started with the first dose and to have been completed when the next dose would otherwise

ARCHES		ENZAMET	
Inclusion criteria	**Exclusion criteria**	**Inclusion criteria**	**Exclusion criteria**
	to participate in the study, which placed the patient at undue risk or complicated the interpretation of data in the opinion of the investigator. 20. Patient had received bisphosphonates or denosumab within 2 weeks prior to day 1 unless administered at stable dose or to treat diagnosed osteoporosis. 21. Patient had shown a hypersensitivity reaction to the active pharmaceutical ingredient or any of the study capsule components, including Labrasol®, butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT). Waivers to the exclusion criteria were not allowed.		have been due, e.g., 12 weeks after the last dose of depot goserelin 10.8 mg. 9. Prior cytotoxic chemotherapy for prostate cancer, but up to 2 cycles of docetaxel chemotherapy for metastatic disease was permitted. 10. Participation in other clinical studies of investigational agents for the treatment of prostate cancer or other diseases.

Source: ARCHES Clinical Study Report[23]; Armstrong *et al*[27]; ENZAMET Clinical Study Report[24]; Davis *et al*[28]
Abbreviations: ADT: Androgen deprivation therapy; ALT: Alanine aminotransferase; AR: Androgen receptor; AST: Aspartate aminotransferase; BHA: Butylated hydroxyanisole; BHT: Butylated hydroxytoluene; CT: Computed tomography; ECG: Electrocardiogram; ECOG: Eastern Cooperative Oncology Group; Hb: Haemoglobin; HRQoL: health-related quality of life; IRB-IEC: Institutional Review Board-Independent Ethics Committee; LHRH: Luteinizing hormone-releasing hormone; MRI: Magnetic resonance imaging; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; PSA: Prostate-specific antigen; RECIST: Response Evaluation Criteria in Solid Tumours; ULN: Upper limit of normal.

Demographics and baseline characteristics of patients in ARCHES and ENZAMET

In ARCHES, demographic and baseline disease characteristics were well balanced between the 2 treatment groups (Table 8). The majority of patients were recruited in Europe (n=685/1150; 59.6%) [redacted] were recruited in the UK centres[23]. Given the low number, the demographics and baseline characteristics of [redacted] are not included in Table 8.

The median age at randomisation was 70.0 years in both treatment groups, with a similar proportion of patients in each age category (enzalutamide plus ADT vs placebo plus ADT: 25.8% vs 26.4% [<65 years]; 44.6% vs 44.3% [65 to <75 years] and 29.6% vs 29.3% [≥75 years]). Most patients in the total population were white (80.5%) and were from Europe (59.6%). The body mass index (BMI) was comparable between both treatment groups (26.65 kg/m^2 and 26.91 kg/m^2 for enzalutamide plus ADT and placebo plus ADT, respectively). At study entry, the majority of patients (77.5%) had an ECOG performance status of 0 in both treatment groups[23].

The median PSA value at baseline was 5.36 ng/mL in the enzalutamide plus ADT group and 5.07 ng/mL in the placebo plus ADT group. The median duration of metastatic prostate cancer until randomisation was similar between the treatment groups: 3.47 months in the enzalutamide plus ADT group and 3.38 months in the placebo plus ADT group. Overall, 36.8% of patients had LVD and 63.2% of patients HVD; the proportion of patients with low or high disease burden was balanced between the treatment groups[23].

Table 8 Demographic and baseline disease characteristics in ARCHES (ITT population)

Parameters Statistics/criteria	ENZA + ADT (n=574)	PLA + ADT (n=576)	Total (n=1,150)
Age category (years), n (%)			
<65	148 (25.8)	152 (26.4)	300 (26.1)
65 to <75	256 (44.6)	255 (44.3)	511 (44.4)
≥75	170 (29.6)	169 (29.3)	339 (29.5)
Age (years)			
Mean (SD)	69.5 (8.0)	69.5 (8.4)	69.5 (8.2)
Median (min, max)	70.0 (46, 92)	70.0 (42, 92)	70.0 (42, 92)
Race†, n (%)			
White	466 (81.2)	460 (79.9)	926 (80.5)
Black or African American	8 (1.4)	8 (1.4)	16 (1.4)
Asian	75 (13.1)	80 (13.9)	155 (13.5)
Other	2 (0.3)	3 (0.5)	5 (0.4)
Missing	23 (4.0)	25 (4.3)	48 (4.2)
Ethnicity†, n (%)			
Hispanic or Latino	46 (8.0)	37 (6.4)	83 (7.2)
Not Hispanic or Latino	504 (87.8)	514 (89.2)	1018 (88.5)
Missing	24 (4.2)	25 (4.3)	49 (4.3)
Geographic region‡, n (%)			
Asia-Pacific	104 (18.1)	113 (19.6)	217 (18.9)
Europe	341 (59.4)	344 (59.7)	685 (59.6)
North America	86 (15.0)	77 (13.4)	163 (14.2)
South America	32 (5.6)	30 (5.2)	62 (5.4)

Parameters Statistics/criteria	ENZA + ADT (n=574)	PLA + ADT (n=576)	Total (n=1,150)
Other	11 (1.9)	12 (2.1)	23 (2.0)
Weight (kg)			
N	573	575	1148
Mean (SD)	81.25 (16.17)	81.26 (16.22)	81.26 (16.19)
Median (min, max)	80.00 (42.7, 163.0)	80.00 (39.1, 157.5)	80.00 (39.1, 163.0)
Body mass index (kg/m^2)			
N	567	570	1137
Mean (SD)	27.20 (4.44)	27.21 (4.61)	27.20 (4.53)
Median (min, max)	26.65 (16.7, 45.2)	26.91 (16.4, 48.8)	26.81 (16.4, 48.8)
ECOG performance status at study entry*, n (%)			
0	448 (78.0)	443 (76.9)	891 (77.5)
1	125 (21.8)	133 (23.1)	258 (22.4)
Baseline serum PSA (ng/mL)**			
N	572	574	1146
Mean (SD)	75.37 (356.36)	104.78 (834.48)	90.10 (641.90)
Median (min, max)	5.36 (0.0, 4823.5)	5.07 (0.0, 19000.0)	5.21 (0.0, 19000.0)
Total Gleason score at initial diagnosis, n (%)			
<8	171 (29.8)	187 (32.5)	358 (31.1)
≥8	386 (67.2)	373 (64.8)	759 (66.0)
Volume of disease§, n (%)			
Low	220 (38.3)	203 (35.2)	423 (36.8)
High	354 (61.7)	373 (64.8)	727 (63.2)
Prior docetaxel therapy use§, n (%)			
None	471 (82.1)	474 (82.3)	945 (82.2)
1 to 5 cycles	14 (2.4)	11 (1.9)	25 (2.2)
6 cycles	89 (15.5)	91 (15.8)	180 (15.7)
Previous use of ADT, n (%)			
None	39 (6.8)	61 (10.6)	100 (8.7)
<3 months	414 (72.1)	394 (68.4)	808 (70.3)
≥3 months	121 (21.1)	120 (20.8)	241 (21.0)
Unknown¶	0	1 (0.2)	1 (0.1)
Duration of prostate cancer# (months)			
N	572	575	1147
Mean (SD)	17.56 (37.47)	19.99 (41.40)	18.78 (39.49)
Median (min, max)	3.47 (0.26, 267.89)	3.38 (0.39, 259.09)	3.45 (0.26, 267.89)
Duration of metastatic disease## (months)			
N	562	571	1133
Mean (SD)	3.40 (6.66)	3.77 (8.34)	3.59 (7.55)
Median (min, max)	2.07 (0.20, 82.83)	2.07 (0.03, 141.21)	2.07 (0.03, 141.21)
Metastasis based on ICR§§, n (%)			
Yes	536 (93.4)	531 (92.2)	1067 (92.8)
No	34 (5.9)	45 (7.8)	79 (6.9)

Parameters Statistics/criteria	ENZA + ADT (n=574)	PLA + ADT (n=576)	Total (n=1,150)
Unknown	4 (0.7)	0	4 (0.3)
Location of metastases based on ICR, n (%)			
Bone only	268 (46.7)	245 (42.5)	513 (44.6)
Soft tissue only	51 (8.9)	45 (7.8)	96 (8.3)
Bone and soft tissue	217 (37.8)	241 (41.8)	458 (39.8)
Location of metastases based on investigator assessment, n (%)			
Bone only	249 (43.4)	241 (41.8)	490 (42.6)
Soft tissue only	64 (11.1)	72 (12.5)	136 (11.8)
Bone and soft tissue	254 (44.3)	258 (44.8)	512 (44.5)
Total number of bone lesions based on ICR, n (%)			
1	83 (14.5)	70 (12.2)	153 (13.3)
2 to 4	151 (26.3)	142 (24.7)	293 (25.5)
5 to 9	95 (16.6)	106 (18.4)	201 (17.5)
10 to 19	111 (19.3)	114 (19.8)	225 (19.6)
≥20 (including TNC)	45 (7.8)	54 (9.4)	99 (8.6)
Total number of bone lesions based on investigator assessment, n (%)			
1	72 (12.5)	59 (10.2)	131 (11.4)
2 to 4	124 (21.6)	126 (21.9)	250 (21.7)
5 to 9	77 (13.4)	74 (12.8)	151 (13.1)
10 to 19	26 (4.5)	28 (4.9)	54 (4.7)
≥20	23 (4.0)	23 (4.0)	46 (4.0)
TNC¶¶	181 (31.5)	189 (32.8)	370 (32.2)

Source: ARCHES Clinical Study Report[23]
Data cut-off date: 14 Oct 2018
All patients who were randomised in this study (ITT population).
† Race/Ethnicity was not collected in France, by country regulations.
‡ Europe includes: Russian Federation, Slovakia, Italy, Denmark, Romania, Spain, the Netherlands, Poland, France, Finland, Belgium, Sweden, Germany and the United Kingdom. North America includes the United States and Canada. South America includes Chile and Argentina. Asia-Pacific includes Japan, Taiwan, Republic of Korea, Australia and New Zealand. Other is Israel.
* ECOG assessed on day 1. Grade 0: Fully active, able to carry on all pre-disease performance without restriction. Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
** PSA levels of 0 were observed, which could have been due to prior treatment with docetaxel and/or use of ADT within 3 months of study start. One patient receiving placebo plus ADT had a baseline PSA level of >19000 ng/mL, which impacts the calculation of mean baseline PSA for this group.
§ Volume of disease and prior docetaxel therapy were stratification factors at randomisation.
# Duration of prostate cancer (months) = [(date of randomisation - date of initial diagnosis) + 1]/(365.25/12)
Duration of metastatic disease (months) = ([date of randomisation - date of metastatic disease] + 1) / (365.25/12)
§§ Enrolment was based on investigator assessment of metastatic disease; ICR confirmation of this assessment was not required prior to entry into the study.
¶ The patient had prior ADT; however, the duration of ADT use is unknown
¶¶ The instructions to the investigators allowed the selection of "too numerous to count" as an alternative to an exact bone lesion count.
Abbreviations: ADT: androgen deprivation therapy; ECOG: Eastern Cooperative Oncology Group; ENZA: enzalutamide; ICR: independent central review; ITT: intent-to-treat; max: maximum; min: minimum; PLA: placebo; PSA: prostate-specific antigen; TNC: too numerous to count.

Table 9 provides an overview of the demographics and baseline characteristics of patients included in the intent to treat (ITT) analysis and the UK patient subgroup in ENZAMET who

did not receive concomitant docetaxel. In ENZAMET, both treatment groups (not on concomitant docetaxel) were generally well balanced with respect to clinically relevant demographic and baseline disease characteristics[24]. The median age at randomisation was [redacted] years in the enzalutamide plus ADT group and [redacted] years in the NSAA plus ADT group. The majority of patients in both treatment arms came from Australia/New Zealand ([redacted]%). Overall, [redacted] of all patients (including those receiving concomitant docetaxel) were recruited in Europe of which [redacted] in the UK (enzalutamide plus ADT: n=[redacted] and NSAA plus ADT: n= [redacted])[24]. Of the [redacted] patients recruited in the UK, [redacted] were not on concomitant docetaxel (enzalutamide plus ADT: n=[redacted]; NSAA plus ADT: n=[redacted]).

The majority of patients had an ECOG performance status score of 0 (n=[redacted]) at study entry and a Gleason score of ≥8 (n=[redacted]) at the time of diagnosis. Overall, [redacted] patients had regional lymph node involvement and [redacted], distal lymph node involvement. For the majority of patients (n=[redacted]), distal metastases were diagnosed within the previous 12 weeks of randomisation with bone being the most frequently reported site for distant metastases (n=[redacted]). Volume of disease (per CHAARTED study criteria*), planned early use of docetaxel, planned antiresorptive therapy and comorbidities based on ACE-27 score were stratification factors. Overall, [redacted] patients had LVD and [redacted]) HVD; the proportion of patients with low or high disease burden was balanced between the treatment groups[24].

The demographic and baseline disease characteristics for the UK ENZAMET patient subgroup are also provided in Table 9. [redacted]

* The patient population included in mHSPC trials markedly differs. CHAARTED compared the efficacy and safety of docetaxel plus ADT vs ADT alone in mHSPC patients (Sweeney et al 2015). Initially conceived to include only patients with HVD, the protocol was subsequently amended to include patients with LVD. In this study, docetaxel showed significant benefit in HVD but not in LVD; this is highlighted in treatment guidelines (Mottet et al 2018). In order to allow comparison with the docetaxel results in GETUG, several studies have analysed data using the CHAARTED criteria which defines HVD as ≥ 4 bone metastases (at least 1 outside the spine or pelvis) AND/OR visceral metastases (Sweeney et al 2015).

Table 9 Demographic and baseline disease characteristics in ENZAMET for patients not on concomitant docetaxel (ITT and UK populations)

	ITT (no concomitant DOC)		UK (no concomitant DOC)	
	ENZA+ADT (n=309)	**ADT+NSAA (n=313)**	**ENZA+ADT (n=[redacted])**	**ADT+NSAA (n=[redacted])**
Sex male	309 (100.0%)	313 (100.0%)	[redacted]	[redacted]
Age (years), n	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Age group, years				
<65	[redacted]	[redacted]	[redacted]	[redacted]
>=65	[redacted]	[redacted]	[redacted]	[redacted]
<75	[redacted]	[redacted]	[redacted]	[redacted]
>=75	[redacted]	[redacted]	[redacted]	[redacted]
<85	[redacted]	[redacted]	[redacted]	[redacted]
>=85	[redacted]	[redacted]	[redacted]	[redacted]
Weight (kg), n	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
BMI (kg/m^2), n	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Region				
Europe	[redacted]	[redacted]	[redacted]	[redacted]
Australia/New Zealand	[redacted]	[redacted]	[redacted]	[redacted]
North America	[redacted]	[redacted]	[redacted]	[redacted]
Volume of disease strata				
High	[redacted]	[redacted]	[redacted]	[redacted]
Low	[redacted]	[redacted]	[redacted]	[redacted]
Anti-resorptive therapy, yes	[redacted]	[redacted]	[redacted]	[redacted]
Visceral metastases, yes	[redacted]	[redacted]	[redacted]	[redacted]
ECOG performance status				
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
Gleason score				
<8	[redacted]	[redacted]	[redacted]	[redacted]
≥8	[redacted]	[redacted]	[redacted]	[redacted]
Unknown or missing	[redacted]	[redacted]	[redacted]	[redacted]
Regional lymph node				
No involvement	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]
Pelvic	[redacted]	[redacted]	[redacted]	[redacted]
Inguinal	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]

	ITT (no concomitant DOC)		UK (no concomitant DOC)	
	ENZA+ADT (n=309)	ADT+NSAA (n=313)	ENZA+ADT (n=[redacted])	ADT+NSAA (n=[redacted])
Distant lymph node				
No involvement	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal	[redacted]	[redacted]	[redacted]	[redacted]
Retroperitoneal	[redacted]	[redacted]	[redacted]	[redacted]
Mediastinal	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Distant metastases first diagnosed				
Within 12 weeks	[redacted]	[redacted]	[redacted]	[redacted]
More than 12 weeks	[redacted]	[redacted]	[redacted]	[redacted]
More than 6 months	[redacted]	[redacted]	[redacted]	[redacted]
More than 12 months	[redacted]	[redacted]	[redacted]	[redacted]
Site of distant metastases				
Bone	[redacted]	[redacted]	[redacted]	[redacted]
Lung	[redacted]	[redacted]	[redacted]	[redacted]
Pleura	[redacted]	[redacted]	[redacted]	[redacted]
Liver	[redacted]	[redacted]	[redacted]	[redacted]
Adrenal	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Number of bone metastases				
None	[redacted]	[redacted]	[redacted]	[redacted]
1 - 3	[redacted]	[redacted]	[redacted]	[redacted]
4 or more	[redacted]	[redacted]	[redacted]	[redacted]
Prior androgen deprivation therapy (including adjuvant)				
No	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]
Prior cytotoxic chemotherapy (including adjuvant)				
No	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Prior radiotherapy (including adjuvant)				
No	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]
NSAA for metastatic disease within 12 weeks prior to randomisation				
No	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]
Bilateral orchidectomy				
No	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]
LHRHa for metastatic disease within 12 weeks prior to randomisation				
No	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel for metastatic disease prior to randomisation				
No	[redacted]	[redacted]		

	ITT (no concomitant DOC)		UK (no concomitant DOC)	
	ENZA+ADT (n=309)	ADT+NSAA (n=313)	ENZA+ADT (n=[redacted])	ADT+NSAA (n=[redacted])
Yes	[redacted]	[redacted]		
Missing	[redacted]	[redacted]		

Source: ENZAMET Clinical Study Report[24]
Data cut-off date: 28 Feb 2019
Abbreviations: ADT: androgen deprivation therapy; DOC: docetaxel; ECOG: Eastern Cooperative Oncology Group; ENZA: enzalutamide; ITT: intent to treat; LHRHa: luteinizing hormone releasing hormone analogue; max: maximum; min: minimum; NSAA: nonsteroidal antiandrogen; PSA: prostate-specific antigen; UK: cohort of patients recruited in the United Kingdom.

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

B.2.4.1 Primary hypothesis

In ARCHES, the null hypothesis was that the radiographic progression-free survival (rPFS) for placebo plus ADT and enzalutamide plus ADT were not different[23]. In ENZAMET, the null hypothesis was that the earlier use of a therapy shown to be effective in the more advanced state of HRPC would not prevent or delay the emergence of castration resistant disease and prolong OS[24].

B.2.4.2 Patient population

In ARCHES, the ITT population, defined as all randomised patients, was used for all efficacy analyses and analyses of demographics, and baseline disease characteristics. The ITT population was analysed by treatment group as randomised (i.e., treatment group based on randomisation assignment) regardless of study drug administration. The safety population was defined as all randomised patients who received at least 1 dose of study drug. The safety population was used to conduct safety analyses by treatment group as treated (i.e., based on the actual study drug the patient received for the greater number of days rather than the study drug to which the patient was randomised).

Similarly, in ENZAMET, the ITT population, defined as all randomised patients, was used for all efficacy analyses, unless stated otherwise, and analyses of demographics and baseline disease characteristics. Safety analyses were conducted on the safety population by treatment group as treated. The safety population included patients that were randomised and received at least 1 dose of study drug (either enzalutamide plus ADT or NSAA plus ADT).

B.2.4.3 Sample size, power calculations

In ARCHES, approximately 1,100 patients (550 patients per treatment group) were planned to be randomised in the study. The final analysis of the primary endpoint (rPFS) was planned to be conducted when a minimum of 262 progression events had occurred, based on the following considerations:

- A target hazard ratio (HR) of 0.67. The expected median rPFS for the placebo plus ADT group was 20 months as measured from the date of randomisation. Under the assumption of an exponential distribution, a target HR of 0.67 corresponded to approximately 50% increase in median rPFS for the enzalutamide plus ADT group relative to the placebo plus ADT group (approximately 30 vs 20 months).
- 262 rPFS events (radiographic progression at any time or death from any cause within 24 weeks after study drug discontinuation, whichever occurred first) provided 90% power to detect the target HR based on a 2-sided log-rank test and a significance level of 0.05.

In addition, the study was powered to detect a meaningful difference in OS. Specifically, 342 death events were required to provide 80% power to detect a target HR of 0.73 with a target difference in Kaplan-Meier estimated median of approximately 15 months (40 months for placebo plus ADT vs 55 months for enzalutamide plus ADT) at the 0.04 significance level under the assumption of an exponential distribution. This significance level was chosen to apply a parallel testing strategy between OS and some other secondary endpoints (with allocated type I error rate of 0.01).

In ENZAMET, 470 deaths were required to provide over 80% power to detect a 25% reduction in the hazard of death with a 2-sided type 1 error of 0.05 (using a log-rank test) assuming a 3-year survival rate of 65% amongst controls. It was estimated that 1,100 patients were needed to observe the 470 deaths.

A 25% reduction in the hazard of death was considered clinically plausible in light of the results of the AFFIRM study of enzalutamide vs placebo in HRPC after chemotherapy, which showed a 37% reduction in the hazard of death[37] and the PREVAIL study of enzalutamide vs placebo for HRPC before chemotherapy, which showed a 29% reduction in the hazard of death[38]. The design incorporated 3 formal interim analyses performed on OS using the Lan-DeMets alpha spending function approach (with an O'Brien-Fleming type boundary shape).

B.2.4.4 Handling of dropouts or missing data

In ARCHES, as a general principle, no imputation of missing data was applied. Exceptions were the start and stop dates of AEs, previous and concomitant medications, the date of initial diagnosis (to estimate the relative study day to calculate cancer duration), dates of cancer treatment (e.g., previous procedure, previous radiotherapy), the last dose date and the date of death. For these dates, imputation differed depending on the variable (Table 10).

Table 10 Imputations applied in ARCHES

Variable	Imputations
Non-prostate cancer related medication dates and/or AEs/TAEs	• Incomplete *start day* from start date and the corresponding *end date* is complete: use the later of (first day of the month, first dosing day if first dosing month); but if later than the end date, then impute the start day as the day of the end date • Incomplete *start day* from start date and incomplete *end day* from end date: use the later of (first day of the month, first dosing day if first dosing month) • Incomplete *end day* from end date: use the earliest of (last day of the month, day of the 30-day follow-up visit if it is the month of the 30-day follow-up visit)

Variable	Imputations
	• Incomplete month or year: no imputation.
Initial diagnosis and prior cancer treatment	• Incomplete day: use the 15th day of the month, if month/year is before first dosing or after last dosing (-for start date imputation- but if later than the end date, then impute the start day as the day of the end date; -for end date imputation- but if earlier than the start date, then impute the end day as the day of the start date) • Incomplete month: use 1st of July if the year is before year of first dosing, otherwise missing • Incomplete year: no imputation, the derived variable is considered to be missing
Last dose of medication	• Incomplete day only: use the earliest of (last day of the month, end of treatment [form] day -if on the same month and year-, day of the 30-day follow-up visit-if on the same month and year-) • If fully missing or Incomplete month or/and year: the date will be imputed by the earliest of (end of treatment [form] date, date of the 30-day follow-up visit)
Date of death	• Incomplete day: use the earliest of (last day of the month, end of study day) • Incomplete month or year: no imputation

Source: ARCHES Clinical Study Report[23]
Abbreviations: AE: adverse event; TEAE: treatment-emergent adverse event.

In ENZAMET, imputation of dates was applied. First day of month was imputed if day was missing (January was imputed if month was also missing) for ADT start date. Last day of month was imputed if day was missing (December if month missing) for ADT end date.

B.2.4.5 Interim analyses and stopping guidelines

In ARCHES, one interim analysis was planned for OS. The interim analysis of OS was to be performed at the time of the rPFS final analysis (i.e., when at least 262 rPFS events had occurred). The exact significance level for this analysis, calculated using the O'Brien-Fleming alpha spending function was used to determine the stopping boundaries based on the number of events observed at the interim analysis and control the overall 2-sided alpha at 0.05 or at 0.04[23].

If the interim analysis of OS had been statistically significant, it would have been reported as the final analysis and no subsequent analysis performed. If the interim analysis of OS was not statistically significant, the final analysis of OS was planned for when approximately 342 deaths were observed to ensure an adequate number of events. At the time of the planned final analysis of OS, no additional analyses of other efficacy endpoints were planned to be conducted[23].

In ENZAMET, the study design included a provision for up to 3 interim efficacy analyses on OS at 50%, 67% and 80% of the maximum number of events being sought (i.e., 470). The interim analyses allowed for early rejection of the null hypothesis according to an alpha spending function with an O'Brien-Fleming boundary shape. The actual number of events observed at the time of the interim analyses was to be used to construct the definitive rejection boundary. Assuming the null hypothesis was not rejected, the conditional power of the study was also to be calculated for OS at the interim analyses. This procedure did not

'spend' any alpha associated with the test of the null hypothesis. The first interim analysis was triggered upon reaching 235 deaths (i.e., 50% of maximum expected) as registered in the study database daily data extract (on 28 Feb 2019)[24].

B.2.4.6 Statistical methods used to compare groups for primary and secondary outcomes

ARCHES:

a. Analysis of the primary endpoint:

The analysis of the primary efficacy endpoint, rPFS, was to be conducted when at least 262 rPFS events had occurred. The effect of enzalutamide plus ADT compared to placebo plus ADT was tested using a stratified log-rank test at the level of significance of 0.05 (2-sided). Stratification factors were the factors used at randomisation, prior docetaxel use (yes vs no) and disease volume (low vs high)[23].

Kaplan-Meier methods were used to estimate the distribution of rPFS events by treatment group. The median rPFS was estimated using the corresponding 50th percentile of Kaplan-Meier estimates. A 2-sided 95% confidence interval (CI) was provided for this estimate by use of the Brookmeyer and Crowley method. The 25th and 75th percentile of rPFS were also provided. A Kaplan-Meier plot by treatment group was presented. The estimates of the event free rate on a 3-monthly basis up to 1 year and every 6 months thereafter were summarised by treatment group, as long as at least 10 patients were at risk. The benefit of enzalutamide plus ADT compared to placebo plus ADT was summarised by a HR with its 95% CI based on a Cox regression model stratified for the prior docetaxel use and disease volume[23].

The null and alternative hypotheses regarding rPFS could be rephrased in terms of the HR, $\lambda_{ArmA} / \lambda_{ArmB}$, where:

- λ_{ArmA} represents the hazard of rPFS for enzalutamide plus ADT and
- λ_{ArmB} represents the hazard of rPFS for placebo plus ADT

A HR of <1 indicates that the rPFS is prolonged for patients randomised to enzalutamide plus ADT compared with patients randomised to placebo plus ADT.

The estimated HR of enzalutamide plus ADT to placebo plus ADT ($\lambda_{ArmA} / \lambda_{ArmB}$) and its 95% CI was determined. If the estimate of the HR (enzalutamide plus ADT/placebo plus ADT) <1 and the results from the log-rank test led to the rejection of the null hypothesis in favour of its alternative, then it could be concluded that enzalutamide plus ADT prolonged rPFS compared to placebo plus ADT.

The rPFS results are provided in the ARCHES Clinical Study Report Addendum[32].

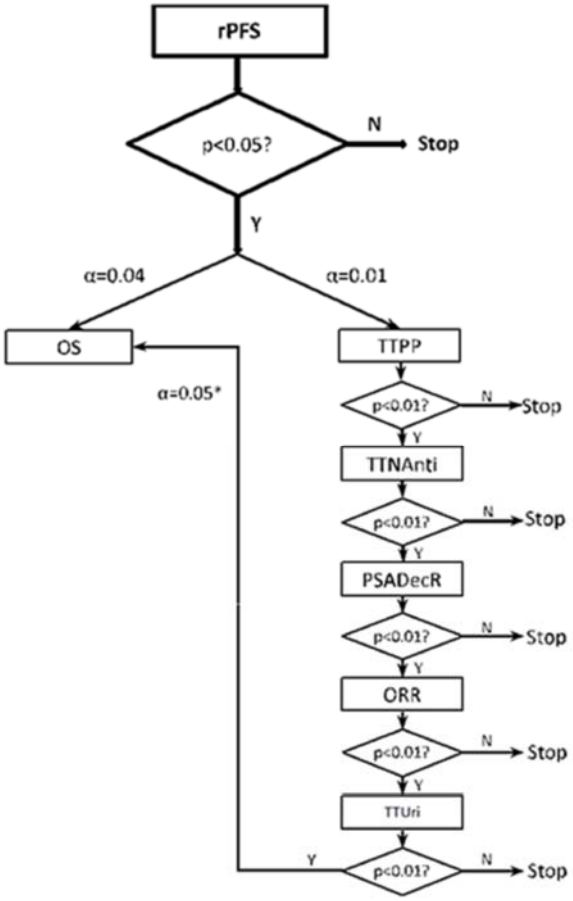
b. Analysis of the secondary endpoint:

All secondary endpoint analyses were performed at the time of the rPFS final analysis (i.e., when at least 262 rPFS events had occurred). If the primary endpoint statistical analysis test, conducted at the level of significance of 0.05 (2-sided), was statistically significant, then the following 6 secondary endpoints were tested using a method to preserve the family-wise 2-sided type I error rate at 0.05[23]:

- OS
- Time to PSA progression
- Time to start of new antineoplastic therapy
- Rate of PSA decline to <0.2 ng/mL
- ORR
- Time to deterioration in urinary symptoms as per the QLQ-PR25

To maintain the family-wise 2-sided type I error rate at 0.05, a parallel testing strategy between OS (with allocated type I error rate 0.04) and the other 5 endpoints (with allocated type I error rate 0.01) was performed (Figure 5).

Figure 5 Testing strategy for the primary and six selected secondary endpoints



Source: ARCHES Clinical Study Report[23]
*OS would have been tested at 0.05 only, if all other 5 secondary endpoints analyses were statistically significant at 0.01.
Abbreviations: rPFS: radiographic progression-free survival; OS: overall survival; TTPP: time to PSA progression; TTNAnti: time to start of new antineoplastic therapy; PSADecR: rate of PSA decline to <0.2 ng/mL; ORR: objective response rate; TTUri: time to deterioration in urinary symptoms from QLQ-PR25.

ENZAMET:

a. Analysis of the primary endpoint:

The primary analysis of OS was performed using unstratified analyses. The treatment difference in OS was assessed by unstratified log-rank test. The HR was calculated using an unstratified Cox proportional hazards model. Median OS and 95% CI were estimated using Kaplan-Meier survival methodology[24].

Regarding exposure, the Kaplan-Meier method was used to summarize time on study drug, with any patients remaining on treatment being censored at the time the most recent dosing was recorded.

B.2.4.7 Methods for additional analyses, such as subgroup analyses and adjusted analyses

ARCHES:

a. Sensitivity analyses:

Sensitivity analyses were performed to evaluate the robustness of the rPFS results by investigating the extent to which the results and conclusions may be affected by various limitations of the data, assumptions and analytic approaches to data analysis[23]:

- Sensitivity analysis 1: impact of study drug discontinuation as an additional event.
- Sensitivity analysis 2: impact of new antineoplastic therapy and occurrence of an SSE as additional events.
- Sensitivity analysis 3: impact of all deaths (with no time limit) as events
- Sensitivity analysis 4: impact of radiographic progressive disease (rPD) documented between per-protocol visits
- Sensitivity analysis 5: 'missing' data impact – last scan not documented as not evaluable
- Sensitivity analysis 6: 'missing' data impact – absence of 2 consecutive scans
- Sensitivity analysis 7: censoring rPD on competing risks: new antineoplastic therapy and occurrence of a symptomatic skeletal event (SSE)
- Sensitivity analysis 8: 'missing' data impact and censoring rPD on competing risks: new antineoplastic therapy, occurrence of an SSE and study drug discontinuation in patients with M1 based on ICR assessments
- Sensitivity analysis 9: limited to M1 patients who were identified from the baseline assessments made by ICR
- Sensitivity analysis 10: impact of rPD documented by the investigators
- Sensitivity analysis 11: impact of rPD according to PCWG2 criteria[39] and documented by the investigators
- Sensitivity analysis 12: impact of rPD according to PCWG2 criteria and documented by ICR.

These sensitivity analyses were conducted on the ITT population using the same analysis methods as described above for the primary analysis. No adjustment was made for the multiple comparisons in the sensitivity analyses.

A forest plot displaying the HR for treatment comparison and 95% CI was presented for the different rPFS sensitivity analyses. The HR was estimated by use of Cox proportional hazards models stratified for the prior docetaxel use and disease volume and treatment as covariate, as in the primary analysis.

b. Subgroup analyses:

Subgroup analyses of rPFS were performed to determine whether the treatment effect was consistent among subgroups. To avoid possible issues related to small numbers of events, subgroup analyses were not adjusted for the stratification factors used at randomisation. A forest plot displaying the HR for treatment comparison and 95% CI was presented by subgroup. The HR was estimated by use of Cox proportional hazards models with treatment as covariate.

The subgroups were defined as follows[23]:

- Age category (<65 and ≥65 years)
- Geographic region (Europe, North America, rest of the world)
- ECOG performance status (0 vs 1) at baseline
- Gleason score (<8 vs ≥8) at initial diagnosis
- Disease location (bone only vs soft tissue only vs both bone and soft tissue) at baseline
- Baseline PSA value (at or below overall median vs above overall median)
- Volume of disease at baseline (low vs high)
- Prior docetaxel use (yes vs no)
- Previous use of ADT or orchiectomy (yes vs no).

ENZAMET:

a. Sensitivity analyses:

Sensitivity analyses was performed using a stratified log-rank test and Cox regression analysis for OS with stratification[24].

b. Subgroup analyses:

Subgroup analyses were performed for geographical region, volume of disease strata, and docetaxel strata. An evaluation of the treatment effect in the subgroup of high-volume disease patients in the docetaxel stratum was also to be performed. These subgroup analyses were performed on OS and repeated for PSA PFS and clinical PFS endpoints[24].

Subgroup analyses on HRQOL endpoints were to be performed by docetaxel strata and by symptom severity on baseline HRQOL.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

A quality assessment of the relevant clinical effectiveness evidence is included in appendix D. The quality assessment was conducted on the clinical study report (CSR) of ARCHES[23] and ENZAMET[24]. This appraisal was conducted using the quality elements suggested by NICE to assess the risk of bias and generalisability in parallel groups RCTs[40].

Overall the quality assessment indicated that ARCHES and ENZAMET were of high quality with little risk of bias.

B.2.6 Clinical effectiveness results of the relevant trials

Unless stated otherwise, all data in this section originate from the ARCHES or ENZAMET CSRs or key publications. The clinical effectiveness results are provided separately for ARCHES and ENZAMET.

B.2.6.1 ARCHES clinical effectiveness results

B.2.6.1.1 Primary endpoint: primary analysis of radiographic progression-free survival

As of the data analysis cut-off date (14 Oct 2018), a total of 292 patients had a progression event as assessed by ICR per protocol-specified criteria, with 91 patients (15.8%) in the enzalutamide plus ADT group and 201 patients (34.9%) in the placebo plus ADT group[32].

The study met its primary endpoint and enzalutamide plus ADT demonstrated a statistically significant reduction (61%) in the risk of a patient experiencing a rPFS event compared with placebo plus ADT (hazard ratio [HR]: 0.39, 95% CI: 0.30, 0.50; p<0.0001). The median time to a rPFS event was not reached in the enzalutamide plus ADT group vs 19.0 months (95% CI: 16.59, 22.24) in the placebo plus ADT group (Table 11). The Kaplan-Meier event-free rate at 12 months was greater for patients in the enzalutamide plus ADT group compared with patients in the placebo plus ADT group (84.16% vs 63.18%, respectively, Table 11).

Table 11 Radiographic PFS - primary efficacy analysis based on ICR assessment (ITT population)

Category Parameter/Statistics	ENZA + ADT (n=574)	PLA + ADT (n=576)
Events, n (%)†	91 (15.85)	201 (34.90)
Kaplan-Meier estimates (months)		
25th percentile	[redacted]	[redacted]
Median (95% CI)‡	NYR	19.0 (16.59, 22.24)
75th percentile	[redacted]	[redacted]
Kaplan-Meier events free rate estimate at 12 months	84.16%	63.18%
Treatment comparison: enzalutamide + ADT vs placebo + ADT		
Cox HR (95% CI)§	0.39 (0.30, 0.50)	
Log-rank p value§	< 0.0001	
Individual components in rPFS events, n (%)¶		
rPD	79 (13.76)	188 (32.64)
Death within 24 weeks after treatment discontinuation	12 (2.09)	13 (2.26)
Censoring, n (%)†		
Censored	[redacted]	[redacted]
First censored reason		
No baseline assessment	[redacted]	[redacted]
No postbaseline assessment	[redacted]	[redacted]
All postbaseline assessments were “Not Evaluable”	[redacted]	[redacted]
No rPFS event before the data cut-off date	[redacted]	[redacted]

Source: Armstrong 2019[27], ARCHES CSR Addendum[32]

Data cut-off date: 14 Oct 2018

† A progression event was defined as objective evidence of radiographic disease progression based on the assessments by ICR or death by any cause within 24 weeks from study drug discontinuation, whichever occurred first. The time to event was calculated from the date of randomisation to the date of occurrence of the first progression event. For patients with no documented progression event, rPFS was censored on the date of the last radiologic assessment performed before the cut-off date.

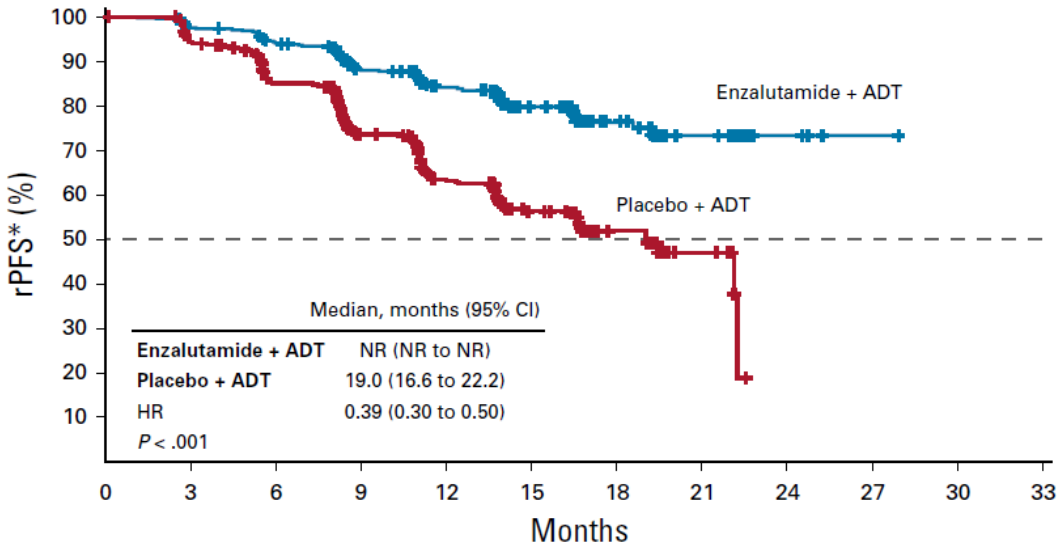
‡ Calculated by Brookmeyer and Crowley method

§ Stratified by volume of disease (low vs high) and prior docetaxel use (yes vs no)

¶ Calculated as a percentage of the total number of randomised patients

Abbreviations: ADT: androgen deprivation therapy; CI: confidence interval; ENZA: enzalutamide; HR: hazard ratio; ICR: independent central review; ITT: intent-to-treat; NYR: not yet reached; rPD: radiographic progressive disease; PLA: placebo; rPFS: radiographic progression-free survival.

Figure 6 Kaplan-Meier plot of rPFS based on ICR assessment (ARCHES - ITT population)



No. at risk												
Enzalutamide + ADT	574	516	493	370	256	144	62	23	4	1	0	0
Placebo + ADT	576	511	445	314	191	106	39	10	0	0	0	0

Source: Armstrong 2019[27]; ARCHES CSR Addendum[32]
Data cut-off date: 14 Oct 2018
Abbreviations: ADT: androgen deprivation therapy; CI: confidence interval; ICR: independent central review; ITT: intent-to-treat; NE: not estimable; rPFS: radiographic progression-free survival.

The robustness of the primary rPFS results was demonstrated through protocol prespecified sensitivity analyses evaluating the effect of various censoring rules (see section B.2.4.6). The HRs for all sensitivity analyses were consistent with the primary rPFS HRs and ranged from [redacted] to [redacted], with similarly narrow confidence intervals[27] (Appendix M).

B.2.6.1.2 Key secondary endpoints

The statistically significant improvement observed in the primary rPFS endpoint allowed testing with multiplicity adjustment of key secondary endpoints (see section B.2.4.6).

As per protocol, all key and additional secondary endpoints were also evaluated at the data cut-off point of approximately 262 rPFS events (i.e., 14 October 2018). These evaluations were final for all endpoints except for OS for which only 84 (24.6%) events of the 342 events expected at the final OS analysis had occurred[23].

B.2.6.1.2.1 Time to PSA progression

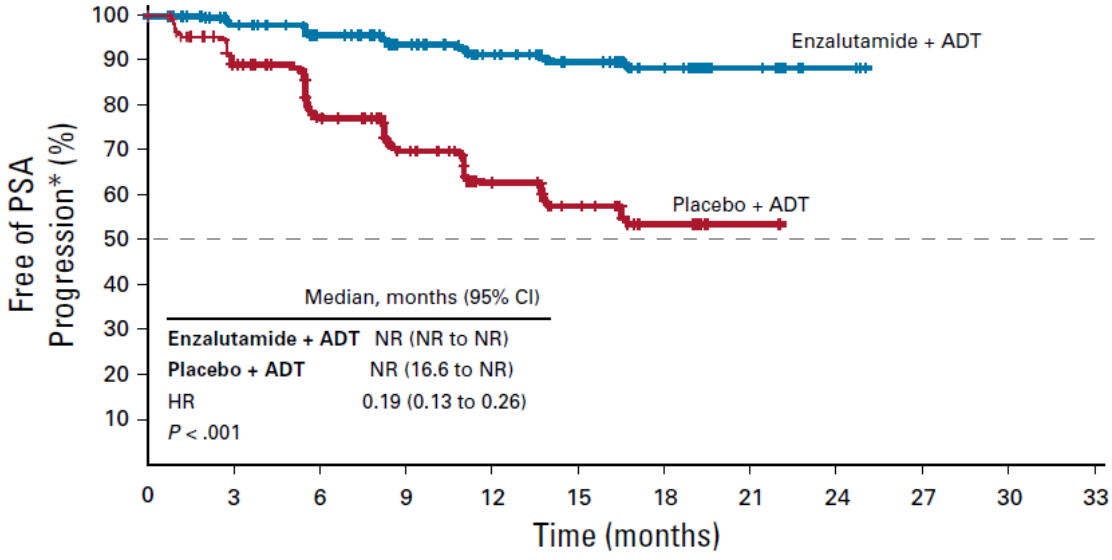
A total of [redacted] patients in the enzalutamide plus ADT group and [redacted] patients in the placebo plus ADT group had PSA progression (Table 12). Treatment with enzalutamide plus ADT was associated with a statistically significant reduction (81%) in the risk of PSA progression compared with placebo plus ADT (HR: 0.19, 95% CI: 0.13, 0.26; p<0.0001)[23, 27]. The median time to PSA progression was not reached for either treatment group. The Kaplan-Meier event-free rate at 12 months was greater for patients in the enzalutamide plus ADT group compared with patients in the placebo plus ADT group ([redacted] vs [redacted], respectively).

Table 12 Time to PSA progression (ITT population)

Category Parameter/Statistics	ENZA + ADT (n=574)	PLA + ADT (n=576)
PSA progression events†, n (%)	[redacted]	[redacted]
Kaplan-Meier estimates for time to PSA progression (months)		
25th percentile	[redacted]	[redacted]
Median (95% CI)‡	NYR	NYR (16.59, NYR)
75th percentile	[redacted]	[redacted]
Kaplan-Meier event-free rate at 12 months	[redacted]	[redacted]
Treatment comparison: enzalutamide vs placebo		
Cox HR (95% CI)§	0.19 (0.13, 0.26)	
Log-rank p value§	<0.0001	

Source: Armstrong 2019[27], ARCHES CSR[23]
Data cut-off date: 14 Oct 2018
† PSA progression was defined as a ≥ 25% increase and an absolute increase of ≥ 2 µg/L (≥ 2 ng/mL) above the nadir, which was confirmed by a second consecutive value at least 3 weeks later. In patients with PSA progression, time to PSA progression was calculated as the time from randomisation to the date of first observation of PSA progression. In patients with no PSA progression, time to PSA progression was censored on the date of the last PSA sample taken (or last value prior to 2 or more consecutive missed PSA assessments).
‡ Calculated by Brookmeyer and Crowley method.
§ Stratified by volume of disease (low vs high) and prior docetaxel use (yes vs no)
Abbreviations: ADT: androgen deprivation therapy; CI: confidence interval; ENZA: enzalutamide; HR: hazard ratio; ITT: intent-to-treat; NYR: not yet reached; PLA: placebo; PSA: prostate-specific antigen.

Figure 7 Kaplan-Meier plot of time to PSA progression (ITT population)



No. at risk:												
Enzalutamide + ADT	574	530	495	371	247	134	58	22	4	0	0	0
Placebo + ADT	576	469	387	257	153	76	25	4	0	0	0	0

Source: Armstrong 2019[27]
Data cut-off date: 14 Oct 2018
PSA progression was defined as a ≥ 25% increase and an absolute increase of ≥ 2 µg/L (≥ 2 ng/mL) above the nadir, which was confirmed by a second consecutive value at least 3 weeks later. In patients with PSA progression, time to PSA progression was calculated as the time from randomisation to the date of first observation of PSA progression. In patients with no PSA progression, time to PSA progression was censored on the date of the last PSA sample taken, or if applicable, prior to 2 or more consecutive missed PSA assessments.
Abbreviations: ADT: androgen deprivation therapy; CI: confidence interval; Cum.: cumulative; ITT: intent-to-treat; NE: not estimable; PSA: prostate-specific antigen.

B.2.6.1.2.2 Time to start of new antineoplastic therapy

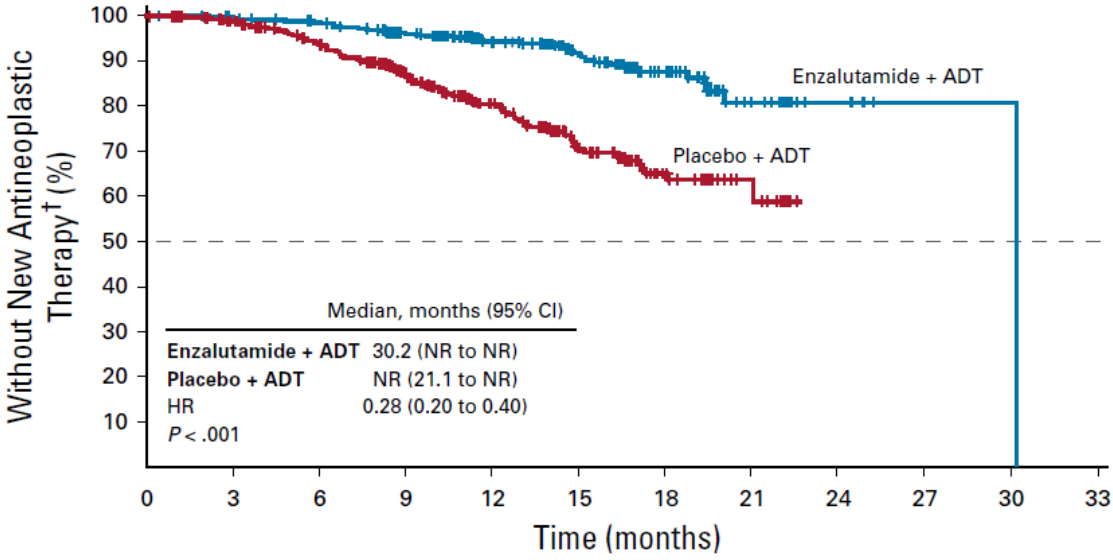
A total of 46 (8.01%) patients in the enzalutamide plus ADT group and 133 (23.09%) patients in the placebo plus ADT group initiated a new antineoplastic therapy (Table 13). Treatment with enzalutamide plus ADT was associated with a statistically significant 72% reduction in the risk of initiation of a new antineoplastic therapy for prostate cancer compared with placebo plus ADT (HR: 0.28, 95% CI: 0.20, 0.40; p<0.0001)[23, 27]. The median was 30.2 months with enzalutamide plus ADT vs not yet reached for the placebo plus ADT group. The Kaplan-Meier event-free rate at 12 months was greater for patients in the enzalutamide plus ADT group compared with patients in the placebo plus ADT group ([redacted] vs [redacted], respectively)[23].

Table 13 Time to start of new antineoplastic therapy (ITT population)

Category Parameter/Statistics	**ENZA + ADT (n=574)**	**PLA + ADT (n=576)**
Patients with new antineoplastic therapy†, n (%)	46 (8.01%)	133 (23.09%)
Kaplan-Meier estimates for time to start of antineoplastic therapy (months)		
25th percentile	[redacted]	[redacted]
Median (95% CI)‡	30.2 (NYR, NYR)	NYR (21.06, NYR)
75th percentile	[redacted]	[redacted]
Kaplan-Meier event-free rate at 12 months	[redacted]	[redacted]
Treatment comparison: enzalutamide vs placebo		
Cox HR (95% CI)§	0.28 (0.20, 0.40)	
Log-rank p value§	<0.0001	

Source: Armstrong 2019[27], ARCHES CSR[23]
Data cut-off date: 14 Oct 2018
† In patients with a new antineoplastic therapy initiated for prostate cancer after randomisation, time to start of a new antineoplastic therapy was defined as the time interval from randomisation to the date of the first dose administration of the first antineoplastic therapy. In patients with no new antineoplastic therapy initiated for prostate cancer after randomisation, time to start of new antineoplastic therapy was censored on the last visit date or the date of randomisation, whichever occurred last.
‡ Calculated of Brookmeyer and Crowley method
§ Stratified by volume of disease (low vs high) and prior docetaxel use (yes vs no)
Abbreviations: ADT: androgen deprivation therapy; CI: confidence interval; ENZA: enzalutamide; HR: hazard ratio; ITT: intent-to-treat; NYR: not reached; PLA: placebo.

Figure 8 Kaplan-Meier plot of time to start of new antineoplastic therapy (ITT population)



No. at risk:												
Enzalutamide + ADT	574	559	548	438	299	174	83	28	7	1	1	0
Placebo + ADT	576	552	515	383	252	140	53	13	0	0	0	0

Source: Armstrong 2019[27]
Data cut-off date: 14 Oct 2018
In patients with a new antineoplastic therapy initiated for prostate cancer after randomisation, time to start of a new antineoplastic therapy was defined as the time interval from randomisation to the date of first dose administration of the first antineoplastic therapy. In patients with no new antineoplastic therapy initiated for prostate cancer after randomisation, time to start of new antineoplastic therapy was censored on the last visit date or the date of randomisation, whichever occurred last.
Abbreviations: ADT: androgen deprivation therapy; CI: confidence interval; Cum.: cumulative; ITT: intent-to-treat; NE: not estimable.

The most frequently used subsequent antineoplastic therapies for prostate cancer were docetaxel (1.9% in the enzalutamide plus ADT group and 9.0% in the placebo plus ADT group) and abiraterone acetate (2.3% in the enzalutamide plus ADT group and 4.9% in the placebo plus ADT group)[23, 27] (Table 14).

Table 14 Selected subsequent antineoplastic therapies for prostate cancer (ITT population)

Therapy. n (%)	ENZA + ADT (n=574)	PLA + ADT (n=576)
Overall	46 (8.0)	133 (23.1)
Docetaxel	11 (1.9)	52 (9.0)
Abiraterone acetate	13 (2.3)	28 (4.9)
Enzalutamide	4 (0.7)	28 (4.9)
Bicalutamide	4 (0.7)	12 (2.1)
Other†	14 (2.4)	15 (2.6)

Source: ARCHES CSR[23], Armstrong *et al*[27]
Data cut-off date: 14 Oct 2018
The table shows the first new antineoplastic prostate cancer therapy used on or after the date of last dose. Percentages are calculated over the ITT population. One patient in the placebo plus ADT group received a combination of docetaxel with carboplatin and another patient in that placebo plus ADT group received a combination of docetaxel with blinded therapy. Both patients are counted in both the docetaxel and the "other" categories.

† Other includes different chemotherapies and vaccines.
Abbreviations: ADT: androgen deprivation therapy; ENZA: enzalutamide; ITT: intent-to-treat; PLA: placebo.

B.2.6.1.2.3 PSA undetectable rate

The PSA undetectable rates are provided in Appendix M.

B.2.6.1.2.4 Objective response rate

Treatment with enzalutamide plus ADT was associated with a statistically significant improvement in objective response rate (ORR) compared with placebo plus ADT. The ORR as assessed by the ICR was 83.1% (147/177) for patients in the enzalutamide plus ADT group and 63.7% (116/182) for patients in the placebo plus ADT group with an absolute difference of [redacted], Table 15)[23, 27]. Similar results were observed for ORR as assessed by the investigator (non-key secondary endpoint) which was [redacted] for patients in the enzalutamide plus ADT group and [redacted] for patients in the placebo plus ADT group (an absolute difference of [redacted].

The proportion of patients with a complete response as assessed by ICR was greater for patients in the enzalutamide plus ADT group compared with the placebo plus ADT group ([redacted])[23].

Table 15 Objective response rate (ITT population)

Best RECIST 1.1 Overall Response	ICR		Investigator	
	ENZA + ADT (n = 574)	PLA + ADT (n = 576)	ENZA + ADT (n = 574)	PLA + ADT (n = 576)
Patients with measurable disease at baseline, n	[redacted]	[redacted]	[redacted]	[redacted]
Objective response† n (%)	147 (83.1)	116 (63.7)	[redacted]	[redacted]
95% CI for rate‡	[redacted]	[redacted]	[redacted]	[redacted]
Difference in rate (95% CI)‡	[redacted]		[redacted]	
P value§	<0.0001		[redacted]	
Categories, n (%)				
CR	65 (36.7)	42 (23.1)	[redacted]	[redacted]
PR	82 (46.3)	74 (40.7)	[redacted]	[redacted]
Stable disease	17 (9.6)	43 (23.6)	[redacted]	[redacted]
Non-CR/ Non-PD	0	0	[redacted]	[redacted]
PD	7 (4.0)	9 (4.9)	[redacted]	[redacted]
NA¶	1 (0.6)	5 (2.7)	[redacted]	[redacted]
Not evaluable	5 (2.8)	9 (4.9)	[redacted]	[redacted]

Source: ARCHES CSR[23], Armstrong *et al*[27]
Data cut-off date: 14 Oct 2018
The best RECIST overall response corresponded to the best assessment made at any time during the treatment period, up to the cut-off date. Patients with no postbaseline assessment at any visit were reported in the "not evaluable" category.
† Objective response: the patient achieved a CR or PR in their soft tissue disease using the RECIST 1.1 criteria.
‡ 95% CI was computed using Clopper-Pearson method based on exact binomial distribution; the asymptotic one was provided on the difference.
§ Cochran-Mantel-Haenszel score test, stratified by volume of disease (low vs high) and prior docetaxel use (yes, vs no).

¶ The ICR reassessed the baseline tumour status of these patients during postbaseline time points.
Abbreviations: ADT: androgen deprivation therapy; CI: confidence interval; CR: complete response; ENZA: enzalutamide; ICR: independent central review; ITT: intent-to-treat; NA: not applicable; PD: progressive disease; PLA: placebo: PR: partial response; RECIST 1.1: Response Evaluation Criteria in Solid Tumours version 1.1.

B.2.6.1.2.5 Time to deterioration of urinary symptoms

In the ITT population, [redacted] patients in the enzalutamide plus ADT group and [redacted] patients in the placebo plus ADT group experienced deterioration of urinary symptoms as assessed with the prostate cancer module of the EORTC QLQ-C30 (i.e., QLQ-PR25)[23]. Treatment with enzalutamide plus ADT reduced by 12% the risk of deterioration in urinary symptoms compared with placebo plus ADT treatment (HR: 0.88, 95% CI: 0.72, 1.08; p=0.2162, Table 16). The median time to deterioration of urinary symptoms was not reached in the enzalutamide plus ADT group vs 16.8 months in the placebo plus ADT group[23,27].

Table 16 Time to deterioration of urinary symptoms based on QLQ-PR25 score (ITT population)

Category **Parameter/Statistics**	**ENZA + ADT (n=574)**	**PLA + ADT (n=576)**
Patients with events†, n (%)	[redacted]	[redacted]
Kaplan-Meier estimates for time to deterioration of QLQ-PR25 score (months)		
25th percentile	[redacted]	[redacted]
Median (95% CI)‡	NYR (19.35, NYR)	16.8 (14.06, NYR)
75th percentile	[redacted]	[redacted]
Kaplan-Meier event-free rate at 12 months	[redacted]	[redacted]
Treatment comparison: enzalutamide vs placebo		
Cox HR (95% CI)§	0.88 (0.72, 1.08)	
Log-rank p value§	0.2162	

Source: ARCHES CSR[23], Armstrong *et al*[27]
Data cut-off date: 14 Oct 2018
† A deterioration in urinary symptoms was defined as an increase in the QLQ-PR25 modified urinary symptoms score (i.e., items 31 to 33) by ≥ 50% of the standard deviation observed in the QLQ-PR25 modified urinary symptoms score at baseline. In patients with deterioration, the time to deterioration was defined as the time interval between randomisation and the first deterioration in urinary symptoms at any postbaseline visit. In patients without deterioration in urinary symptoms, the time to deterioration in urinary symptoms was censored on the date the last urinary symptoms QLQ-PR25 score was calculable.
‡ Calculated by Brookmeyer and Crowley method
§ Stratified by volume of disease (low vs high) and prior docetaxel use (yes vs no)
Abbreviations: ADT: androgen deprivation therapy; CI: confidence interval; ENZA: enzalutamide; HR: hazard ratio; ITT: intent-to-treat; NYR: not yet reached; PLA: placebo; QLQ-PR25: Quality of Life Questionnaire-Prostate 25 Module.

B.2.6.1.2.6 Overall survival

Only data from the interim analysis were available at the time of submission. After a median follow-up of 14.4 months, the interim analysis of OS was based on a total of 84 deaths, i.e., 24.6% of the 342 events required for the final analysis[23,27]. There were 39 (6.8%) deaths in the enzalutamide plus ADT group and 45 (7.8%) deaths in the placebo plus ADT group. The interim analysis of OS showed a 19% reduction in the risk of death in patients treated with

enzalutamide plus ADT vs placebo plus ADT but this difference was not statistically significant (HR: 0.81, 95% CI: 0.53, 1.25; p=0.3361, Table 17). However, this was not unexpected, as the trial was not powered to show a significant OS difference at the interim analysis.

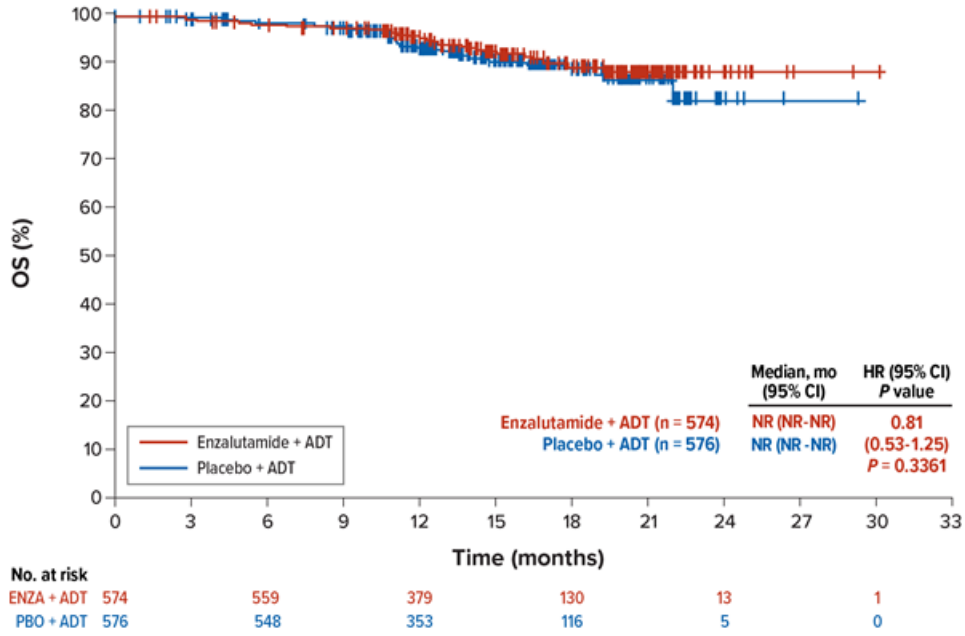
A relatively small number of death events were reported, and median OS was not reached in either treatment group. The data are considered to be immature at this time, preventing a robust characterisation of treatment effect on OS. OS data collection is ongoing and will be analysed as planned in the final analysis.

Table 17 Overall survival (ITT population)

Category **Parameter/Statistics**	**ENZA + ADT (n=574)**	**PLA + ADT (n=576)**
Deaths from any cause, n (%)	39 (6.79)	45 (7.81)
Kaplan-Meier estimates[†] (months)		
25th percentile	[redacted]	[redacted]
Median (95% CI)[‡]	NYR	NYR
75th percentile	[redacted]	[redacted]
Kaplan-Meier event-free rate at 12 months	[redacted]	[redacted]
Treatment comparison: enzalutamide vs placebo		
Cox HR (95% CI)[§]	0.81 (0.53, 1.25)	
Log-rank p value[§]	0.3361	
Primary reason for death, n (%)		
Radiographic progression	[redacted]	[redacted]
Other	[redacted]	[redacted]
Median follow-up (months)	14.4	

Source: ARCHES CSR[23], Armstrong *et al*[27]
Data cut-off date: 14 Oct 2018
[†] Time from randomisation to death from any cause. For patients still alive at the date of the analysis cut-off point, overall survival was censored on the last date the patient was known to be alive.
[‡] Calculated by Brookmeyer and Crowley method.
[§] Stratified by volume of disease (low vs high) and prior docetaxel use (yes vs no).
Abbreviations: ADT: androgen deprivation therapy; CI: confidence interval; ENZA: enzalutamide; HR: hazard ratio; ITT: intent-to-treat; NYR: not yet reached; PLA: placebo.

Figure 9 **Kaplan-Meier plot of overall survival – key secondary efficacy analysis (ITT population)**



Source: ARCHES CSR[23], Armstrong *et al*[27]
Data cut-off date: 14 Oct 2018
Time from randomisation to death from any cause. For patients still alive at the date of the analysis cut-off point, overall survival was censored on the last date the patient was known to be alive.
Abbreviations: ADT: androgen deprivation therapy; CI: confidence interval; ITT: intent-to-treat; NE: not estimable.

B.2.6.1.3 Other secondary endpoints

B.2.6.1.3.1 Time to first symptomatic skeletal event

A total of [redacted] patients in the enzalutamide plus ADT group and [redacted] patients in the placebo plus ADT group had a symptomatic skeletal event (SSE†), which was defined as radiation to bone, a surgery to bone, a clinically apparent pathological bone fracture or a spinal cord compression. Treatment with enzalutamide plus ADT was associated with a 48% reduction in the risk of a patient experiencing an SSE compared with placebo plus ADT treatment (HR: 0.52, 95% CI: 0.33, 0.80; nominal p=0.0026, Table 18). The median time to the first SSE was not reached for either treatment group[23, 27].

Table 18 **Time to first symptomatic skeletal event (ITT population)**

Category **Parameter/Statistics**	**ENZA + ADT (n=574)**	**PLA + ADT (n=576)**
Patients with SSEs†, n (%)	[redacted]	[redacted]
Kaplan-Meier estimates for time to first SSE (months)		
25th percentile	[redacted]	[redacted]
Median (95% CI)‡	NYR	NYR
75th percentile	[redacted]	[redacted]

† The definition of a SSE in ARCHES matches the definition of a skeletal-related event. In section B2, we use the same term as in ARCHES but in B3, the term skeletal-related event is used.

Category Parameter/Statistics	ENZA + ADT (n=574)	PLA + ADT (n=576)
Kaplan-Meier event-free rate at 12 months	[redacted]	[redacted]
Treatment comparison: enzalutamide vs placebo		
Cox HR (95% CI)	0.52 (0.33, 0.80)	
Log-rank p value, nominal	0.0026	

Source: ARCHES CSR[23], Armstrong *et al*[27]
Data cut-off date: 14 Oct 2018
† An SSE was defined as a radiation or surgery to bone, clinically apparent pathological bone fracture or spinal cord compression, whichever occurred first. Time to first SSE was the time from randomisation to the occurrence of the first SSE. In patients with no SSE by the time of the data cut-off point, time to SSE was censored on the last visit date or the date of randomisation, whichever occurred last.
‡ Calculated by Brookmeyer and Crowley method.
Abbreviations: ADT: androgen deprivation therapy; CI: confidence interval; ENZA: enzalutamide: HR: hazard ratio; ITT: intent-to-treat;
NYR: not yet reached; SSE: symptomatic skeletal event.

B.2.6.1.3.2 Time to castration resistance

A total of [redacted] patients in the enzalutamide plus ADT group and [redacted] patients in the placebo plus ADT group developed castration resistance, which was defined as the occurrence, in the presence of castrate levels of testosterone (<50 ng/dL), of any of the following: radiographic progressive disease (rPD), PSA progression or an SSE. Treatment with enzalutamide plus ADT was associated with a 72% reduction in the risk of a patient experiencing a castration resistance event compared with placebo plus ADT treatment (HR: 0.28, 95% CI: 0.22, 0.36; nominal p<0.0001, Table 19). The median time to castration resistance was not reached in the enzalutamide plus ADT group vs 13.9 months in the placebo plus ADT group[23, 27].

Table 19 Time to castration resistance (ITT population)

Category Parameter/Statistics	ENZA + ADT (n=574)	PLA + ADT (n=576)
Patients with castration resistance events†, n (%)	[redacted]	[redacted]
Kaplan-Meier estimates for time to castration resistance (months)		
25th percentile	[redacted]	[redacted]
Median (95% CI)‡	NYR	13.9 (11.40, 17.18)
75th percentile	[redacted]	[redacted]
Kaplan-Meier event-free rate at 12 months	[redacted]	[redacted]
Treatment comparison: enzalutamide vs placebo		
Cox HR (95% CI)	0.28 (0.22, 0.36)	
Log-rank p value, nominal	< 0.0001	
Individual components in castration resistance events (i.e., events that occurred with castrate levels of testosterone [< 50 ng/dL]), n (%)		
PSA progression	[redacted]	[redacted]
Radiographic disease progression and PSA progression	[redacted]	[redacted]

Category Parameter/Statistics	ENZA + ADT (n=574)	PLA + ADT (n=576)
Radiographic disease progression	[redacted]	[redacted]
SSE	[redacted]	[redacted]

Source: ARCHES CSR[23], Armstrong *et al*[27]
Data cut-off date: 14 Oct 2018
† 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 by ICR, PSA progression or SSE, whichever occurred first. In patients with castration resistance event, time to castration resistance was defined as the time from randomisation to the first castration-resistant event. In patients with no documented castration resistance event, the time to castration resistance was censored on the latest date from: the date of last radiologic assessment, the last PSA sample taken prior to the start of any new prostate cancer therapy and prior to 2 or more consecutive missed PSA assessments (if applicable), and the last visit date performed.
‡ Calculated by Brookmeyer and Crowley method.
Abbreviations: ADT: androgen deprivation therapy; CI: confidence interval; ENZA: enzalutamide; HR: hazard ratio; ICR: independent central review; ITT: intent-to-treat; NYR: not yet reached; PLA: placebo; PSA: prostate-specific antigen; SSE: symptomatic skeletal event.

B.2.6.1.3.3 Time to deterioration of HRQoL based on FACT-P

A total of 280 (48.78%) patients in the enzalutamide plus ADT group and 274 (47.57%) patients in the placebo plus ADT group had at least a 10-point decrease from baseline FACT-P total score[23,27,30]. The median time to deterioration of HRQoL based on the FACT-P total score was 11.3 months in the enzalutamide plus ADT group and was 11.1 months in the placebo plus ADT group. No significant difference was observed in time to deterioration of HRQoL based on the FACT-P total score between treatment arms (HR: 0.96, 95% CI: 0.81, 1.14; nominal p=0.6548, Table 20).

Table 20 Time to deterioration of HRQoL based on FACT-P Total Score (ITT population)

Category Parameter/Statistics	ENZA + ADT (n=574)	PLA + ADT (n=576)
Patients with deterioration of QoL†, n (%)	280 (48.78)	274 (47.57)
Kaplan-Meier estimates for time to deterioration of QoL based on FACT-P total score (months)		
25th percentile	5.5	3.2
Median (95% CI)‡	11.3 (11.04, 13.83)	11.1 (8.48, 13.83)
75th percentile	NYR	22.1
Kaplan-Meier event-free rate at 12 months	46.87%	47.30%
Treatment comparison: enzalutamide vs placebo		
Cox HR (95% CI)	0.96 (0.81, 1.14)	
Log-rank p value, nominal	0.6548	

Source: ARCHES CSR[23], Armstrong *et al*[27], Stenzl *et al*[30]
Data cut-off date: 14 Oct 2018
† A deterioration of QoL was defined as a decrease of at least 10 points decrease in the FACT-P total score from baseline. In patients with QoL deterioration, the time to deterioration of QoL was defined as the time interval from the date of randomisation to the first date a decline from baseline of 10 points or more in the FACT-P total score was recorded. In patients without FACT-P progression, the time to deterioration of QoL was censored on the date of the last FACT-P total score was calculable.
‡ Calculated by Brookmeyer and Crowley method
Abbreviations: ADT: androgen deprivation therapy; CI: confidence interval; ENZA: enzalutamide; FACT-P: Functional Assessment of Cancer Therapy – Prostate; HR: hazard ratio; ITT: intent-to-treat; NYR: not yet

reached; PLA: placebo; QoL: quality of life.

B.2.6.1.3.4 Time to pain progression as measured with BPI-SF

A total of 324 (56.45%) patients in the enzalutamide plus ADT group and 329 (57.12%) patients in the placebo plus ADT group experienced pain progression, defined as an increase of ≥30% from baseline in the average BPI-SF item scores[23,27]. Median time to pain progression was 8.3 months in both treatment groups. A trend towards a delay in time to pain progression was observed with enzalutamide (HR: 0.92, 95% CI: 0.78, 1.07; nominal p=0.2715, Table 21)[23,30].

Table 21 Time to pain progression based on BPI-SF (ITT population)

Category **Parameter/Statistics**	**ENZA + ADT (n=574)**	**PLA + ADT (n=576)**
Patients with pain progression†, n (%)	324 (56.45)	329 (57.12)
Kaplan-Meier estimates for time to pain progression (months)		
25th percentile	2.9	2.8
Median (95% CI)‡	8.3 (8.25, 10.91)	8.3 (5.65, 8.38)
75th percentile	19.5	19.4
Kaplan-Meier event-free rate at 12 months	37.83%	35.04%
Treatment comparison: enzalutamide vs placebo		
Cox HR (95% CI)	0.92 (0.78, 1.07)	
Log-rank p value, nominal	0.2715	

Source: ARCHES CSR[23], Armstrong *et al*[27], Stenzl *et al*[30]
Data cut-off date: 14 Oct 2018
† Pain progression was defined an increase of ≥ 30% from baseline in the average BPI-SF item scores. In patients with pain progression, time to pain progression was defined as time from randomisation to the first pain progression event. In patients with no pain progression event, time to pain progression was censored on the last visit date where BPI-SF was collected.
‡ Calculated by Brookmeyer and Crowley method
Abbreviations: ADT: androgen deprivation therapy; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; ENZA: enzalutamide; HR: hazard ratio; ITT: intent-to-treat; PLA: placebo.

B.2.6.1.4 Other efficacy endpoints

Other efficacy endpoints include EQ-5D-5L analyses, time to treatment discontinuation (TTD), combined response (soft tissue and bone lesions) and PSA reduction from baseline. The results associated to additional EQ-5D and TTD are presented here while the results of the other two endpoints are provided in Appendix M.

B.2.6.1.4.1 EQ-5D-5L

Completion rates of EQ-5D-5L were high at baseline (enzalutamide plus ADT: [redacted]; placebo plus ADT: [redacted]) and remained high (>[redacted]) for patients who remained in the study through week 97 in both treatment groups, with unadjusted completion rates of [redacted] and [redacted], for the enzalutamide plus ADT and placebo plus ADT groups respectively at week 73[33]. The completion rate during long-term follow-up was lower and ranged between [redacted] and [redacted] in the enzalutamide plus ADT group and between [redacted] and [redacted] in the placebo plus ADT

group[33]. PROs were collected during the long-term follow-up only if patients were seen in the clinic; this may have reduced the number of patients with post-progression PRO data.

Baseline scores for the items of the EQ-5D-5L suggest that patients had a relatively good quality of life at baseline and this was maintained by many patients in both arms throughout the study. The proportion of patients that scored 1 (no problems) on these items ranged between approximately [redacted] ([redacted]) – [redacted] ([redacted]) among the enzalutamide plus ADT group and between [redacted] ([redacted]) – [redacted] ([redacted]) and was comparable between patient groups. The majority of patients in both treatment arms (approximately [redacted]) did not show any change in score during the first 73 weeks[33].

Treatment with enzalutamide plus ADT [redacted] delayed median time to first clinically meaningful deterioration based on EQ-5D-5L VAS compared to the placebo plus ADT group (median time [redacted] vs. [redacted] months; HR: [redacted])[33]. [redacted][33].

Improvement rates in each treatment arm were compared using logistic regression analyses. Improvement was defined as confirmed clinical meaningful improvement at some point during the study. Only patients with baseline values above certain thresholds were included in these analyses[33]. With the primary threshold definition, improvement rates ranged from [redacted] (UK utility – mapping algorithm) to [redacted] (EQ-5D-5L VAS) among the enzalutamide plus ADT group and from [redacted] (UK utility – mapping algorithm) to [redacted] (EQ-5D-5L VAS) among the placebo plus ADT group. Similar results were observed for confirmed clinical meaningful improvement[33].

Table 22 EQ-5D-5L in ARCHES

Analysis	ENZA + ADT (n=574)	PLA + ADT (n=576)	Clinically meaningful threshold
Baseline score, mean (SD)			
VAS	[redacted]	[redacted]	[redacted]
Mapping algorithm	[redacted]	[redacted]	[redacted]
UK value set	[redacted]	[redacted]	[redacted]
Time to deterioration, median [95% CI]; HR [95% CI], p-value			
First event			
VAS	[redacted]	[redacted]	[redacted]
	[redacted]		
Mapping algorithm	[redacted]	[redacted]	[redacted]
	[redacted]		
UK value set	[redacted]	[redacted]	[redacted]
	[redacted]		
Confirmed event			
VAS	[redacted]	[redacted]	[redacted]
	[redacted]		

Analysis	ENZA + ADT (n=574)	PLA + ADT (n=576)	Clinically meaningful threshold
Mapping algorithm	[redacted]	[redacted]	[redacted]
UK value set	[redacted]	[redacted]	[redacted]
Improvement rate, n (%); OR [95% CI], p-value			
Primary threshold			
VAS*	[redacted]	[redacted]	[redacted]
Mapping algorithm†	[redacted]	[redacted]	[redacted]
UK value set#	[redacted]	[redacted]	[redacted]
Sensitivity threshold			
VAS&	[redacted]	[redacted]	[redacted]

Source: Astellas PRO report[33]. *Among patients with a baseline score ≤93. †Among patients with a baseline score ≤0.91. #Among patients with a baseline score ≤0.93. &Among patients with a baseline score ≤90.
Abbreviations: ADT: androgen deprivation therapy; CI: confidence interval; ENZA: enzalutamide; HR: hazard ratio; OR: odds ratio; PLA: placebo; VAS: visual analogue scale.

B.2.6.1.4.2 Time to treatment discontinuation

TTD was calculated for modelling purposes as “treatment end date” – “treatment start date” + 1. All patients were considered to have an event (discontinuation), unless their treatment was ongoing at the time of data cut-off, in which case these patients were censored (Figure 10).

TTD was statistically significantly longer for enzalutamide plus ADT (HR: [redacted]) with a median time to study drug discontinuation [redacted] in the enzalutamide plus ADT arm versus [redacted] months (95% CI: [redacted]) in the placebo plus ADT arm. At the data analysis cut-off date (14 Oct 2018), [redacted]) patients in the enzalutamide plus ADT group and [redacted]) patients in the placebo plus ADT group had discontinued the randomised treatment.

Figure 10 Kaplan-Meier curves for TTD (ITT population)

Source: ARCHES extrapolation report[41]

B.2.6.1.5 Key conclusions

- ARCHES was a randomised double-blind placebo-controlled study comparing enzalutamide plus ADT to placebo plus ADT in adults with mHSPC
- The primary endpoint of rPFS was met, along with most key secondary endpoints, with the exception of time to deterioration of urinary symptoms and OS. For the latter, the OS analysis was immature with only approximately 25% of the total pre-specified number of expected events having occurred at time of this analysis

Primary endpoint

- Enzalutamide plus ADT demonstrated a statistically significant 61% reduction in the risk of a patient experiencing a rPFS event compared with placebo plus ADT treatment (HR: 0.39, 95% CI: 0.30, 0.50; p<0.0001)
- The HRs for all prespecified sensitivity analyses were consistent with the primary rPFS HRs (HRs ranging from [redacted] to [redacted]), suggesting that the rPFS results are robust

Key secondary endpoints

- Compared to placebo plus ADT, treatment with enzalutamide plus ADT was also associated with[27]:
    - A statistically significant 81.0% reduction in the risk of PSA progression (HR: 0.19, 95% CI: 0.13, 0.26; p<0.0001)

- A statistically significant 72% reduction in the risk of start of a new antineoplastic therapy for prostate cancer (HR: 0.28, 95% CI: 0.20, 0.40; p<0.0001)
- A significantly higher percentage of patients with a PSA decline to an undetectable level (<0.2 ng/mL) among patients with a detectable PSA level at baseline (treatment difference: 50.5%, 95% CI: 45.3, 55.7; p<0.0001)
- A significantly higher ORR as assessed by the ICR in patients with measurable disease (absolute difference: 19.3%, 95% CI: 10.4, 28.2; p<0.0001)
- Trend towards a delay in time to deterioration in urinary symptoms (HR: 0.88, 95% CI: 0.72, 1.08; p=0.2162)

- OS data were immature at this analysis with only 24.6% of deaths required for the final analysis of OS. After a median follow-up of 14.4 months, there were 39 (6.8%) deaths in the enzalutamide plus ADT group and 45 (7.8%) deaths in the placebo plus ADT group (HR: 0.81, 95% CI: 0.53, 1.25; p=0.3361). OS data collection is ongoing and will be analysed as planned in the final analysis.

Other secondary endpoints

- Compared to placebo plus ADT, treatment with enzalutamide plus ADT was also associated with:
  - A 48% reduction in the risk of a patient experiencing an SSE (HR: 0.52, 95% CI: 0.33, 0.80; nominal p=0.0026)
  - A 72% reduction in the risk of a patient experiencing a castration-resistance event (HR: 0.28, 95% CI: 0.22, 0.36; nominal p<0.0001)
  - A [redacted] reduction in the risk of treatment discontinuation (HR: [redacted])
  - Maintenance of good HRQoL and functioning based on FACT-P total score and individual scores. No significant differences were observed for time to deterioration of HRQoL based on the FACT-P total score (HR: 0.96, 95% CI: 0.81, 1.14; nominal p=0.6548)
  - Significantly delayed time to EQ-5D VAS deterioration (HR: [redacted])
  - Trend towards delaying time to pain progression based on BPI-SF worst pain (HR: 0.92, 95% CI: 0.78, 1.07; nominal p=0.2715).

B.2.6.2 ENZAMET clinical effectiveness results

Overall, 241 (42.8%) and 235 (42.1%) patients in the enzalutamide plus ADT and NSAA plus ADT arms, respectively received concomitant docetaxel[24, 28]. Given the current use of enzalutamide in clinical practice (with ADT only) and the expected label indication for enzalutamide, only results for patients on enzalutamide plus ADT and no concomitant

docetaxel are considered relevant. These are the results reported here unless stated otherwise.

Randomisation was stratified by planned use of docetaxel. In addition, the protocol prespecified subgroup analysis for patients not on concomitant docetaxel in any treatment arm. Thus, only the comparison between patients on enzalutamide plus ADT and no docetaxel vs patients on ADT plus NSAA and no docetaxel is reported here. Comparison between the enzalutamide plus ADT with no concomitant docetaxel subgroup and the placebo plus ADT with concomitant docetaxel would be biased because of enrichment for LVD (LVD: [redacted]) and lower Gleason score (≥8: [redacted]) in the enzalutamide arm.

The ENZAMET CSR[24] provides only data regarding the primary endpoint (OS) and safety. However, the other endpoints have either been published in Davis *et al*[28] or provided by the sponsor after finalisation of the CSR.

B.2.6.2.1 Primary endpoint: overall survival (interim analysis)

As of the data cut-off date of 28 February 2019, and with a median follow-up of 37.3 months for patients not on concomitant docetaxel, 50 (16.2%) and 88 (28.1%) deaths occurred in the enzalutamide plus ADT (no concomitant docetaxel) and the NSAA plus ADT (no concomitant docetaxel) arms respectively (Table 23). A statistically 47.2% significant reduction (HR: 0.528, 95% CI 0.370, 0.743, unstratified p=0.0002) in the risk of death was observed with enzalutamide plus ADT vs NSAA plus ADT (no concomitant docetaxel; Figure 11)[24, 28].

Similar results were observed for the overall population (i.e., with and without concomitant docetaxel) with 102 (18.1%) and 143 (25.4%) deaths in the enzalutamide plus ADT and the NSAA plus ADT groups, respectively. In the overall ITT population, enzalutamide plus ADT reduced the risk of death by 33% vs NSAA plus ADT (HR: 0.67, 95% CI: 0.52, 0.86; p=0.002). A sensitivity analysis using a stratified log-rank test and Cox regression model showed an HR of 0.68 (95% CI: 0.52, 0.87, p= 0.0008) demonstrating the robustness of the primary OS result. Median OS was not reached in any arm (Table 23)[24, 28].

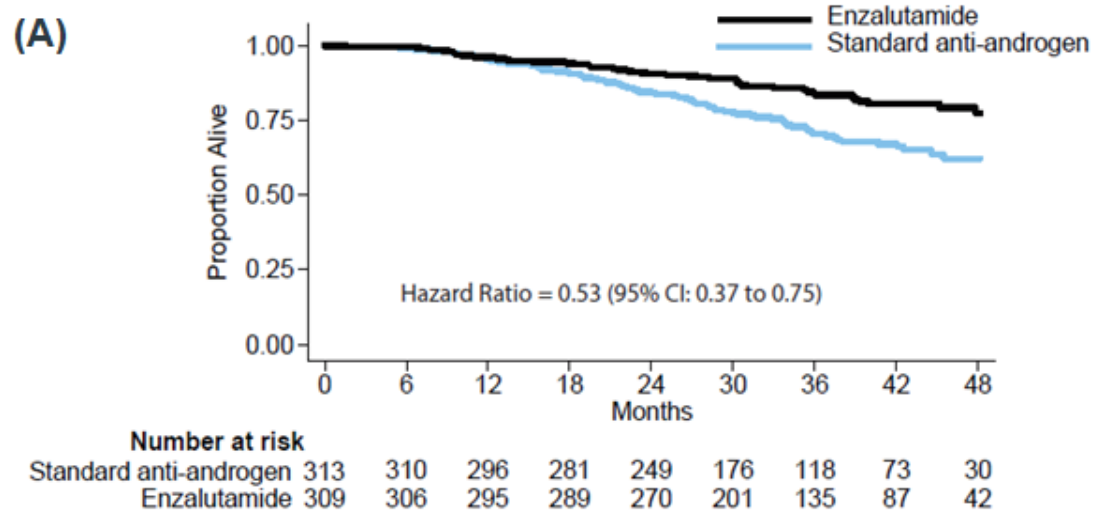
Table 23 Interim analysis of overall survival (ITT population and patients not on docetaxel)

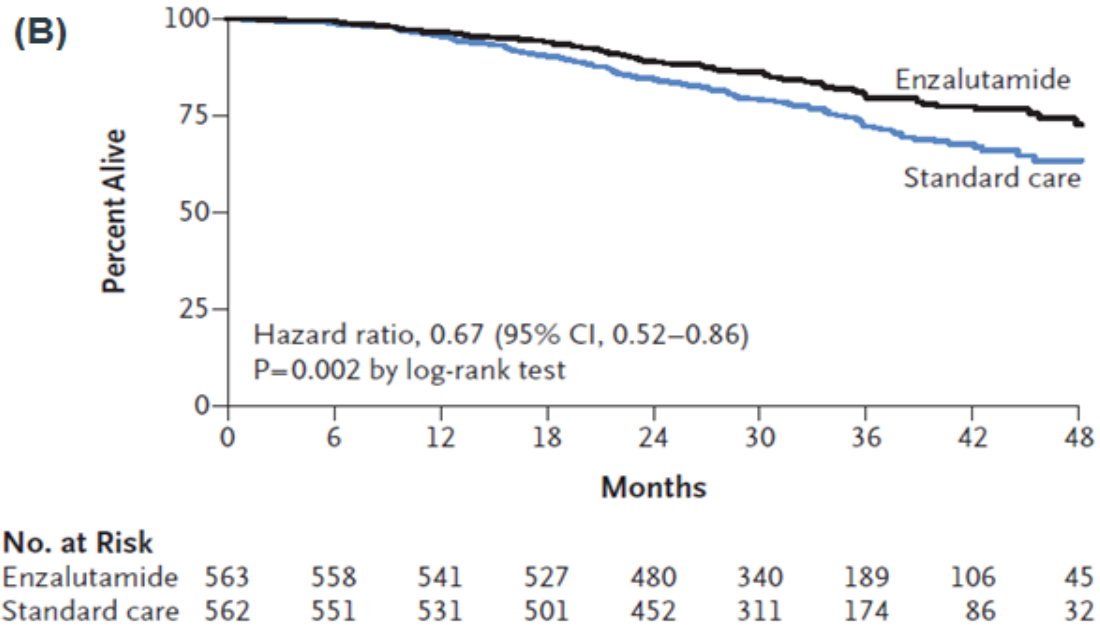
	Patients not on concomitant DOC		ITT (regardless of concomitant DOC)	
Category Parameter/statistic	**ENZA + ADT**	**Conventional NSAA + ADT**	**ENZA + ADT**	**Conventional NSAA + ADT**
Subgroup with no concomitant docetaxel				
N patients	309	313	593	562
Deaths, n (%)	50 (16.2%)	88 (28.1%)	102 (18.1)	143 (25.4)
Censored at the cut-off date, n (%)			461 (81.9)	419 (74.6)
Overall survival, Kaplan-Meier estimate (months)				
25th percentile (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Median (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
75th percentile (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment comparison: ENZA + ADT vs NSAA + ADT				
Unstratified analysis†				
Cox HR (95% CI)	0.528 (0.370, 0.743)		0.669 (0.518, 0.862)	
Log-rank 2-sided p value	0.0002		0.0018	

	Patients not on concomitant DOC		ITT (regardless of concomitant DOC)	
Category Parameter/statistic	**ENZA + ADT**	**Conventional NSAA + ADT**	**ENZA + ADT**	**Conventional NSAA + ADT**
Stratified analysis‡				
Cox HR (95% CI)§	Not available		0.675 (0.522, 0.870)	
Log-rank 2-sided p value			0.0008	
Overall survival rate, % (95% CI)¶				
Month 36	[redacted]	[redacted]	[redacted]	[redacted]
Median FU, months	Not available	Not available	33.84	33.84
Combined median FU, months	37.3		33.84	

Source: ENZAMET CSR[24]; Davis *et al*[28]
All patients randomly assigned to treatment (Intention-to-Treat Population)
Data cut-off date: 28 Feb 2019
Overall survival in months was defined as (death [or censoring] date - randomisation date)/(30.4375).
† Based on a Cox proportional hazards model. Assuming proportional hazards, HR < 1 indicated a reduction in hazard rate in favour of the enzalutamide arm.
‡ Stratification factors were volume of disease (high, low), use of early docetaxel planned (yes, no), use of antiresorptive therapy (yes, no), Adult Comorbidity Evaluation score (0 to 1, 2 to 3) and region (Europe, Australia/New Zealand, North America). If patients were incorrectly stratified at the time of randomisation, data in the electronic case report form corrected by the site were used in analysis.
§ Based on an adjusted Cox model that included the stratification factors as covariates. Assuming proportional hazards, HR < 1 indicated a reduction in hazard rate in favour of the enzalutamide arm
¶ Survival rate and 95% CI were estimated using the Kaplan-Meier method and Greenwood formula.
Abbreviations: ADT: androgen deprivation therapy; CI: confidence interval; DOC: docetaxel; ENZA: enzalutamide; FU: follow-up; HR: hazard ratio; NE: not estimable; NSAA: nonsteroidal antiandrogen

Figure 11 Kaplan-Meier plot of overall survival in (A) patients not on concomitant docetaxel and (B) overall population (ITT population)





No. at Risk									
Enzalutamide	563	558	541	527	480	340	189	106	45
Standard care	562	551	531	501	452	311	174	86	32

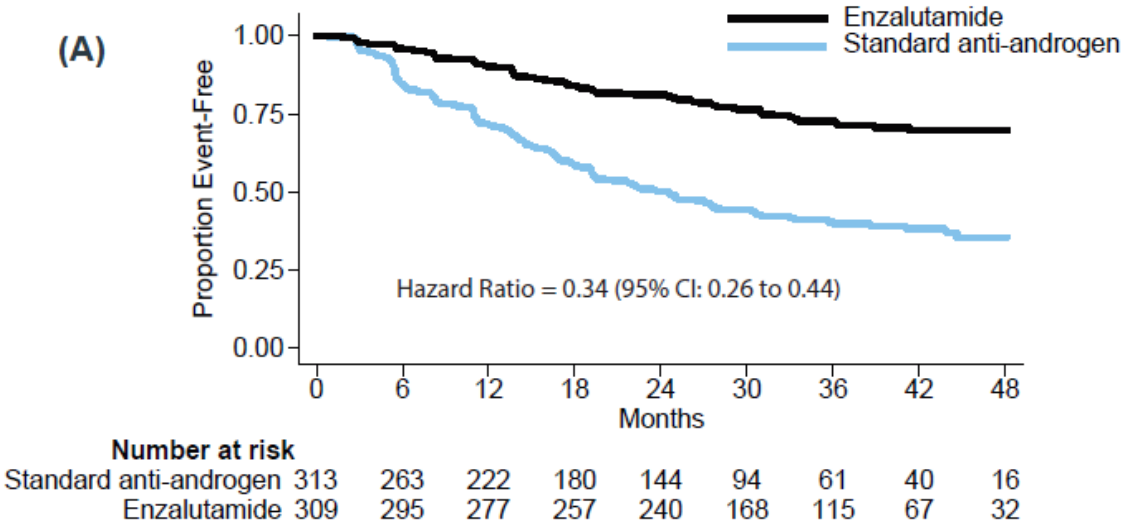
Source: Davis *et al* 2019[28]
Data cut-off date: 28 Feb 2019

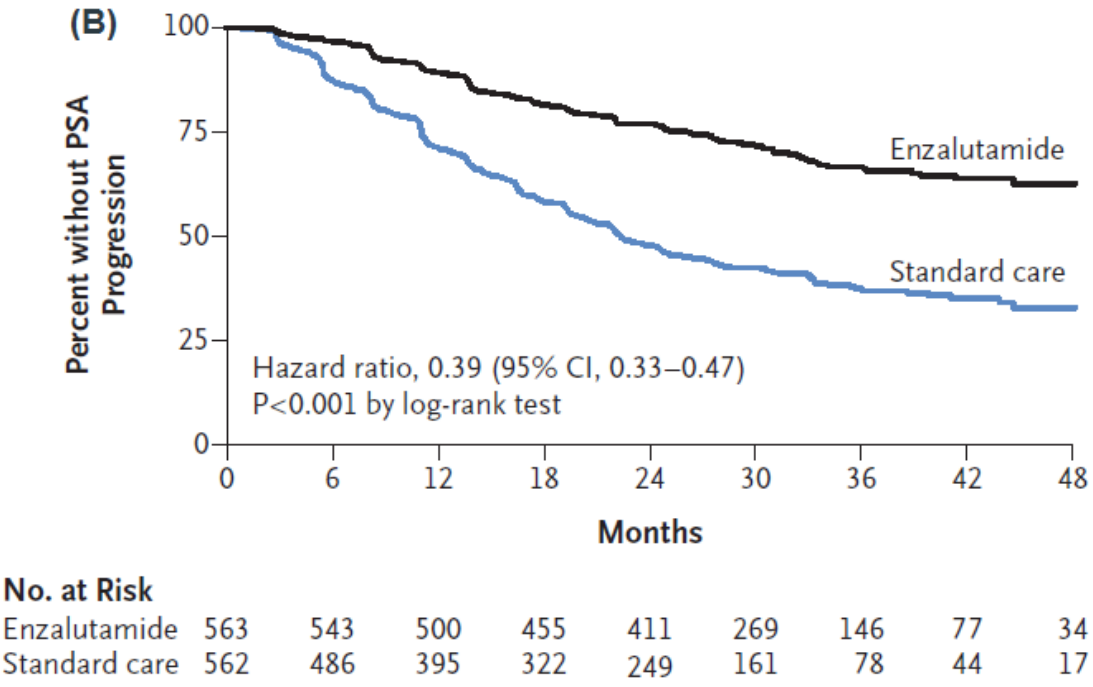
B.2.6.2.2 Secondary endpoints

B.2.6.2.2.1 PSA progression-free survival

Enzalutamide plus ADT (no docetaxel) significantly reduced by 76% the risk of PSA PFS events (HR: 0.34, 95% CI 0.26, 0.44) compared to NSAA plus ADT (no docetaxel; Figure 12A). Similar benefit was also observed in the overall population with a risk reduction of 61% (HR: 0.39, 95% CI 0.33, 0.47; p<0.001)(Figure 12B)[24, 28].

Figure 12 Kaplan-Meier plot of PSA progression-free survival in (A) patients not on concomitant docetaxel and (B) overall population (ITT population)



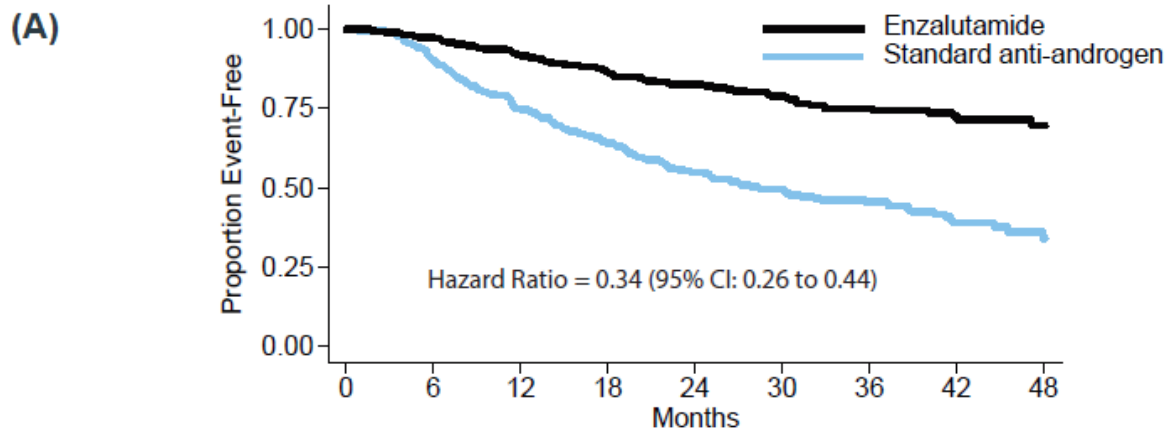


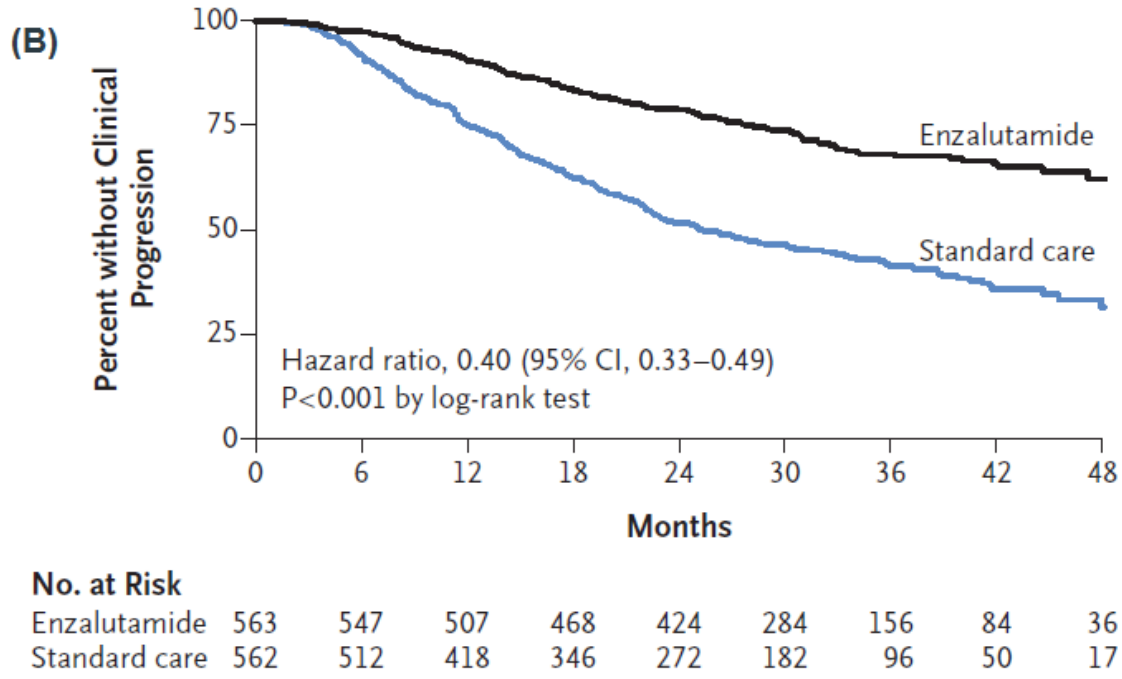
Source: Davis *et al* 2019[28]
Data cut-off date: 28 Feb 2019

B.2.6.2.2.2 Clinical progression-free survival

Enzalutamide plus ADT (no concomitant docetaxel) significantly reduced the risk of clinical PFS events by 66% (HR: 0.34, 95% CI 0.26, 0.44) compared to NSAA plus ADT (no concomitant docetaxel; Figure 13A). Similar benefit was also observed in the overall population with a risk reduction of 60% (HR: 0.40, 95% CI 0.33, 0.49; p<0.001) (Figure 13B)[24, 28].

Figure 13 Kaplan-Meier plot of clinical progression-free survival in (A) patients not on concomitant docetaxel and (B) overall population (ITT population)





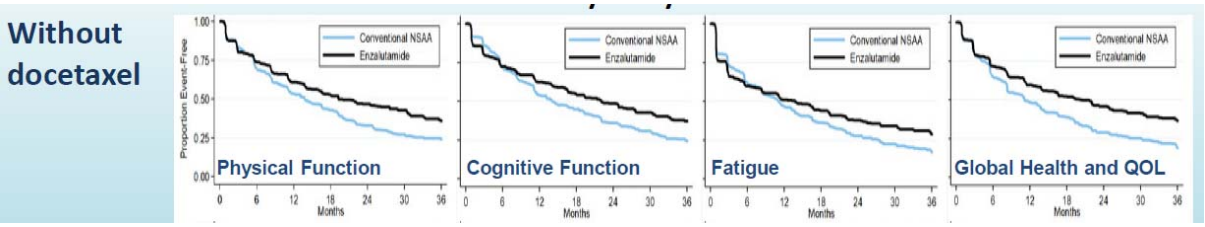
Source: Davis *et al* 2019[28]
Data cut-off date: 28 Feb 2019

B.2.6.2.2.3 HRQoL

HRQoL-related data were presented at ESMO. Data on time to deterioration for physical function, cognitive function, fatigue and global health and HRQoL for ENZAMET patients not on concomitant docetaxel were provided. Time to HRQoL deterioration was defined as the earliest of death, clinical progression, cessation of study treatment, or a 10-point worsening from baseline[35].

As shown in Figure 14, the time to deterioration consistently favoured enzalutamide plus ADT over NSAA plus ADT in the four domains[35].

Figure 14 Time to deterioration in EORTC QLQ-C30 physical function, cognitive function, fatigue and global health and quality of life in ENZAMET (cohort of patients not on docetaxel)



Source: Stockler *et al*[35]

B.2.6.2.2.4 Time to treatment discontinuation

TTD was calculated using the same assumptions as for ARCHES (see section B.2.6.1.5). All patients were considered to have an event (discontinuation), unless their treatment was ongoing at the time of data cut-off, in which case these patients were censored (Figure 15).

TTD was statistically significantly longer for enzalutamide plus ADT (HR: [redacted]) with a median time to study drug discontinuation [redacted] in the enzalutamide plus ADT arm versus [redacted] months (95% CI: [redacted]) in the NSAA plus ADT arm. At the data analysis cut-off date (28 February 2019), [redacted]) patients in the enzalutamide plus ADT group and [redacted]) patients in the NSAA plus ADT group had discontinued the randomised treatment.

Figure 15 Kaplan-Meier curves for TTD (ITT population)

[redacted]

Source: ENZAMET extrapolation report[42]

B.2.6.2.3 Key conclusions

- ENZAMET was a randomised open-label study comparing enzalutamide plus ADT to NSAA plus ADT in adult males with mHSPC.
- The primary endpoint of OS was met in patients with no concomitant docetaxel and in the overall population. Compared with NSAA plus ADT (no concomitant docetaxel), enzalutamide plus ADT reduced the risk of death by 47.2% (HR: 0.528, 95% CI 0.370, 0.743, unstratified p=0.0002)[28]
- Compared to NSAA plus ADT (no concomitant docetaxel), treatment with enzalutamide plus ADT was also associated with[28]:
    - A statistically significant 76% decrease in the risk of PSA PFS events (HR: 0.34, 95% CI 0.26, 0.44)‡
    - A statistically significant 66% decrease in the risk of clinical PFS events (HR: 0.34, 95% CI 0.26, 0.44)‡
    - A [redacted] reduction in the risk of treatment discontinuation (HR: [redacted])
    - Longer time to deterioration on EORTC QLQ-C30 physical functioning, cognitive functioning, fatigue and quality of life[35].

B.2.7 Subgroup analysis

B.2.7.1 ARCHES subgroup analyses

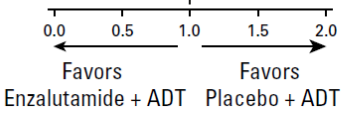
The treatment effect on rPFS of enzalutamide plus ADT vs placebo plus ADT as measured by the estimated HR was consistently favourable across all prespecified subgroups, including volume of disease at baseline, age, geographic region, baseline ECOG performance status, Gleason score at initial diagnosis, disease location at baseline, baseline PSA level, prior docetaxel use and prior use of ADT or orchiectomy[23, 27].

The HRs, using the Cox proportional hazards model, ranged from 0.20 to 0.53 for all subgroups. The upper bounds of the 95% CI for each subgroup were less than 1.0, with the exception of the small subgroup of patients with only soft tissue metastases noted at study entry (5 vs 12 events in the enzalutamide plus ADT vs placebo plus ADT groups, respectively). Importantly, subgroups of patients with high or low volume of disease, and patients with or without prior docetaxel therapy showed a strong benefit in favour of enzalutamide (95% CI excluded 1.0) (Figure 16)[23, 27]. Post hoc analyses were also conducted for other key endpoints in several patient subgroups (Table 24)[41].

‡ Estimation of the p-value for the subgroup of patients not on concomitant docetaxel was not preplanned.

Figure 16 Forest plot of rPFS - subgroup analysis (ITT population)

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)



Source: Armstrong *et al* 2019[27], ARCHES CSR addendum[32]. Data cut-off date: 14 Oct 2018
Abbreviations: ADT: androgen deprivation therapy; CI: confidence interval; E: number of events; ECOG: Eastern Cooperative Oncology Group; ITT: intent-to-treat; N: number of patients; NYR: not yet reached; PSA: prostate-specific antigen; rPFS: radiographic progression-free survival.

Table 24 Post-hoc ARCHES analyses on efficacy endpoints in mHSPC patient subgroups

Outcome	ND (n=512)	Recurrent (n=316)	Previously tx with DOC	NDHRk (n=350)	HVD (n=727)	LVD (n=423)	HRk (n=511)	LRk (n=566)
PFS[#]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS[#]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to SSE[#]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to CR[#]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TINAP[#]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to PSA progression[#]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ORR*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to pain progression[#]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Extrapolation report for ARCHES[41]

In bold, statistically significant. [#]Data are presented as hazard ratio [95% CI]; p-value. *Data are given as the difference enzalutamide plus ADT minus placebo plus ADT.

Abbreviations: CR: castration-resistance; DOC: docetaxel; HRk: high-risk; HVD: high volume disease; LRk: low risk; LVD: low volume disease; ND: newly diagnosed; NDHRk: newly diagnosed high-risk; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PSA: prostate specific antigen; TINAP: time to initiation of new antineoplastic therapy tx: treatment

.

B.2.7.2 ENZAMET subgroup analyses

For the subgroup population of patients with no concomitant docetaxel, further subgroup analyses based on the disease volume were conducted for OS, clinical PFS and TTD. Statistical significance was observed for all endpoints in both, high and low volume disease (Table 25).

Regarding OS, enzalutamide plus ADT significantly reduced the risk of mortality by 35% (HR: 0.65, 95% CI 0.42, 0.99) and 62% (HR: 0.38, 95% CI 0.21, 0.69) in high and low-volume disease patients, respectively.

Regarding clinical PFS, enzalutamide plus ADT significantly reduced the risk of clinical disease progression events by 62% (HR: 0.38, 95% CI 0.27, 0.55) and 72% (HR: 0.28, 95% CI 0.18, 0.42) in high and low-volume disease patients, respectively.

Table 25 Post-hoc ENZAMET analyses on efficacy endpoints in mHSPC patient subgroups (not on concomitant docetaxel)

Outcome	HVD (n=232)	LVD (n=390)
Clinical PFS[#]	0.38 [0.27; 0.55]; <0.001	0.28 [0.18; 0.42]; <0.0001
OS[#]	0.65 [0.42; 0.99]; 0.0450	0.38 [0.21;0.69]; 0.0015
TTD	[redacted]	[redacted]

Source: ENZAMET extrapolation analysis[42]; Davis 2019[28]
[#]Data are presented as hazard ratio [95% CI]; unstratified p-value. Abbreviations: HVD: high volume disease; LVD: low volume disease; OS: overall survival; PFS: progression-free survival; TTD: time to treatment deterioration

B.2.8 Meta-analysis

The SLR identified two RCTs assessing enzalutamide in addition to ADT in the treatment of patients with mHSPC (see Sections B.2.1 and B.2.2). No meta-analysis has been performed, but a pooled analysis of ARCHES and ENZAMET has been conducted for the total population of ARCHES and the patient subgroup with no concomitant docetaxel in ENZAMET[43].

The pooled analysis was conducted for the following endpoints: OS, TTD, and clinical PFS. For the pooled analysis these endpoints were defined as[43]:

- OS was defined as the time from randomisation to death from any cause. All events of death were included
- Clinical PFS was defined as the interval from the date of randomisation to the date of first clinical evidence of disease progression or death from any cause whichever occurs first, or the date of last known follow-up without clinical progression (at which point the observation is censored). Clinical progression was defined by progression on imaging, development of symptoms attributable to cancer progression, or initiation of other anticancer treatment for prostate cancer. An attempt to adjust the ARCHES PFS definition to match the ENZAMET clinical PFS definition was conducted by defining PFS in ARCHES as death, rPFS (according to PCWG2 criteria and documented by investigators) or start of new antineoplastic treatment. However, the definition could not be successfully matched to that in ENZAMET because no data

are available for development of symptoms attributable to cancer progression in ARCHES

- TTD was derived as follows: treatment end date – treatment start date + 1. All patients were considered to have an event (treatment discontinuation), unless their treatment was ongoing at the time of data cut-off, in which case these patients were censored.

Regarding OS, survival after a median of 14.4 months was comparable between ARCHES and ENZAMET. Based on the Kaplan-Meier method, the percentage of patients alive after a median follow-up of 14.4 months was 92.9% and 91.4% in the enzalutamide plus ADT and the ADT alone arms, respectively in ARCHES, and [redacted] and [redacted] in the enzalutamide plus ADT and the ADT plus NSAA arms, respectively in ENZAMET. This suggests that the differences in OS observed between the studies is likely due to differences in median follow-up.

The results of the pooled analyses are summarised in Table 26 and Figure 17.

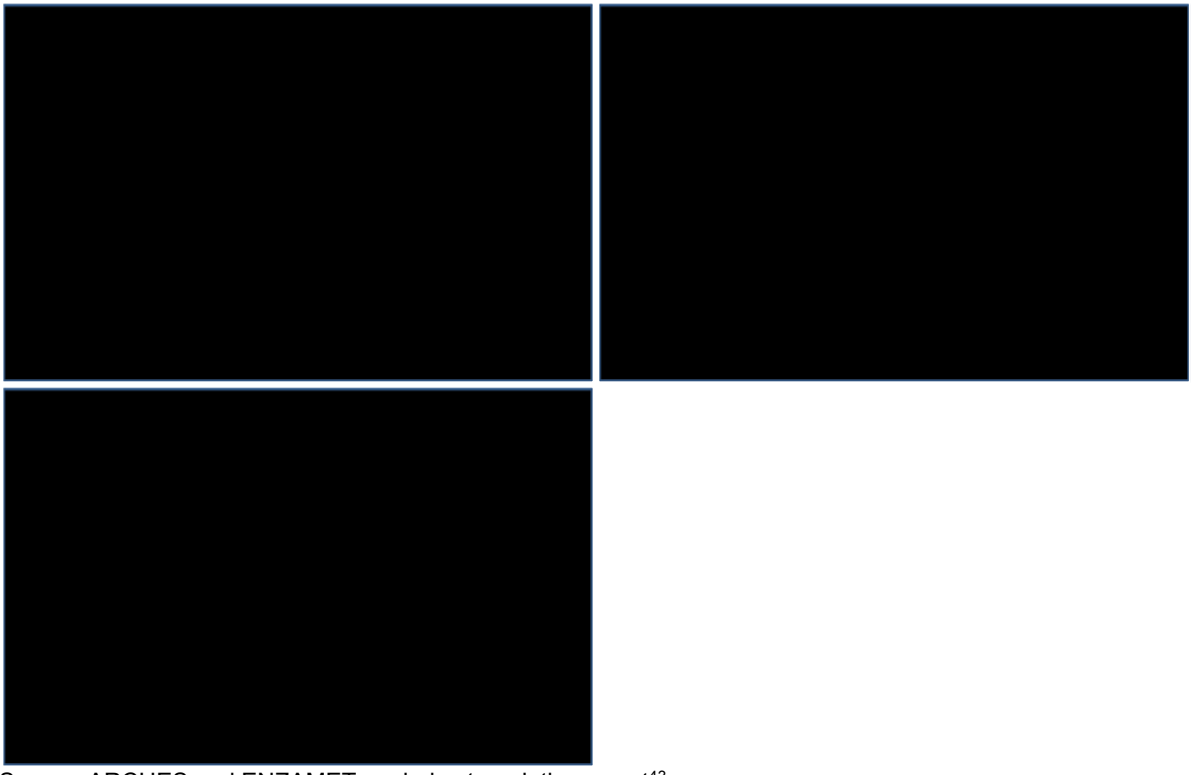
Table 26 Results of the pooled ARCHES and ENZAMET data

Outcome		All patients (no concomitant DOC)	
		ENZA+ADT	ADT±NSAA
OS	N	[redacted]	[redacted]
	N events	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	HR [95% CI]; p-value*	[redacted]	
Clinical PFS	N	[redacted]	[redacted]
	N events	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	HR [95% CI]; p-value*	[redacted]	
TTD	N	[redacted]	[redacted]
	N events	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	HR [95% CI]; p-value*	[redacted]	

Source: ARCHES and ENZAMET pooled extrapolation report[43]

*Cox regression model with stratification. Abbreviations: ADT: androgen deprivation therapy; CI: confidential interval; DOC: docetaxel; ENZA: enzalutamide; HR: hazard ratio; NSAA: non-steroidal anti-androgen; NYR: not yet reached; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation.

Figure 17 Kaplan Meier for the (A) OS, (B) clinical PFS and (C) TTD for the pooled analysis



Source: ARCHES and ENZAMET pooled extrapolation report[43]
Abbreviations: OS: overall survival; PFS: progression-free survival; TTD: time to treatment deterioration.

B.2.9 Indirect and mixed treatment comparisons

Twenty[§] studies meeting the selection criteria for the network meta-analysis (NMA) relevant to this submission were identified using the strategy described in appendix D. No additional searches were conducted for the NMA. Following identification of relevant studies, the next stage was to assess the comparability of the trials and to determine whether it would be appropriate to combine the trials in an NMA.

The NMA was conducted as part of due diligence to prepare for European submissions including the NICE submission. The NMA included comparators that are not relevant for this submission (e.g., abiraterone, apalutamide or radiotherapy). Only those studies informing the comparisons relevant for this submission are discussed. Unless stated otherwise, all information provided for the NMA in this section relates to the NMA comparisons relevant for this submission.

B.2.9.1 Trial selection and inclusion

Details of the inclusion criteria and rationale employed for the NMA are presented in Table 27. For this submission the relevant interventions were ADT alone (including orchiectomy or LHRH analogues, such as goserelin, buserelin and leuprorelin), monotherapy with bicalutamide and docetaxel. As already discussed in Table 1, abiraterone was not

considered a relevant comparator because it was not standard of care at the time of this submission.

Table 27 Eligibility criteria for the network meta-analysis

PICOS	Inclusion criteria	Rationale
Population	• Adult patients (≥18y) with mHSPC*	The goal is to assess the relative efficacy of enzalutamide vs current standard of care in the mHSPC setting and treatments expected to be standard of care in the near future[#]
Intervention	• ADT alone including orchiectomy or LHRH analogues, such as goserelin, buserelin and leuprorelin[#] • Abiraterone[†] • Docetaxel[#] • Antiandrogens (e.g. bicalutamide, flutamide, nilutamide)[#] • Apalutamide[&] • Darolutamide[&] • Radiotherapy[&]	[#]These are the currently licensed or under development therapies in the mHSPC setting however only ADT alone, docetaxel and abiraterone are of interest for the cost effectiveness model
Comparator	• All above interventions • Placebo	
Outcome	• Radiographic progression-free survival • Overall survival • Time for first symptomatic skeletal event • Time to castration-resistance • Time to first use of new antineoplastic therapy • Time to PSA progression • Time to treatment discontinuation	These outcomes are considered the most relevant ones in the context of the cost effectiveness model
Study design	• Randomised clinical trials (RCTs) with any blinding status	RCTs are the gold standard of clinical evidence, minimising the risk of confounding and allowing the comparison of the relative efficacy of interventions

Source: Astellas NMA[44]
*In case of studies including mixed populations only those reporting outcomes separately for mHSPC patients were included. [#]For this submission the comparators for the network evidence were limited to ADT alone, monotherapy with bicalutamide and docetaxel. [†]Although abiraterone was not a relevant comparator for this submission, studies comparing abiraterone plus ADT to ADT alone were included in the evidence network. [&]These were included in the network meta-analysis conducted to support European health technology appraisals but are not within the remit of this submission.
Abbreviations: ADT: androgen deprivation therapy; LHRH: luteinising hormone--releasing hormone; mHSPC: metastatic hormone-sensitive prostate cancer; PSA: prostate-specific antigen; RCTs: randomised clinical trials

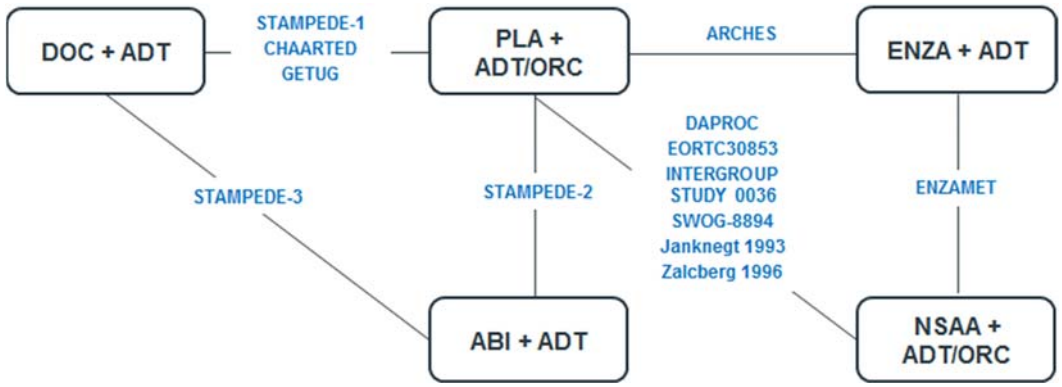
Out of the 41 studies identified in the SLR, 20[§] studies (24 publications) comparing five treatments met the selection criteria for the NMA base case (i.e., for the total mHSPC population). However, seven of the studies comparing CAB/MAB to ADT alone were deemed non-eligible for inclusion to the NMA evidence due to limited information on the

[§] Each STAMPEDE arm comparison is considered a single study. STAMPEDE-1 corresponds to the comparison between docetaxel plus ADT vs SoC, STAMPEDE-2 corresponds to the comparison between abiraterone plus ADT vs SoC, and STAMPEDE-3 corresponds to the comparison between abiraterone plus ADT vs docetaxel plus ADT.

patient characteristics and/or number of patients at risk or number of events been given in the publications, small sample size or cross-switching that would bias the results. Overall, only 13 studies comparing 5 treatments were included in the NMA relevant to this submission and only these studies are discussed in this report.

The evidence network informing this submission is provided in Figure 18. Studies comparing abiraterone plus ADT vs ADT alone were included in the evidence network to enrich it but abiraterone is not considered a relevant comparator for this submission.

Figure 18 Evidence network used for this submission for the full mHSPC population



Source: edited from NMA Report[44]
Abbreviations: ABI: abiraterone; ADT: androgen deprivation therapy; DOC: docetaxel; ENZA: enzalutamide; NSAA: non-steroidal antiandrogen; ORC: orchiectomy; PLA: placebo.

B.2.9.2 Comparability of the 20 studies eligible studies and heterogeneity

Heterogeneity was defined as variability among studies such that it could influence the observed intervention effects, making them differ from each other more than it would be expected due to random error alone.

Statistical heterogeneity was assessed for each outcome. For each pairwise comparison that was informed by at least two trials, an ordinary meta-analysis was performed (using the standard frequentist approach to pairwise meta-analysis). In addition to the statistical heterogeneity, an explorative analysis was carried out, in order to list all the potential sources of heterogeneity. The potential heterogeneity sources were partitioned in two distinct classes:

- Clinical heterogeneity refers to the potential sources originating from differences in patient characteristics that could influence study-specific effect estimates. In particular, these differences can be due to varying inclusion and exclusion criteria among the trials or to peculiar characteristics of the sampled individuals;
- Methodological heterogeneity on the other hand includes potential causes of bias explained by study design and variation in the definition of the outcomes of interest.

Based on the findings of the clinical and methodological heterogeneity, only 13 of the 20 studies were included in the master evidence network for NMA. An overview of the studies eligible for the NMA and that informed the treatment comparisons relevant for this submission is provided in Table 28.

Table 28 Overview of the eligible studies for the NMA

Study	Study design	Interventions	Primary endpoint	Source
ARCHES	Ph III RCT, DB, MN	ENZA+ADT (n=574) PLA+ADT (n=576)	rPFS	CSR[23]
CHAARTED	Ph III RCT, DB	DOC+ADT (n=397) PLA+ADT (n=393)	OS	Sweeney 2015[17] Kyriakopoulos 2018[45] Gravis 2018[46]
GETUG-AFU 15	Ph III RCT, OL	DOC+ADT (n=192) PLA+ADT (n=193)	OS	Gravis 2013[15] Gravis 2016[47] Gravis 2018[46]
ENZAMET	Ph III RCT, OL	ENZA+ADT (n=309) NSAA+ADT (n=313)	OS	CSR[24] Davis 2019[28]
STAMPEDE-1*	Ph II OL, multi-centre, RCT	DOC+ADT (M1: n=362/592; 61%) PLA+ADT (M1: n=724/1184; 61%)	OS	James 2016[48]
STAMPEDE-2		ABI+ADT (M1: n=500/960=52%) PLA+ADT (M1: n=502/957=53%)		James 2017[49] Hoyle 2018[50]
STAMPEDE-3		DOC+ADT (M1: n=115/189=61%) ABI+ADT (M1: n=227/377=60%)		Sydes 2018[51]
DAPROC	RCT	GOS+FLU (n=129) ORC (n=133)	Objective assessment of disease progression	Iversen 1990[52]
EORTC 30852	Ph III, RCT, MN	GOS+FLU (n=164) ORC (n=163)	Not specified	Denis 1990[53],1991[54], 1993[55]
IPCSG	RCT	GOS+FLU (M1/M0: n=11/15) GOS (M1/M0: n=11/13)	Not specified	Jurincic 1991[56]
Tyrrell 1991	RCT, MN	GOS+FLU (M1/M0: n=149/138) GOS (M1/M0: n=151/133)	Not specified	Tyrrell 1991[57]
INTERGROUP STUDY 0036	Ph III RCT, DB	LEU+FLU (n=303) LEU+PLA (n=300)	OS	Benson 1991b [58] Crawford 1990a[59] Crawford 1990b[60]
Navratil 1987	RCT, DB	BUS+NIL (n=23) BUS+PLA (n=26)	Not specified	Navratil 1987[61]
NTR130	RCT	INT (CPA) (n=131) CONT (CPA) (n=127)	Time to PSA progression	Verhagen 2014[62]
Beland 1991a Beland 1991c	RCT, DB	ORC+NIL (n=105) ORC+PLA (n=103)	Not specified	Beland 1991a[63] Beland 1991c[64]

Study	Study design	Interventions	Primary endpoint	Source
SWOG-8894	RCT, DB	ORC+FLU (n=700) ORC+PLA (n=687)	Death from any cause	Eisenberger 1998[65]
Janknegt 1993 Dijkman 1991	RCT, DB, MN	ORC+NIL (n=225) ORC+PLA (n=232)	Not specified	Janknegt 1993[66] Dijkman 1991[67]
Beland 1988	RCT, DB	ORC+NIL/BUS+NIL (n=107) ORC+PLA (n=77)	Not specified	Beland 1988[68]
Namer 1990/1988	RCT, DB	ORC+GOS (M1/M0: n=65/7) ORC+PLA (M1/M0: n=64/14)	Not specified	Namer 1990[69] Namer 1988[70]
Zalcberg 1996	RCT, DB	ORC+FLU (n=112) ORC+PLA (n=110)	Not specified	Zalcberg 1996[71]

*The study included locally advanced and metastatic patients. The ample size mentioned in the table corresponds to the metastatic patient subgroup. Abbreviations: ADT: androgen deprivation therapy, APA: apalutamide, BUS: buserelin, DB: double-blind; ENZA: enzalutamide, FLU: flutamide, GOS: goserelin, LEU: leuprorelin, M0: non-metastatic subgroup; M1: metastatic subgroup; MN: multinational; NIL: nilutamide, NSAA: non-steroidal antiandrogen, OL: open label; ORC: orchiectomy, PLA: placebo; Ph: phase, RCT: randomised clinical trial; RT: radiotherapy

Clinical heterogeneity:

The clinical heterogeneity of the clinical studies eligible for the NMA was analysed.

The study population differed across studies. The STAMPEDE trial randomised metastatic and non-metastatic HSPC patients however, only results from the metastatic subgroup was considered for this analysis. Metastatic and non-metastatic patients were also included in IPCSG[56], Tyrrell 1991[57] and Namer 1990[69] but only data for the metastatic cohort was used in the NMA. The remaining studies included a heterogenous population of mHSPC patients that included high and low risk.

In terms of patient characteristics, in GETUG-AFU 15[15, 47], more patients had ECOG 0 while fewer had high-volume disease and a Gleason score ≥8 than in the other studies included in the NMA (Table 29); these data suggest that patients in GETUG-AFU 15 may have had a better prognosis. For this reason, GETUG-AFU 15 was included in the base case but a sensitivity scenario was run excluding it. Gravis 2018[46] published pooled OS results from GETUG-AFU 15 and CHAARTED and stated that there was no statistical heterogeneity between subgroups defined by high and low volume, although the proportions were different in the two studies. This reinforces our proposal to include GETUG-AFU 15 in the base case, despite the lower percentage of high-volume patients.

For the 13 studies comparing CAB/MAB vs ADT alone, very limited patient characteristics were available in the corresponding publications, thus a heterogeneity assessment was not possible. Three out of 13 studies did not state neither HRs nor include Kaplan-Meier (KM) curves of all-cause mortality, thus they could not be used in the analysis. For the remaining ten articles that included KM-curves, four were further excluded for the following reasons:

- IPCSG (Jurincic 1999): sample size was 11 patients per arm in the metastatic population, thus the KM curves were highly uncertain[56]
- Tyrrell 1991: neither number at risk, nor the total number of events was reported, thus estimations using the algorithm published by Guyot *et al* 2012 would provide highly uncertain results, as the authors stated[72].
- Beland 1991a: authors stated that patients on placebo switched to nilutamide when they progressed, thus this KM-curve was excluded as treatment switching would potentially have confounded any treatment effect[63]
- Namer 1988: similar to Tyrrell 1991, neither number at risk, nor the total number of events was reported[70].

There was some variation in the definitions of “previous local therapy” in the different studies:

- ARCHES and CHAARTED: primary radiation or prostatectomy
- ENZAMET: included local surgeries (radical prostatectomy, TURP procedure), local radiotherapy (prostate including lymph nodes, prostate not including lymph nodes), or other local treatment (NanoKife™, green light laser prostatectomy, low dose rate brachytherapy, high-intensity focused ultrasound, or laser cryoablation).

Regarding concomitant treatment, in ENZAMET, patients were allowed up to 6 cycles of concomitant docetaxel (75 mg/m^2), as long as the decision to use early docetaxel was made

and specified prior to randomisation and the patients had received no more than 2 cycles prior to randomisation. Given the current use of enzalutamide in clinical practice (with ADT only) and the expected label indication, the combination of enzalutamide plus ADT and docetaxel was not considered a relevant comparator for the NMA. Only results for patients on enzalutamide plus ADT and no concomitant docetaxel were included in the NMA.

Regarding endpoints, PFS results from the studies assessing CAB/MAB were not used in this NMA, as the definitions provided in the articles were unclear, and imaging techniques and frequency of scanning were markedly different to the recent prostate cancer studies. The CAB/MAB studies were all older than the other studies and reporting was less clear than the recent ones.

Table 29 Patient characteristics for the eligible studies for the NMA

Study	ECOG=0 (%)	Gleason Score ≥8 (%)	High volume disease (%)	Previous local therapy (%)	Previous Docetaxel use (%)
ARCHES	ENZA+ADT: 78% PLA+ADT: 77%	ENZA+ADT: 67% PLA+ADT: 65%	ENZA+ADT: 62% PLA+ADT: 65%	ENZA+ADT: 21% PLA+ADT: 22%	ENZA+ADT: 17.9% PLA+ADT: 17.7%
CHAARTED	DOC+ADT: 70% PLA+ADT: 69%	DOC+ADT: 61% PLA+ADT: 62%	DOC+ADT: 66% PLA+ADT: 64%	DOC+ADT: 27% PLA+ADT: 27%	Exclusion criteria: Prior chemotherapy in adjuvant or neoadjuvant setting
GETUG-AFU 15	DOC+ADT: 99% PLA+ADT: 96%	DOC+ADT: 55% PLA+ADT: 59%	DOC+ADT: 48% PLA+ADT: 47%	DOC+ADT: 32% PLA+ADT: 24%	Exclusion criteria: previous chemotherapy for metastatic disease Allowed: In the neo adjuvant and adjuvant settings or in the context of isolated PSA increase, previous chemotherapy or ADT, or both, were allowed, with the condition that the treatment had been discontinued at least 12 months before inclusion in the study and no metastases or PSA increase had been documented during this period. The number of patients receiving (neo)adjuvant treatment was not reported.
ENZAMET	[redacted]	[redacted]	[redacted]	[redacted]	Patients who had already commenced docetaxel prior to study entry were eligible if they were tolerating full doses of docetaxel (75 mg/m^2) with ADT and met all eligibility criteria for the study while receiving docetaxel and had no more than 2 cycles prior to randomisation. However, data on patients taking concurrent docetaxel were excluded from the NMA
STAMPEDE-1	DOC+ADT: 78% PLA+ADT: 78%	DOC+ADT: 74% PLA+ADT: 68%	Overall: 60-64%	DOC+ADT: 4% PLA+ADT: 5%	Exclusion criteria: Prior chemotherapy for prostate cancer (excluding patients receiving docetaxel as part of the new SOC)
STAMPEDE-2	ABI+ADT: 78% PLA+ADT: 78%	ABI+ADT: 74% PLA+ADT: 75%	Overall: 55.4%	ABI+ADT: 7% PLA+ADT: 5.2%	
STAMPEDE-3	DOC+ADT: 79% ABI+ADT: 80%	DOC+ADT: 81% ABI+ADT: 75%	NR	DOC+ADT: 5.2% ABI+ADT: 11.9%	
DAPROC	NR	NR	NR	NR	NR
EORTC 30852	NR	NR	NR	NR	NR
IPCSG	NR	NR	NR	NR	NR
Tyrrell 1991	NR	NR	NR	NR	NR

Study	ECOG=0 (%)	Gleason Score ≥8 (%)	High volume disease (%)	Previous local therapy (%)	Previous Docetaxel use (%)
INTERGROUP STUDY 0036	LEU+FLU: 93% LEU+PLA: 94%	NR	NR	NR	NR
Navratil 1987	NR	NR	NR	NR	NR
NTR130	NR	NR	NR	38 patients from the total population	NR
Beland 1991a Beland 1991c	NR	NR	NR	NR	NR
SWOG-8894 Eisenberg 1998	NR	NR	NR	NR	NR
Janknegt 1993 Dijkman 1997	NR	ORC+NIL 41% ORC+PLA 42%	NR	ORC+NIL 10% ORC+PLA 12%	NR
Neland 1988	NR	NR	NR	NR	NR
Namer 1988 Namer 1990	NR	NR	NR	NR	NR
Zalcberg 1996	ORC+FLU: 52% ORC+PLA: 45%	NR	NR	NR	NR

*Only relevant for the newly diagnosed high-risk analyses.
Abbreviations: ABI: abiraterone, ADT: androgen deprivation therapy, AR: androgen receptor; ENZA: enzalutamide, FLU: flutamide, LEU: leuprorelin, LHRH: luteinizing hormone–releasing hormone; NIL: nilutamide, NMA: network meta-analysis; NR: not reported; NSAA: non-steroidal antiandrogen, ORC: orchiectomy, PLA: placebo; PSA: prostate-specific antigen.

Methodological heterogeneity:

Methodological heterogeneity in terms of study design and variation in the definition of the outcomes of interest was also assessed.

In CHAARTED[17], a clinical PFS endpoint was used and defined as the time until increasing symptoms of bone metastases; progression according to RECIST, version 1.0; or clinical deterioration due to cancer according to the investigator's opinion. This definition could not be considered equivalent to the rPFS used in other studies, therefore results from clinical progression were not used in the NMA.

In ENZAMET, a clinical PFS endpoint was also used and defined as the interval from the date of randomisation to the date of first clinical evidence of disease progression or death from any cause, whichever occurred first, where clinical progression was defined by progression on imaging, development of symptoms attributable to cancer progression, or initiation of other anticancer treatment for prostate cancer. This definition could not be considered equivalent to the rPFS used in other studies and therefore the clinical PFS results were also excluded from the NMA.

In STAMPEDE-1 and STAMPEDE-2 disease progression was defined as failure-free survival (FFS) which included biochemical failure (Table 30). FFS was not included in the NMA. In contrast, STAMPEDE-3 provided results for two definitions for PFS:

- Progression-free survival (PFS) was defined as time from randomisation to the first of: new disease or progression of: distant metastases, lymph nodes or local disease; or death from prostate cancer.
- Metastatic PFS (MPFS) was defined as time from randomisation to death from any cause, new metastases or progression of distant metastases.

Results from both definitions were used in the NMA in all analyses with MPFS considered the base case.

The definitions for PFS in the other studies were considered similar (Table 30).

Table 30 PFS definitions used in the non-CAB/MAB studies included in the NMA

Study Treatments	PFS definition
ARCHES ENZ vs PLA	rPFS defined as the time from randomisation to the first objective evidence of: 1. Radiographic disease progression as assessed by central review or 2. Death (defined as death from any cause within 24 weeks from study drug discontinuation), whichever occurs first. Radiographic disease progression was defined as progressive disease by RECIST version 1.1 for soft tissue disease or by appearance of 2 or more new lesions on bone scan.
CHAARTED DOC vs PLA	The time to clinical progression was defined as the time until: 1. Increasing symptoms of bone metastases 2. Progression according to RECIST, version 1.0; 3. Clinical deterioration due to cancer according to the investigator's opinion. Death was not included.
GETUG DOC vs PLA	rPFS included radiographic progression and death (Gravis 2016)[15]

Study Treatments	PFS definition
ENZAMET ENZ vs NSAA	Clinical PFS: defined as the interval from the date of randomisation to the date of first clinical evidence of disease progression or death from any cause, whichever occurs first, where clinical progression: defined by progression on imaging, development of symptoms attributable to cancer progression, or initiation of other anticancer treatment for prostate cancer.
STAMPEDE DOC, ABI, SOC	FFS was defined as time from randomisation to first evidence of at least one of: • Biochemical failure (a rise of 50% above the within-24-week nadir and above 4 ng/mL and confirmed by retest or treatment) • Progression either locally, in lymph nodes, or in distant metastases • Death from prostate cancer. PFS was defined as time from randomisation to the first of: • New disease or • Progression of: distant metastases, lymph nodes or local disease; or • Death from prostate cancer. MPFS was defined as time from randomisation to • Death from any cause • New metastases or • Progression of distant metastases.
LATITUDE* ABI vs PLA	Time from randomisation to the occurrence of: • Radiographic progression or • Death from any cause. Radiographic progression of soft-tissue lesions was evaluated by either CT or MRI on the basis of RECIST, version 1.1. Progression on bone scanning was assessed by adaptation of Prostate Cancer Working Group 2 criteria

*Only relevant for the newly diagnosed high-risk patient subgroup analysis.
Abbreviations: ABI: abiraterone; DOC: docetaxel; ENZA: enzalutamide, FFS: failure-free survival; MPFS: metastasis progression-free survival; NSAA: non-steroidal antiandrogen, PLA: placebo; rPFS: radiographic progression-free survival; RECIST: response evaluation criteria in solid tumours; SOC: standard of care.

B.2.9.3 Methods

The NMA was performed using Bayesian methods principles. The underlying assumption for the NMA was that while studies comparing treatments A and B may have different baseline hazards (due to differences in patients or study characteristics), the true underlying difference between A and B was either constant across studies (leading to the use of a fixed-effect model) or exchangeable (leading to the use of a random-effects model). It was assumed that there was no variation between studies that could influence the size of the treatment effect (such characteristics are commonly referred to as “effect modifiers”)[44].

Both a fixed-effect (FE) model and a random-effect (RE) model were developed. Random-effect models were fitted only for the networks where >1 study informed at least one comparison[44].

B.2.9.3.1 Fixed-effect model

A FE model for the log HR was developed as described in the NICE technical Decision Support Unit (DSU) Technical Support Document 2[73]. It was assumed that the log HR follows a normal distribution. For each study, it was necessary to define a baseline treatment

to which all other treatments were compared. For ease of interpretation it was placebo (unless the study did not include placebo), however, the choice of baseline treatment did not affect the results.

- Define L_{jkb} as the observed log HR for treatment k relative to treatment b in trial j;
- Define σ_{jkb} as the standard error of the log HR for treatment k relative to treatment b in trial j.

For each treatment, other than the baseline treatment:

$L_{jkb} \sim \text{Normal}(\theta_{kb}, \sigma_{jkb}^2)$ (Equation 1)

where:

$\theta_{kb} = \delta_k - \delta_b$ (Equation 2)

The parameters δ_k and δ_b were the true log HRs for treatment k relative to placebo, and treatment b relative to placebo. The parameters δ_k and δ_b were given vague prior distributions:

$\text{Normal}\ (0,100^2)$.

B.2.9.3.2 Random-effect model

The RE model assumed that the true treatment effect observed in each trial was itself the realisation of a random variable which was usually assumed to be normally distributed. The variability of each trial estimate was increased due to the addition of this between-trial uncertainty. The random-effect model allows for the between-trial variability to be accounted for in the overall estimate and its standard error (SE).

The fixed-effects model can be extended to a random-effects model by replacing θ_{kb} in equation 1 with γ_{kbj}, where γ_{kbj} was the difference between active treatment k and baseline treatment b for trial j.

For the random-effects model:

$$\gamma_{kbj} \sim \text{Normal}(\theta_{kb}, \varphi^2)$$

Where θ_{kb} was defined as for the fixed effects model and φ^2 was the between-study variance. It was assumed that the between-study variance was the same for each pairwise comparison. In theory, we could assume a separate between-study variance for each comparison, however, in this case, there were not enough data to estimate separate variances.

It was necessary to define a prior distribution for the between-study variance φ^2. NMA can be sensitive to the choice of prior distribution for this parameter[74]. Hence it was important to assess the sensitivity of the model to the choice of prior distribution. Common choices in NMA include the vague prior distribution $1/\varphi^2 \sim$Gamma (0.001,0.001) and the weakly informative prior distribution $\varphi \sim$ Uniform (0,5).

For the purposes of this analysis the primary prior distribution was:

$\varphi \sim$ Uniform (0,5).

This distribution was chosen as the primary prior distribution as it was the one recommended in Woods *et al*[75].

B.2.9.3.3 Adjustment for multi-arm studies

This was not needed in this NMA given that none of the studies included more than two arms. The only exception was STAMPEDE which included several treatment arms but as already mentioned, comparisons between arms were conducted at different data cut-offs and each comparison was considered a different study.

B.2.9.3.4 Model assessment

To be able to check for convergence and analyse the dependency on the initial values, two parallel chains were run for each model. To lessen the influence of the starting values and wait for the chains to converge to the target distribution, the first 50,000 iterations were discarded as a burn-in period. To reduce the autocorrelation of the series a thinning of 10 was applied, in other words discarding 9 values out of 10 simulated by the chains. These were run long enough to collect 50,000 values for each chain after the burn-in, for a total of 100,000 values sampled from each outcome-specific posterior distribution. To assess the convergence of the Markov chain Monte Carlo models, trace plots and the Brooks-Gelman-Rubin diagnostic were reviewed[76].

The fixed-effect and random-effects models were compared using the Deviance Information Criterion (DIC)[77]. The DIC, an extension of the AIC (Akaike Information Criterion) used in the Frequentist setting, was a measure that takes into account the trade-off between goodness of fit and model complexity. The DIC does not only measure the difference in deviance but makes use of another index, indicated as p_D, the effective number of parameters. This was defined as $p_D \coloneqq \overline{D}_{model} - D(\hat{\theta})$, where $\overline{D}_{model}$ indicates the posterior mean deviance for a given model and $D(\hat{\theta})$ the deviance calculated in correspondence of a specific value $\hat{\theta}$, that in WinBUGS was the posterior mean of the parameters[78].

The DIC was defined as:

$$DIC = D(\hat{\theta}) + 2p_D = \overline{D}_{model} + p_D$$

The DIC can then be used to compare two models fitting the same data, with a lower value indicating preference. It had been suggested that differences in DIC over 5 were important, while for differences less than 3 in DIC, the change in model fit penalised for model complexity was negligible[73].

B.2.9.3.5 Assessment of inconsistency

Differences between direct and indirect estimates (inconsistency) were assessed by the Bucher method as described in the NICE DSU Technical Support Document 2[73]. For a particular treatment comparison, with estimates based on both direct evidence and indirect evidence, the statistical significance of the difference between the direct and indirect evidence was tested. Specifically, if d_d was the direct evidence estimate and d_i was the indirect evidence estimate, then the significance of their differences can be obtained from the following z-statistic:

$$z = \frac{d_d - d_i}{\sqrt{Var(d_d) + Var(d_i)}}$$

The two-sided p-value was calculated as: $2 \times \Phi(|z|)$ where $\Phi(x)$ was the cumulative distribution function of the normal distribution.

B.2.9.3.6 Sensitivity analyses

A comparison of the patient characteristics for these studies revealed some degree of heterogeneity. For this reason and due to the limited number of studies informing each comparison, except for the NSAA+ADT vs ADT comparison, two ways were identified to deal with the heterogeneity: sensitivity analyses including and excluding certain studies, and subgroup analyses on certain populations of interest.

B.2.9.3.7 Proportionality of hazards check

Proportionality of hazards was assessed for all outcomes with a KM-curve available. The KM-curve was first digitised using DigitizeIt software version 2.3.2.

The proportionality of hazards assumption check was performed using three formal statistical tests and two graphical methods as indicated in Table 31. These tests are described in Appendix D.

Table 31 Summary of the methods assessing the validity of the PH assumption

	PH assumption holds if
Statistical testing	
Cox	P-value >0.05
Schoenfeld residuals method	P-value >0.05
Martingale-based cumulative residuals or Score process method	P-value >0.05
Graphical inspection	
Log-cumulative hazard plots	Curves are parallel
Simulation graph produced by the martingale residuals	Observed score are in between the simulated ones

Source: Astellas NMA[44]. Abbreviations: PH: Proportionality of hazards

B.2.9.4 NMA input parameters

B.2.9.4.1 Total population

In addition to the base case which included the GETUG-AFU 15 and the CAB/MAB studies, three different sensitivity analyses were conducted:

- Sensitivity 1 excluding the GETUG-AFU 15 trial
- Sensitivity 2 including GETUG-AFU 15 and considering that the efficacy of ADT alone or with placebo is the same as for ADT plus a NSAA

- Sensitivity 3 excluding GETUG-AFU 15 and considering that the efficacy of ADT alone or with placebo is the same as for ADT plus a NSAA.

The input data included in the base case and different sensitivity analyses are provided in Table 32 for the studies that include the comparators of relevance for this submission and in Table 33 for the non-enzalutamide studies including a CAB/MAB arm. The latter studies were not included in the sensitivity analysis 2 and 3.

Table 32 Data available per outcome (HR [95% CI]) for non-CAB/MAB studies - total population

Outcome	ARCHES[23] ENZ vs PLA	STAMPEDE-1[48] DOC vs -	STAMPEDE-2[49] ABI vs -	STAMPEDE-3[51] ABI vs DOC	CHAARTED[45] DOC vs PLA	GETUG[15, 47] DOC vs PLA	ENZAMET[24, 28] ENZ vs NSAA	Feasible comparison
Base case and SA2								
rPFS	0.39 (0.30, 0.50)	NA	NR	PFS: 0.69 (0.50,0.95) MPFS: 0.76(0.55,1.04)	NR	0.69 (0.55,0.87)	NR	ENZ vs DOC
OS	0.81 (0.53, 1.25)	0.76 (0.62,0.92)	0.61 (0.49, 0.75)	1.13 (0.77, 1.66)	0.72 (0.59, 0.89)	0.88 (0.68,1.14)	0.53 (0.37, 0.74)	ENZ vs DOC ENZ vs NSAA
TSSE	0.52 (0.33, 0.80)	NR	0.45 (0.36, 0.58)	0.82 (0.53, 1.25)	NR	NR	NR	ENZ vs DOC
TCR	0.28 (0.22, 0.36)	NR	NR	NR	0.61 (0.52, 0.73)	NR	NR	ENZ vs DOC
TINAT	0.28 (0.20, 0.40	NR	NR	NR	NR	No HR or KM-curve available*	NR	None
TPSA	0.19 (0.13, 0.26)	NR	NR	NR	NR	0.70 (0.55, 0.89)	NR	ENZ vs DOC
TTD	[redacted]	NR	NR	NR	NR	NR	NR	None
SA1 – SA3								
rPFS	0.39 (0.30, 0.50)	NR	NR	PFS: 0.69(0.50,0.95) MPFS: 0.76(0.55,1.04)	NR	Excluded	NR	None
OS	0.81 (0.53, 1.25)	0.76 (0.62,0.92)	0.61 (0.49, 0.75)	1.13 (0.77,1.66)	0.72 (0.59, 0.89)	Excluded	0.53 (0.37, 0.74)	ENZ vs DOC ENZ vs NSAA
TSSE	0.52 (0.33, 0.80)	NR	0.45 (0.36,0.58)	0.82 (0.53,1.25)	NR	Excluded	NR	ENZ vs DOC
TCR	0.28 (0.22, 0.36)	NR	NR	NR	0.61 (0.52, 0.73)	Excluded	NR	ENZ vs DOC
TINAT	0.28 (0.20, 0.40)	NR	NR	NR	NR	Excluded	NR	None
TPSA	0.19 (0.13, 0.26)	NR	NR	NR	NR	Excluded	NR	None
TTD	[redacted]	NR	NR	NR	NR	Excluded	NR	None

Source: Astellas NMA[44]

*Only median times are reported. [a]Progression-free survival. [b]Metastases progression-free survival. Abbreviation: ABI: abiraterone; DOC: docetaxel; ENZA: enzalutamide; MPFS: metastasis progression-free survival; NR: not reported; NSAA: non-steroidal antiandrogen; OS: overall survival; PLA: placebo; PFS: progression-free survival; rPFS: radiographic progression-free survival; SA: sensitivity analysis; TSSE: time to symptomatic skeletal event; TCR: time to castration resistance; TINAT: time to initiation of new antineoplastic therapy; TPSA: time to PSA progression; TTD: time to treatment discontinuation.

Table 33 Data available per outcome (HR [95% CI]) for CAB/MAB studies - total population

Outcome	DAPROC[52] GOS+FLU vs ORC	EORTC30853[55] GOS+FLU vs ORC	Intergroup[58-60] LEU+FLU vs LEU+PLA	SWOG8894[65] ORC+FLU vs ORC+PLA	Janknegt 1993[66, 67] ORC+NIL vs ORC+PLA	Zalcberg 1996[71] ORC+FLU vs ORC+PLA
rPFS	NR	NR	NR	NR	NR	NR
OS	1.20 (0.89, 1.62)	0.76 (0.59, 0.99)	0.78 (0.26, 2.3)	0.91 (0.81, 1.01)	0.80 (0.65, 0.97)	1.15 (0.84, 1.57)
TSSE	NR	NR	NR	NR	NR	NR
TCR	NR	NR	NR	NR	NR	NR
TINAT	NR	NR	NR	NR	NR	NR
TPSA	NR	NR	NR	NR	NR	NR
TTD	NR	NR	NR	NR	NR	NR

Source: Astellas NMA[44]

Abbreviations: FLU: flutamide; GOS: goserelin; LEU: leuprorelin; NIL: nilutamide; NR: not reported; PLA: placebo; rPFS: radiographic progression-free survival; ORC: orchiectomy; OS: overall survival; TSSE: time to symptomatic skeletal event; TCR: time to castration resistance; TINAT: time to initiation of new antineoplastic therapy; TPSA: time to PSA progression; TTD: time to treatment discontinuation.

B.2.9.5 Results

A summary of the results from the NMA for the primary, as well as the sensitivity FE and RE analyses for total population are provided in the Table 34.

The NMA results for the comparison of enzalutamide plus ADT vs ADT with or without placebo are in line with the results observed in the two enzalutamide studies. Compared to ADT alone (or with placebo), enzalutamide significantly reduced the risk of disease progression by [redacted] (HR: [redacted]) in the base case and scenarios. In addition, it significantly the risk of time to symptomatic skeletal event by [redacted] (HR: [redacted]), the risk of castration resistance by [redacted] (HR: [redacted]) and the risk of PSA progression by [redacted] (HR: [redacted]) in the base case (scenarios could not be conducted for these endpoints). Regarding OS, enzalutamide significantly reduced the risk of death in the base case and all sensitivity analyses when using the FE model with HRs between [redacted] and [redacted]. When using the RE model, the HRs ranged between [redacted] and [redacted] but only reached statistical significance in the base case and sensitivity analysis 1.

NMA results for the comparison of enzalutamide plus ADT to ADT plus a NSAA were only available for OS. The statistically significantly benefit of enzalutamide plus ADT over CAB/MAB on OS was similar to that observed over ADT alone (or with placebo) with a HR of [redacted]. The NMA also showed no statistically significantly difference between ADT alone (or with placebo) and CAB/MAB in terms of OS with a HR of [redacted] (95% CrI [redacted]) with the FE model and [redacted] (95% Cr, [redacted]) with the RE model.

The NMA results for the comparison between enzalutamide and docetaxel consistently favoured enzalutamide for all endpoints and analyses (base case and sensitivity analyses). However, this benefit reached statistical significance only for [redacted], [redacted] and [redacted]. No statistical significance was observed for [redacted] or [redacted].

Table 34 NMA results (FE/RE model) for the total mHSPC population

Endpoint	Type of analysis	Model	HR (95% CrI)		
			ENZA+ADT vs ADT±PLA	ENZA+ADT vs DOC+ADT	ENZA+ADT vs NSAA+ADT
rPFS	Base case	FE	[redacted]	[redacted]	[redacted]
	Sensitivity 1	FE	[redacted]	[redacted]	[redacted]
	Sensitivity 2	FE	[redacted]	[redacted]	[redacted]
OS	Base case	FE	[redacted]	[redacted]	[redacted]
		RE	[redacted]	[redacted]	[redacted]
	Sensitivity 1	FE	[redacted]	[redacted]	[redacted]
		RE	[redacted]	[redacted]	[redacted]
	Sensitivity 2	FE	[redacted]	[redacted]	[redacted]
		RE	[redacted]	[redacted]	[redacted]
	Sensitivity 3	FE	[redacted]	[redacted]	[redacted]
		RE	[redacted]	[redacted]	[redacted]
TSSE	Base case	FE	[redacted]	[redacted]	[redacted]
TCR	Base case	FE	[redacted]	[redacted]	[redacted]
TPSA	Base case	FE	[redacted]	[redacted]	[redacted]

Source: Astellas NMA[44]
Abbreviations: ADT: androgen deprivation therapy, CrI: credible interval; DOC: docetaxel, ENZA: enzalutamide, FE: fixed effect; HR: hazard ratio; NA: not available; NMA: network meta-analysis; NSAA: non-steroidal antiandrogen, OS: overall survival; PLA: placebo; PSA: prostate specific antigen; RE: random effect; rPFS: radiographic progression-free survival. In bold, statistically significant differences.

B.2.9.6 Conclusions and uncertainties

A traditional NMA using Bayesian methods principles as described in the NICE DSU document 2[73] was performed. The NMA was informed by an SLR[26], conducted according to a pre-specified protocol with extensive searches in a range of databases.

The comparators included in the NMA for the total population were: ADT alone and docetaxel.

The main NMA findings for the total population can be summarised as:

- [redacted].

In the total mHSPC population, [redacted].

The NMA findings should be considered in the context of several limitations that were identified. Some degree of heterogeneity was revealed among the studies included in the NMA with respect to ECOG scores, HVD and LVD proportions, as well as previous local therapy or metastatic disease being newly diagnosed. The GETUG-AFU 15[15] study included patients with better prognosis, however, Gravis 2018[46] published pooled OS results from GETUG-AFU 15 and CHAARTED and stated that there was no statistical heterogeneity between subgroups defined by high and low volume, although the proportions were different in the two studies[46]. For this reason, GETUG-AFU 15 was included in the base case, however a sensitivity scenario excluding GETUG was also run for the total population and results were similar. Additionally, the studies comparing NSAA to placebo were older and provided very little information on the patient characteristics, thus it was unknown how comparable these populations were to the rest of the more recent studies in the NMA. Absence of all patient characteristics that may be considered treatment-effect modifying variables prevents the use of population-adjusted methods.

The ENZAMET study compared enzalutamide plus ADT to NSAA plus ADT. For the total population, there were studies comparing NSAA plus ADT to ADT alone or placebo, allowing to incorporate evidence from ENZAMET into the indirect comparisons of enzalutamide vs other comparators.

Finally, standard Bayesian NMA methods assume proportionality of hazards. This was tested for all outcomes that were relevant to the cost effectiveness model, i.e., rPFS, OS and TTD, and was found to hold for all cases.

The impact of potential publication bias was not explored in the NMA.

B.2.10 Safety results

This section provides safety data from ARCHES and ENZAMET. Unless stated otherwise, all data in this section originates from the ARCHES CSR[23] and the ENZAMET CSR[24]. The safety data provided for ENZAMET in this section relate to the group of patients who did not receive concomitant docetaxel unless stated otherwise.

B.2.10.1 ARCHES safety results

B.2.10.1.1 Treatment-emergent adverse events

An overview of the safety profile of enzalutamide and placebo in ARCHES is presented in Table 35.

The median duration of treatment was 12.8 and 11.6 months in the enzalutamide plus ADT and placebo plus ADT groups, respectively. The percentage of patients with any grade (85.1% vs 85.9%) or grade 3 or higher (23.6% vs 24.7%) treatment-emergent adverse event (TEAE) was comparable between both treatment groups. Similarly, the incidence rates of serious TEAEs were comparable. The percentage of patients with TEAEs leading to death was higher in the enzalutamide arm (2.4% vs 1.7%) but the percentage of total deaths was higher in the placebo arm (6.8% vs 7.8%).

Table 35 Overview of the safety profile in ARCHES (safety population)

	ENZA + ADT (n=572)		PLA + ADT (n=574)	
	n (%)	# Events	n (%)	# Events
Any TEAE	487 (85.1)	2475	493 (85.9)	2221
NCI-CTC grade 3 and 4 TEAEs	135 (23.6)	231	142 (24.7)	225
Drug-related† TEAEs	303 (53.0)	856	268 (46.7)	624
Serious TEAEs‡	104 (18.2)	189	112 (19.5)	185
Drug-related† serious TEAEs‡	22 (3.8)	34	16 (2.8)	23
TEAEs leading to death	14 (2.4)	18	10 (1.7)	11
Drug-related† TEAEs leading to death	0	0	1 (0.2)	1
TEAEs leading to permanent discontinuation of study drug	41 (7.2)	50	30 (5.2)	37
Drug-related† TEAEs leading to permanent discontinuation of study drug	16 (2.8)	19	12 (2.1)	15
TEAEs leading to dose reduction	25 (4.4)	38	11 (1.9)	13
Deaths§	39 (6.8)	NA	45 (7.8)	NA

Source: Armstrong 2019[27]; ARCHES CSR[23]
Data cut-off date: 14 Oct 2018
All randomised patients who received at least 1 dose of study drug (safety population).
A TEAE was defined as an AE that occurred or worsened at any time from the first study drug intake up to the date of end of treatment plus 30 days, study discontinuation or the start of new antineoplastic therapy, whichever occurred first. AE grading was based on NCI-CTCAE v4.03.
†Possible or probable, as assessed by the investigator, or records where relationship was missing.
‡Included SAEs upgraded by the sponsor based on review of the sponsor's list of Always Serious terms, if any

upgrade was done.
§All reported deaths after the first study drug administration.
Abbreviations: ADT: androgen deprivation therapy; AE: adverse event; #: number; ENZA: enzalutamide; NA: not applicable; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; PLA: placebo; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

TEAEs of any grade or relationship reported in at least 5% of patients in either treatment group during the study are presented in Table 36.

The most commonly reported TEAEs (≥10% of patients in either treatment group) were hot flush, fatigue, arthralgia and back pain. All-causality adverse events (all grades) with an event rate >2% higher in the enzalutamide plus ADT group compared with the placebo plus ADT group were hot flush, fatigue, hypertension, and musculoskeletal pain. Back pain was the only adverse event with an event rate >2% higher in the placebo plus ADT group compared with the enzalutamide plus ADT group. There was no all-causality adverse event reported with a 10% difference higher in the enzalutamide plus ADT group compared to the placebo plus ADT arm.

Table 36 Treatment-emergent adverse events reported in at least 5% of patients in either treatment group (safety population)

	Overall Incidence, n (%)	
MedDRA v21.0 - Preferred Term	**ENZA + ADT (n=572)**	**PLA + ADT (n=574)**
Overall	**487 (85.1)**	**493 (85.9)**
Hot flush	155 (27.1)	128 (22.3)
Fatigue	112 (19.6)	88 (15.3)
Arthralgia	70 (12.2)	61 (10.6)
Back pain	43 (7.5)	62 (10.8)
Weight increased	35 (6.1)	44 (7.7)
Hypertension	46 (8.0)	32 (5.6)
Diarrhoea	34 (5.9)	33 (5.7)
Oedema peripheral	29 (5.1)	38 (6.6)
Nausea	37 (6.5)	29 (5.1)
Asthenia	31 (5.4)	28 (4.9)
Constipation	28 (4.9)	31 (5.4)
Musculoskeletal pain	36 (6.3)	23 (4.0)
Dizziness	29 (5.1)	20 (3.5)

Source: Armstrong 2019[27]; ARCHES CSR[23]
Data cut-off date: 14 Oct 2018
All randomised patients who received at least 1 dose of study drug (safety population).
Abbreviations: ADT: androgen deprivation therapy; ENZA: enzalutamide PLA: placebo.

Grade 3 or 4 TEAEs reported in at least 1% of patients in either the enzalutamide plus ADT group or the placebo plus ADT group are presented in Table 37.

Of the grade 3 or 4 events that were reported in at least 1% of patients in either treatment group, events that occurred at a higher incidence in the enzalutamide plus ADT group compared with the placebo plus ADT group were hypertension (3.3% vs 1.7%), asthenia (1.0% vs 0.5%) and syncope (1.0% vs 0.2%).

Table 37 Grade 3 or 4 treatment-emergent adverse events reported in at least 1% of patients in either treatment group (safety population)

MedDRA v21.0 Preferred term	ENZA + ADT (n=572)	PLA + ADT (n=574)
Overall	135 (23.6)	142 (24.7)
Hypertension	19 (3.3)	10 (1.7)
Asthenia	6 (1.0)	3 (0.5)
Syncope	6 (1.0)	1 (0.2)
Anaemia	5 (0.9)	6 (1.0)
Fatigue	5 (0.9)	6 (1.0)
Urinary retention	2 (0.3)	6 (1.0)

Source: Armstrong 2019[27]; ARCHES CSR[23]
Data cut-off date: 14 Oct 2018
All randomised patients who received at least 1 dose of study drug (safety population).
Adverse event grading was based on NCI-CTCAE v4.03.
Abbreviations: ADT: androgen deprivation therapy; ENZA: enzalutamide; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; PLA: placebo.

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B.2.10.1.2 Deaths, other serious TEAEs and TEAEs leading to permanent discontinuation of study drug

TEAEs leading to death (grade 5 TEAEs) were reported to be higher in the enzalutamide plus ADT group compared with the placebo plus ADT group (2.4% vs 1.7%) (Table 38). The most commonly TEAEs leading to death in the enzalutamide pus ADT arm were [redacted] and [redacted] while the most commonly reported ones in the placebo plus ADT arm were [redacted].

Table 38 Treatment-emergent adverse events leading to death (safety population)

System organ class Preferred term	Overall Incidence, n (%)	
	ENZA + ADT (n=572)	PLA + ADT (n=574)
Overall	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Cardio-respiratory arrest	[redacted]	[redacted]
Cardiopulmonary failure	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Duodenal ulcer perforation	[redacted]	[redacted]
Gastritis erosive	[redacted]	[redacted]
Pneumoperitoneum	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]

System organ class Preferred term	Overall Incidence, n (%)	
	ENZA + ADT (n=572)	PLA + ADT (n=574)
Euthanasia	[redacted]	[redacted]
General physical health deterioration	[redacted]	[redacted]
Sudden death	[redacted]	[redacted]
Death	[redacted]	[redacted]
Sudden cardiac death	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Septic shock	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
Road traffic accident	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	[redacted]	[redacted]
Malignant neoplasm progression	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Cerebrovascular accident	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]
Completed suicide	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]

Source: ARCHES CSR[23]
Data cut-off date: 14 Oct 2018
All randomised patients who received at least 1 dose of study drug (safety population).
Sorting order: ascending order by system organ class code and descending by the number of patients of total group by preferred term. In case of ties ascending order by preferred term code is applied.
Abbreviations: ADT: androgen deprivation therapy; ENZA: enzalutamide; PLA: placebo.

TEAEs leading to permanent discontinuation of study drug were reported to be higher in the enzalutamide plus ADT group compared with the placebo plus ADT group (7.2% vs 5.2%). Results are presented in Table 39. None of the TEAEs leading to permanent discontinuation of study drug occurred in more than 2 (0.3%) patients in either treatment group[27].

Table 39 Treatment-emergent adverse events leading to permanent discontinuation of study drug in at least 2 patients in either treatment group (safety population)

MedDRA v21.0 Preferred term	Overall Incidence, n (%)	
	ENZA + ADT (n=572)	PLA + ADT (n=574)
Overall	**41 (7.2)**	**30 (5.2)**
Fatigue	[redacted]	[redacted]
Sudden death	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Bone pain	[redacted]	[redacted]
Malignant neoplasm progression	[redacted]	[redacted]
Seizure	[redacted]	[redacted]

MedDRA v21.0 Preferred term	Overall Incidence, n (%)	
	ENZA + ADT (n=572)	PLA + ADT (n=574)
Pulmonary embolism	[redacted]	[redacted]

Source: ARCHES CSR[23]
Data cut-off date: 14 Oct 2018
All randomised patients who received at least 1 dose of study drug (safety population).
Sorting order: ascending order by system organ class code and descending by the number of patients of total group by preferred term. In case of ties ascending order by preferred term code is applied.
Abbreviations: ADT: androgen deprivation therapy; ENZA: enzalutamide; PLA: placebo.

TEAEs leading to dose reduction were reported to be higher in the enzalutamide plus ADT group than placebo plus ADT group (4.4% vs 1.9%; Table 40). The most frequently reported TEAE leading to dose reduction was fatigue. TEAEs leading to dosing interruptions were comparable across both treatment groups (7.3% in the enzalutamide plus ADT group and 6.3% in the placebo plus ADT group). The TEAEs leading to dosing interruption reported in at least 2 patients of the enzalutamide plus ADT group with at least 2-fold higher incidence than the placebo plus ADT group were [redacted].

Table 40 Treatment-emergent adverse events reported leading to dose reduction in at least 2 patients in either treatment group (safety population)

MedDRA v21.0 Preferred term	Overall Incidence, n (%)	
	ENZA + ADT (n=572)	PLA + ADT (n=574)
Overall	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Memory impairment	[redacted]	[redacted]
Hot flush	[redacted]	[redacted]

Source: ARCHES CSR[23]
Data cut-off date: 14 Oct 2018
All randomised patients who received at least 1 dose of study drug (safety population).
Sorting order: ascending order by system organ class code and descending by the number of patients of total group by preferred term. In case of ties ascending order by preferred term code is applied.
Abbreviations: ADT: androgen deprivation therapy; ENZA: enzalutamide; PLA: placebo.

B.2.10.1.3 Adverse events of special interest

The frequency of adverse events of special interest (all grades) were 56.6% (324/572) in the enzalutamide plus ADT group and 50.7% (291/574) in the placebo plus ADT group[27]. Based on pre-specified combinations of preferred terms (MedDRA 21.0) related to the adverse event of special interest forming categories, the only adverse events of special interest that were grade 5 were in the enzalutamide plus ADT group (ischemic heart disease, n=1; other selected cardiovascular events, n=1; Table 41). All-causality adverse events of special

interest (all grades) that were reported at an event rate >2% higher in the enzalutamide plus ADT group compared with the placebo plus ADT group included hypertension, cognitive/memory impairment, fatigue, and fractures. The only all-causality grade ≥3 adverse event that occurred at an event rate >1% higher in enzalutamide + ADT group compared with the placebo + ADT group was hypertension[27].

The change in terminology from seizures (used in previous enzalutamide studies) to convulsions was meant to align with Medical Directory for Regulatory Activities (MedDRA) terminology. MedDRA is used to code adverse events both in clinical trials and in the post-market setting. Seizure is a MedDRA-preferred term that represents a singular event of seizure, while convulsion is a grouped term called a standardised MedDRA query (SMQ) and is composed of numerous preferred terms characteristic of a seizure event. The convulsion SMQ was used since there is no seizure SMQ available within MedDRA. Further, because the convulsion SMQ has a much broader scope, it is more likely to identify adverse events of this type and, therefore, represents a more appropriate and conservative approach to ongoing pharmacovigilance for enzalutamide.

Table 41 Overview of treatment-emergent adverse events of special interest (safety population)

MedDRA v21.0 Category	ENZA + ADT (n=572)	PLA + ADT (n=574)
	n (%)	n (%)
Convulsion	2 (0.3)	2 (0.3)
Hypertension	**49 (8.6)**	**36 (6.3)**
Neutrophil count decreased	5 (0.9)	4 (0.7)
Cognitive/memory impairment	**26 (4.5)**	**12 (2.1)**
Ischemic heart disease	10 (1.7)	8 (1.4)
Other selected cardiovascular events	13 (2.3)	9 (1.6)
Posterior reversible encephalopathy syndrome	0	0
Fatigue	**138 (24.1)**	**112 (19.5)**
Fall	21 (3.7)	15 (2.6)
Fractures	**37 (6.5)**	**24 (4.2)**
Loss of consciousness	9 (1.6)	1 (0.2)
Thrombocytopenia	3 (0.5)	3 (0.5)
Musculoskeletal events	151 (26.4)	159 (27.7)
Severe cutaneous adverse reactions	0	1 (0.2)
Angioedema	7 (1.2)	1 (0.2)
Rash	15 (2.6)	9 (1.6)
Second primary malignancies	11 (1.9)	11 (1.9)

Source: Armstrong 2019[27]; ARCHES CSR[23]
Data cut-off date: 14 Oct 2018
All randomised patients who received at least 1 dose of study drug (safety population).
All second primary malignancies recorded after the study treatment start are reported, including those recorded after the treatment-emergent period.
In bold, adverse events (all grades) that occurred at a rate > 2% higher in the enzalutamide + ADT group compared with the placebo + ADT group.
Abbreviations: ADT: androgen deprivation therapy; ENZA: enzalutamide; PLA: placebo.

B.2.10.2 ENZAMET safety results

Safety-related information for the ENZAMET patient subgroup who did not receive concomitant docetaxel is limited. An overview of the safety profile in ENZAMET for patients not on concomitant docetaxel is presented in Table 42. The percentage of patients with grade 3 or higher adverse events and serious adverse events tended to be higher with enzalutamide plus ADT than with ADT plus NSAA.

Table 42 Overview of the safety profile in ENZAMET (safety population excluding patients on concomitant docetaxel)

	ENZA + ADT (n=309)	ADT + NSAA (n=312)
AE with grade 3 or 4 and SAE of any grade	[redacted]	[redacted]
AE grade 3 or 4	[redacted]	[redacted]
SAE	[redacted]	[redacted]
SAE grade 3 or 4	[redacted]	[redacted]
SAE grade 3 or higher	[redacted]	[redacted]
Study drug-related SAE*	[redacted]	[redacted]
Study drug-related SAE leading to discontinuation of study drug	[redacted]	[redacted]
Study drug-related fatal SAE*	[redacted]	[redacted]
SAE leading to discontinuation of study drug	[redacted]	[redacted]
SAE leading to dose interruption	[redacted]	[redacted]
SAE leading to dose reduction	[redacted]	[redacted]
Fatal SAE	[redacted]	[redacted]
Death#	[redacted]	[redacted]

Source: ENZAMET CSR[24]

*Relatedness was based on investigator's assessment. #Only deaths occurred prior to or on the cut-off date.
Abbreviations: ADT: androgen deprivation therapy; AE: adverse even; ENZA: enzalutamide; NSAA: non-steroidal antiandrogen; SAE: serious adverse event.

B.2.10.2.1 Adverse events of grade 3 or 4

An overview of grade 3 or 4 adverse events is presented in (Table 43). Overall, the rate of grade 3 or 4 adverse events was higher in the enzalutamide plus ADT group than NSAA plus ADT group [redacted].

Grade 3 or 4 adverse events that occurred in >1% of patients (not on docetaxel) in either group an which were more commonly reported with enzalutamide plus ADT included [redacted].

Table 43 Overall summary of grade 3 or 4 adverse events occurring in >1% of patients in either group (safety population excluding patients on concomitant docetaxel)

	ENZA + ADT (n=309)	ADT + NSAA (n=312)
Overall	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]
Cataract	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Pain	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Lung infection	[redacted]	[redacted]
Skin infection	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
Fracture	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Arthritis	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Syncope	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]
Nephrolithiasis	[redacted]	[redacted]
Urinary retention	[redacted]	[redacted]
Haematuria	[redacted]	[redacted]
Reproductive system and breast disorders	[redacted]	[redacted]
Erectile dysfunction	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]

Source: ENZAMET CSR[24]
Data cut-off date: 28 Feb 2019
Abbreviations: ADT: androgen deprivation therapy; ENZA: enzalutamide; NSAA: nonsteroidal antiandrogen

B.2.10.2.2 Serious adverse events

Overall, [redacted] of patients in the enzalutamide and ADT arm and [redacted] of patients in the ADT plus NSAA arm reported an adverse event that met the serious adverse event (SAE) criteria. An overview of those SAEs of any grade that were reported for >1% of patients in either arm is provided in Table 44.

Those SAEs that were more frequently reported in the enzalutamide plus ADT arm than in the ADT plus NSAA arm included [redacted].

Table 44 Serious adverse events of any grade by preferred term in >1% of patients in either treatment group (safety population excluding patients on concomitant docetaxel)

	ENZA + ADT (n=309)	ADT + NSAA (n=312)
Overall	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Pain	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Lung infection	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Skin infection	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
Fracture	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Arthritis	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Cerebrovascular accident	[redacted]	[redacted]
Seizure	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]
Haematuria	[redacted]	[redacted]
Urinary retention	[redacted]	[redacted]
Urinary tract obstruction	[redacted]	[redacted]

Source: ENZAMET CSR[24]
Data cut-off date: 28 Feb 2019
Abbreviations: ADT: androgen deprivation therapy; ENZA: enzalutamide; NSAA: nonsteroidal antiandrogen

B.2.10.2.5 Key conclusions- safety

The adverse event profile observed for enzalutamide plus ADT in ARCHES and ENZAMET is broadly consistent with the known safety profile of enzalutamide. Enzalutamide has been available as a treatment for mHRPC since 2012 in the US and 2013 in Europe and more recently for nmHRPC. As of April 2019, approximately 384,000 patients had been treated worldwide with enzalutamide. No new safety signals were observed in ARCHES or ENZAMET.

B.2.11 Ongoing studies

The ARCHES trial is still ongoing for OS and will be analysed as planned in the final analysis. In ARCHES, as of the interim analysis data cut-off date, a total of 84 deaths occurred which corresponds to 24.6% of the 342 events required for the final analysis.

The ENZAMET trial is also still ongoing for OS. An updated OS analysis is planned when approximately 470 deaths have been reported.

No additional study with enzalutamide is known to be currently ongoing with nmHRPC patients.

B.2.12 Innovation

Enzalutamide is expected to obtain marketing authorisation for the totality of the mHSPC patient population in Europe. At present there is a clear unmet need for mHSPC patients. In England and Wales treatment of mHSPC patients relies on ADT and docetaxel. Clinical evidence show that ADT alone is less efficacious than docetaxel plus ADT[17, 47, 79]. However, not all mHSPC patients are suitable for docetaxel. Given its toxicity, patients need to be sufficiently fit and with no serious comorbidities. In addition, not all patients may be willing to accept chemotherapy. 'Estimations from the Cancer Drugs Fund show that only approximately 50% of people presenting with mHSPC are not sufficiently fit or willing to receive docetaxel and thus they receive ADT alone[80].

Abiraterone was granted marketing authorisation in newly diagnosed high-risk mHSPC patients at the end of 2017[81]. However, it is not yet recommended for commissioning by NICE in England, and thus, it is not used in routine clinical practice in England.

Enzalutamide has shown OS benefit in a heterogenous mHSPC patient population including newly diagnosed/de novo as well as recurrent patients. In addition, it has shown PFS benefit in different mHSPC patient subgroups regardless of risk level (high and low risk), and metastatic disease volume (HVD and LVD). This overcomes the uncertainty related to lack of consensus on the subgroup definitions to be used for patient selection[82]. The definitions of risk level and disease volume used in previous studies heavily rely on the number of metastases. The number of identified metastases may depend on the sensitivity of the imaging tests used and may differ across centres.

Treatment duration with docetaxel is shorter (6 cycles of 21 days) than with enzalutamide (treatment to be maintained until progression) which is an advantage for docetaxel, however docetaxel is associated with several disadvantages over enzalutamide e.g., need to go to hospital to receive intravenous treatment (unlike enzalutamide which is orally administered), need for regular monitoring for full blood cell count and liver function tests during treatment and risk of specific serious adverse events such as (febrile) neutropenia or thrombocytopenia or of burdensome adverse events such as sensory and motor peripheral neuropathy, which can persist for a long time once the treatment has been discontinued. In addition, not all patients with newly diagnosed mHSPC are suitable for docetaxel. In the abiraterone NICE assessment, the Cancer Drugs Fund's clinical lead noted that around 50% of people presenting with mHSPC are not fit enough for docetaxel and have ADT alone[80]. In addition, some eligible patients may simply refuse to receive chemotherapy. These patients have an important unmet need.

Compared to ADT alone, the main benefit of enzalutamide is its superior efficacy as demonstrated by the results of both ARCHES and ENZAMET.

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Overall conclusions

Enzalutamide is expected to receive regulatory approval for the treatment of the overall mHSPC population in Europe. In the UK, current management of mHSPC patients relies on docetaxel if they have newly diagnosed mHSPC and do not have any significant comorbidities/objections to receiving chemotherapy, or ADT alone for the majority of other mHSPC patients[2]. NICE has an on-going appraisal for abiraterone in the treatment of newly diagnosed high-risk mHSPC patients. But this appraisal has been on-hold for over 12 months for pricing negotiations, and so this therapy is not yet routinely available or used in the treatment of patients with mHSPC in England.

The efficacy and safety of enzalutamide in mHSPC have been evaluated in two large phase III studies (ARCHES and ENZAMET) against active control which included ADT alone or with NSAA. ARCHES included 1,150 patients with mHSPC stratified by volume of disease (high vs. low) and prior docetaxel therapy for prostate cancer (none, 1-5 cycles, or 6 cycles)[23, 27]. ENZAMET included 1,125 patients with mHSPC stratified by volume of disease (low vs. high), early use of docetaxel, anti-resorptive therapy, study sites, and comorbidities[28]. In both studies, enzalutamide showed an important treatment benefit over both ADT alone[27] or with a NSAA[28] in the overall population as well as in pre-specified patient subgroups.

In ARCHES, after a median follow-up time of 14.4 months, enzalutamide plus ADT significantly reduced the risk of radiographic disease progression (primary endpoint) by 61% (HR: 0.39; 95% CI, 0.30-0.50; p<0.001) in the overall patient population[23, 27]. Enzalutamide plus ADT also demonstrated statistically significant benefit vs. placebo plus ADT in the secondary endpoints of time to castration resistance, PSA undetectable rate, ORR, start of a new anti-neoplastic therapy, and reduction in the risk of an SSE[23, 27]. The treatment benefit of enzalutamide plus ADT vs placebo plus ADT was consistently favourable across all prespecified subgroups. The OS data were immature and failed to show a significant OS benefit in the interim analysis conducted after 84 deaths, i.e., 24.6% of the 342 events required for the final analysis. At the interim analysis, 39 (6.8%) and 45 (7.8%) deaths had occurred in the enzalutamide plus ADT and placebo plus ADT arms, respectively (HR: 0.81, 95% CI: 0.53, 1.25; p=0.3361)[23, 27]. These findings show a non-statistically significant trend towards better OS with enzalutamide; this will be confirmed or rejected in the final OS analysis expected in 2023. Given the advanced age of patients participating in the ARCHES trial (median: 70 years), a high number of OS events are needed to differentiate between age related death, which should be the same in both groups, and disease specific death, that is likely to be lower in the enzalutamide group than in the placebo arms. The median follow-up (14.4 months) at this initial analysis was likely too short to observe any marked differences. Mortality observed in the first 12 months are likely due to the advanced aged of these patients rather than the underlying metastatic disease which is expected to result in death at a later stage (after 12 months)[83].

For ENZAMET, only the evidence for those patients who did not receive concomitant docetaxel is considered in this submission. Enzalutamide is indicated with concomitant ADT but not with concomitant docetaxel[1]. Concomitant use does not reflect current clinical

practice in the UK. In ENZAMET, enzalutamide plus ADT demonstrated a statistically significant improvement in OS compared with NSAA plus ADT both in the overall population (HR: 0.67, 95% CI [0.52, 0.86]; p=0.002) and patients not on concomitant docetaxel (HR: 0.53, 95% CI 0.37, 0.74], p=0.0002)[24, 28]. After a median follow-up of 34 months for the total population, 102 (18.1%) and 143 (25.4%) deaths had occurred in the enzalutamide plus ADT and the NSAA plus ADT groups, respectively. In the subgroup with no concomitant docetaxel, the number of deaths was 50 (16.2%) and 88 (28.1%), respectively (after a median of 37 months). The median survival time was not yet determined in either treatment group. Enzalutamide plus ADT also demonstrated statistically significant benefit vs. NSAA plus ADT in the secondary endpoints of improvement in PSA PFS and clinical PFS[24, 28]. In both studies, enzalutamide plus ADT showed no new safety signals in patients with mHSPC.

In addition to benefits in efficacy and safety, enzalutamide plus ADT maintained the baseline levels of good HRQoL and functioning throughout the study. Men enrolled in ARCHES were generally asymptomatic, had low urinary symptom burden, and had good HRQoL at the start of the study. There was no evidence to suggest that enzalutamide plus ADT meaningfully worsened symptoms, functioning, or HRQoL relative to placebo plus ADT over the duration of the study. In addition, treatment with enzalutamide plus ADT showed a significant protective effect on time to progression of worst pain, mean pain severity, and time to clinically meaningful deterioration in HRQoL as measured by EQ-5D-5L VAS. In combination with the results of the primary study objective, this means that enzalutamide plus ADT provides a robust benefit on disease progression while the patient's experience of their quality of life is not compromised and, on some levels, even remains better as compared to placebo plus ADT.

An NMA was conducted to assess the relative effectiveness of enzalutamide plus ADT vs docetaxel which is recommended for patients with newly diagnosed mHSPC.

The NMA was associated with marked limitations (section B.2.9.6) that question the robustness of the results. The NMA findings should therefore be interpreted with caution. The results for all endpoints favoured enzalutamide plus ADT over docetaxel plus ADT. [redacted]

There is a particular unmet need for treatments that delay disease progression and extend survival for patients with mHSPC who cannot take docetaxel plus ADT, either because they are not fit enough to tolerate it or are not willing to take chemotherapy. Based on the Cancer Fund Drug, only 50% of patients to whom docetaxel would be recommended receive it. The remaining patients are currently treated with ADT alone which has consistently demonstrated worse efficacy than docetaxel and enzalutamide. Overall, the results of ARCHES and ENZAMET show that enzalutamide plus ADT is effective in all subtypes of mHSPC patients, regardless of volume of disease, risk level and prior use of docetaxel.

B.2.13.2 Strengths and limitations

A key strength of the ARCHES and ENZAMET studies is that the use of enzalutamide in these trials reflect its intended use in UK clinical practice. The efficacy, safety and tolerability profile expected for enzalutamide in clinical practice are the same as those observed in these two trials.

The ARCHES and ENZAMET trials are two large, robust and clinically relevant studies comparing enzalutamide plus ADT to either ADT alone or with NSAA that have been published in peer-reviewed journals[27, 28]. Both studies demonstrated the treatment benefit of enzalutamide plus ADT on several endpoints that are relevant to patients and clinicians.

Enzalutamide plus ADT demonstrated a robust benefit in delaying disease progression over ADT alone or with NSAA. Despite the markedly different definition of PFS used in ARCHES (rPFS) and ENZAMET (clinical PFS), enzalutamide plus ADT significantly delayed both clinical and radiographic progression. Patients recruited in ARCHES and ENZAMET had relatively good HRQoL and functioning at baseline. This is in line with other studies with mHSPC patients[84, 85]. However, as the disease progresses, patients may experience bone pain, skeletal-related events (SREs) and SSEs, which include vertebral collapse or deformity, pathological fractures, and spinal cord compression[86, 87]. Pain from metastasis is a major disease component. In patients with bone metastases, SREs and SSEs are a source of significant pain and decreased HRQoL. Delaying disease progression is an important goal in the treatment of mHSPC. In line with the benefit in (radiographic and clinical) PFS, enzalutamide plus ADT also significantly delayed onset of SSEs (HR: 0.52, 95% CI: 0.33, 0.80), castration-resistance (HR: 0.28, 95% CI: 0.22, 0.36) and initiation of a new antineoplastic treatment for prostate cancer (HR: 0.28, 95% CI: 0.20, 0.40). Importantly, the benefit of enzalutamide plus ADT was consistent across prespecified patient subgroups. In addition, as already mentioned (section B.2.13.1), despite the limitations of the NMA, the NMA results favour enzalutamide plus ADT vs docetaxel plus ADT.

An additional strength of enzalutamide is that its safety profile is well established. The safety profile of enzalutamide plus ADT was comparable in ARCHES[23, 27] and ENZAMET[24, 28]. The side-effect profile of enzalutamide in these two trials is consistent with that observed in previous enzalutamide studies and extensive post-marketing experience with no new or unexpected safety signals.

Several limitations can be identified including the different comparator arm used in ARCHES (ADT alone) and ENZAMET (NSAA plus ADT) and the implications of this in the NMA and pooled analysis. NSAA plus ADT is not currently recommended in NICE guidelines as first-line therapy. Several SLRs comparing the efficacy of ADT alone vs that of CAB/MAB in advanced and metastatic patients have concluded that there are no statistically significant differences in the efficacy of CAB/MAB vs ADT alone [88, 89]. This is further supported by the NMA conducted for this submission which shows only a small numerical benefit for OS for NSAA over ADT. Considering efficacy of NSAA plus ADT to be the same as for ADT alone is not expected to introduce any bias to the results or at worst, would underestimate the treatment benefit of enzalutamide plus ADT over ADT alone.

Another important limitation relates to the length of the follow-up required to have accumulated sufficient OS events to perform an adequately powered analysis. Median follow-up in ARCHES was too short (14.4 months) to demonstrate benefit on OS. However, statistically significant benefit on OS was clearly demonstrated in ENZAMET for the overall population as well as in the cohort of patients not on concomitant docetaxel.

Another limitation is the post-progression treatment in ARCHES and the lack of information regarding post-progression treatment in ENZAMET. OS may be impacted by post-progression treatment. The number of patients with post-progression treatment is very low in ARCHES (enzalutamide arm: n=46; placebo arm: n=133). Post-progression treatment in the

enzalutamide arm differed from what patients would be expected to receive in clinical practice in the UK. As of the data analysis cut-off date (14 Oct 2018), 0.7% and 2.3% of patients in the enzalutamide arm received enzalutamide and abiraterone, respectively after disease progression. However, given the low number of patients receiving these treatments in the enzalutamide plus ADT arm, the impact on OS is likely to be very limited. No data are available regarding post-progression treatment in ENZAMET which was sponsored by the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP) and The University of Sydney (USYD), Australia. A larger number of patients receiving post-progression treatment is expected in ENZAMET than in ARCHES but the data has not yet been disclosed by the trial sponsor.

Related to post-progression treatment, neither ARCHES nor ENZAMET allows us to measure the impact on OS of the different treatment sequences used in the UK. This is a limitation.

Additional limitations also increase the uncertainty of the NMA results for the overall population. The evidence network included the two enzalutamide studies, three docetaxel studies (CHAARTED, GETUG-AFU 15 and STAMPEDE) and 12 studies comparing ADT alone vs CAB/MAB. The study population markedly differed across those studies that report disease volume or risk level. In addition, the studies comparing CAB/MAB to ADT alone do not provide any information on these disease characteristics. Given the difference prognosis of HVD vs LVD, differences in the proportion of HVD and LVD patients across studies may have biased the results.

As already mentioned, for ENZAMET only data for those patients who did not receive concomitant docetaxel have been considered relevant for this submission. This reduced the sample size (from 1,155 in the overall ENZAMET population to 622). In addition, exclusion of patients on concomitant docetaxel resulted in an enrichment for LVD patients compared to the overall population. However, the percentage of LVD patients was comparable between arms (enzalutamide arm: 63.1%; NSAA arm: 62.3%) and thus, it reduces the risk for any bias.

Finally, another limitation is the low number of patients recruited in the UK ([redacted] in ARCHES and [redacted] in ENZAMET). The number of patients recruited in Europe in ENZAMET was also low (n=89, 14.3%) but more than 50% of patients in ARCHES were recruited in Europe (n=685, 59.6%).

Despite the limitations, the overall efficacy and safety results support a positive benefit/risk assessment of the use of enzalutamide at a daily dose of 160 mg plus ADT in adult men with mHSPC. In ARCHES and ENZAMET, enzalutamide was associated with a significantly longer time to disease progression while maintaining a low symptom burden, good HRQoL and good functioning and an acceptable safety profile.

B.3 Cost effectiveness

B.3.1 Published cost effectiveness studies

An SLR of cost effectiveness studies in mHSPC in the UK was conducted[26]. For the full details of the SLR methods and outcomes, see Appendix G. The SLR identified 13 cost effectiveness studies in mHSPC. However, of these, only 3 studies were specific to the UK. Therefore, this section will only address the following studies:

- Lu *et al*, 2012[90], which explored the cost effectiveness of degarelix vs triptorelin in the full mHSPC population in the UK
- James *et al*, 2018[91] and Woods *et al*, 2018[92], which explored the cost effectiveness of 6 cycles of docetaxel in addition to ADT vs ADT alone non-metastatic HSPC and mHSPC patients in the UK. However, separate results were provided for the mHSPC patient cohort
- NICE ID945[80] which explored the cost effectiveness of abiraterone plus ADT versus ADT alone in newly identified mHSPC patients in the UK.

Of these publications, James *et al*, 2018[91] and Woods *et al*, 2018[92] refer to the same study; Woods *et al*, 2018 is the publication in a peer-reviewed journal and James *et al*, 2018 a congress presentation. However, the congress presentation provides additional data to the peer-reviewed publication.

These studies performed a cost effectiveness analysis whereby the costs and benefits were modelled based on a Markov, semi-Markov, or undefined approach. The health states captured in the model structure applied in Lu *et al*, 2012[90] included stable disease, disease progression and death. In NICE ID945, the progressed health state was further divided into separate health states based on treatment lines[80]. The model structure developed by James *et al*, 2018 and Woods *et al*, 2018 study included five health states: hormone-sensitive, HRPC M0 or M1 lymph node, HRPC M1 bone, HRPC M1 bone plus SRE, and HRPC M1 visceral[91, 92]. Patients who entered the hormone sensitive health state with metastatic disease would go to the HRPC M1 bone state directly upon disease progression. In contrast, patients with nmHSPC would go to HRPC M0 or M1 lymph node when they progressed. The perspective was from the UK healthcare payer in all studies.

The time horizon differed across studies and ranged between 10 years in Lu *et al*, 2012[90] and 20 years in NICE ID945[80]. In James *et al*, 2018 and Woods *et al*, 2018 the time horizon was lifetime[91, 92] (Table 45).

Lu *et al*, 2012 assessed the cost effectiveness of degarelix vs triptorelin in the management of mHSPC from a UK NHS perspective[90]. Degarelix treatment resulted in 0.0128 additional QALYs and £758 additional cost vs triptorelin. Based on a willingness-to-pay (WTP) threshold of £30,000 per QALY, degarelix was not considered cost effective vs triptorelin. The probability of being cost effective at a WTP threshold of £30,000 was 9.6% (Table 45).

James *et al*, 2018[91] and Woods *et al*, 2018[92] assessed the cost effectiveness of docetaxel plus ADT vs ADT alone both in nmHSPC and mHSPC patients. However, only the mHSPC results are considered relevant for this appraisal. Docetaxel resulted in 0.50 incremental

QALYs in mHSPC specifically. This health benefit came at an incremental cost of £2,787 resulting in an ICER of £5,514. Based on a WTP threshold of £30,000 per QALY, docetaxel plus ADT was considered cost effective vs ADT alone with a probability of being cost effective of >99% (Table 45).

In NICE ID945[80], evaluated the addition of abiraterone to ADT, specifically in the newly diagnosed high risk subpopulation. The company claimed that the addition of abiraterone to ADT compared to ADT alone or with docetaxel resulted in a gain of LYs (+1.56 vs ADT and +0.67 vs docetaxel plus ADT) and QALYs (+1.09 vs ADT alone and +0.60 vs docetaxel plus ADT) (Table 45). Abiraterone was considered cost effective with an company reported ICER of £17,418 per QALY vs ADT alone and £17,828 per QALY vs docetaxel plus ADT[80]. However, the appraisal committee did not accept the company reported ICERs based on the critique that the company's model structure did not reflect the treatment pathway for mHSPC and modelled implausible survival estimates. The committee therefore was unable to determine a plausible ICER for abiraterone plus ADT compared with ADT alone or with docetaxel plus ADT. The committee argued that If the model were to accurately reflect the treatment pathway, the committee would expect the benefits of abiraterone plus ADT in delaying progression to be balanced by the potential benefits of the treatment options available to patients once they have progressed to hormone-relapsed disease. It concluded that, without a plausible ICER, it could not recommend abiraterone as a cost effective use of NHS resources.

Table 45 Design and outcomes of the identified cost effectiveness studies

Study	Year	Summary of model	Population (average age)	QALYs	Costs	ICER (per QALY gained)
NICE ID945	2018	Markov • Health states: mHSPC progression-free, mHSPC PD, mHRPC 1L, mHRPC 2L, mHRPC 3L • Perspective: NHS UK • Time horizon: 20 years • Discounting: 3.5% per year	Newly diagnosed mHSPC (age 67)	ABI + ADT vs ADT (ERG case) • ABI + ADT QALYs: 3.455 • ADT QALYs: 2.379 • Incremental QALYs: 1.077 ABI + ADT vs DOC + ABI (ERG case) • ABI + ADT QALYs: 3.455 • DOC + ADT QALYs: 2.863 • Incremental QALYs: 0.592	ABI + ADT vs ADT (ERG case) • Incremental Costs: £27,185 ABI + ADT vs DOC + ABI (ERG case) • Incremental Costs: £19,195	ABI + ADT vs ADT alone (ERG case) • ICER: £25,241* ABI + ADT vs DOC + ADT (ERG case) • ICER: £32,424*
Lu *et al*, 2012	2012	Decision analytic; with decision tree and Markov • 3 health states: Response; Progression; Death • Payer's perspective • Time horizon: 10 years • Discounting: 3.5% per year	mHSPC (age 70)	DEG vs TPT • Incremental QALY: 0.0128 (2.4548 vs 2.4419)	DEG vs TPT • Incremental cost: £758 (£3,883 vs £3,125)	DEG vs TPT • ICER: £59,012 • Probability of cost effectiveness (WTP of £30,000): 9.6%
James *et al*, 2018 and Woods et al, 2018	2018	Patient-level simulation • Five health states: HSPC; nm- or mHRPC lymph node; mHRPC Bone; mHRPC Bone+SRE; mHRPC Visceral • Perspective: NHS UK • Time horizon: lifetime • Discounting: 3.5% per year	STAMPEDE patients (nmHSPC and mHSPC) treated with DOC+ADT or ADT alone (age 65)	LYG (discounted) • Total – SOC: 4.90 – DOC: 5.79 • Incremental: 0.89 QALYs (discounted) • Failure-free – SOC: 1.40 – DOC: 2.02 – Incremental: 0.63	Costs (discounted) • Total – SOC: £52,466 – DOC: £55.253 • Incremental: £2787 • Savings were much greater for nmHSPC patients as patients allocated to docetaxel arm spend a much	ICER DOC vs ADT • £5,514/QALY • Q1: £4,479 • Q2: £6,062 • Q3: £5,454 • Q4: £5,686 • Probabilistic sensitivity analysis for DOC being

Study	Year	Summary of model	Population (average age)	QALYs	Costs	ICER (per QALY gained)
				• Post-failure – SOC: 1.61 – DOC: 1.49 – Incremental: -0.12 • Total – SOC: 3.01 – DOC: 3.51 – Incremental: 0.51	shorter period in HRPC (i.e. extensions to FFS do not fully translate to increased OS)	cost effective vs ADT: >99%

* The ICERs were not reported in the appraisal consultation document due to the level of uncertainty. The reported ICERs are calculated based on the incremental costs and QALYs from the appraisal consultation document, and should be interpreted with caution.

Abbreviations: AA: antiandrogen; ABI: abiraterone; ADT: androgen-deprivation therapy; AE: adverse event; CE: cost effectiveness; HRPC: hormone-relapsed prostate cancer; DEG: degarelix; DOC: docetaxel; ERG: evidence review group; ICER: incremental cost effectiveness ratio; LYG: life-year gained; mHRPC: metastatic hormone-relapsed prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; NHS: national health services NICE: National Institute for Health and Care Excellence; nmHSPC: non-metastatic hormone-sensitive prostate cancer; OS: overall survival; PFS: progression-free survival; QALY: quality-adjusted life year; UK: United Kingdom; vs: versus; WTP: willingness-to-pay threshold;

B.3.2 Economic analysis

An economic evaluation was conducted to assess the cost effectiveness of enzalutamide plus ADT versus ADT alone or docetaxel plus ADT, in adult men with mHSPC. This population is aligned to the patient population studied in the phase III clinical study of enzalutamide (ARCHES[23]).

The analysis was conducted using a survival-based cost effectiveness model.

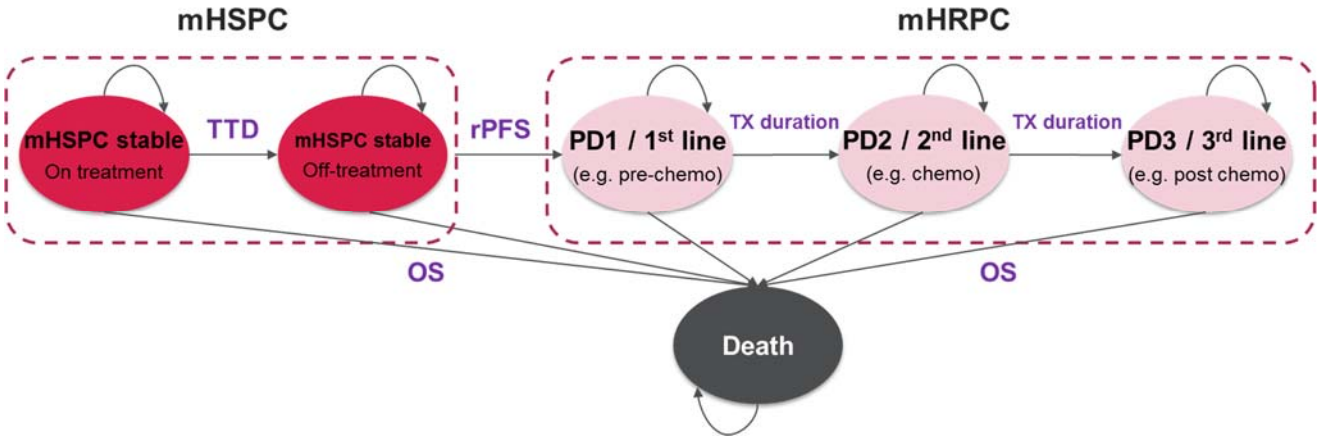
B.3.2.1 Patient population

In line with ARCHES and ENZAMET participants, the patient group entering the economic model consists of men with mHSPC. This population includes both patients with mHSPC who are newly diagnosed, and patients who have relapsed with metastasis following local therapy.

B.3.2.2 Model structure

The base case model structure is presented in Figure 19 and builds upon the economic models in NICE TA316, NICE TA377 and NICE TA580 which related to enzalutamide plus ADT in the post-chemotherapy, chemotherapy-naïve mHRPC, and high-risk nmHRPC setting respectively[93-95]. The model was divided into a series of mutually exclusive health states (i.e. a patient can only be in one particular health state at each point in time). Its design was based on the standard three-state structure that is commonly used in oncology (i.e. stable disease, progressed disease and death) and emulates the natural progression of disease from mHSPC to mHRPC and death. Taking into account the existing indications and the progressive nature of the disease, the mHRPC health state was further divided into three additional progressed disease (PD1-3) sub-health states allowing for the incorporation of different treatment sequences and gradually declining utility values (Figure 19).

Figure 19 Model structure



Abbreviations: mHRPC: metastatic hormone-relapsed prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; PD: progressed disease

In the model, all patients start in the mHSPC (stable disease) health state receiving their initial treatment. ARCHES and ENZAMET results suggest that the average patient receiving

enzalutamide plus ADT discontinues treatment a little time before progressing (i.e., TTD appears to be slightly shorter than rPFS and cPFS). Patients who discontinue active treatment before progression are assumed to receive ADT alone (mHSPC stable, off-treatment). This transition is informed by TTD. Upon progression, as informed by rPFS, patients progress to the mHRPC health states. Finally, all health states are subject to mortality, informed by OS, with death being the absorbing final health state of the model. Patient propagation between the health states of the model is based on the assumption that the individual progression steps are irreversible. As an example, patients cannot move back to the mHSPC health state after progressing to mHRPC (i.e., after developing resistance).

The model follows a partitioned survival (PartSA) approach. Time-to-event data from the studies has been used to calculate the areas-under-the-curves or between the curves, which allows the model to determine health state memberships. In the model, the area under the TTD curve represents the mHSPC on treatment health state, everything between rPFS and OS represents mHRPC and everything above OS represents death.

Metastatic HRPC is divided into three sub-states, PD1-3. No time-to-event data from ARCHES or ENZAMET is available, however, to inform the model when patients would start second- (PD2) or third-line (PD3) mHRPC therapy. This makes it difficult to split the mHRPC health state into three PD sub-states in the PartSA model. To capture the differences in costs and health benefits that patients will experience in the gradually worsening progressive disease health state, the model has a built-in Markov structure to more accurately model the outcomes attributable to post-progression treatments received. The distribution of patients across the PD1-PD3 states at any point in time (model cycle) in the built-in Markov structure is used to inform this split in the PartSA model. To test the impact of modelling the PD1-3 sub-states a scenario analysis has been performed that combines PD1-3 (i.e., one combined mHRPC health state with no difference in cost and health benefits as patients progress through mHRPC) in the PartSA approach.

B3.2.3 Intervention technology and comparators

The model is designed to evaluate the cost effectiveness of enzalutamide plus ADT compared to docetaxel plus ADT, or ADT alone in mHSPC. These represent the initial treatment when patients enter the model. ADT is a collective term that comprises LHRH agonists and antagonists. In this analysis, decapeptyl, zoladex LA depot, and prostap 3 prolonged release are included as ADT options. A weighted average of these treatments, based on net ingredient costs as per the July 2019 Prescription Cost Analysis (PCA), was used to calculate the average ADT costs in the model[96]. A list of ADT applied in the model is provided in Table 46. As discussed in section B1, the comparison against abiraterone was not performed as abiraterone is currently not approved by NICE or part of standard of care for mHSPC patients in England.

Table 46 Most common endocrine baseline treatments given in ARCHES

Androgen deprivation therapies	Brand	Price per day	Market share to derive ADT cost	Net ingredient costs - July 2019
LHRH (goserelin)	Zoladex	£2.50	5.7%	£173,390
LHRH (goserelin)	Zoladex LA	£2.80	38.4%	£1,171,937
LHRH agonist (leuprorelin acetate)	Prostap SR DCS	£2.49	4.2%	£127,833

Androgen deprivation therapies	Brand	Price per day	Market share to derive ADT cost	Net ingredient costs - July 2019
LHRH agonist (leuprorelin acetate)	Prostap 3 DCS	£2.49	34.1%	£1,041,468
LHRH agonist (triptorelin)	Decapeptyl SR	£2.28	17.7%	£540,458
Average daily ADT costs applied in the model				**£2.57**

Source: Prescription Cost Analysis – July 2019[96]
Abbreviations: ADT: androgen-deprivation therapy; DCS: Dual Chamber Pre-filled Syringe; LA: long-acting; LHRH: Luteinizing hormone releasing hormone SR: sustained release.

Other features of the economic analysis along with the justification are listed in Table 47.

Table 47 Features of the economic analysis

Factor	Previous appraisals - Abiraterone in mHSPC (ID945)[97]	Current appraisal	
	Chosen values	**Chosen values**	**Justification**
Time horizon	Lifetime horizon implemented as 20 years	Lifetime horizon implemented as 30 years	As per NICE guidance, the time horizon in an economic evaluation should be long enough to reflect all important differences in costs or outcomes between the technologies being compared. As enzalutamide may have an impact on survival of mHSPC patients and given the typical age a patient is diagnosed with mHSPC (the median age at baseline was 70 years in ARCHES and 69 years in ENZAMET), a time horizon of 30 years (corresponding to a lifetime horizon for these patients) is therefore deemed appropriate.
Cycle length	1 week for first year, monthly thereafter	1 month	According to good research practice guidelines for state-transition modelling[98], the choice of cycle length should be based on the clinical problem, remaining life expectancy, and computational efficiency. It should be short enough to represent the frequency of key clinical events and interventions, which should occur at most once per cycle. The clinical events that underlie the main transitions in the model, i.e. progression and death, can occur only once and at any given time. The frequency of administration for different prostate cancer drugs varies. Oral tablets of enzalutamide, abiraterone and bicalutamide are taken daily. Leuprorelin and goserelin are the LHRH agonists that are used most commonly for ADT. Leuprorelin acetate is available in 1- or 3-month depot formulations in the UK, whereas goserelin acetate implants are injected every 28 days or 12 weeks (the latter being the long-acting formulation). Docetaxel is administered as a 1-hour infusion once every 3 weeks. As in the

Factor	Previous appraisals - Abiraterone in mHSPC (ID945)[97]	Current appraisal	
	Chosen values	Chosen values	Justification
			previous XTANDI models, a cycle length of one month was considered appropriate (assuming 365.2425 days/12 = 30.44 days per month)[93, 94].
Were health effects measured in QALYs; if not, what was used?	Yes	Yes	In line with NICE reference case[40]
Discount for utilities and costs	3.5%	3.5%	In line with NICE reference case[40]
Perspective (NHS/PSS)	The NHS and PSS in England	The NHS and PSS in England	In line with NICE reference case[40]
Half-cycle correction	NA	NA	Not applicable in a PartSA model
Treatment waning effect?	NA	NA	No treatment waning effect was observed in either the ARCHES or ENZAMET studies[42, 43]
Source of utilities	LATITUDE[25], NICE TA387[99]	ARCHES[23], AFFIRM[100]	Most utilities were derived from the ARCHES trial, as this is the trial informing the modelled time spent in the progression free health state (i.e., PFS), which largely determines the survival benefits for enzalutamide plus ADT. AFFIRM trials were used for later stages of the disease and literature for AEs and SRE-related utilities
Source of costs	NHS reference costs	NHS reference costs	In line with NICE reference case[40]

Abbreviations: AE: adverse event; mHSPC: metastatic hormone-sensitive prostate cancer NA: not applicable; NHS: National Health Service; PSA: prostate-specific antigen; PSS: personal social services; QALYs: quality-adjusted life years; SRE: skeletal-related event.

B.3.3 Clinical parameters and variables

As far as possible, all clinical parameters included in the model (PFS, TTD, OS) are derived from ARCHES and ENZAMET. Where available, external data were used to validate, and if needed, to augment the ARCHES and ENZAMET data. A summary of the extrapolation methodology is available in the sections below. A detailed description of the extrapolation procedure is included as a reference in this submission[41-43].

Given the variation in duration and follow-up between the two studies, clinical data for time to event outcomes was extrapolated to facilitate modelling of survival benefits for a lifetime horizon (i.e., 30 years). In line with NICE DSU Technical Support Document 14[101], treatment effects were modelled extrapolating patient-level data per arm. For each outcome of the above-mentioned outcomes (PFS, TTD, OS), six standard parametric models (i.e. exponential, Weibull, log-logistic, log-normal, generalised gamma and Gompertz) were fitted for each treatment group separately[41, 42]. To determine the best model fit in line with the recommendations in the NICE DSU Technical Support Document 14[101], the following steps were undertaken[41, 42]:

- **Akaike information criterion (AiC) and Bayesian information criterion (BiC)** - Model fits were evaluated using AiC and BiC statistics. Lower AiC and BiC figures are indicative of a better statistical fit of the survival function of the Kaplan-Meier data.
- **Visual Inspection** - Visual inspection was carried out by plotting the projected survival curves overlaid with the Kaplan-Meier survival functions.
- **Clinical Validity** - The clinical plausibility of the proportion of patients estimated to be surviving at the tails of the curve was examined.

Inclusion and extrapolation of each clinical outcome is detailed in the following sections.

B.3.3.1 Progression modelling

TTD and PFS are used to inform the progression to mHSPC off-treatment and first-line mHRPC (PD1), respectively, in the base case of the model. As discussed in Sections B.2.6 and B.2.8, three distinct sources can inform PFS and TTD in the model: ARCHES, ENZAMET and the pooled ARCHES and ENZAMET data. The pooling of ARCHES and ENZAMET data makes maximal use of available information. However, combining PFS from both studies was difficult as the definitions differed between the studies. To address these differences, the ARCHES PFS definition was modified to match the cPFS definition in ENZAMET as closely as possible. However, it was not feasible to completely match the ENZAMET cPFS definition because:

- Differences in the frequency and type of imaging tests between ARCHES and ENZAMET
- Differences in the comparator (ARCHES: ADT alone vs ENZAMET: ADT plus NSAA). Although ADT and NSAA are comparable in clinical practice in terms of OS, external experts have indicated that using ADT or NSAA could affect PFS[83]
- No data on clinically meaningful deterioration of symptoms was collected in ARCHES.

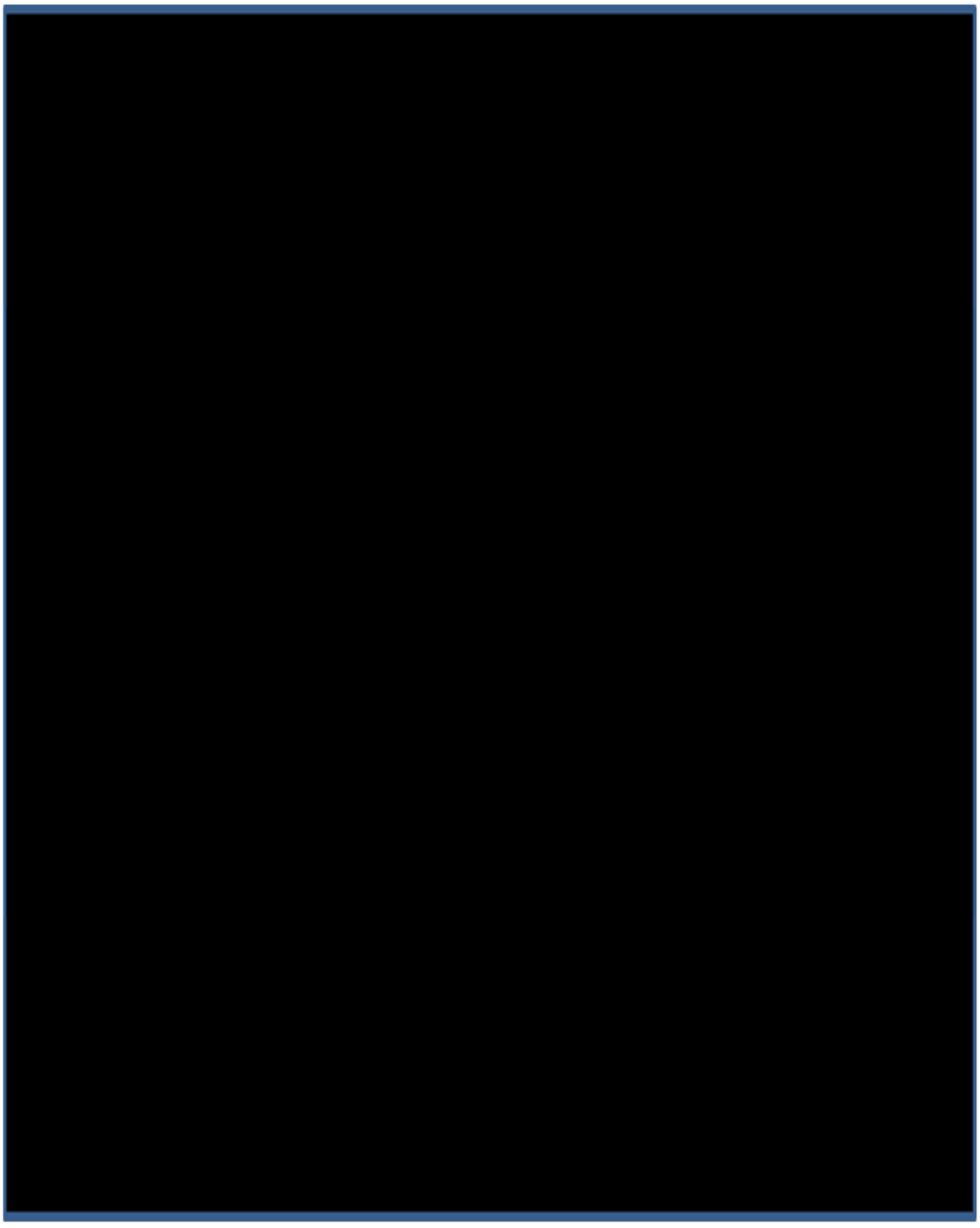
Given the failure to align the PFS definition in ARCHES to that of ENZAMET, it was decided that pooling PFS data would not be an appropriate approach to inform the transition to mHRPC. ARCHES rPFS was preferred over ENZAMET cPFS because the ARCHES rPFS definition is more aligned with what is commonly used in clinical trials, including all docetaxel plus ADT studies, making the comparison vs docetaxel more robust. In addition, rPFS was the primary endpoint in ARCHES while a secondary endpoint in ENZAMET. In addition,

although NSAA does not affect patient survival when added to ADT, it could have a small impact on PFS[44, 83], making ARCHES more suitable to accurately model progression in the UK than ENZAMET. To test the impact of this choice, scenarios using pooled and ENZAMET PFS and TTD have been presented.

B.3.3.1.1 ARCHES PFS extrapolation

Figure 20 shows the ARCHES PFS extrapolations with the six standard parametric models (i.e. exponential, Weibull, log-logistic, log-normal, generalised gamma and Gompertz) for enzalutamide plus ADT and ADT alone. Of these curves, log-normal had the best statistical fit to the data followed by generalised gamma and log-logistic[41]. Long-term PFS estimates from STAMPEDE[49, 91], and GETUG[46] suggested that at 5-years, 19%-28% of patients in the standard of care arm remained progression-free. Based on these data, generalised gamma would provide the most clinically plausible fit, as it predicts a 5-year PFS of [redacted][41]. However, the consulted UK clinical expert commented that the long-term PFS estimates for enzalutamide plus ADT (28.9% PFS free after 10-years) were not clinically plausible and advised log-normal be applied to the base case. In line with best modelling practices, which recommend that the same parametric fit is applied to both arms of the model, the log-normal curve for both ADT and enzalutamide plus ADT was selected in the base case[101]. A scenario analysis using ARCHES PFS generalised gamma for both curves has been included to assess the sensitivity of the results to the chosen PFS curve.

Figure 20 ARCHES PFS extrapolated by the 6 standard parametric models



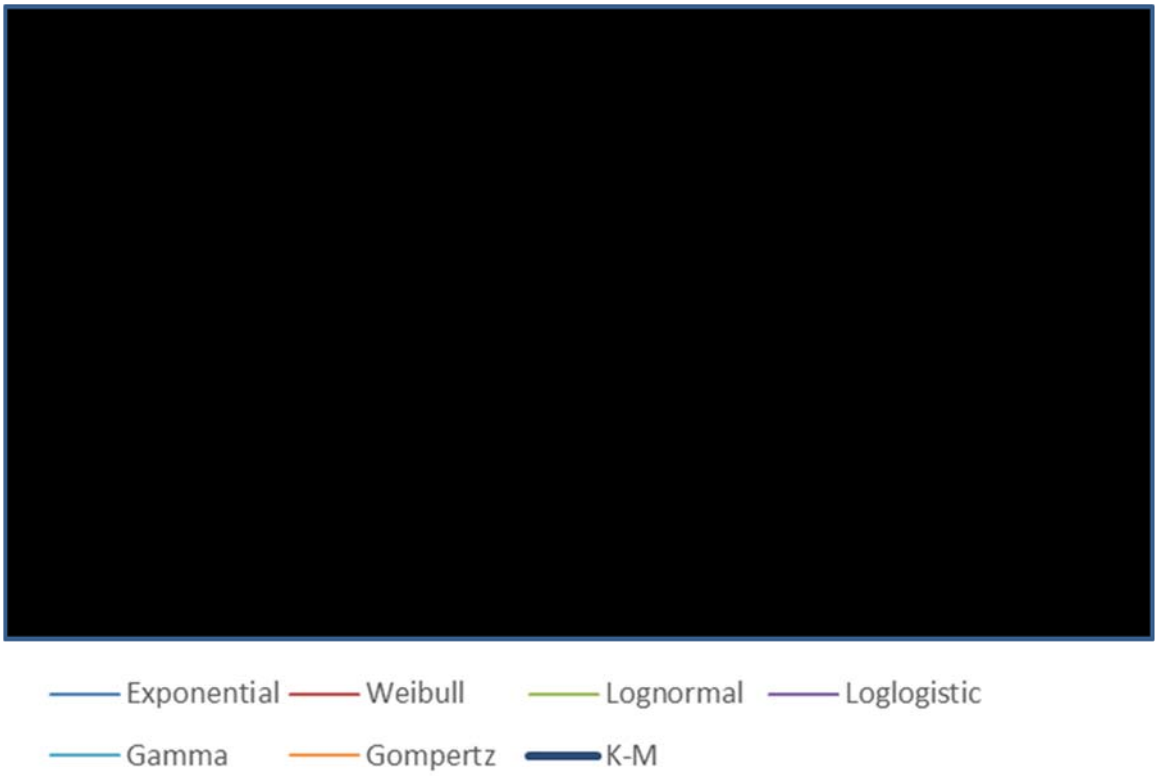
Abbreviations: ADT: androgen-deprivation therapy; K-M: Kaplan-Meier.

B.3.3.1.2 ARCHES TTD extrapolation

The most appropriate TTD curve was selected based on the best statistical fit to the data as well as the position relative to the selected PFS curve to avoid crossing curves. The model with the best statistical fit for ARCHES TTD was exponential, closely followed by log-logistic and Weibull (Figure 21)[41]. Of these, the exponential curve closely follows the PFS curve without crossing it, especially for the first 4 years of the analysis when most people will be in the mHSPC health states (Figure 22). Weibull and log-logistic on the other hand either

crossed or diverged from the ARCHES PFS curve leading to clinically implausible survival estimates. Consequently, the exponential extrapolation for ARCHES TTD was selected for the base case analysis.

Figure 21 ARCHES enzalutamide plus ADT TTD extrapolated by the 6 standard parametric models



Abbreviations: ADT: androgen-deprivation therapy; K-M: Kaplan-Meier; TTD: time to treatment discontinuation.

Figure 22 Modelled ARCHES TTD extrapolations relative to the base case rPFS OS curves

Abbreviations: OS: overall survival; rPFS: radiographic progression-free survival; TTD: time to treatment discontinuation

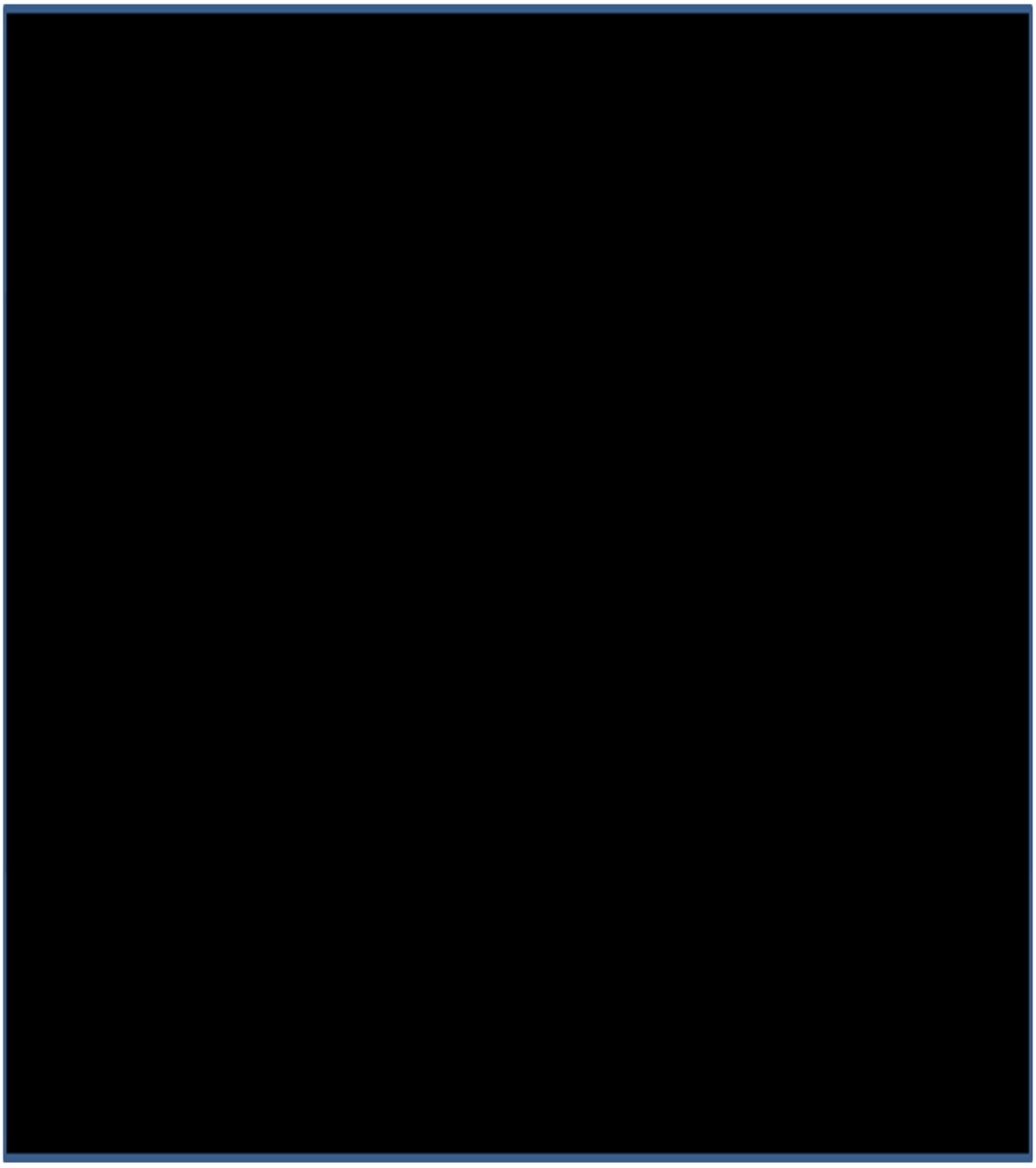
B.3.3.2 Survival modelling

The pooled ARCHES and ENZAMET (those patients not receiving concurrent docetaxel) data was considered the most appropriate data source to inform survival in the model. Since OS is not prone to differences in endpoint definition, pooling of OS data from ARCHES and ENZAMET is less prone to bias, if patient population and treatment protocol are consistent. In addition, the use of NSAA plus ADT in ENZAMET has no significant effect on OS as indicated by the NMA and confirmed by the consulted UK clinical expert[44, 83], so the difference in comparator is unlikely to affect the ARCHES and ENZAMET OS results. Furthermore, pooled OS makes the best use of all available data, by combining the data from ARCHES and ENZAMET, making it the most reliable source to inform survival in the model. To test the impact of changing this assumption, scenarios using ARCHES and ENZAMET OS projections in isolation have also been performed. One caveat of using pooled ARCHES and ENZAMET OS data may be the longer follow-up observed in ENZAMET (median follow-up of 14.4 months in ARCHES and 33.8 months in ENZAMET). At median follow-up for ARCHES, the survival in ENZAMET was comparable to that observed in ARCHES with an OS at 14.4 months of 92.9% and [redacted]% for enzalutamide vs 91.4% and [redacted]% for ADT and/or NSAA in ARCHES and ENZAMET, respectively, indicating that the longer follow-up time is not a source of bias when pooling the data.

Figure 23 shows the pooled OS extrapolations with the six standard parametric models (i.e. exponential, Weibull, log-logistic, log-normal, generalised gamma and Gompertz) for enzalutamide plus ADT and ADT alone. The OS curves were adjusted for background mortality, by increasing the mortality rate in any cycle to the age-matched population mortality rate, if the population mortality was higher[102]. Consequently, the exponential, log-normal, log-logistic and generalised gamma curves are virtually identical, as all have crossed

background mortality at some point in the extrapolation period and subsequently follow the background mortality curve. The model with the best fit for pooled OS was log-normal for both enzalutamide plus ADT and ADT alone. However, the differences were only minor and Weibull, log-logistic and generalised gamma also showed adequate statistical fits[43]. Long-term survival estimates from STAMPEDE[91], CHAARTED[45] and GETUG[46] suggested a 7-year survival in the standard of care arm of 27%-34%. Based on these data, log-logistic provided the most clinically plausible fit predicting a 7-year survival of [redacted] for ADT alone (Figure 23)[43]. However, the consulted UK clinical expert commented that log-logistic resulted in unrealistically high OS estimates at 16 years for the enzalutamide arm[83]. Therefore, Weibull was selected for the model base case. To test the impact of this choice a scenario using the log-logistic extrapolation has been performed.

Figure 23 Pooled OS extrapolated by the 6 standard parametric models



*The shown curves are adjusted for background-mortality. Consequently, the exponential, log-normal, log-logistic and generalised gamma curves overlap, as all have crossed background mortality in the extrapolation period.
Abbreviations: KM: Kaplan Meier; OS: overall survival.

B.3.3.3 Health state transitions

Time-to-event data from the ARCHES and ENZAMET studies were used to calculate the areas-under-the-curves and between the curves, allowing the model to determine health state memberships for mHSPC, mHSPC off-treatment, mHRPC (i.e. PD1-3), and death. The comparator arms in ARCHES and ENZAMET are assumed to reflect ADT alone in UK clinical practice. Since there is no direct data for docetaxel plus ADT in the model, the HRs vs ADT obtained from the NMA in the total population (Table 34) were applied to the ADT alone reference curve to model docetaxel plus ADT efficacy. The efficacy for enzalutamide plus ADT can both be modelled using the enzalutamide plus ADT curves directly (within trial comparison) or by applying the NMA HRs to the ADT reference curve. However, given the NMA caveats discussed in B.2.9.6, the within trial approach provides the most robust comparison, as it uses the trial data directly. A scenario where enzalutamide plus ADT efficacy is informed by applying the enzalutamide plus ADT NMA HRs to the ADT reference curve and has also been included.

Since there is no direct trial data to inform progression in PD1-3, median times to progression or treatment discontinuation were used to model the mHRPC transition probabilities from PD1 to PD2 and PD3, using the built in Markov structure of the PartSA model. These were based on the median treatment durations and/or number of treatment cycles (e.g. for chemotherapy) observed in pivotal trials of these treatments (e.g. PREVAIL[103], TROPIC[104], TAX-327[105]) or the SmPC for radium-223[106]. These durations were used to calculate the probability per month to discontinue (Table 48).

Table 48 Mean treatment durations used in model for mHRPC health states (PD1-PD3)

	Median Tx duration (months [95% CI])	Prob. per month to discontinue	Source
Probabilities for progression in PD1			
Probability to progress on 2nd line enzalutamide	[redacted]	[redacted]	PREVAIL[103] Median TTD Enza arm (Extrapolation report v4 - Table 3)
Probability to progress on 2nd line ADT	[redacted]	[redacted]	PREVAIL[103] Median TTD placebo arm (Extrapolation report v4 - Table 3)
Probability to progress on 2nd line abiraterone	[redacted]	[redacted]	Assumed identical to enzalutamide
Probability to progress on 2nd line docetaxel	6.58 [5.92; 7.23]	0.100	TAX 327[105] 9.5 cycles of 21 days
Probability to progress on 2nd line radium-223	5.54 [4.98; 6.09]	0.118	Xofigo SmPC[106] 6 injections at 4-week intervals
Probabilities for progression in PD2			

Probability to progress on 3rd line docetaxel in PD2	6.58 [5.92; 7.23]	0.100	TAX 327[105] 9.5 cycles of 21 days
Probability to progress on 3rd line radium-223	5.54 [4.98; 6.09]	0.118	Xofigo SmPC[106] 6 injections at 4-week intervals
Probability to progress on 3rd line cabazitaxel	4.15 [3.74; 4.57]	0.154	TROPIC[104] 6 cycles of 21 days

Abbreviations: ADT: androgen deprivation therapy; PD: progressed disease; Prob: probability; Tx: treatment.

B.3.4 Measurement and valuation of health effects

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

The health state utility values used in the base case analysis of the model were measured using the EQ‑5D instrument in key enzalutamide clinical trials and are summarised in Table 49. Mean utilities derived from all pre-rPFS progression measurements and all post-rPFS values from both arms of ARCHES[23] have been used in the mHSPC and PD1 health state, respectively. Although EQ-5D was also collected in ENZAMET this data was not yet available at the time of the NICE submission. Baseline utility values from the AFFIRM[100] study were used to inform utility values in PD3. No gradual decline in HRQoL was observed for the mHRPC utilities. Therefore, a pragmatic decision was made to take the average of P1-PD3 to calculate the PD2 value, a mean of the PD1 and PD3 values is being used (i.e. average of [redacted]). Based on the last utility assessment before death (OS) conducted in both arms of ARCHES, it is assumed that patients have a utility value of [redacted] in the last 3 months of life.

Table 49 Utility values used in the cost effectiveness model

Health state		N	Mean	SD	Source
mHSPC (stable disease & off Tx)		[redacted]	[redacted]	[redacted]	ARCHES EQ-5D-5L + Van Hout algorithm[107] All pre-rPFS progression values, both arms
mHRPC	**PD1, mapped value**	[redacted]	[redacted]	[redacted]	ARCHES EQ-5D-5L + Van Hout algorithm[107] All post rPFS values, both arms
	PD2	-	[redacted]	-	Assumption Mean value of PD1 and PD3 utilities
	PD3	209	0.688	0.282	AFFIRM EQ-5D-3L Baseline values, both arms
End-of-life utility		[redacted]	[redacted]	[redacted]	ARCHES EQ-5D-5L + Van Hout algorithm[107] Last assessment before death (OS), both arms

Health state	N	Mean	SD	Source
Death	0	-	-	Definition

Abbreviations: CSR: clinical study report; HEOR: health economics and outcomes research; HRQoL: health-related quality of life; PD: progressed disease; SA: sensitivity analysis.

B.3.4.2 Mapping

EQ‑5D is the preferred instrument to measure HRQoL in adults for use in health economic models to be submitted to NICE and various other HTA agencies. The 3L version of the instrument has been used in AFFIRM, whereas the EQ-5D-5L questionnaire has been used in the more recent ARCHES study. As per the NICE position statement on the EQ-5D-5L, health state utility values based on ARCHES HRQoL data have been derived by mapping the observed EQ-5D-5L to the UK tariff EQ-5D-3L value sets using the scoring algorithm by van Hout *et al*[107].

B.3.4.3 Health-related quality-of-life studies

A total of 13 studies (six in the initial SLR and seven in the SLR update) met the selection criteria for the utility weights SLR in mHSPC.

Eight of these studies are cost effectiveness models[91, 108-113]. The SLR also identified a publication providing the EQ-5D results in the LATITUDE trial for mHSPC patients[84], a data-on-file document providing the EQ-5D results in the ARCHES trial for mHSPC patients[33], a time to trade-off study specifically designed to capture UK societal utility values for high-risk HSPC and burdensome treatment-related adverse events[114, 115] and an EQ-5D 5L cross-sectional study[116].

The utility weights reported in the reviewed sources including mHSPC patients ranged between 0.64 for mHSPC patients on docetaxel[115] to 0.93 after 12 months of 1-month depot of goserelin[112]. In mHRPC utilities are lower ranging from 0.612 for patients on docetaxel[108] to 0.9 reported by Parikh *et al*, 2019[110]. Overall, the utility values used in the model appeared to be in line with the mHSPC and mHRPC utility values found in the literature.

Several studies report a decrease in the utility weight for patients on docetaxel plus ADT vs ADT alone. In Hall *et al*, the utility weight for patients on docetaxel plus ADT was 0.64 ± 0.27 vs 0.71 ± 0.26 for mHSPC patients on ADT alone[115]. In our model, a conservative approach was taken and no utility decrement for patients receiving docetaxel was applied.

In the studies identified in the SLR, the utility weight further decreased with disease progression with a utility weight of 0.54-0.56 in the last year of life[112].

B.3.4.4 Adverse reactions

B.3.4.4.1 Adverse event rates

As discussed in Section B.2.10, TEAEs in ARCHES and ENZAMET were infrequent and generally well tolerated. TEAE rates for enzalutamide plus ADT and ADT alone in mHSPC

are integrated based on ARCHES safety results for the enzalutamide and placebo arm respectively[23]. For the other mHSPC and mHRPC treatments in the model, AE rates were sourced from the following clinical trials:

- mHSPC treatments:
    - Docetaxel plus ADT: GETUG-AU 15[15]
- mHRPC treatments:
    - ADT alone: PREVAIL (same as in NICE TA580[94])
    - Enzalutamide plus ADT: PREVAIL (same as in NICE TA580[94])
    - Docetaxel plus ADT: TAX327[105]
    - Abiraterone plus ADT and prednisone: COU-AA-302[117]
    - Cabazitaxel plus ADT: TROPIC[104]
    - Radium-22 plus ADT 3: ALSYMPCA[118].

For each of the relevant TEAE, the number of events was obtained from the ARCHES CSR[23] for enzalutamide plus ADT and ADT alone, and from the respective clinical study's main publication for other comparators. The model takes into account TEAEs of grade 3-4, those reported in ≥2% of patients, and TEAEs of special interest (i.e. those with a high impact on costs and health). Annual TEAE rates were subsequently calculated by dividing this absolute number of TEAEs by the follow-up time expressed in patients-years, whenever this information was available (Table 50). For various comparators, the number of patient-years was not reported, and a proxy was calculated by multiplying the median exposure time by the number of patients in the respective study arm.

Table 50 Adverse events frequencies for enzalutamide and comparators

	mHSPC			mHRPC					
	ARCHES		GETUG	PREVAIL		COU-AA-302	TAX 327	TROPIC	ALSYMPCA
	ENZA	PLA	DOC	ENZA	PLA	ABI	DOC	CAB	RAD
Patient years	635.6	579.4	370.1	1180.1	541.6	707.5	1194.0	913.0	370.1
AE	n (events)								
Abdominal pain	[redacted]							7	
ALT increase	[redacted]		3						
Alopecia	[redacted]		5						
Anaemia	[redacted]		4	29	25		17	39	76
Anorexia	[redacted]								9
Arthralgia	[redacted]					11		4	
AST increase	[redacted]		3						
Asthenia	[redacted]							17	
Back pain	[redacted]			22	25			14	
Bone pain	[redacted]			12	20			3	125
Decreased libido	[redacted]		12						
Deterioration in general physical health	[redacted]			18	10				16
Diarrhoea	[redacted]							23	9
Dyspnoea	[redacted]		4			13		5	12
Erectile dysfunction	[redacted]		16						
Fatigue	[redacted]		13			13	17	18	24
Febrile neutropenia	[redacted]		14				10	28	
Haematuria	[redacted]							7	
Hot flushes	[redacted]		8						

	mHSPC			mHRPC					
	ARCHES		GETUG	PREVAIL		COU-AA-302	TAX 327	TROPIC	ALSYMPCA
	ENZA	PLA	DOC	ENZA	PLA	ABI	DOC	CAB	RAD
Hypertension	[redacted]	[redacted]		59	19	23			
Hypokalaemia	[redacted]	[redacted]				14			
Infection with neutropenia	[redacted]	[redacted]	4						
Leukopenia	[redacted]	[redacted]						253	
Nail change	[redacted]	[redacted]	5						
Nausea	[redacted]	[redacted]						7	10
Neutropenia	[redacted]	[redacted]	61				106	303	13
Fluid retention	[redacted]	[redacted]				5			10
Pain	[redacted]	[redacted]						4	
Pain in extremity	[redacted]	[redacted]						6	
Peripheral oedema	[redacted]	[redacted]	2						
Pneumonia	[redacted]	[redacted]							13
Sensory neuropathy	[redacted]	[redacted]	3						
Thrombocytopaenia	[redacted]	[redacted]						15	39
Urinary retention	[redacted]	[redacted]							9
Vomiting	[redacted]	[redacted]						7	10

Abbreviations: ABI: abiraterone; AE: adverse event; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CAB: cabazitaxel; DOC: docetaxel; ENZA: enzalutamide; mHRPC: metastatic hormone-relapsed prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; PLA: placebo; RAD: radium-223

B.3.4.4.2 Skeletal-related event rates

One of the most distinct and severe symptoms experienced by metastatic prostate cancer patients are SREs, which can have a significant impact on the patient's HRQoL and treatment costs. As in previous prostate cancer models, SREs have been categorised in four types: spinal cord compression, pathological bone fractures, radiation to the bone, and surgery to the bone.

Data from ARCHES, PREVAIL, AFFIRM, and COU-AA-301 have been used to inform SRE rates for the mHSPC, PrePD1, PD1 and PD2, PD3 health states, respectively (Table 51). Identical SRE rates have been assumed for all comparators (based on enzalutamide data), except for ADT alone (based on data from the control arm of ARCHES and PREVAIL) in the mHSPC, PrePD1 and PD1 health states. In alignment with previous enzalutamide models, pooled data from AFFIRM and COU-AA-301 was used to inform SRE rates for all comparators In PD2 and PD3 and equal rates were assumed for enzalutamide plus ADT and ADT alone.

Upon the primary analysis of ARCHES data, 31 and 56 SREs had occurred in the enzalutamide and placebo arm of ARCHES, respectively[11]. At the time of writing this submission, however, it was not known how these events were distributed across the 4 types of SREs. Therefore, the same distribution was assumed as in the PREVAIL stable disease population.

Table 51 SRE frequencies in trials relevant to the model

	mHSPC		**mHRPC (PD1)**		**mHRPC (PD2-3)**	
	ARCHES		**PREVAIL**		**AFFIRM + COU-AA-301**	
	ENZA	**PLA**	**ENZA**	**PLA**	**ENZA/ABI**	**PLA**
Patient years	635.6	579.4	1149.7	494.9	1572.2	1572.2
SRE	n (events)					
Spinal cord compression	[redacted]	[redacted]	38	21	176	176
Pathologic bone fractures	[redacted]	[redacted]	41	15	100	100
Radiation to bone	[redacted]	[redacted]	130	83	586	586
Surgery to bone	[redacted]	[redacted]	15	9	39	39
Total, n (rate)	**31 (0.049)**	**56 (0.097)**	**224 (0.195)**	**128 (0.259)**	**901 (0.573)**	**901 (0.573)**

Abbreviations: ABI: abiraterone; ENZA: enzalutamide; mHRPC: metastatic hormone-relapsed prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; PD: progressed disease; PLA: placebo; SRE: Skeletal-related event.

B.3.4.4.3 Adverse event and SRE disutilities

In general, TEAEs and SREs have a negative impact on the HRQoL of patients. Due to the nature of the adverse events reported in ARCHES, it is assumed that most TEAEs will be resolved within two weeks[23]. In ARCHES, PROs were collected every 12 weeks with tools that have a recall period of 7 or fewer days. Therefore, it is unlikely that the impact of TEAEs and SRE on HRQoL was captured in the on-treatment benefit. To better model the impact of

TEAEs and SREs on patient's HRQoL, disutility values were applied for the most relevant TEAEs (i.e., grade 3 or higher) and SREs. In the absence of disutility data from ARCHES, the disutilities of experiencing an TEAEs and SREs were sourced from the published literature and the NICE submission for enzalutamide in chemotherapy-naïve mHRPC patients. When disutility estimates were identified in different sources, an average was taken and this value was used to inform the model. The disutilities and durations used in the model are reported in Table 52 and Table 53. The duration of the disutilities correspond to the average duration of the acute phase of the corresponding TEAE.

Table 52 Duration and disutilities of adverse events

AE	Disutility	Duration disutility (days)	Utility Source	Duration Source
Abdominal pain	-0.069	10.5	Assumed same as pain and arthralgia (Doyle *et al*[119])	NICE ERG report on pre-chemo enzalutamide TA377[120]; also reported in NICE ERG report on post-chemo abiraterone TA259[121]
ALT Increase	0.000	28.0	Assumed equal to zero	NICE TA320[122]
Alopecia	-0.040	182.5	Hall *et al*[115]	Assumption
Anaemia	-0.119	10.5	Swinburn *et al*[123]	NICE ERG report on pre-chemo enzalutamide TA377[120]; also reported in NICE ERG report on post-chemo abiraterone TA259[121]
Anorexia	-0.131	91.25	Assumed equal to asthenia	Assumed equal to asthenia
Arthralgia	-0.069	10.5	Doyle *et al*[119]	NICE ERG report on pre-chemo enzalutamide TA377; also reported in NICE ERG report on post-chemo abiraterone TA259
AST increase	0.000	28.0	Assumed equal to ALT increase	Assumed equal to ALT increase
Asthenia	-0.131	91.25	Assumed equal to fatigue: Lloyd *et al*[124], Nafees *et al*[125], Swinburn *et al*[123]	NICE ERG report on pre-chemo enzalutamide TA377[93]; also reported in NICE ERG report on post-chemo abiraterone TA259[121]
Back pain	-0.069	10.5	Doyle *et al*[119]	
Bone pain	-0.069	10.5	Doyle *et al*[119]	
Decreased libido	-0.137	50.0	Assumed equal to erectile disfunction	Assumed equal to erectile disfunction
Deterioration in general physical health	-0.131	91.25	assumed equal to fatigue	Assumed equal to fatigue
Diarrhoea	-0.137	10.5	Nafees *et al*[125], Swinburn *et al*[123], Lloyd *et al*[124]	NICE ERG report on pre-chemo enzalutamide TA377[93]; also reported in NICE ERG report on post-chemo abiraterone TA259[121]
Dyspnoea	-0.050	10.5	Doyle *et al*[119]	
Erectile dysfunction	-0.137	50.0	Lee *et al*[126]	Lee *et al* (2019)

AE	Disutility	Duration disutility (days)	Utility Source	Duration Source
Fatigue	-0.131	91.25	Lloyd *et al*[124], Nafees *et al*[125], Swinburn *et al*[123]	NICE ERG report on pre-chemo enzalutamide TA377[93]; also reported in NICE ERG report on post-chemo abiraterone TA259[121]
Febrile neutropenia	-0.120	10.5	Lloyd *et al*[124] and Nafees *et al*[125]	
Haematuria	0.000	10.5	No (dis-)utilities available	Assumed equal to neutropenia
Hot flushes	0.000	10.5	Assumed equal to zero	NICE TA320[122]
Hypertension	-0.153	10.5	Swinburn *et al*[123]	NICE ERG report on pre-chemo enzalutamide TA377[93]; also reported in NICE ERG report on post-chemo abiraterone TA259[121]
Hypokalaemia	0.000	30.42	No (dis-)utilities available	
Infection with neutropenia	-0.131	10.5	Assumed equal to neutropenia: Nafees *et al*[125]	Assumed equal to neutropenia: Nafees *et al*[125]
Leukopenia	-0.090	91.25	Assumed equal to neutropenia: Nafees *et al*[125]	NICE ERG report on pre-chemo enzalutamide TA377[93]; also reported in NICE ERG report on post-chemo abiraterone TA259[121]
Nail change	0.000	30.4	Assumed equal to zero	Assumed equal to hypokalaemia
Nausea	-0.152	10.5	Nafees *et al*[125], Swinburn *et al*[123]	NICE ERG report on pre-chemo enzalutamide TA377[93]; also reported in NICE ERG report on post-chemo abiraterone TA259[121]
Neutropenia	-0.090	10.5	Nafees *et al*[125]	
Oedema Peripheral or Fluid retention	-0.070	10.5	Hall *et al*[115], (equal to fluid retention)	
Pain	-0.069	10.5	Doyle *et al*[119]	
Pain in extremity	-0.069	10.5	Doyle *et al*[119]	
Peripheral oedema	-0.070	10.5	Assumed equal to fluid retention	Assumed equal to fluid retention
Pneumonia	-0.200	10.5	Beusterien *et al*[127]	Assumed equal to nausea
Sensory neuropathy	-0.080	91.25	Hagiwara *et al*[128]	Assumed equal to fatigue
Thrombocytopaenia	-0.090	10.5	Assumed same as neutropenia: Nafees *et al*[125]	NICE ERG report on pre-chemo enzalutamide TA377[93]; also reported in NICE ERG report on post-chemo abiraterone TA259[121]
Urinary retention	-0.110	10.5	Armstrong *et al*[129]	Assumed equal to haematuria
Vomiting	-0.076	10.5	Lloyd *et al*[124] and Nafees *et al*[125]	NICE ERG report on pre-chemo enzalutamide TA377[93]; also reported in NICE ERG report on post-chemo abiraterone TA259[121]

Abbreviations: AE: adverse event; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ERG: evidence review group; TA: technology appraisal.

Table 53 Duration and disutilities of SREs

SREs	Disutility	Duration of disutility (days)	Source of duration	Source of disutility
Spinal Cord Compression	-0.237	30.42	Botteman *et al*[130]	: NICE ERG report on pre-chemo enzalutamide TA377[93]
Pathological Bone Fracture	-0.201	30.42		
Radiation to the Bone	-0.056	30.42		
Surgery to the Bone	-0.056	30.42		

Abbreviations: EQ-5D: EuroQol 5-dimensions; PRO: patient reported outcome; SRE: skeletal-related event.

B.3.4.5 Health-related quality-of-life data used in the cost effectiveness analysis

A summary of the utility values included in the model is provided in Table 54.

Table 54 Summary of utility values for cost effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
mHSPC	[redacted]	[redacted]	Table 49, page 130	ARCHES is the main source of utility weight values for mHSPC and mHRPC patients (see section B.3.4.3)
PD1	[redacted]	[redacted]	Table 49, page 130	
PD2	[redacted]	[redacted]	Table 49, page 130	Average from PD1 and PD3 to model gradual utility decline (see section B.3.4.3)
PD3	0.706	0.688-0.723	Table 49, page 130	AFFIRM is the main source of utility weight values for post-chemo mHRPC patients. Its results were in line with several other publications (see section B.3.4.3)
End-of-life utility	[redacted]	[redacted]	Table 49, page 130	ARCHES utility value based on final HRQoL assessment before death (see section B.3.4.3)
AE disutilities	See Table 52, pages 136-137			Literature values were used as impact of individual AEs could not be measured in ARCHES due to frequency of HRQoL measurements
Spinal cord compression	-0.237	SE = 0.079	Table 53, page 138	Disutilities reported for different types of SREs in patients with bone metastases
Pathological bone fracture	-0.201	SE = 0.080	Table 53, page 138	
Radiation to the bone	-0.056	SE = 0.021	Table 53, page 138	

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Surgery to the bone	-0.056	SE = 0.021	Table 53, page 138	

Abbreviations: AE: adverse event; CSR: clinical study report; HEOR: health economics and outcomes report; HRQoL: health related quality of life; mHSPC: metastatic hormone-sensitive prostate cancer; PD: progressed disease; SE: standard error.

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

The perspective of the economic assessment is the NHS England and Personal Social Services perspective[40]. Therefore, only direct medical costs (e.g. drug acquisition costs, inpatient bed days, emergency room [ER] visits, diagnostics, TEAEs, etc.) relevant to mHSPC and progression to mHRPC have been taken into consideration.

A SLR was performed to identify mHSPC cost and healthcare resource use (HRU) data for the UK. Detailed information on the identified studies can be found in Appendix I. The results of this SLR did not identify HRU specific for mHSPC patients in the UK. The only HRU-related study identified was Li *et al*[131], which reports the HRU collected in the LATITUDE trial for high-risk mHSPC patients. Li *et al* concluded that abiraterone plus ADT leads to fewer patients needing overnight hospitalisations and imaging than placebo plus ADT[131]. In contrast, no statistically significant differences were observed for need of ER visits, radiotherapy, surgery, specialist visits, general practitioner visits. However, considering that this study was conducted in high-risk mHSPC, rather than the total population, the results of this study are not considered relevant and the model assumes equal HRU between patients on enzalutamide plus ADT and ADT alone, to provide a conservative estimate. The measurement of HRU for patients on enzalutamide plus ADT was based on previous NICE TAs in mHRPC for enzalutamide and validated with a UK clinician[83, 93, 94].

HRU in the model was based on previous NICE TA for enzalutamide in mHRPC and nmHRPC, and further refined by clinical experts[83, 93, 94]. Since no specific ADT alone data is available, the model assumes equal HRU between enzalutamide and ADT at mHRPC health states. Different HRU are reported for enzalutamide and abiraterone for mHRPC patients, with more frequent monitoring for patients on abiraterone[93]. In addition the model also assumes a higher HRU for patients on ADT alone or enzalutamide plus ADT in mHRPC than in mHSPC, informed by the UK clinical expert[83].

B.3.5.1 Health-state unit costs and resource use

The following direct medical costs have been considered in the model: 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, hospitalisation costs, all follow-up treatment costs and costs for nursing care. HRU frequencies used in the model (Table 55 - Table 59) were validated with a UK clinical expert[83] and are largely in line with the ERG report of the NICE appraisal of

enzalutamide in pre-chemo mHRPC (TA377)[120]. Patients who discontinue docetaxel after 6 cycles and continue on ADT alone are assumed to have the same HRU as ADT alone. HRU for docetaxel is assumed to be identical between mHSPC and mHRPC.

Table 55 Visits and testing frequencies included as HRU for ADT alone and enzalutamide plus ADT in mHSPC

Service mHSPC	Enzalutamide plus ADT and ADT alone			Reference
	% of patients	No. of visits	Every x weeks	
Outpatient visit oncologist	50%	1	8	ERG report TA377[93] and TA580[94]ta5 (control arm), UK clinical expert[83]
Outpatient visit nurse	50%	1	8	
Community nurse visit	100%	0	6	
CT scan	80%	1	39	
Radiographic or MRI scan	5%	1	12	
ECG	0%	-	-	
Ultrasound	0%	-	-	
Bone scan	80%	1	39	
Full blood count	100%	1	8	
Liver function test	100%	1	8	
Kidney function test	100%	1	8	
PSA	100%	1	8	

Abbreviations: ADT: androgen deprivation therapy; CT: Computer tomography ECG: electrocardiogram; ERG: evidence review group; mHSPC: metastatic hormone-sensitive prostate cancer; PD: progressed disease; PSA: prostate-specific antigen; pts: patients; TA: technology appraisal.

Table 56 Visits and testing frequencies included as HRU for ADT alone and enzalutamide plus ADT in mHRPC

Service PD1-3	Enzalutamide plus ADT and ADT alone			Reference
	% of patients	No. of visits	Every x weeks	
Outpatient visit oncologist	50%	1	8	ERG report TA377[93] and TA580[94](control arm), UK clinical expert[83]
Outpatient visit nurse	50%	1	8	
Community nurse visit	100%	0	6	
CT scan	100%	1	39	
Radiographic or MRI scan	5%	1	12	
ECG	0%	1	6	
Ultrasound	0%	1	6	
Bone scan	100%	1	39	
Full blood count	100%	1	8	
Liver function test	100%	1	8	
Kidney function test	100%	1	8	
PSA	100%	1	8	

Abbreviations: ADT: androgen deprivation therapy; CT: Computer tomography ECG: electrocardiogram; ERG: evidence review group; mHRPC: metastatic hormone-relapsed prostate cancer; no.: number; PD: progressed disease; PSA: prostate-specific antigen; pts: patients; TA: technology appraisal.

Table 57 Visits and testing frequencies included as HRU for docetaxel plus ADT in mHSPC and mHRPC

Service mHSPC, PD1-3	Docetaxel plus ADT			Reference
	% of patients	No. of visits	Every x weeks	
Outpatient visit oncologist	67%	1	3	ERG report TA377[93] and TA316[95] (docetaxel arm), UK clinical expert[83]
Outpatient visit nurse	33%	1	3	
Community nurse visit	100%	0	3	
CT scan	100%	1	18	
Radiographic or MRI scan	5%	1	12	
ECG	0%	1	6	
Ultrasound	0%	1	6	
Bone scan	100%	1	18	
Full blood count	100%	1	3	
Liver function test	100%	1	3	
Kidney function test	100%	1	3	
PSA	100%	1	3	

Abbreviations: CT: Computer tomography ECG: electrocardiogram; ERG: evidence review group; mHSPC: metastatic hormone-sensitive prostate cancer; mHRPC: metastatic hormone-relapsed prostate cancer; no.: number; PD: progressed disease; PSA: prostate-specific antigen; pts: patients; TA: technology appraisal.

Table 58 Visits and testing frequencies included as HRU for abiraterone (mHRPC)

Service PD1-3	Abiraterone plus ADT			Reference
	% of patients	No. of visits	Every x weeks	
Outpatient visit oncologist	50%	1	4	ERG report TA377[93] and TA580[94] (abiraterone arm)
Outpatient visit nurse	50%	1	4	
Community nurse visit	50%	1	4	
CT scan	100%	3	66.7	
Radiographic or MRI scan	-	-	-	
ECG	-	-	-	
Ultrasound	-	-	-	
Bone scan	20%	1	12	
Full blood count	100%	1	4	
Liver function test	50%	1	4	
Kidney function test	100%	1	4	
PSA	100%	1	4	

Abbreviations: CT: Computer tomography ECG: electrocardiogram; ERG: evidence review group; mHRPC: metastatic hormone-relapsed prostate cancer; no.: number; PD: progressed disease; PSA: prostate-specific antigen; pts: patients; TA: technology appraisal.

Table 59 Visits and testing frequencies included as HRU for Cabazitaxel, Radium-223 (mHRPC)

Service PD1-3	Cabazitaxel and Radium-223 plus ADT			Reference
	% of patients	No. of visits	Every x weeks	
Outpatient visit oncologist	100%	1	3	ERG report TA377[93] and TA580[94] (cabazitaxel arm)
Outpatient visit nurse	-	-	-	
Community nurse visit	-	-	-	
CT scan	5%	1	6	
Radiographic or MRI scan	5%	1	6	
ECG	5%	1	6	
Ultrasound	5%	1	6	
Bone scan	5%	1	6	
Full blood count	100%	1	3	
Liver function test	100%	1	3	
Kidney function test	100%	1	3	
PSA	100%	1	3	

Abbreviations: CT: Computer tomography ECG: electrocardiogram; ERG: evidence review group; mHRPC: metastatic hormone-relapsed prostate cancer; no.: number; PD: progressed disease; PSA: prostate-specific antigen; pts: patients; TA: technology appraisal.

Concomitant medication use applied for each health state is based on the concomitant medications as reported in TA580 for patients receiving enzalutamide plus ADT, ADT alone and abiraterone plus ADT[94], and TA391 for patients receiving docetaxel, radium-223, and cabazitaxel plus ADT (Table 60)[132].

Table 60 Type and frequency of concomitant treatment use

Product	% of patients requiring concomitant treatment per treatment					
	ADT alone[23]	Enzalutamide [23]	Docetaxel[a]	Abiraterone[b]	Radium-223[a]	Cabazitaxel [132]
ADT	NA	100%	100%	100%	100%	100%
Antihistamine	8%	9%	100%	9%	100%	100%
H2-antagonist	4%	5%	100%	5%	100%	100%
Anti-emetic	6%	5%	100%	5%	100%	100%
Steroid (prednisolone)	4%	4%	100%	100%	100%	100%
G-CSF	0%	0%	25%	0%	25%	25%
Bisphosphonate	4%	4%	47%	4%	47%	47%

a. Assumed equal to cabazitaxel

b. Assumed equal to enzalutamide + prednisone

Abbreviations: ADT: androgen deprivation therapy; G-CSF: Granulocyte-colony stimulating factor.

B.3.5.2 Intervention and comparator costs and resource use

After patients progress to mHRPC, various treatment options become available. To give an accurate representation of the costs that are incurred in mHRPC, three distinct PD health states were included to capture distinct costs and HRQL impact across three lines of treatment for increasingly progressive disease. The respective treatment sequence in these health states were informed by UK clinical guidelines and validated by an external clinical expert (Table 61).

Table 61 Overview of treatment sequences considered for mHSPC and mHRPC

Health states	Enzalutamide arm	ADT arm	Docetaxel arm
mHSPC	Enzalutamide	ADT	Docetaxel
PD1	20% ADT 60% Docetaxel 20% Radium-223	20% ADT 35% Enzalutamide 10% Docetaxel 35% Abiraterone	10% ADT 35% Enzalutamide 25% Docetaxel 30% Abiraterone
PD2	25% BSC 15% Docetaxel 30% Radium-223 30% Cabazitaxel	30% BSC 10% Enzalutamide 30% Docetaxel 5% Abiraterone 20% Radium-223 5% Cabazitaxel	25% BSC 5% Enzalutamide 5% Abiraterone 30% Radium-223 35% Cabazitaxel
PD3	80% BSC 10% Radium-223 10% Cabazitaxel	85% BSC 10% Radium-223 5% Cabazitaxel	80% BSC 10% Radium-223 10% Cabazitaxel

Source: UK expert[83]
Note: ADT is included in all treatment lines
Abbreviations: ADT: androgen deprivation therapy; mHSPC: metastatic hormone-sensitive prostate cancer; PD: progressed disease.

Drug acquisition costs for generic products were sourced from eMIT[133], with the remainder of drug acquisition costs sources from the British National Formulary (BNF)[7].

Unit costs for all other HRU components were sourced from NHS reference costs tables[134] and the Personal Social Services Research Unit (PSSRU)[135]. If available, lower and upper quartiles have been used for sensitivity analyses.

Table 62 and Table 63 provide an overview of drug acquisition and administration costs, and costs for visits and testing, respectively.

Table 62 Drug unit costs

Drug	Brand	NHS Price per pack (£)	Price per day	Reference
Active treatments				
Enzalutamide	Xtandi	£2,734.67	£97.67	BNF Publication last updated on 10-Sep-2019
Androgen deprivation therapies (ADT)				

Drug	Brand	NHS Price per pack (£)	Price per day	Reference
Luteinizing hormone releasing hormone (LHRH) (goserelin)	Non-proprietary	£235.00	£2.80	BNF Publication last updated on 10-Sep-2019
LHRH agonist (leuprorelin acetate)	Non-proprietary	£75.24	£2.49	BNF Publication last updated on 10-Sep-2019
LHRH agonist (leuprorelin acetate)	Non-proprietary	£225.72	£2.49	BNF Publication last updated on 10-Sep-2019
LHRH agonist (triptorelin)	Non-proprietary	£207.00	£2.28	BNF Publication last updated on 10-Sep-2019
Next line treatments				
Abiraterone	Zytiga	£2,735.00	£97.68	BNF Publication last updated on 10-Sep-2019
Docetaxel	Non-proprietary	.£25.59	£1.15	eMit database April 2019, NPC code DHC046
Cabazitaxel	Jevtana	£3,696.00	£221.10	BNF Publication last updated on 10-Sep-2019
Concomitant treatments				
Bisphosphonates (Zoledronic acid)	Non-proprietary	£3.44	£0.16	eMit database April 2019 NPC code DFF024
Antihistamine (chlorphenamine)	Non-proprietary	£0.24	£0.01	eMit database April 2019 NPC code DCD050
H2-antagonist (ranitidine)	Non-proprietary	£0.82	£0.01	eMit database April 2019 NPC code DAE018
Anti-emetic (ondansetron)	Non-proprietary	£0.86	£0.03	eMit database April 2019 NPC code DDF028
G-CSF: Filgrastim	Neupogen	£52.70	£35.13	BNF Publication last updated on 10-Sep-2019
Prednisone	Non-proprietary	£0.27	£0.02	eMit database April 2019 NPC code DHC046

Abbreviations: BNF: British national formulary; eMIT: electronic market information tool; GCSF: Granulocyte colony-stimulating factor; LHRH: Luteinizing hormone releasing hormone; NHS: National Health Service.

Table 63 Visits and testing unit costs

Variable	Code	Unit Cost	Reference
Outpatient visit consultant - follow-up	section 15.5	£108.00	PSSRU 2018[135]
Outpatient visit nurse	section 10.2	£42.00	PSSRU 2018[135]
Community nurse visit	section 10.2	£36.00	PSSRU 2018[135]
CT scan	IMAGOP RD22Z	£132.66	NHS Reference Costs 2017-2018[134]
Radiographic or MRI scan	IMAGOP RD03Z	£199.33	NHS Reference Costs 2017-2018[134]

Variable	Code	Unit Cost	Reference
ECG	OPROC EY51Z Urology	£299.56	NHS Reference Costs 2017-2018[134]
Ultrasound less than 20 min	IMAGOP RD40Z	£54.12	NHS Reference Costs 2017-2018[134]
Ultrasound more than 20 min	IMAGOP RD42Z	£66.41	NHS Reference Costs 2017-2018[134]
Bone scan	NMOP RN16A	£237.93	NHS Reference Costs 2017-2018[134]
Full blood count	DAPS DAPS05	£2.51	NHS Reference Costs 2017-2018
Liver function test (5 tests required: 5 times DAPS04)	DAPS DAPS04	£5.55	NHS reference costs 2017-2018[134]. 5 tests required as reported in abiraterone manufacturer submission (TA259[121])
Kidney function test	DAPS DAPS04	£11.09	NHS Reference Costs 2017-2018. Assumed 10 tests, similar to abiraterone manufacturer submission (TA259[121])
PSA	DAPS DAPS04	£1.11	NHS Reference Costs 2017-2018[134]
Echocardiogram	IMAGOP RD51A	£107.84	NHS Reference Costs 2017-2018[134]
Home care visit (cost 1-hour visit)	section 11.5 Home care	£22.50	PSSRU 2018 Average of daytime and evening[135]
Hospice centre (cost per day)	SPAL IP SD03A	£117.84	NHS Reference Costs 2017-2018[134]
Palliative care centre (cost per day)	SPAL IP SD03A	£117.84	NHS Reference Costs 2017-2018[134]
Administration			
Chemotherapy (IV; per cycle); first attendance	CHEM SB12Z	£247.74	NHS Reference Costs 2017-2018[134]
Chemotherapy (IV; per cycle); subsequent elements	CHEM SB15Z	£312.34	NHS Reference Costs 2017-2018[134]

Abbreviations: CT: Computer tomography ECG: electrocardiogram; NHS: National Health Service; PSA: prostate-specific antigen; PSSRU: Personal Social Services Research Unit.

B.3.5.3 Adverse event unit costs and resource use

Adverse events- and SRE-related costs are shown in Table 64 and Table 65, respectively. Adverse events cost information has been obtained from NHS reference costs 2017-2018[134] and NICE ERG report of post-chemo abiraterone[136], whereas SRE cost information was informed by Ford *et al*[137] and inflated to 2019 prices based on the methods described in section B.3.5.5.

Table 64 TEAE-related unit costs

AE	Cost	Source
Abdominal pain	£1,437.60	NHS reference costs 2017-2018[134]; NEL: Weighted average:FD05A, FD05B
ALT increase	£0	Assumed to have no costs
Alopecia	£0	Assumed to have no costs, considering the age and duration of alopecia
Anaemia	£2,158.87	NHS reference costs 2017-2018[134]; NEL: Weighted average of SA04G, SA04H, SA04J, SA04K, SA04L
Anorexia	£12.00	Costs are not available in NHS reference costs 2017-2018[134]; assumed equal to asthenia: NICE ERG report abiraterone (post-chemo), table 24, p. 64. IQR assumed ±25%
Arthralgia	£69.70	Costs assumed to be equal to pain: NHS Reference Costs 2017-2018[134]; NCL: WF02B; service code: 191 (Pain management, Multiprofessional Non-Admitted Non Face to Face Attendance, First)
AST increase	£0	Assumed equal to ALT increase
Asthenia	£12.00	NICE ERG report abiraterone (post-chemo)[121], table 24, p. 64. IQR assumed ±25%
Back pain	£424.55	NHS reference costs 2017-2018[134]; NES: Weighted average of HC32H, HC32J, HC32K
Bone pain	£615.70	NHS reference costs 2017-2018[134]; NES[134]: Weighted average of HD40D, HD40E, HD40F, HD40G, HD40H
Decreased libido	£609.84	Assumed equal to erectile disfunction
Deterioration in general physical health	£12.00	Costs are not available in NHS Reference Costs 2017-2018[134]; assumed to be equal to fatigue: NICE ERG report abiraterone (post-chemo), table 24, p. 64. IQR assumed ±25%
Diarrhoea	£2,689.81	Costs are not available in NHS reference costs 2017-2018[134]; assumed equal to vomiting: NHS reference costs 2016-2017; NEL: Weighted average of PF28A, PF28B, PF28C, PF28D, PF28E
Dyspnoea	£0.00	NICE ERG report abiraterone (post-chemo)[121], table 24, p. 64.
Erectile dysfunction	£609.84	NHS reference costs 2017-2018[134]; DC: LB43Z
Fatigue	£12.00	NICE ERG report abiraterone (post-chemo)[121], table 24, p. 64. IQR assumed ±25%
Febrile neutropenia	£5,858.41	NHS reference costs 2017-2018[134]: NEL: Weighted average of PM45A, PM45B, PM45C, PM45D (Paediatric Febrile Neutropenia with Malignancy)
Haematuria	£406.85	NHS reference costs 2017-2018[134]; NEL: Weighted average of LB38C, LB38D, LB38E, LB38F, LB38G, LB38H
Hot flushes	£0	Assumed to have negligible or no cost
Hypertension	£364.49	NHS reference costs 2017-2018[134]; NES: EB04Z
Hypokalaemia	£321.05	NHS reference costs 2017-2018[134]; HCD: HICD0285 (Outpatients; Parenteral Nutrition)
Infection with neutropenia	£1,193.08	NHS reference costs 2017-2018[134]; Weighted average of FD01F-J
Leukopenia	£59.02	Costs are not available in NHS reference costs 2017-2018; assumed to be equal to neutropenia: NHS reference costs 2017-2018[134]; HCD: Weighted average of HICD0164, HICD0230, HICD0234, HICD0291 (Admitted Patient Care)

AE	Cost	Source
Nail change	£0	Assumed to have negligible or no costs
Nausea	£2,689.81	Costs are not available in NHS reference costs 2017-2018; assumed to be equal to vomiting: NHS reference costs 2017-2018[134]: NEL: Weighted average of PF28A, PF28B, PF28C, PF28D, PF28E (Paediatric, Feeding Difficulties or Vomiting)
Neutropenia	£59.02	NHS reference costs 2017-2018[134]; HCD: Weighted average of HICD0164, HICD0230, HICD0234, HICD0291 (Admitted Patient Care)
Oedema or Fluid retention	£914.00	NICE ERG report abiraterone (post-chemo)[121], table 24, p. 64
Pain	£69.70	NHS Reference Costs 2017-2018[134]; NCL: WF02B; service code: 191 (Pain management, Multiprofessional Non-Admitted Non Face to Face Attendance, First)
Pain in extremity	£69.70	Costs are not available in NHS reference costs 2017-2018; assumed to be equal to arthralgia and pain: NHS Reference Costs 2017-2018[134]; NCL: WF02B; service code: 191 (Pain management, Multiprofessional Non-Admitted Non Face to Face Attendance, First)
Peripheral oedema	£914.00	NICE ERG report abiraterone (post-chemo), table 24, p. 64
Pneumonia	£2,526.61	NHS reference costs 2017-2018[134]; NEL: Weighted average of DZ11K-DZ11V
Sensory neuropathy	£136.53	Costs are not available in NHS reference costs 2017-2018[134]; NHS reference costs 2016-2017; XD47Z
Thrombocytopaenia	£516.95	NHS reference costs 2017-2018[134]; NES: Weighted average of SA12G, SA12H, SA12J, SA12K
Urinary retention	£1,989.26	NHS reference costs 2017-2018[134]; NEL: Weighted average of LB16D, LB16E, LB16F, LB16G, LB16H, LB16J, LB16K
Vomiting	£2,689.81	NHS reference costs 2017-2018[134]: NEL: Weighted average of PF28A, PF28B, PF28C, PF28D, PF28E (Paediatric, Feeding Difficulties or Vomiting)

Abbreviations: AE: adverse event; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ERG: evidence review group; NEL: non-elective long stay; NES: non-elective short stay; NHS: National Health Service.

Table 65 SRE-related unit costs

SREs	Cost (inflated to 2019)	Source
Spinal Cord Compression	£7,683.84	Ford *et al*[137].
Pathological Bone Fracture	£985.31	Ford *et al*[137]
Radiation to the Bone	£695.76	Ford *et al*[137]
Surgery to the Bone	£7,639.69	Ford *et al*[137]
NEL Vertebral fractures	£308.99	Ford *et al*[137]
Non-vertebral fractures	£1,661.63	Ford *et al*[137]

Abbreviations: HRG: Healthcare Resource Group; NEL: non-elective long stay; NES: non-elective short stay; NHS: National Health Service; SRE: skeletal-related event.

B.3.5.4 Miscellaneous unit costs and resource use

End of life or terminal treatment costs have been included based on data adapted from TA387[138], which were also used in the enzalutamide pre-chemo NICE submission. No palliative care health state was applied in the economic assessment for enzalutamide in mHSPC but rather an average one-off cost of £3,598 for end-of-life treatment incurred for all mHRPC-related deaths[99].

B.3.5.5 Discounting and inflation of costs

Costs have been discounted at an annual rate of 3.5% in the reference-case analysis, as per NICE recommendations[139]. A scenario analysis demonstrating the impact of discounting rate on the results has been performed.

When possible, the model uses the latest information to inform costs in the model. Aggregated costs with a paucity of information around individual components or costs from alternative sources were unable to be updated from national databases. In these cases, costs with a price year of 2007 or more recent were inflated using PSSRU inflation indices. Based on PSSRU recommendations, the 'New Health Services Index using Consumer Price Index' values were used to inflate prices between 2014-2018 with the 'Hospital and Community Health Services Index' (HCHS) prior to 2014. All prices prior to 2007 have been inflated to the year 2019 based on the consumer price inflation tables provided by the UK's Office of National Statistics.

B.3.6 Summary of base case analysis inputs and assumptions

B.3.6.1 Summary of base case analysis inputs

Table 66 gives a summary of the main variables applied in the economic model.

Table 66 Summary of variables applied in the economic model

Variable description	Base-case value	Uncertainty and distribution	Reference
General Inputs (based on Table 47)			
Cycle length in years	0.0833	None	1-month cycle was chosen as a clinically meaningful time interval
Time horizon in years	30	None	30 years time horizon was assumed to be sufficient to capture the remaining life time of a mHSPC patient
Discount rate effects and costs	3.5%	None	NICE guidelines
Average age at model entry	70	Normal	ARCHES CSR[33]
Average body area for patients on chemotherapy	2.01	[1.6; 2.4]; Normal	NICE ERG report on post chemo abiraterone[121]
Maximum number of 3-week cycles given as 1st line therapy in mHSPC	6	None	NICE clinical guidelines
Costs (based on input from Table 46 and Table 62, in £)			

Variable description	Base-case value	Uncertainty and distribution	Reference
Daily drug costs for enzalutamide (no PAS)	97.67	None	BNF Publication last updated on 10-Sep-2019
Daily drug costs for docetaxel	1.15	None	eMit database April 2019 DHC046
Daily drug costs for ADT	2.57	[2.31; 2.83]; Gamma	Aggregate value
Daily drug costs for abiraterone	97.68	None	BNF Publication last updated on 10-Sep-2019
Daily drug costs for cabazitaxel	221.10	None	BNF Publication last updated on 10-Sep-2019
Daily drug costs for radium-223	144.29	None	BNF Publication last updated on 10-Sep-2019
Costs of chemotherapy administration per model cycle	452.39	[407.15; 497.63]; Gamma	Assuming an average body area of 2.01m2 for patients on chemotherapy; NHS reference costs 2017-2018[134]
Monitoring costs per cycle (based on input from Table 55-Table 59 and Table 63, in £)			
Monthly health state costs for patients on enzalutamide in mHSPC	88.14	[71.71; 106.23]; Gamma	Aggregate value. For probabilistic SA, standard error is assumed 10%
Monthly health state costs for patients on enzalutamide in PD1-3	96.37	[78.41; 116.16]; Gamma	Aggregate value. For probabilistic SA, standard error is assumed 10%
Monthly health state costs for patients on docetaxel	246.61	[200.65; 297.24]; Gamma	Aggregate value. For probabilistic SA, standard error is assumed 10%
Monthly health state costs for patients on BSC	512.72	[417.17; 617.98]; Gamma	Aggregate value. For probabilistic SA, standard error is assumed 10%
Monthly health state costs for patients on ADT in mHSPC	88.14	[71.71; 106.23]; Gamma	Aggregate value. For probabilistic SA, standard error is assumed 10%
Monthly health state costs for patients on ADT in PD1-3	96.37	[78.41; 116.16]; Gamma	Aggregate value. For probabilistic SA, standard error is assumed 10%
Monthly health state costs for patients on abiraterone in PD1-3	162.00	[131.81; 195.25]; Gamma	Aggregate value. For probabilistic SA, standard error is assumed 10%
Monthly health state costs for patients on cabazitaxel in PD1-3	671.00	[545.95; 808.75]; Gamma	Aggregate value. For probabilistic SA, standard error is assumed 10%
Monthly health state costs for patients on radium-223 in PD1-3	218.61	[177.87; 263.48]; Gamma	Aggregate value. For probabilistic SA, standard error is assumed 10%
Terminal care costs	3,598.00	[2,698.50; 4,497.50]; Gamma	Healthcare resource utilisation for the last 3 months of a patient's life. Source: Abiraterone NICE pre-chemo submission[99]. Applied as transition cost to patients

Variable description	Base-case value	Uncertainty and distribution	Reference
			moving to the death health state
Concomitant medication (based on input from Table 60 and Table 62, in £)			
Monthly costs of concomitant medications for patients on enzalutamide	78.57	[60.16; 99.39]; Gamma	Table 12.2.2.6 in ARCHES CSR[23]
Monthly costs of concomitant medications for patients on docetaxel, cabazitaxel or radium-223	349.93	[267.96; 442.67]; Gamma	Same as cabazitaxel in NICE appraisal (TA391)[132]
Monthly costs of concomitant medications for patients on ADT	3.53	[2.70; 4.46]; Gamma	Table 12.2.2.6 in ARCHES CSR[23]
Monthly costs of concomitant medications for patients on abiraterone	79.13	[60.59; 100.10]; Gamma	Assumed equal to enzalutamide, with prednisone
Utilities (based on Table 49)			
Utility value in mHSPC	[redacted]	[redacted]; Beta	ARCHES EQ-5D-5L + Van Hout algorithm All pre-rPFS progression values, both arms
Utility value in PD1	[redacted]	[redacted]; Beta	ARCHES EQ-5D-5L + Van Hout algorithm All post rPFS values, both arms
Utility value in PD2	[redacted]	[redacted]; Beta	Mean of PD1 and PD3
Utility value in PD3	0.688	[0.649; 0.726]; Beta	AFFIRM baseline utility values (pooled arms) - EQ-5D-3L[100]
Utility value for end-of-life period	[redacted]	[redacted]; Beta	ARCHES EQ-5D-5L + Van Hout algorithm Last assessment before death (OS), both arms
Duration for end-of-life utility value in months	3		Assumption
Data input (based on selected parametric fit in section B.3.3)			
OS ADT	Intercept: [redacted] Scale: [redacted]	Intercept: [redacted]; Multivariate Scale: [redacted]; Multivariate	Pooled analysis Extrapolation Report[43]; Weibull extrapolation
OS enzalutamide	Intercept: [redacted] Scale: [redacted]	Intercept: [redacted]; Multivariate Scale: [redacted]; Multivariate	Pooled analysis Extrapolation Report[43]; Weibull extrapolation
rPFS ADT	Intercept: [redacted] Scale: [redacted]	Intercept: [redacted]; Multivariate Scale: [redacted]; Multivariate	ARCHES CSR[23], rPFS addendum[32]; ARCHES Extrapolation Report[41]; Lognormal extrapolation

Variable description	Base-case value	Uncertainty and distribution	Reference
rPFS enzalutamide	Intercept: [redacted] Scale: [redacted]	Intercept: [redacted]; Multivariate Scale: [redacted]; Multivariate	ARCHES CSR[23], rPFS addendum[32]; ARCHES Extrapolation Report[41]; Lognormal extrapolation
TTD enzalutamide	Intercept: [redacted]	Intercept: [redacted]; Multivariate	ARCHES CSR[23]; ARCHES Extrapolation Report[41]; Exponential extrapolation
Hazard ratios (based on Table 34)			
Docetaxel PFS NMA HR to ADT	[redacted]	[redacted]	ARCHES NMA report[44]
Docetaxel OS NMA HR to ADT	[redacted]	[redacted]	ARCHES NMA report[44]
Monthly probabilities for AEs and SREs (based on inputs from Table 50 and Table 51)			
Monthly AE probability on ADT in mHSPC	[redacted]	None	Aggregate value, individual AEs varied in OWSA and PSA
Monthly AE probability on ADT in mHRPC (PD1-3)	0.01523	None	Aggregate value, individual AEs varied in OWSA and PSA
Monthly AE probability on enzalutamide in mHSPC	[redacted]	None	Aggregate value, individual AEs varied in OWSA and PSA
Monthly AE probability on enzalutamide in mHRPC (PD1-3)	0.00989	None	Aggregate value, individual AEs varied in OWSA and PSA
Monthly AE probability on docetaxel in mHSPC	0.03535	None	Aggregate value, individual AEs varied in OWSA and PSA
Monthly AE probability on docetaxel in mHRPC (PD1-3)	0.06846	None	Aggregate value, individual AEs varied in OWSA and PSA
Monthly AE probability on abiraterone in mHRPC (PD1-3)	0.00931	None	Aggregate value, individual AEs varied in OWSA and PSA
Monthly AE probability on radium-223 in mHRPC (PD1-3)	0.15060	None	Aggregate value, individual AEs varied in OWSA and PSA
Monthly AE probability on cabazitaxel in mHRPC (PD1-3)	0.49381	None	Aggregate value, individual AEs varied in OWSA and PSA
Monthly AE probability on BSC in mHRPC (PD1-3)	0	None	Aggregate value, individual AEs varied in OWSA and PSA
Monthly SRE probability on ADT in mHSPC	[redacted]	None	Aggregate value, individual AEs varied in OWSA and PSA
Monthly SRE probability on all other treatments in mHSPC	[redacted]	None	Aggregate value, individual AEs varied in OWSA and PSA
Monthly SRE probability on ADT in PD1	0.02155	None	Aggregate value; identical to NICE TA377[93]
Monthly SRE probability on all other treatments in PD1	0.01624	None	Aggregate value; identical to NICE TA377[93]
Monthly SRE probability on all treatments in PD2-3	0.04776	None	Aggregate value; identical to NICE TA377[93]
AE and SRE costs (based on input from Table 50, Table 51, Table 64 and Table 65; in £)			
Average cost to treat an AE on ADT in mHSPC	[redacted]	None	Aggregate value, individual AEs varied in OWSA and PSA
Average cost to treat an AE on ADT in mHRPC (PD1-3)	847.93	None	Aggregate value, individual AEs varied in OWSA and PSA

Variable description	Base-case value	Uncertainty and distribution	Reference
Average cost to treat an AE on enzalutamide in mHSPC	[redacted]	None	Aggregate value, individual AEs varied in OWSA and PSA
Average cost to treat an AE on enzalutamide in mHRPC (PD1-3)	721.83	None	Aggregate value, individual AEs varied in OWSA and PSA
Average cost to treat an AE on docetaxel in mHSPC	754.75	None	Aggregate value, individual AEs varied in OWSA and PSA
Average cost to treat an AE on docetaxel in mHRPC (PD1-3)	678.30	None	Aggregate value, individual AEs varied in OWSA and PSA
Average cost to treat an AE on abiraterone in mHRPC (PD1-3)	232.54	None	Aggregate value, individual AEs varied in OWSA and PSA
Average cost to treat an AE on radium-223 in mHRPC (PD1-3)	1067.86	None	Aggregate value, individual AEs varied in OWSA and PSA
Average cost to treat an AE on cabazitaxel in mHRPC (PD1-3)	540.03	None	Aggregate value, individual AEs varied in OWSA and PSA
Average cost to treat an AE on BSC in mHRPC (PD1-3)	0.00	None	Aggregate value, individual AEs varied in OWSA and PSA
Average cost to treat an SRE on ADT in mHSPC+PD1	[redacted]	None	Aggregate value, individual SREs varied in OWSA and PSA
Average cost to treat an SRE on other treatments in mHSPC+PD1	[redacted]	None	Aggregate value, individual SREs varied in OWSA and PSA
Average cost to treat an SRE on all treatments in PD2-3	2393.51	None	Aggregate value, individual SREs varied in OWSA and PSA
AE and SRE disutilities (based on input from Table 50, Table 51, Table 52 and Table 53)			
Average disutility due to AE on ADT in mHSPC	[redacted]	None	Aggregate value, individual AEs varied in OWSA and PSA
Average disutility due to AE on ADT in mHRPC (PD1-3)	-0.00591	None	Aggregate value, individual AEs varied in OWSA and PSA
Average disutility due to AE on enzalutamide in mHSPC	[redacted]	None	Aggregate value, individual AEs varied in OWSA and PSA
Average disutility due to AE on enzalutamide in mHRPC (PD1-3)	-0.00725	None	Aggregate value, individual AEs varied in OWSA and PSA
Average disutility due to AE on docetaxel in mHSPC	-0.00860	None	Aggregate value, individual AEs varied in OWSA and PSA
Average disutility due to AE on docetaxel in mHRPC (PD1-3)	-0.00615	None	Aggregate value, individual AEs varied in OWSA and PSA
Average disutility due to AE on abiraterone in mHRPC (PD1-3)	-0.00730	None	Aggregate value, individual AEs varied in OWSA and PSA
Average disutility due to AE on radium-223 in mHRPC (PD1-3)	-0.00663	None	Aggregate value, individual AEs varied in OWSA and PSA
Average disutility due to AE on cabazitaxel in mHRPC (PD1-3)	-0.01064	None	Aggregate value, individual AEs varied in OWSA and PSA
Average disutility due to AE on BSC in mHRPC (PD1-3)	0.00000	None	Aggregate value, individual AEs varied in OWSA and PSA

Variable description	Base-case value	Uncertainty and distribution	Reference
Average disutility due to SRE on ADT in mHSPC+PD1	[redacted]	None	Aggregate value, individual AEs varied in OWSA and PSA
Average disutility due to SRE on other treatments in mHSPC+PD1	[redacted]	None	Aggregate value, individual AEs varied in OWSA and PSA
Average disutility due to SRE on all treatments in PD2-3	-0.00895	None	Aggregate value; identical to NICE TA377[93]

Abbreviations: AE: adverse event; ADT: androgen deprivation therapy; BNF: British national formulary; BSC: best supportive care; CI: confidence interval; CSR: clinical study report; EQ-5D-3L: European Quality of Life-5 Dimensions-3 Levels; mHSPC: metastatic hormone-sensitive prostate cancer; mHRPC: metastatic hormone-relapsed prostate cancer; NHS: national health services PSA: probabilistic sensitivity analysis; OS: overall survival; OWSA: one-way sensitivity analysis; PAS: patient access scheme; PD: progressed disease; SRE: skeletal-related event; TTD: time to treatment discontinuation.

B.3.6.2 Assumptions

The assumptions taken for the model were based on the ARCHES trial[23], UK clinical practice, published literature and expert opinion[83] (Table 67).

Table 67 Summary of key assumptions in the economic model

Assumption	Justification	Source
It is assumed that ADT is continued indefinitely regardless of the treatment arm	European guidelines recommend ADT to be maintained indefinitely in HSPC patients[140]. The consulted UK clinical expert confirmed that this is in line with UK clinical practice[83].	Clinical expert opinion[83] Treatment guidelines[140]
Various treatment options exist for patients with mHRPC. The model reflects the expected treatment algorithm to be applied in the UK once enzalutamide is available for the mHSPC setting. Costs for treatment and/or drug acquisition, administration, monitoring, and AEs, as well as treatment durations and AE disutilities are taken into account for these treatments. However, OS outcomes of the model are not adjusted based on post-baseline (i.e. PD1-PD3) treatments, since neither ARCHES nor ENZAMET were powered to perform these adjustments.	In UK clinical practice, patients who have received enzalutamide are not permitted to receive abiraterone or enzalutamide again later in the disease course. Informed by expert opinion, it was assumed that these patients would primarily receive docetaxel (60%). The remaining patients would receive ADT alone or radium-223[83]. Current SoC for patients progressing on ADT alone or docetaxel plus ADT in mHSPC would be to primarily receive enzalutamide or abiraterone. The remaining patients would either receive ADT alone, docetaxel (including re-challenge)[83]. All later line treatments were also informed by UK clinical expert opinion[83]v.	Clinical expert opinion[83]
In the model, no assumptions about dosing intensities, compliance and capped treatment durations have been taken into account.	The model assumed that patients remain on the full label dosage for all treatments as per reported times to progression. However, in reality patients and their physicians might choose to (temporarily) reduce the dosage or (temporarily) interrupt treatment altogether, which might reduce actual treatment costs. The effect of treatment interruption is further explored in a scenario analysis.	NA

Assumption	Justification	Source
The ARCHES and ENZAMET clinical trials provide the most reliable data source to inform progression and survival in the model. Limitations to the data maturity (i.e. finite follow-up period) can be addressed using publicly available external reference data.	While there is no alternative data source that would provide a more reliable reference curve for either of the model outcomes, there are data that can be used for external validation of the extrapolations. Data from the STAMPEDE[49, 91], CHAARTED[45], and GETUG[46] were used to validate the long term PFS and OS extrapolations. The plausibility of the selected curves was later validated by UK clinical experts and the sensitivity of the model to these curves was explored in a series of scenarios, to ensure an accurate long-term representation of the disease progression.	STAMPEDE[49, 91], CHAARTED[45], GETUG[46]; Discussion with a clinical expert[83]
It is methodologically acceptable to pool ARCHES and ENZAMET OS data and to combine rPFS data from ARCHES with pooled OS data, considering the caveats in pooling PFS from both studies	To increase the robustness of the data and to make use of all patient data across both trials (n=1,772), OS data from ARCHES and ENZAMET was pooled. OS is a hard endpoint which should not differ between trials. It was therefore considered methodologically sound to pool OS data. In addition the long-term OS extrapolations were validated with a UK clinical expert[83]. For PFS, pooling was considered implausible, due to the differences in PFS definition between ARCHES and ENZAMET and the effect that NSAA has on PFS. ARCHES PFS was preferred over pooled or ENZAMET PFS, to enable a robust comparison versus docetaxel and since the ARCHES PFS definition is more aligned with that in similar trials and PFS was the primary endpoint in ARCHES[83].	Discussion with a UK clinical and a HTA experts[83]
Patients have a short gap between mHSPC and first-line mHRPC in which they only receive ADT. This is informed by TTD in the model	In both ARCHES and ENZAMET, there was a difference between the respective TTD and PFS outcomes, indicating that patients spend a short time off-treatment before progression. This was confirmed by a UK clinical expert 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[83].	Discussion with a UK clinical expert[83]
Transition rates between the mHRPC health states (PD1, PD2, and PD3) are informed by the median TTD for each respective treatment.	Due to the uncertainty around (future) mHRPC treatment sequences and the lack of alternative data that could inform transition rates in this stage of the disease, TTD drives the transition between mHRPC health states. This assumption was previously accepted in mHRPC models.	Discussion with a UK economist[83]

Abbreviations: ADT: androgen deprivation therapy; ERG: evidence review group; HTA: health technology assessment; mHRPC: metastatic hormone-relapsed prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; OS: overall survival; PD: progressed disease; PFS: progression-free survival; TA: technology appraisal; TTD: time to treatment discontinuation.

B.3.6.3 Scenario analyses

Several scenario analyses were performed to explore the uncertainties and the robustness of the model. Table 68 provides an overview of the scenarios that were performed, along with a justification.

Table 68 Scenarios included in the cost effectiveness analysis

No	Scenario analysis	Scenario description	Justification
1	Markov version of the base case analysis	Run the base case analysis using the built-in Markov structure only	To demonstrate robustness of the modelling technique by showing that results from the PartSA model are similar to the results from the build in Markov model
2	Scenario using second best fitting parametric curves for OS	Run the base case analysis using the log-logistic pooled OS curve to model survival	Weibull distribution was selected as the base case curve fit for OS based on validation of clinical plausibility. Alternatively, log-logistic showed a good fit for pooled OS based on statistical validity tests, but clinical experts informed that it resulted in unrealistic enzalutamide extrapolations. This scenario explores the impact of the distribution applied to model OS.
3	Scenario using second best fitting parametric curves for PFS and TTD	Run the base case analysis using the gamma ARCHERS PFS and log-logistic TTD curves to model progression	Gamma distribution showed a good fit for ARCHES PFS based on statistical validity tests and resulted in realistic long-term ADT PFS predictions. However, it also resulted in crossing of curves for PFS and OD in the enzalutamide arm. Further, clinical experts opinion indicated that it resulted in unrealistic enzalutamide extrapolations, therefore log-normal distribution was applied. This scenario explores the impact of the distribution applied to model PFS. TTD was also varied to match the PFS curve.
4	Scenario using only ENZAMET data	Run the base case analysis using ENZAMET log-logistic OS, Weibull PFS and exponential TTD	Investigate the sensitivity of results to alternative source of data
5	Scenario using only ARCHES data	Run the base case analysis using ARCHES log-logistic OS data	Investigate the sensitivity of results to alternative source of data
6	Scenario using only pooled data	Run the base case analysis using Pooled exponential PFS and TTD data	Investigate the sensitivity of results to alternative source of data
7	Scenario excluding off-treatment mHSPC health state	The model assumes that some patients and their physicians may choose to temporarily interrupt treatments. In this scenario, all patients remain on their initial treatment until they progress, by excluding treatment discontinuation from the model	To explore the impact of excluding treatment modifications as observed in ARCHES
8	Scenario using a combined PD1-3 health state	This scenario explores the effect of using one combined health PD1-3 health state.	In the base case progressed disease health states are separated into 3 sub-states PD1, PD2, PD3 using the Markov calculation. This scenario was performed to demonstrate the impact of capturing the costs and HRQL impact of increasingly progressive disease

No	Scenario analysis	Scenario description	Justification
9	Scenario using NMA HRs to model enzalutamide	Modelling ENZA efficacy by applying the NMA HRs vs ADT ([redacted]) to the ADT curves, excluding off treatment	The current base case uses enzalutamide curve to model efficacy based on the trial data. It is also possible to inform enzalutamide efficacy using the NMA HR, which reflects the methodology for the comparison with docetaxel although with caveats to the NMA methodology as described above in section B.2.9
10	Scenario using ARCHES PD1 treatments	Model the treatments in PD1 based on the first post-progression treatment observed in ARCHES	To explore uncertainty in results due to the assumptions for post-progression treatments use
11	Scenario including dose-interruptions	The enzalutamide dose is corrected with the observed mean dose in ARCHES (158.3mg)	Although enzalutamide is recommended at a daily dose of 160 mg, in daily practice this dose would be expected to be lower due to dose-interruptions. This scenario assessed the sensitivity of results to dose interruptions
12	Scenario using a shorter time horizon	A time horizon of 10 and 20 years instead of 30 years was used	Shorter time horizons were tested to show the impact of the long-term survival extrapolation.
13	Scenario using a lower discount rate (1.5%)	Replace 3.5% discount rates for cost and outcomes with 1.5% rate	Investigate the long-term uncertainty and impact of discounting

Abbreviations: ADT: androgen deprivation therapy; ERG: evidence review group; HTA: health technology assessment; mHRPC: metastatic hormone-relapsed prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; OS: overall survival; PD: progressed disease; PFS: progression-free survival; TA: technology appraisal; TINAT: time to initiation of new antineoplastic therapy; TTD: time to treatment discontinuation.

B.3.7 Base case results

B.3.7.1 Base case incremental cost effectiveness analysis results

The base case cost effectiveness results are presented in Table 69.

On average, a patient treated with enzalutamide plus ADT gains [redacted] additional LYs and [redacted] additional QALYs (discounted) compared to a patient treated with ADT. Compared to docetaxel plus ADT, a patient treated with enzalutamide plus ADT gains an additional [redacted] LYs and [redacted] QALYs (discounted). The additional LYs and QALYs with enzalutamide plus ADT are achieved at an incremental cost of [redacted] and [redacted] versus ADT and docetaxel plus ADT, respectively. Enzalutamide plus ADT treatment for mHSPC patients is more effective, but also more costly than both ADT alone or docetaxel plus ADT, with an ICER of £19,911 and £22,877, respectively. Additional clinical outcomes and disaggregated costs are summarised in Appendix J.

Table 69 Base case cost effectiveness results

Treatment	Total Costs (£)	Total LYs	Total QALYs	Incr. Costs (£)	Incr. LYs	Incr. QALYs	ICER (£)
Enzalutamide plus ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

Treatment	Total Costs (£)	Total LYs	Total QALYs	Incr. Costs (£)	Incr. LYs	Incr. QALYs	ICER (£)
ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,911
Docetaxel plus ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,877

Abbreviations: ADT: androgen deprivation therapy; incr.: incremental; LYG: life-years gained; PD: progressed disease; QALY: quality-adjusted life years.

B.3.8 Sensitivity analyses

B.3.8.1 Deterministic sensitivity analysis

Two distinct univariate one-way sensitivity analyses (OWSA) have been conducted by varying input parameters within their 95% confidence interval or their most plausible ranges, one for enzalutamide vs ADT, and one for enzalutamide vs docetaxel. Variables for which no confidence interval and/or standard deviation or error was available have been varied by an arbitrary range of ±25%. Drug costs have been varied by ±10% in this analysis.

The most important drivers of the model have been plotted in a tornado diagram and summarised in a table for the comparison between enzalutamide plus ADT and ADT (Figure 24, Table 70) and for enzalutamide plus ADT vs docetaxel (Figure 25, Table 71). Overall, the spread in ICERs suggest the results for cost effectiveness of enzalutamide plus ADT vs ADT and docetaxel plus ADT are relatively stable when key parameters are varied across their standard error or reported upper and lower ranges. PFS was the most important driver of results. This is not surprising since PFS plays an important role in determining the incremental costs in the model given that the disease pathway following progression is modelled consistently across intervention and comparators. A longer PFS raises the costs in the enzalutamide arm of the model (since patients stay longer on enzalutamide) while decreasing the costs in the ADT and docetaxel plus ADT arms, as patients remain longer on ADT alone for the comparators. Other influential parameters were OS, treatment costs, treatment durations, and health state costs.

Figure 24 Tornado diagram for enzalutamide plus ADT vs ADT alone one-way SA

Abbreviations: ADT: androgen deprivation therapy; Enza: enzalutamide; PD: progressed disease; PPS: post-progression survival; PrePS: pre-progression survival; SA: sensitivity analysis.

Table 70 One-way SA results for enzalutamide plus ADT vs ADT alone

Parameter	Model Input (BC)	Low	High	ICER Low	ICER High
Base case	NA	NA	NA	£19,911	
Enza PFS extrapolation, intercept value	[redacted]	[redacted]	[redacted]	£24,382	£14,473
Enza OS extrapolation, intercept value	[redacted]	[redacted]	[redacted]	£25,113	£18,300
Enza TTD extrapolation, intercept value	[redacted]	[redacted]	[redacted]	£16,882	£22,842
Enza PFS extrapolation, scale value	[redacted]	[redacted]	[redacted]	£22,005	£18,620
Placebo PFS extrapolation, intercept value	[redacted]	[redacted]	[redacted]	£18,338	£21,675
Placebo PFS extrapolation, scale value	[redacted]	[redacted]	[redacted]	£18,785	£21,048
Enza OS extrapolation, scale value	[redacted]	[redacted]	[redacted]	£21,174	£19,092
Median treatment duration for ABI in PD1	[redacted]	[redacted]	[redacted]	£20,393	£19,450
Average body area	[redacted]	[redacted]	[redacted]	£19,524	£20,302
Enza mHSPC health state costs	[redacted]	[redacted]	[redacted]	£19,550	£20,312
Enza concomitant medication costs	[redacted]	[redacted]	[redacted]	£19,560	£20,312

Parameter	Model Input (BC)	Low	High	ICER Low	ICER High
Placebo OS extrapolation, scale value	[redacted]	[redacted]	[redacted]	£19,560	£20,294
BSC health state costs	[redacted]	[redacted]	[redacted]	£19,583	£20,277
PD3 utility value	[redacted]	[redacted]	[redacted]	£20,148	£19,691
PD1 utility value	[redacted]	[redacted]	[redacted]	£19,742	£20,083

Abbreviations: ABI: abiraterone; ADT: androgen deprivation therapy; BC: base case; BSC: best supportive care; Enza; enzalutamide ICER: incremental cost effectiveness ratio; mHSPC: metastatic hormone-sensitive prostate cancer; PD: progressed disease; PFS: progression-free survival; OS: overall survival; QALY: quality-adjusted life years; SA: sensitivity analysis.

Figure 25 Tornado diagram for enzalutamide plus ADT vs docetaxel plus ADT one-way SA

Abbreviations: ADT: androgen deprivation therapy; Enza: enzalutamide; MFS: metastasis-free survival; PD: progressed disease; PPS: post-progression survival; PrePS: pre-progression survival; SA: sensitivity analysis.

Table 71 One-way SA results for enzalutamide plus ADT vs docetaxel plus ADT

Parameter	Model Input (BC)	Low	High	ICER Low	ICER High
Base case	NA	NA	NA	£22,877	
Enza OS extrapolation, intercept value	[redacted]	[redacted]	[redacted]	£41,528	£19,654
PFS NMA HR for docetaxel	[redacted]	[redacted]	[redacted]	£30,526	£16,206
Enza PFS extrapolation, intercept value	[redacted]	[redacted]	[redacted]	£29,394	£15,264

Parameter	Model Input (BC)	Low	High	ICER Low	ICER High
Enza TTD extrapolation, intercept value	[redacted]	[redacted]	[redacted]	£18,662	£26,949
Placebo PFS extrapolation, intercept value	[redacted]	[redacted]	[redacted]	£19,850	£26,189
Placebo PFS extrapolation, scale value	[redacted]	[redacted]	[redacted]	£19,888	£25,592
Enza PFS extrapolation, scale value	[redacted]	[redacted]	[redacted]	£25,880	£21,038
Enza OS extrapolation, scale value	[redacted]	[redacted]	[redacted]	£24,601	£21,794
Placebo OS extrapolation, scale value	[redacted]	[redacted]	[redacted]	£22,443	£24,574
Placebo OS extrapolation, intercept value	[redacted]	[redacted]	[redacted]	£24,174	£22,478
OS NMA HR for docetaxel	[redacted]	[redacted]	[redacted]	£22,370	£23,449
Enza concomitant medication costs	[redacted]	[redacted]	[redacted]	£22,372	£23,432
Enza mHSPC health state costs	[redacted]	[redacted]	[redacted]	£22,495	£23,297
BSC health state costs	[redacted]	[redacted]	[redacted]	£23,273	£22,498
Median treatment duration for ABI in PD1	[redacted]	[redacted]	[redacted]	£22,498	£23,273

Abbreviations: ABI: abiraterone; ADT: androgen deprivation therapy; BC: base case; BSC: best supportive care; Enza; enzalutamide ICER: incremental cost effectiveness ratio; mHSPC: metastatic hormone-sensitive prostate cancer; PD: progressed disease; PFS: progression-free survival; OS: overall survival; QALY: quality-adjusted life years; SA: sensitivity analysis.

B.3.8.2 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 characterised using probability distributions and analysed using a Monte Carlo simulation using 10,000 simulations.

An overview of the probabilistic sensitivity analysis results for the cost effectiveness of enzalutamide plus ADT vs ADT and vs docetaxel plus ADT are shown in Table 72 and Table 73, respectively. Overall, the probabilistic sensitivity analysis results produce mean values similar to those presented within the base case analysis with an average ICER of £20,758/QALY for enzalutamide plus ADT vs ADT and £24,167/QALY for enzalutamide plus ADT vs docetaxel plus ADT.

Table 72 Probabilistic SA statistical results vs ADT

	Enzalutamide plus ADT		ADT		Incremental		
	Costs	QALYs	Costs	QALYs	Costs	QALYs	CE ratio
Deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,911

	Enzalutamide plus ADT		ADT		Incremental		
	Costs	QALYs	Costs	QALYs	Costs	QALYs	CE ratio
Probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,758
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,994
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
95% LCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
95% UCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

Abbreviations: ADT: androgen deprivation therapy; CE: cost effectiveness; LCI: lower confidence interval; NA: not available; SA: sensitivity analysis; QALY: quality-adjusted life years StDev: standard deviation UCI: upper confidence interval.

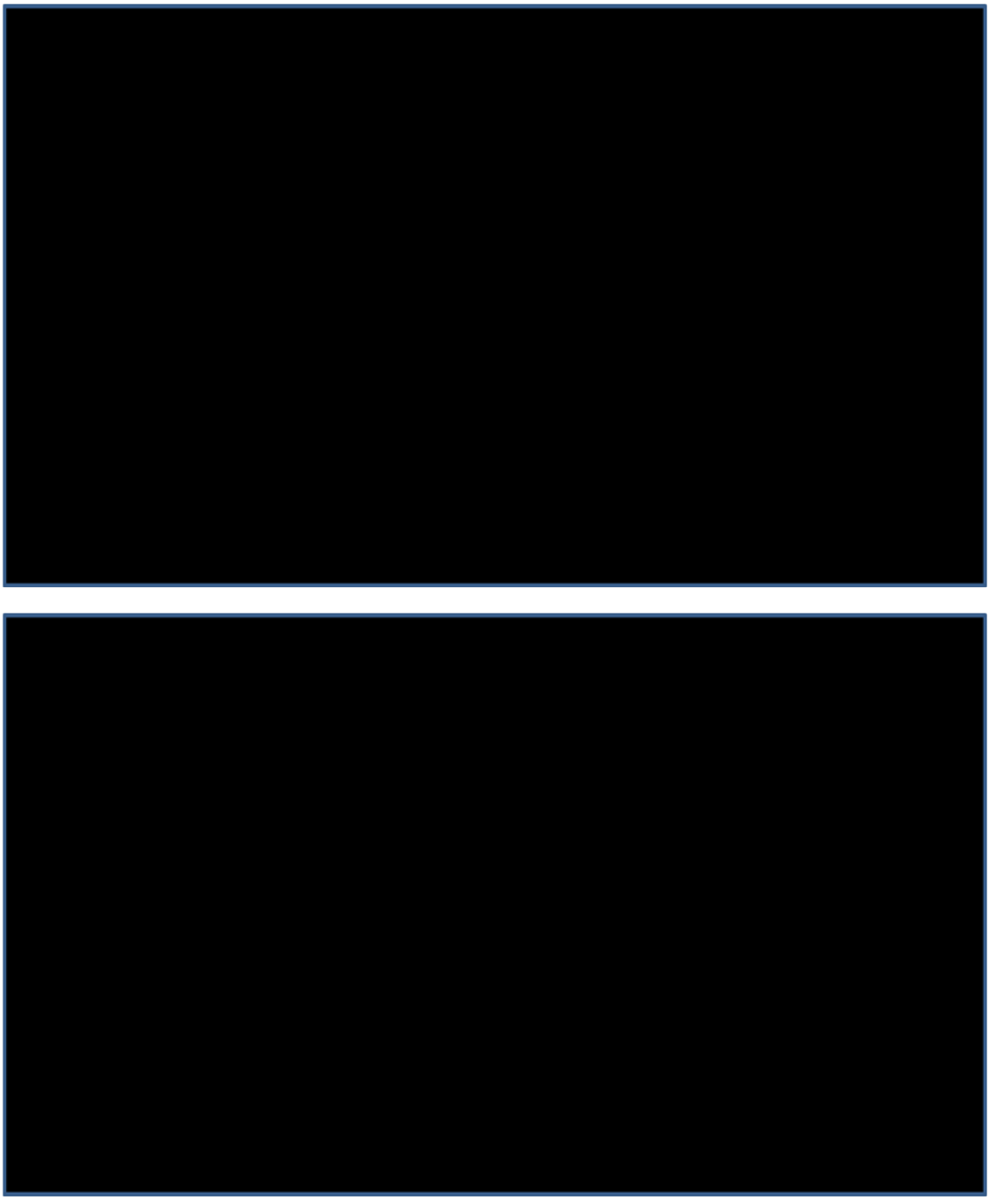
Table 73 Probabilistic SA statistical results vs docetaxel

	Enzalutamide plus ADT		Docetaxel plus ADT		Incremental		
	Costs	QALYs	Costs	QALYs	Costs	QALYs	CE ratio
Deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,877
Probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,167
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,371
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
95% LCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
95% UCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

Abbreviations: ADT: androgen deprivation therapy; CE: cost effectiveness; LCI: lower confidence interval; NA: not available; SA: sensitivity analysis; QALY: quality-adjusted life years StDev: standard deviation UCI: upper confidence interval.

The individual results of the probabilistic sensitivity analysis were plotted in cost effectiveness planes to visualise the distribution of possible ICERs relative to the selected comparator (Figure 26). Each dot resembles one Monte Carlo simulation where the effectiveness input parameters are sampled from their distributions. A total of 10,000 of such simulations were performed. The black line represents a WTP threshold of £30,000 per QALY gained.

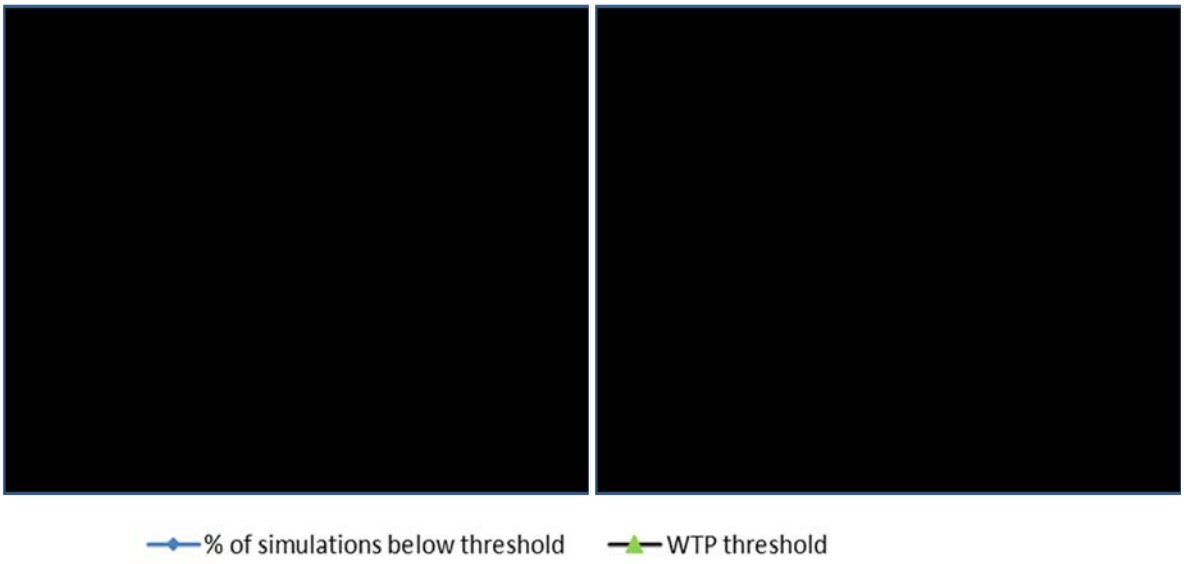
Figure 26 Cost effectiveness plane enzalutamide plus ADT vs ADT (top) and vs docetaxel plus ADT (bottom)



Abbreviations: ADT: androgen deprivation therapy; QALY: quality-adjusted life years; WTP: willingness to pay.

At the list price with the PAS applied, the probability of enzalutamide plus ADT being cost effective versus ADT alone and docetaxel plus ADT at a £30,000 per QALY threshold is [redacted] and [redacted], respectively (Figure 27).

Figure 27 Cost effectiveness acceptability curve enzalutamide vs ADT (left) and vs docetaxel (right)



Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost effectiveness ratio; WTP: willingness to pay.

B.3.8.3 Scenario analyses

Table 74 Scenario analysis results

No.	Description	Enzalutamide			ADT				Docetaxel			
		Costs	QALY	LYG	Costs	QALY	LYG	ICER vs ADT	Costs	QALY	LYG	ICER vs Doc
	Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,911	[redacted]	[redacted]	[redacted]	£22,877
1	Markov version of the base case analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,025	[redacted]	[redacted]	[redacted]	£22,546
2	Second best parametric fit for OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,904	[redacted]	[redacted]	[redacted]	£25,977
3	Second best parametric fit for PFS and TTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,740	[redacted]	[redacted]	[redacted]	£30,482
4	Using only ENZAMET data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,639	[redacted]	[redacted]	[redacted]	£37,049
5	Using only ARCHES data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,446	[redacted]	[redacted]	[redacted]	£30,022
6	Using only pooled data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,027	[redacted]	[redacted]	[redacted]	£29,629
7	Excluding off-treatment health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,020	[redacted]	[redacted]	[redacted]	£29,794
8	Using NMA HRs to model enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,453	[redacted]	[redacted]	[redacted]	£55,074
9	Using a combined PD1-3 health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,867	[redacted]	[redacted]	[redacted]	£27,418
10	Using ARCHES PD1 treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,216	[redacted]	[redacted]	[redacted]	£26,500
11	Including dose-interruptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,667	[redacted]	[redacted]	[redacted]	£22,538
12.1	Using a shorter time horizon (20 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,804	[redacted]	[redacted]	[redacted]	£24,325
12.2	Using a shorter time horizon (10 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,199	[redacted]	[redacted]	[redacted]	£35,652
13	Using a lower discount rate (1.5%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,398	[redacted]	[redacted]	[redacted]	£20,830

Abbreviations: ADT: androgen-deprivation therapy HR: hazard ratio: NMA: network meta-analysis; PD: progressed disease; TINAT: time to imitation of first antineoplastic therapy

Table 74 shows an overview of the scenario analysis results. The resulting ICERs ranged from £18,398 to £33,453 for the comparison vs ADT and from £20,830 to £55,074 for the comparison vs docetaxel plus ADT. Most scenarios resulted in ICERs that were only marginally different from the base case, further illustrating the robustness of base case results for cost effectiveness.

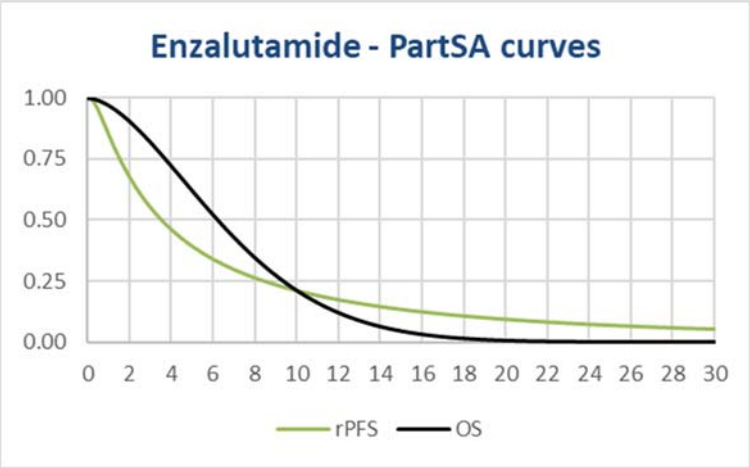
Scenarios 2 and 3 explore the uncertainty in results that could be explained by the survival models selected for PFS and OS. As discussed in section B.3.3, the consulted clinical expert[83] advised different survival models to be most clinically plausible for enzalutamide plus ADT and ADT. Since good modelling practices recommend that all treatment arms considered in the model should be fitted with the same parametric curve, the chosen base case curves for both enzalutamide plus ADT and ADT alone are based on the most plausible OS and PFS extrapolations for enzalutamide as advised by external experts[83]. The second best fitting survival model for PFS represents a scenario based on an overestimation of PFS and hence clinically implausible as per the clinical expert advice. It is therefore not surprising that the ICERs increase int his scenario since an increase in PFS increases the costs of enzalutamide plus ADT.

Scenarios 4, 5 and 6 explore the uncertainty in results that could be explained by the efficacy input using the either only ENZAMET, only ARCHES or only pooled data to model OS, PFS and TTD. The scenario using only ENZAMET or ARCHES data represent an oversimplification as they do not make use of all evidence available for OS. Relying only on ARCHES or ENZAMET data in isolation (as depicted in scenarios 4 and 5) is arguably too simplistic on account of excluding a key source of OS data. On the other hand, using only pooled data (as in scenario 6) provides unrealistic PFS predictions.

Scenario 7 explores the uncertainty in results that could be explained by the inclusion of a treatment gap within the model structure. When excluding the mHSPC treatment discontinuation health state, the ICER increases to £25,020 vs ADT and £29,794 vs docetaxel plus ADT. It is, however, unlikely that not allowing for a treatment gap would be plausible in UK daily practice based on clinical expert opinion.

The scenario with the most significant effect on the model was scenario 8 using the NMA HR to model enzalutamide, which resulted in an ICER of 33,453 vs ADT and £55,074 vs docetaxel plus ADT. However, as discussed in section B.2.9.6, there are several limitations that should be considered when interpreting the NMA results, such as the synthesis of evidence originating from heterogeneous patient populations (with respect to ECOG scores, HVD and LVD, previous therapies and newly diagnosed or metastatic disease), the fact that many older studies (a number of which pre-date the 2000's) informed the NSAA analysis suggesting the evidence is based on practices that are not the current standard of care for mHSPC, and the incomplete reporting of data for some of the included studies.

Figure 28 OS and PFS curves in the scenario where the NMA HRs are used to model enzalutamide



Abbreviations: OS: overall survival; HR: hazard ratio; NMA: network meta-analysis; PartSA: partitioned survival analysis; rPFS: radiographic progression-free survival

Scenarios 9 and 10 explore the uncertainty in results that could be explained by the way in which the PD health states are modelled, either by assuming only one combined PD health state or varying the PD1 treatment sequence. There are important limitations to both scenarios that should be noted. For scenario 9, the combined PD1 health state assumes that patients can only receive one post-progression treatment and that the benefits of such treatment are consistent regardless of line of therapy. Consequently, it was assumed that patients receive the same treatment until death, which leads to unrealistically long treatment durations and unrealistically stable utilities. For Scenario 10, PD1 treatments were modelled in line with the first antineoplastic therapy observed in ARCHES . However, this scenario is not reflective of the NICE guidelines for mHRPC, and hence UK treatment practice, since a small number of patients received abiraterone or enzalutamide after enzalutamide (4 and 13 out of 574 patients received post-progression enzalutamide and abiraterone, respectively).

Table 75 First subsequent antineoplastic therapies observed in the ARCHES trial

	ENZA + ADT (n=574)		PLA + ADT (n=576)	
Therapy	**Observed (n)**	**% assumed in scenario 8**	**Observed (n)**	**% assumed in scenario 8**
Overall	46	-	135	-
Docetaxel	11	34.4%	52	43.4%
Abiraterone acetate	13	40.6%	28	23.3%
Enzalutamide	4	12.5%	28	23.3%
Bicalutamide[a]	4	12.5%	12	10.0%
Other[b]	14	-	15	-

a. Bicalutamide was included as ADT
b. Other includes various treatments, including other chemotherapies and vaccines, and is therefore excluded from the calculations
Abbreviations: ADT: androgen deprivation therapy

Scenarios 12.1 and 12.2 explore the uncertainty in the results that could be explained by the modelled time-horizon. As discussed in section B.3.2, a 30-year time horizon for the model was selected as it is sufficiently long to capture all life-time costs and benefits of treatment for mHSPC, which is in line with NICE guidance. The 10 and 20 year scenarios are unlikely to capture all costs and benefits of treatment for mHSPC, since 34.3% and 7% of patients on enzalutamide remain alive after 10 and 20 years, respectively.

B.3.9 Subgroup analysis

No subgroup analysis has been conducted. Although high-risk was proposed as a subgroup in the decision problem, the available evidence base for enzalutamide plus ADT in mHSPC does not permit such an analysis.

B.3.10 Validation

B.3.10.1 Technical quality control of the cost effectiveness model

A check of internal validity was performed by the model developers using a quality control process. This involved checks on the selection and results of different modelling options, calculation spot checks, cross checks against source data and extreme value scenarios to check if the model behaved logically (see Appendix L for the details of quality checks performed by the model developers).

The quality check explored the following general aspects of the model:

- Top down tests. This involved systematic variation of the model input parameters to establish whether changes in inputs results in predictable changes in the model outputs. These tests were designed to identify failures in model logic or material computation errors
- Model internal functionality (e.g. testing of all key model parameters, extreme value testing). The following aspects of the spreadsheet were identified as key areas for detailed checking: Markov traces; translation of drug prices, complications and resource use into state costs
- Internal consistency. Accuracy of input data. This was checked by comparing the model inputs in Excel against the data sources referenced.

Overall, the validation identified no major issues with the computational accuracy of the model. A number of small inaccuracies were identified and rectified.

B.3.10.2 Comparison of model and clinical trial outcomes

As part of the validation process, results from the model were compared with outcomes from the enzalutamide plus ADT clinical trial program. A summary of this comparison in terms of OS and PFS is presented in Table 76. The results show close alignment between model and outcomes.

Table 76 Comparison of base case model and trial outcomes

Outcome	Data source	3 months	6 months	12 months	18 months	24 months
Enzalutamide outcomes: model versus trials						
OS (Pooled Weibull)	ARCHES	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ENZAMET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS (ARCHES LogNormal)	ARCHES	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADT outcomes: model versus trials						
OS (Pooled Weibull)	ARCHES	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ENZAMET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS (ARCHES LogNormal)	ARCHES	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADT: androgen deprivation therapy; PFS: progression-free survival; OS: overall survival.

Clinical data on docetaxel at set time intervals is not often reported, making an external check for docetaxel less reliable. All available data comes from GETUG[15] and STAMPEDE[79], which reported 3-year survival of 64·2% and 5-year survival of 49%, respectively. The model provides [redacted] 5-year survival estimates (49% vs [redacted]), [redacted] the 3 year survival ([redacted] in the model vs 64.2% in GETUG). This could indicate that the approach to model docetaxel survival by applying the NMA HR to the ADT arm overestimates docetaxel survival and therefore provides a conservative ICER estimate.

B.3.10.3 External validation of the cost effectiveness model

For internal validity, the assumptions employed in the model were made in a manner consistent with the published literature and previous NICE appraisals. In particular, the model structure closely follows the structure of the thoroughly reviewed model used for the NICE submissions of enzalutamide in mHRPC[93] and high-risk nmHRPC[94]. Additionally, health economic model and its inputs were validated with a clinical expert and a health economic expert[83]. The

Some uncertainty remains regarding the extrapolation of the ARCHES and ENZAMET data. However, as described in section B.3.3, for most extrapolations, reliable external reference data were available to ensure the extrapolations gave clinically plausible outcomes. These included the phase III studies STAMPEDE[49, 91], CHAARTED[45] and GETUG[46] to validated the PFS and OS extrapolations. Furthermore, the model fits and the plausibility of clinical outcomes for all extrapolations were validated by UK clinical and health economic experts[83].

B.3.11 Interpretation and conclusions of economic evidence

The base analysis results suggest that enzalutamide plus ADT is cost effective compared to ADT alone and docetaxel plus ADT in mHSPC as it leads to a favourable deterministic ICER of £19,911 and £22,877 vs ADT and vs docetaxel plus ADT, respectively. The probabilistic sensitivity analysis further resulted in consistent ICERs of £20,758 and £24,167 vs ADT and docetaxel plus ADT, respectively. Enzalutamide plus ADT remained cost effective in the majority of the probabilistic scenario analysis runs, with the probability of enzalutamide plus ADT being cost effective versus ADT alone and docetaxel plus ADT at a £30,000 per QALY threshold at [redacted] and [redacted], respectively. Assessment of parameter uncertainty by means of scenario analyses showed that the results are most sensitive to the source and distribution applied when extrapolating PFS and OS. As OS is a key contributor to decision making uncertainty, uncertainty could be reduced if enzalutamide for mHSPC would be made available in a timely manner via the Cancer Drugs Fund.

Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

The model base-case predicted results for survival with ADT and docetaxel plus ADT were compared to results of similar studies in the published literature. The modelled LYG of [redacted] and [redacted] for ADT alone and docetaxel plus ADT, respectively, were [redacted] the only published cost effectiveness model in the total mHSPC population, by Woods *et al*, 2018[92] [redacted]. From the perspective of the modelled median OS results, however, the results of the analysis presented here were found to differentiate from that reported in STAMPEDE and Woods *et al*, 2018[92], reporting a median OS outcomes of 43.2 months for SoC and 59.1 months for docetaxel vs the modelled results for the base case analysis in this submission showing a median OS of 56.3 and 66.6 months for ADT alone and docetaxel plus ADT, respectively. This difference is likely caused by differences in the patient characteristics between the STAMPEDE, ARCHES and ENZAMET studies (Table 77). Most importantly, STAMPEDE patients represent a cohort with a higher proportion of high-risk patients, as shown by the higher proportion of patients with a Gleason score of ≥8. Furthermore, the patients in STAMPEDE were younger, potentially leading to a longer tail in OS. This coincides with the resulting survival curves in both models, with [redacted] (Figure 29). In addition, the difference between both survival curves already arises at the start of the curve which is still informed by the KM data. This indicates that the mHSPC model presented in this submission gives accurate OS predictions, but models a slightly older, lower-risk patient population than what is reported in the literature. The results presented in this submission are based on a population of mHSPC patients that are more similar in baseline characteristics to the UK daily practice setting (see section below) compared with the available literature and should therefore be given more credence than the published literature.

Table 77 Patient characteristics differences in ARCHES, ENZAMET and STAMPEDE

	ARCHES	ENZAMET (no doc)	STAMPEDE (M1 only)

Patient characteristics	ENZA	ADT	ENZA	NSAA	Doc	SoC
Median age	70	71	[redacted]	[redacted]	65	65
Gleason <8	29.8%	32.5%	[redacted]	[redacted]	18%	22%
Gleason ≥8	67.2%	64.8%	[redacted]	[redacted]	70%	66%
Gleason NA	3.0%	2.7%	[redacted]	[redacted]	12%	12%

Abbreviations: ADT: androgen deprivation therapy; ENZA: enzalutamide; Doc; docetaxel; M1: metastatic; NA: not available; NSAA: non-steroidal anti-androgen; SoC: standard of care.

Figure 29 Survival curve comparison between Woods *et al* and the presented cost effectiveness model

Abbreviations: ADT: androgen deprivation therapy; CEM: cost effectiveness model; Doc; docetaxel; KM: Kaplan-Meier; SoC: standard of care.

Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem?

The economic evaluation presented in this submission is relevant to all mHSPC patients who could potentially use the technology as the base case analysis considers the full mHSPC population as reflective of the decision problem. The results do not provide an estimate of cost effectiveness in a subgroup of high-risk mHSPC patients as there is currently no clinical rationale for assessing this subgroup in isolation given that the currently available treatments in UK daily practice are not stratified based on the presence of high-risk disease.

How relevant (generalisable) is the analysis to clinical practice in England?

The presented cost effectiveness analysis is generalizable to UK practice, both in terms of eligible patient population and treatment approach. The average age of onset of prostate cancer in the UK is 70.9[141], which aligns with the modelled baseline age of 70. Therefore, the modelled results in this submission are reflective of the UK prostate cancer population, and even more so compared to the analyses submitted for abiraterone and docetaxel in mHSPC patients (ages 65-67, Table 45). Baseline characteristics of the modelled mHSPC population

were further validated with the consulted UK clinical expert who confirmed that the ARCHES and ENZAMET patient populations were in line with UK practice, both in terms of relapsed disease and previous therapy, with the exception of a higher proportion of patients presenting with low-volume disease in ENZAMET than would be expected in UK daily practice. However, since the proportion of low-volume patients is consistent over both arms, this is unlikely to have an important impact on the observed benefit of enzalutamide.

Regarding treatment approaches, the modelled results were designed to reflect the UK clinical practice as per the most recently available NICE guidelines, which only recommend docetaxel plus ADT and ADT alone in mHSPC, while abiraterone and radiotherapy are not currently recommended[2]. It should also be noted that the comparator in ENZAMET represents ADT plus NSAA relative to the NSAA not commonly used in UK clinical practice for treatment of mHSPC. The addition of NSAA could have improved the efficacy of the comparator in the ENZAMET trial, leading to a dilution of the true comparative effectiveness for enzalutamide plus ADT vs ADT alone in mHSPC. Consequently, the comparative effectiveness evidence underpinning the modelled benefits for enzalutamide plus ADT reflect a more conservative approach with the health benefits likely greater in UK practice in the absence of NSAA. For mHRPC, several treatments are currently approved and it is known that docetaxel, abiraterone and enzalutamide are most commonly prescribed, which is in line with what was observed in ARCHES (Table 75) and subsequently the modelled treatment sequences for mHRPC. While 17 patients received either enzalutamide or abiraterone after enzalutamide, this is unlikely to have a significant effect on trial outcomes, due to the low number of patients receiving this treatment.

What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The strengths of the economic assessment include:

- Model structure builds upon previously validated models submitted in the nmHRPC setting (NICE TA580[94]) and pre-chemo (NICE TA377[93]);
- Efficacy is based on pooling of two large clinical trials;
- The evaluation presented adheres as closely as possible to the stipulated NICE reference case, uses previously accepted methods and in doing this maintains transparency for decision makers;
- A number of alternative modelling methodologies and scenarios are presented allowing for assessment of uncertainty, including alternative modelling approach, source of efficacy, evidence synthesis.

Regarding limitations, an important limitation is the immaturity of the input data. Particularly OS from ARCHES is immature with only approximately 25% of the total pre-specified number of expected events having occurred at time of this analysis. Although ARCHES and ENZAMET OS data were pooled to increase the robustness of the data, OS still had to be extrapolated over an extended period to match the 30-year horizon of the model. This introduced additional uncertainty to the model, since none of the distribution fits showed realistic long-term OS predictions for both ADT and enzalutamide plus ADT. The uncertainty due to immature OS was explored by means of a scenario with the second-best OS fits, which resulted in only a minor impact on modelled results.

Another limitation in the model is introduced by limited access to ENZAMET data. Due to this, the PRO analysis informing the economic assessment was limited to only ARCHES EQ-

5D utility data. The omission of ENZAMET trial-based PRO data, however, is unlikely to impact the cost effectiveness analysis as demonstrated by the deterministic sensitivity analysis where changes in the utilities did not results in a meaningful impact on the results.

What further analyses could be carried out to enhance the robustness or completeness of the results?

The immaturity of OS contributes the majority of the uncertainty in decision-making for enzalutamide plus ADT in mHSPC. As OS is still being collected as part of the long-term follow-up phase of the ARCHES trial, more mature OS data will be available in the final ARCHES data-cut expected early 2023. Inclusion of long-term survival data in the economic assessment via the long-term follow-up of the ARCHES trial, and UK daily practice as part of the re-assessment phase should enzalutamide be made available in a timely manner via the Cancer Drugs Fund, would greatly reduce uncertainty in decision-making for enzalutamide in mHSPC.

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B.5 Appendices

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

C1.1 SmPC

The SmPC submitted to EMA for the proposed extension indication for enzalutamide is provided in the Reference Pack as reference 1.

C1.2 EPAR

The EPAR submitted to EMA for the proposed extension indication for enzalutamide is provided in the Reference Pack as reference 1.

D1.1 Identification and selection of relevant studies

A SLR was conducted in May 2019 to identify the clinical evidence (efficacy and safety) of enzalutamide and standard of care in the management of mHSPC[26]. The SLR was conducted in two stages: an initial SLR in September 2018 and an update in May 2019. However, given that the search strategy for the clinical SLR was modified during the SLR update, all searches in the key databases (Cochrane, Embase and Medline) were rerun during the SLR update with no time limits[26].

D1.1.1 Search strategy

The research question for the clinical SLR was: what is the clinical efficacy and safety of enzalutamide, current licensed drugs and drugs in phase III development for the management of adult patients with mHSPC?

The databases searched and provider used to identify clinical evidence are provided in Table 78. No timeframe, country or language limit was applied to the clinical effectiveness searches.

Table 78 Databases searched and provider used for the clinical SLR

Database / information source	Interface / URL
PubMed*	http://www.ncbi.nlm.nih.gov/pubmed
Medline and Medline in Process	OvidSP
EMBASE	OvidSP
CDSR in the Cochrane Library	Cochrane Library/Wiley Interscience
CENTRAL in the Cochrane Library	Cochrane Library/Wiley Interscience
DARE in the in Cochrane Library	Cochrane Library/Wiley Interscience
American Society of Clinical Oncology (ASCO)	http://www.asco.org/
American Society of Clinical Oncology Genitourinary Cancers symposium (ASCO-GU)	http://gucasym.org/
American Urological Association (AUA)	https://www.auanet.org/
European Association of Urology (EAU)	http://www.uroweb.org/
European Society for Medical Oncology (ESMO)	http://www.esmo.org/
European CanCer Organisation (ECCO)	http://www.ecco-org.eu/
International Society for Pharmacoeconomics and Outcomes Research	http://www.ispor.org/
ClinicalTrials.gov portal	http://www.ClinicalTrials.gov
ClinicalTrialsRegister portal	http://www.clinicaltrialsregister.eu

Source: SLR report[26]
*PubMed was searched to complement the searches in Embase and Medline. The initial search strategy built for Embase and Medline yielded more than 16,000 hits and the titles/abstracts could not be downloaded.
Abbreviations: CDRS: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects.

The complete search strategies used for PubMed, Cochrane, and Medline, including all the search terms: textwords (free text), subject index headings (for example, MeSH), the relationship between the search terms (for example, Boolean) when applicable, and the number of hits for each search are given in Table 79, Table 80, and Table 81, respectively.

Table 79 Search strategy in PubMed for the clinical review

Concept	ID	Search string	Hits
Disease	#1	"prostatic neoplasms"[MeSH Terms]	121,473
	#2	prostat*[Title/Abstract]	204,440
	#3	"cancer"[Title/Abstract] OR carcinoma[Title/Abstract] OR malignant[Title/Abstract] OR malignancy[Title/Abstract] OR tumor[Title/Abstract] OR tumoral[Title/Abstract] OR tumour[Title/Abstract] OR adenocarcinoma[Title/Abstract]	2,802,285
	#4	#2 AND #3	147,261
	#5	#4 OR #1	166,436
	#6	"metastatic"[Title/Abstract] OR mHSPC[Title/Abstract] OR "metastasized"[Title/Abstract] OR "metastasised"[Title/Abstract] OR “advanced”[Title/Abstract] OR “disseminated”[Title/Abstract]	625,489
	#7	#5 AND #6	28,786
Therapies	#8	“Enzalutamide“[Title/Abstract] OR “Xtandi“[Title/Abstract]	1,386
	#9	“Abiraterone”[Title/Abstract] OR “Zytiga”[Title/Abstract]	1,759
	#10	“Docetaxel“[Title/Abstract] OR “Taxotere“[Title/Abstract] OR “Docecad“[Title/Abstract] OR “Docefrez“[Title/Abstract] OR “Zytax“[Title/Abstract]	14,275
	#11	“Apalutamide”[Title/Abstract] OR “Erleada”[Title/Abstract]	60
	#12	“Darolutamide”[Title/Abstract]	24
	#13	"radiotherapy"[Title/Abstract] or "radiation"[Title/Abstract]	464,905
	#14	“androgen deprivation therapy”[Title/Abstract] OR “anti-androgen therapy“[Title/Abstract] OR antiandrogen[Title/Abstract] OR “anti androgen”[Title/Abstract] OR “anti-androgen”[Title/Abstract] OR “androgen antagonist”[Title/Abstract] OR “androgen ablation”[Title/Abstract] OR “androgen-ablation”[Title/Abstract] OR “androgen blockade”[Title/Abstract] OR “androgen-blockade”[Title/Abstract] OR “androgen suppression”[Title/Abstract] OR “androgen deprivation”[Title/Abstract] OR “ADT”[Title/Abstract]	14,466
	#15	“luteinizing hormone”[Title/Abstract] OR “luteinising hormone” OR “gonadotropin-releasing hormone”[Title/Abstract] OR “gonadotropin releasing hormone”[Title/Abstract] OR “Lhrh”[Title/Abstract] OR “Gnrh”[Title/Abstract]	53,393
	#16	“Leuprolide“[Title/Abstract] OR “Leuprorelin“[Title/Abstract] OR “Lupron“[Title/Abstract] OR “Viadur“[Title/Abstract] OR “Eligard“[Title/Abstract] OR “Prostap“[Title/Abstract] OR “Buserelin“[Title/Abstract] OR “Sepretact“[Title/Abstract] OR “Cinnafact“[Title/Abstract] OR “Metrelef“[Title/Abstract] OR “Aminoglutethimide“[Title/Abstract] OR “Cytadren“[Title/Abstract] OR “Goserelin“[Title/Abstract] OR “Zoladex“[Title/Abstract] OR “Triptorelin“[Title/Abstract] OR “Decapeptyl“[Title/Abstract] OR “Diphereline“[Title/Abstract] OR “Gonapeptyl“[Title/Abstract] OR “Trelstar“[Title/Abstract] OR “Variopeptyl“[Title/Abstract] OR	9,527

Concept	ID	Search string	Hits
		“Histrelin“[Title/Abstract] OR “Vantas“[Title/Abstract] OR “Supprelin“[Title/Abstract] OR “Degarelix“[Title/Abstract] OR “Firmagon“[Title/Abstract] OR “Flutamide“[Title/Abstract]	
	#17	“Eulexin“[Title/Abstract] OR “Cytomid“[Title/Abstract] OR “Chimax“[Title/Abstract] OR “Drogenil“[Title/Abstract] OR “Flucinom“[Title/Abstract] OR “Flutamin“[Title/Abstract] OR “Fugerel“[Title/Abstract] OR “Niftolide“[Title/Abstract] OR “Sebatrol“[Title/Abstract] OR “Bicalutamide“[Title/Abstract] OR “Casodex“[Title/Abstract] OR “Cosudex“[Title/Abstract] OR “Calutide“[Title/Abstract] OR “Kalumid“[Title/Abstract] OR “Nilutamide“[Title/Abstract] OR “Nilandron“[Title/Abstract] OR “Anandron“[Title/Abstract] OR “Estrogen“[Title/Abstract] OR “Oestrogen“[Title/Abstract]	134,652
	#18	“Ketoconazole“[Title/Abstract] OR “Nizoral“[Title/Abstract] OR “Diethylstilbestrol“[Title/Abstract] OR “Ethinylestradiol“[Title/Abstract] OR “Cyproterone“[Title/Abstract] OR “Zoledronic acid”[Title/Abstract] OR Zometa[Title/Abstract] OR zoledronate[Title/Abstract]	23,217
	#19	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	686,961
Study design	#20	"randomized controlled trials as topic"[MeSH Terms]	127,787
	#21	"double-blind method"[MeSH Terms]	152,276
	#22	"cohort studies"[MeSH Terms]	1,877,565
	#23	"randomized controlled trial":pt	6,306
	#24	“double blind”[Title/Abstract] OR “double blinded”[Title/Abstract] OR RCT[Title/Abstract] OR Randomi*[Title/Abstract] OR controlled[Title/Abstract] OR controled[Title/Abstract] OR control[Title/Abstract] OR Placebo[Title/Abstract] OR Trial[Title/Abstract]	3,472,854
	#25	(Study[Title/Abstract] OR studies[Title/Abstract]) AND (open[Title/Abstract] OR open-label[Title/Abstract] OR non-randomised[Title/Abstract] OR non-randomized[Title/Abstract] OR "cohort"[Title/Abstract])	598,758
	#26	#20 OR #21 OR #22 OR #23 OR #24 OR #25	5,260,373
All	#27	#7 AND #19 AND #26	4,937

Source: SLR report[26]
This search was conducted on the 22nd of May 2019 and no time restriction was applied.

Table 80 Search strategy in Cochrane for the clinical review

Concept	ID	Search string	Hits
Disease	#1	"prostatic neoplasms"[MeSH Terms]	4,916
	#2	prostat*:ti,ab,kw	19,643
	#3	"cancer":ti,ab,kw OR carcinoma:ti,ab,kw OR malignant:ti,ab,kw OR malignancy:ti,ab,kw OR tumor:ti,ab,kw OR tumoral:ti,ab,kw OR tumour:ti,ab,kw OR adenocarcinoma:ti,ab,kw	183,166
	#4	#2 AND #3	12,984

Concept	ID	Search string	Hits
	#5	#4 OR #1	13,286
	#6	"metastatic":ti,ab,kw OR mHSPC:ti,ab,kw OR "metastasized":ti,ab,kw OR "metastasised":ti,ab,kw OR “advanced”:ti,ab,kw OR “disseminated”:ti,ab,kw	66,760
	#7	#5 AND #6	4,004
Therapies	#8	“Enzalutamide“:ti,ab,kw OR “Xtandi“:ti,ab,kw	479
	#9	“Abiraterone”:ti,ab,kw OR “Zytiga”:ti,ab,kw	593
	#10	“Docetaxel“:ti,ab,kw OR “Taxotere“:ti,ab,kw OR “Docecad“:ti,ab,kw OR “Docefrez“:ti,ab,kw OR “Zytax“:ti,ab,kw	6,372
	#11	“Apalutamide”:ti,ab,kw OR “Erleada”:ti,ab,kw	57
	#12	“Darolutamide”:ti,ab,kw	19
	#13	"radiotherapy":ti,ab,kw or "radiation":ti,ab,kw	43,788
	#14	“androgen deprivation therapy”:ti,ab,kw OR “anti-androgen therapy“:ti,ab,kw OR antiandrogen:ti,ab,kw OR “anti androgen”:ti,ab,kw OR “anti-androgen”:ti,ab,kw OR “androgen antagonist”:ti,ab,kw OR “androgen ablation”:ti,ab,kw OR “androgen-ablation”:ti,ab,kw OR “androgen blockade”:ti,ab,kw OR “androgen-blockade”:ti,ab,kw OR “androgen suppression”:ti,ab,kw OR “androgen deprivation”:ti,ab,kw OR “ADT”:ti,ab,kw	3,482
	#15	“luteinizing hormone”:ti,ab,kw OR “luteinising hormone” OR “gonadotropin-releasing hormone”:ti,ab,kw OR “gonadotropin releasing hormone”:ti,ab,kw OR “Lhrh”:ti,ab,kw OR “Gnrh”:ti,ab,kw	7,138
	#16	“Leuprolide“:ti,ab,kw OR “Leuprorelin“:ti,ab,kw OR “Lupron“:ti,ab,kw OR “Viadur“:ti,ab,kw OR “Eligard“:ti,ab,kw OR “Prostap“:ti,ab,kw OR “Buserelin“:ti,ab,kw OR “Sepreface“:ti,ab,kw OR “Cinnafact“:ti,ab,kw OR “Metrelef“:ti,ab,kw OR “Aminoglutethimide“:ti,ab,kw OR “Cytadren“:ti,ab,kw OR “Goserelin“:ti,ab,kw OR “Zoladex“:ti,ab,kw OR “Triptorelin“:ti,ab,kw OR “Decapeptyl“:ti,ab,kw OR “Diphereline“:ti,ab,kw OR “Gonapeptyl“:ti,ab,kw OR “Trelstar“:ti,ab,kw OR “Variopeptyl“:ti,ab,kw OR “Histrelin“:ti,ab,kw OR “Vantas“:ti,ab,kw OR “Supprelin“:ti,ab,kw OR “Degarelix“:ti,ab,kw OR “Firmagon“:ti,ab,kw OR “Flutamide“:ti,ab,kw	3,786
	#17	“Eulexin“:ti,ab,kw OR “Cytomid“:ti,ab,kw OR “Chimax“:ti,ab,kw OR “Drogenil“:ti,ab,kw OR “Flucinom“:ti,ab,kw OR “Flutamin“:ti,ab,kw OR “Fugerel“:ti,ab,kw OR “Niftolide“:ti,ab,kw OR “Sebatrol“:ti,ab,kw OR “Bicalutamide“:ti,ab,kw OR “Casodex“:ti,ab,kw OR “Cosudex“:ti,ab,kw OR “Calutide“:ti,ab,kw OR “Kalumid“:ti,ab,kw OR “Nilutamide“:ti,ab,kw OR “Nilandron“:ti,ab,kw OR “Anandron“:ti,ab,kw OR “Estrogen“:ti,ab,kw OR “Oestrogen“:ti,ab,kw	12,625
	#18	“Ketoconazole“:ti,ab,kw OR “Nizoral“:ti,ab,kw OR “Diethylstilbestrol“:ti,ab,kw OR “Ethinylestradiol“:ti,ab,kw OR “Cyproterone“:ti,ab,kw OR “Zoledronic acid”:ti,ab,kw OR Zometa:ti,ab,kw OR zoledronate:ti,ab,kw	4,275

Concept	ID	Search string	Hits
	#19	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	73,462
Study design	#20	"randomized controlled trials as topic"[MeSH Terms]	13,804
	#21	"double-blind method"[MeSH Terms]	130,980
	#22	"cohort studies"[MeSH Terms]	141,474
	#23	"randomized controlled trial":pt	469,470
	#24	“double blind”:ti,ab,kw OR “double blinded”:ti,ab,kw OR RCT:ti,ab,kw OR Randomi*:ti,ab,kw OR controlled:ti,ab,kw OR controled:ti,ab,kw OR control:ti,ab,kw OR Placebo:ti,ab,kw OR Trial:ti,ab,kw	1,139,457
	#25	(Study:ti,ab,kw OR studies:ti,ab,kw) AND (open:ti,ab,kw OR open-label:ti,ab,kw OR non-randomised:ti,ab,kw OR non-randomized:ti,ab,kw OR "cohort":ti,ab,kw)	127,696
	#26	#20 OR #21 OR #22 OR #23 OR #24 OR #25	1,218,299
All	#27	#7 AND #19 AND #26	2,659

Source: SLR report[26]
The search was conducted on the 22nd of May 2019 and no time restriction was applied.

Table 81 Search strategy in Medline, Medline in Process and Embase for the clinical review

ID	Search string	Hits
1	exp prostate tumor/	227,208
2	exp Prostatic Neoplasms/	348,651
3	prostat*.ab,ti.	492,104
4	(cancer or carcinoma or malignant or malignancy or tumor or tumoral or tumour or adenocarcinoma).ti,ab.	6,501,642
5	1 or 2 or (3 and 4)	430,870
6	(hormone-sensitive or hormone-dependent or androgen-sensitive or androgen-dependent or castration-naive or castration-sensitive or HSPC or ADPC).ti,ab.	37,252
7	exp hormone sensitivity/	3,164
8	5 and (6 or 7)	11,168
9	(metastatic or mHSPC or metastasized or metastasised or advanced or disseminated).ab,ti.	1,543,110
10	exp metastasis/	779,190
11	exp Neoplasm Metastasis/	779,190
12	8 and (9 or 10 or 11)	3,787
13	exp androgen antagonists/ or exp gonadotropin releasing hormone/ or exp abiraterone acetate/ or exp antiandrogen/ or exp gonadorelin/	140,961
14	exp enzalutamide/ or (Enzalutamide or Xtandi).mp.	6,424
15	(Abiraterone or Zytiga).mp.	7,950
16	(Docetaxel or Taxotere or Docecad or Docefrez or Zytax).mp. or exp docetaxel/	72,417

ID	Search string	Hits
17	('androgen deprivation therapy' or 'anti-androgen therapy' or antiandrogen or 'anti androgen' or anti-androgen or 'androgen antagonist' or 'androgen ablation' or 'androgen-ablation' or 'androgen blockade' or androgen-blockade or 'androgen suppression' or 'androgen deprivation' or ADT).ab,ti.	36,888
18	('luteinizing hormone' or 'luteinising hormone' or 'gonadotropin-releasing hormone' or 'gonadotropin releasing hormone' or Lhrh or Gnrh).ab,ti.	115,936
19	(Leuprolide or Leuprorelin or Lupron or Viadur or Eligard or Prostap or Buserelin or Seprefact or Cinnafact or Metrelef or Aminoglutethimide or Cytadren or Goserelin or Zoladex or Triptorelin or Decapeptyl or Diphereline or Gonapeptyl or Trelstar or Variopeptyl or Histrelin or Vantas or Supprelin or Degarelix or Firmagon or Flutamide).mp.	47,376
20	(Eulexin or Cytomid or Chimax or Drogenil or Flucinom or Flutamin or Fugerel or Niftolide or Sebatrol or Bicalutamide or Casodex or Cosudex or Calutide or Kalumid or Nilutamide or Nilandron or Anandron or Estrogen or Oestrogen).mp.	414,004
21	(Ketoconazole or Nizoral or Diethylstilbestrol or Ethinylestradiol or Cyproterone or Zoledronic acid or Zometa or zoledronate).mp.	117,357
22	(Apalutamide or darolutamide or radiotherapy or radiation).mp.	1,818,872
23	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	2,534,223
24	exp "randomized controlled trial (topic)"/	164,405
25	exp randomized controlled trials as topic/	292,116
26	('double blind' or 'cohort study' or 'cohort studies' or 'randomized controlled trial' or 'randomized clinical trial').mp.	2,021,100
27	('double blind' or 'double blinded' or RCT or Randomi* or controlled or controled or control or Placebo or Trial).ab,ti.	8,016,517
28	((Study or studies) and (open or open-label or non-randomised or non-randomized or cohort)).ab,ti.	1,554,536
29	24 or 25 or 26 or 27 or 28	9,558,256
30	12 and 23 and 29	929
31	remove duplicates from 30	659

Source: SLR report[26]
The search in Medline, Medline in Process and Embase for the clinical component was conducted on the 9th of August 2019. The timeframe covered was: Embase: 1974 to August 09, 2019, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R): 1946 to August 09, 2019.

Searches were also conducted in the following congress websites: American Society of Clinical Oncology (ASCO) (http://www.asco.org/) and American Society of Clinical Oncology Genitourinary Cancers symposium (ASCO-GU) (http://gucasym.org/), American Urological Association (AUA) (https://www.auanet.org/), European Association of Urology (EAU) (http://www.uroweb.org/), European Society for Medical Oncology (ESMO) (http://www.esmo.org/), International Society for Pharmacoeconomics and Outcomes Research (http://www.ispor.org/).

In the initial SLR, no additional relevant abstracts other than those already retrieved in the Medline and EMBASE databases were identified in any of the congresses listed above or the clinical evidence component of the SLR.

Searches were conducted on May 22, 2019 in the same websites as in the initial SLR. In addition to those abstracts already identified in the Medline and EMBASE databases, the following were also identified:

- 62 ISPOR presentations since September 2018 with the keyword “prostate cancer”
- 109 ASCO presentations since September 2018 with the keyword “prostate cancer”[26].

D1.1.2 Study selection

The inclusion and exclusion criteria of the SLR, including the comparators of interest are presented in Section B.2.1; Table 4. The PRISMA flow diagram is shown in Section B.2.1, Figure 2.

Of the 41 studies identified in the clinical SLR, only 18 were relevant for this submission. Of these, 11 were included in the NMA. The results for the studies include in the NMA are presented in section B.2.9. An overview of the study design of these studies is provided in Table 82.

Table 82 Summary of studies identified by clinical SLR and included in the NMA

Study acronym - NCTC ID	Country	Duration	Study design	Aim of the study	Study population	Intervention (n randomised)	Comparator (n randomised)
ARCHES[23]	Global*	March 2016 – Ongoing	Phase III, RCT, DB with OP extension after primary endpoint analysis	To determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by rPFS based on ICR	mHSPC	ENZA + ADT	PLA + ADT
STAMPEDE-1[48, 79]	UK and Switzerland	July 2005 – Ongoing	Phase II open-label multi-centre, multi-arm, RCT	Compare several interventions to SoC in metastatic or high-risk non-metastatic prostate cancer	mHSPC and nmHSPC	Arm C: SoC + DOC	Arm A: SoC
STAMPEDE-2[49, 50]						Arm G: ABI + SoC	Arm A: SoC
STAMPEDE-3[51]						Arm C: SoC + DOC	Arm G: ABI + SoC
CHAARTED[17]	N/A	July 2006 to December 2012	Phase III, open-label, RCT	Test hypothesis that mOS is 33.3% longer when adding DOC to ADT	790 men with mHSPC (ND and previously treated)	ADT + DOC 75mg/m^2/3w	ADT
GETUG[47]	France, Belgium	October 2004 to December 2008	Phase III open-label RCT	Investigate effects of the addition of DOC to ADT for mHSPC	385 men with mHSPC (newly diagnosed: 71%)	ADT + DOC 75mg/m^2/3w (n=192)	ADT (n=193)
ENZAMET[24]	Australia, New Zealand, Canada, Ireland, UK, US	March 2014 - March 2017	Phase III open-label multi-center RCT	To determine the effects of adding enzalutamide to first-line treatment that included testosterone suppression with or without early DOC	mHSPC patients on 1L ADT	ENZA + ADT ± DOC (n = 563)	NSAA + ADT ± DOC (n = 562)
DAPROC[52]	Denmark	June 1986 - December 1987	RCT	To further assess the efficacy of CAB/MAB in mHSPC	Untreated HSPC (M0/M1)	GOS + FLU (n = 129)	ORC (n = 133)

Study acronym - NCTC ID	Country	Duration	Study design	Aim of the study	Study population	Intervention (n randomised)	Comparator (n randomised)
EORTC30853[53-55]	Belgium, UK, Portugal, Italy, Germany, France, The Netherlands	March 1986 - May 1988	Phase III, RCT	To compare the efficacy and side effects of bilateral orchiectomy versus a combination of a goserelin acetate plus flutamide, in patients with metastatic prostate cancer.	Untreated mHSPC	GOS + FLU (n = 164)	ORC (n = 163)
Intergroup STUDY 0036[58-60]	USA	March 1985 - April 1986	Phase III, RCT, DB	To test the effectiveness of combined androgen blockade in men with metastatic prostate cancer who had received no prior therapy.	Newly diagnosed mHSPC (ECOG 0-3)	LEU + FLU (n = 303)	LEU + PLA (n = 300)
SWOG8894[65]	US	December 1989 to September 1994	RCT, DB	To compare FU plus bilateral ORC with placebo plus ORC	mHSPC	FLU + ORC (n = 700)	PLA + ORC (n = 687)
Janknegt 1993[66, 67]	15 countries [not specified]	June 1986 - March 1988	RTC, DB	To study the long-term efficacy and tolerability of NIL, a nonsteroidal antiandrogen, combined with ORC in patients with advanced prostate cancer.	Untreated mHSPC (stage D2)	ORC + NIL (n = 225)	ORC + PLA (n = 232)
Zalcberg 1996	Australia	1985 - onwards	RCT, DB	To investigate the hypothesis that maximal androgen blockade improves the outcome of patients with metastatic prostate cancer	Untreated mHSPC (stage D) - ECOG 0-3	ORC+FLU (n=111)	ORC+PLA (n=110)

Source: SLR report[26]
Abbreviations: ABI: abiraterone; ADT: androgen deprivation therapy; CAB/MAB: compete/maximal androgen blockade; DB: double blinded; DOC: docetaxel; ECOG: Eastern Cooperative Oncology Group; ENZA: enzalutamide; FLU: flutamide; FU: follow-up; GOS: gosrelin; HSPC: hormone sensitive prostate cancer; ICR: independent central review; LEU: leuprorelin; M0/M1: non-metastatic/metastatic: mHSPC: metastatic hormone-sensitive prostate cancer; mOS: median overall survival; N/A: not reported; ND: newly diagnosed; NIL: nilutamide; nmHSPC: non-metastatic hormone-sensitive prostate cancer; NSAA: non-steroidal antiandrogen; OP: open label period; ORC: orchiectomy; PLA: placebo; RCT: randomised controlled study; rPFS: radiographic progression-free survival; SoC: standard of care; UK: United Kingdom; USA: United Stated of America.

Methods and outcomes of studies included in indirect or mixed treatment comparisons

As discussed in Section B.2.9.1, from the 41 studies identified by the SLR and relevant for this submission, only 13 were included in the NMA.

Methods of analysis of studies included in the indirect or mixed treatment comparison

The method of analysis for the ITC is discussed in Section B.2.9.1.

Programming language for the indirect or mixed treatment comparison

The NMA was programmed in WinBUGs. The WinBUGs code is provided below:

```
# Model for pairwise and network meta-analysis
# Normal likelihood, identity link, trial-level data given as treatment differences
# Fixed effects model
# From NICE DSU Report 2, p. 93 & 94 (last updated April 2014)

model{                                  # *** PROGRAM STARTS
for(i in 1:ns) {                        # LOOP THROUGH 2-ARM STUDIES
   y[i,2] ~ dnorm(delta[i,2],prec[i,2])  # normal likelihood for 2-arm trials
   var[i,2] <- pow(se[i,2],2)           # calculate variances
   prec[i,2] <- 1/var[i,2]              # set precisions
   delta[i,2] <-  d[t[i,2]] - d[t[i,1]]
   dev[i,2] <- (y[i,2]-delta[i,2])*(y[i,2]-delta[i,2])*prec[i,2]  #Deviance contribution
  }
totresdev <- sum(dev[,2])               #Total Residual Deviance
d[1]<-0                                 # treatment effect is zero for reference treatment
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }         # vague priors for treatment effects

#Output
# pairwise treatment effect for all possible pair-wise comparisons, if nt>2
for (c in 1:nt) {
    for (k in 1:nt)  {
        Dt[c,k] <- (d[k]-d[c])
           HR[c,k]<-exp(d[k]-d[c])
           better_b[c,k]<- step(-Dt[c,k]) # assumes a positive result is bad
        better_g[c,k]<- step(Dt[c,k]) # assumes a positive result is good
                    }
    }

# ranking on relative scale
for (k in 1:nt) {
     Rk_g[k] <- nt+1-rank(d[],k)                  # assumes events are "good"
     Rk_b[k] <- rank(d[],k)                    # assumes events are "bad"
     best_g[k] <- equals(Rk_g[k],1)    #calculate probability that treat k is best
     best_b[k] <- equals(Rk_b[k],1)    #calculate probability that treat k is best
   for (i in 1:nt){
```

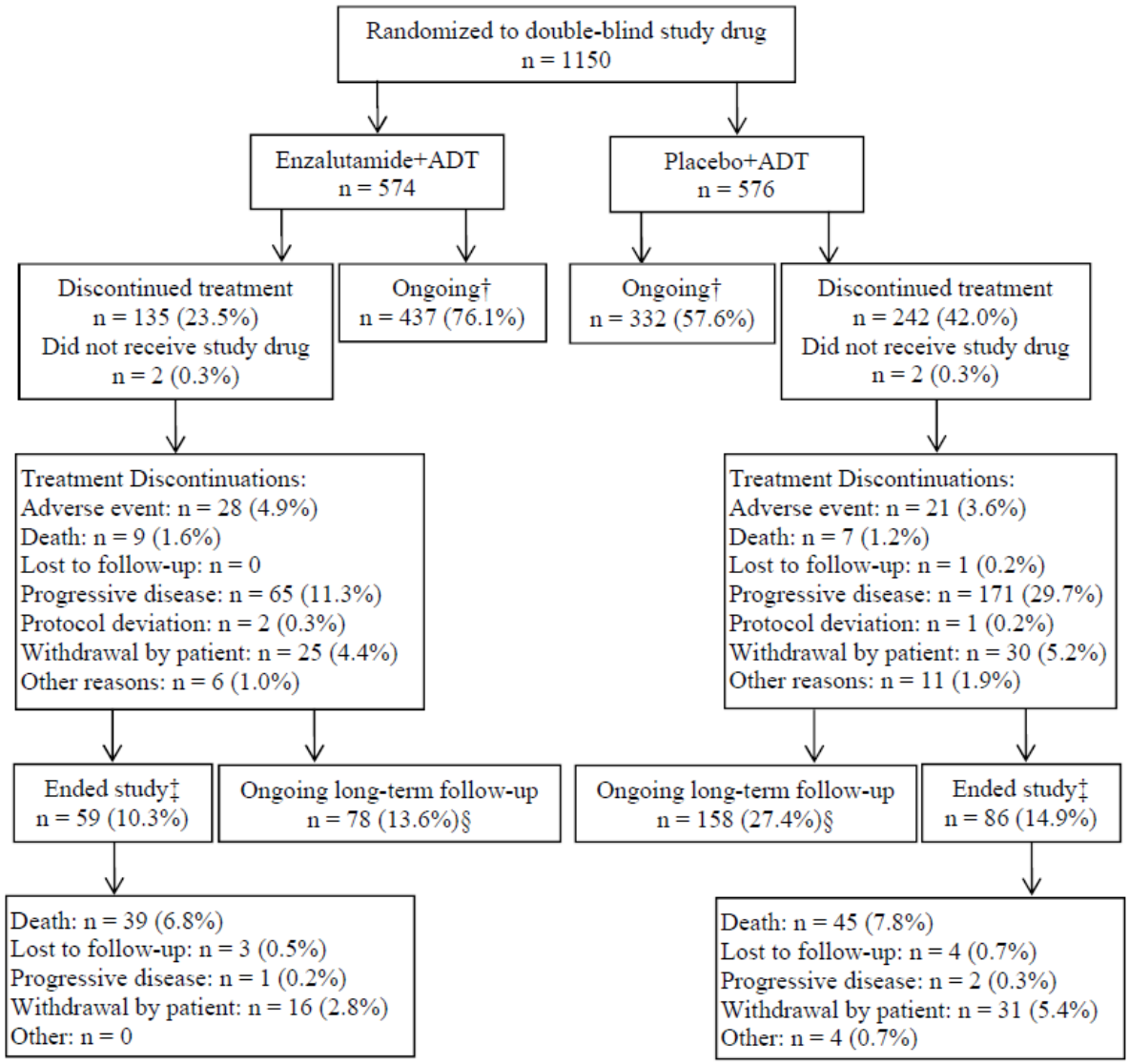


```
      prk_g[k,i] <- equals(Rk_g[k],i)      #calculate probability of treat k being each rank i
      prk_b[k,i] <- equals(Rk_b[k],i)      #calculate probability of treat k being each rank i
     }
}

for(k in 1:nt) {
 for(i in 1:nt) {
    cumprk_g[k,i]<- sum(prk_g[k,1:i])
    cumprk_b[k,i]<- sum(prk_b[k,1:i])
 }
}

#SUCRA
for(k in 1:nt) {
          SUCRA_g[k]<- sum(cumprk_g[k,1:(nt-1)]) /(nt-1)
       SUCRA_b[k]<- sum(cumprk_b[k,1:(nt-1)]) /(nt-1)
}

}
}                              # *** PROGRAM ENDS
```

D1.2 Participant flow in the relevant randomised control trials

The participant flow of the two enzalutamide randomised trials (ARCHES and ENZAMET) is given in Figure 30 and Figure 31.

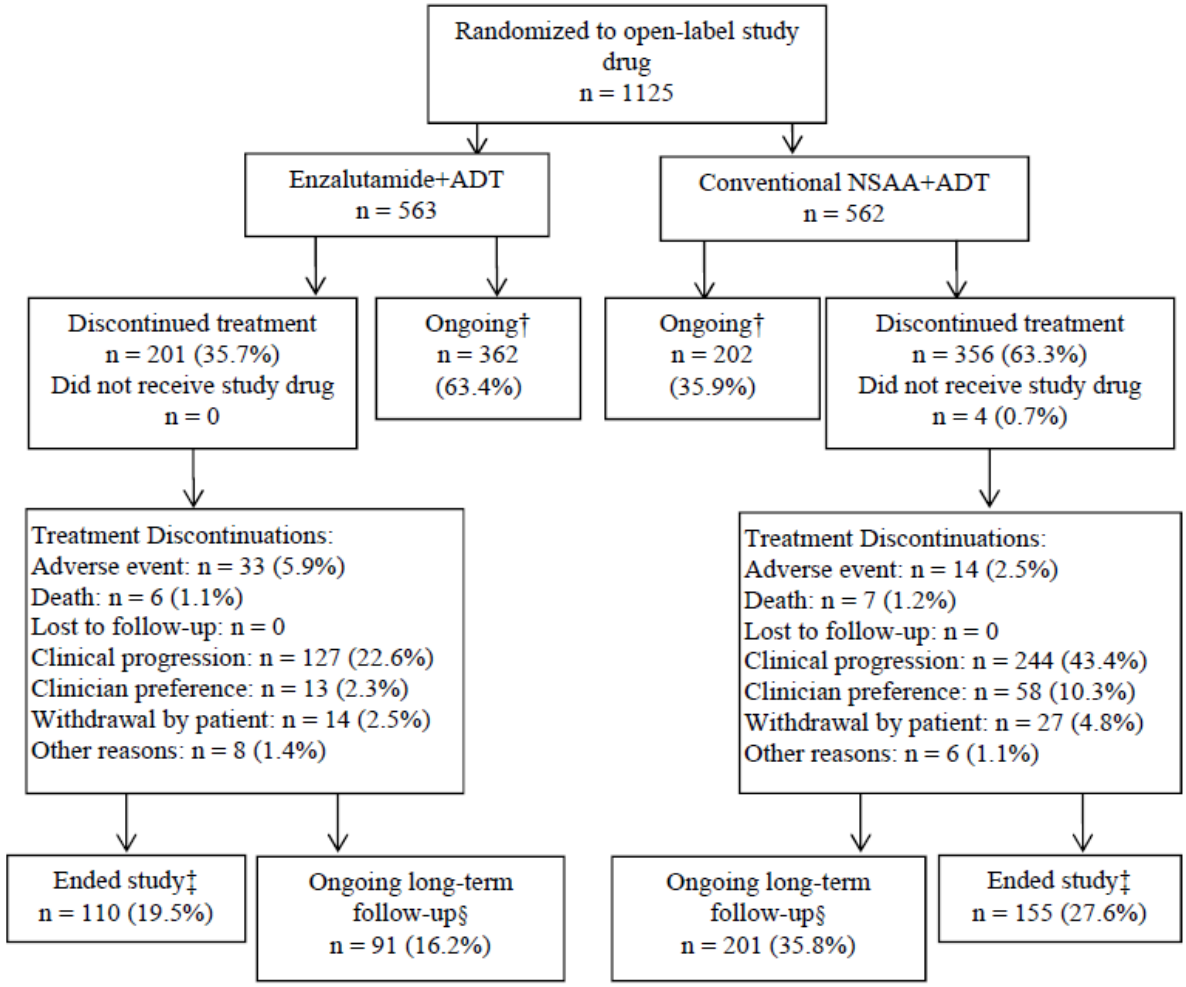
Figure 30 ARCHES participant flow as of 14 October 2018



Source: ARCHES Clinical study report[23]

†Patients were still on-treatment by the cut-off date (or no documentation of treatment discontinuation was received). ‡Includes patients who did not complete any long-term follow-up visits or ended their participation in the long-term follow-up. § Patients in long-term follow-up after treatment discontinuation

Figure 31 ENZAMET participant flow as of 28 February 2019



Source: ENZAMET Clinical study report[24]
†Patients were still on-treatment by the cut-off date (or no documentation of treatment discontinuation was received). ‡Includes patients who did not complete any long-term follow-up visits or ended their participation in long-term follow-up. §Patients in long-term follow-up after treatment discontinuation

D1.3 Quality assessment for each trial

The quality appraisals of the 11 studies included in the NMA to assess the risk of bias and generalisability in parallel group RCTs are shown in Table 83. The quality appraisal was based on the key publication.

Table 83 Quality assessment results for PROSPER and STRIVE

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
ARCHES (CSR)	Y	Y	Y	Y	Y	Y	N	N	Y	Y
CHAARTED / E3805	Y	N	N	N	Y	Y	Y	Y	Y	N/C
DAPROC	N/C	N/C	N	N/C	N	N	N	Y	Y	N/C
ENZAMET (CSR)	y	n	N	N	N/C	Y	N	N	Y	Y

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
EORTC 30853	N/C	N/C	N	N/C	N/C	Y	N	Y	Y	N/C
GETUG-AFU 15	Y	N	N	N	Y	Y	N	N	Y	N/C
INTERGROUP STUDY 0036	N/C	N/C	N/C	N/C	N	N	N	Y	Y	N/C
Janknegt 1983	N/C	N/C	N/C	N/C	Y	Y	N	Y	Y	N/C
STAMPEDE	Y	N	N	N	N	Y	N	N	Y	N/C
SWOG-8894 [Eisenberger 1998]	Y	N/C	N/C	N	N	N	N	N/C	N/C	N/C
Zalcberg 1996	N/C	Y	N/C	N/C	N	Y	N	Y	Y	N/C

Source: SLR report[26]

*Published as an abstract only. Abbreviations: Question 1: Was randomisation carried out appropriately? Question 2: Was the concealment of treatment allocation adequate?; Question 3: Was the blinding of participants and personnel sufficient?; Question 4: Was the blinding of the outcome assessment sufficient?; Question 5: Was the outcome data complete?; Question 6: Was reporting performed appropriately?; Question 7: Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?; Question 8: Is there any evidence to suggest that the authors measured more outcomes than they reported?; Question 9: Did the analysis include an intention-to-treat analysis?; Question 10: If there was an ITT, was this appropriate and were appropriate methods used to account for missing data? N/A: Not Applicable; N/C: Not Clear; Y: Yes; N=No.

NMA related information

Proportionality of hazard

The proportionality of hazards assumption check was performed using three formal statistical tests and two graphical methods. These methods are described below.

Time-dependent effects (Cox 1972[142])

Cox proposed assessing departure from the PH assumption by introducing a constructed time-dependent variable, that is, by adding an interaction term that involves time to the Cox model, and test for its significance[142].

A time-dependent variable was created by forming an interaction (product) term between the predictor, X (continuous or categorical), and a function of time t (f(t) = t, t^2, log(t), ...). Testing for non-proportionality of the hazards was equivalent to testing if the interaction was significantly different from zero.

Test of Harrel and Lee (1986[143]) - Schoenfeld residuals

This method consists of testing for correlation between partial residuals with ranks of survival time. For each predictor in the model, Schoenfeld residuals were defined for every subject who had an event. The idea was that if the PH assumption holds for a particular covariate, then the Schoenfeld residuals for that covariate was not related to survival time[143, 144].

- **Step 1** A Cox PH model was run and the Schoenfeld residuals for each predictor were obtained.
- **Step 2** A variable that ranks the order of failures was created. The subject who had the first (earliest) event gets a value of 1, the next gets a value of 2, and so on.

- **Step 3** The correlation between the variables created in the first and second steps was tested. The null hypothesis was that the correlation between the Schoenfeld residuals and ranked failure time was zero.

Martingale or cumulative residuals

The cumulative sum of Schoenfeld residuals, or equivalently the observed score process can also be used to assess PH. Graphically, the observed score process was plotted versus time for each variable of the model, together with simulated processes assuming the underlying Cox model was true, that is, assuming proportional hazards. Any departure of the observed score process from the simulated ones was evidence against proportionality. These plots can then be used to assess when the lack of fit was present. In particular, an observed score well above the simulated process was an indication of an effect higher than the average one, and conversely[145]. A goodness-of-fit test (supremum test) can also complement the procedure.

Log-cumulative hazard plot

A graph of –ln(-ln(Survival)) vs time over different categories of a covariate (in our case, treatment) can reveal deviations from the PH assumption. As when observing the Kaplan-Meier curves for each treatment, parallelism should be detected. This was a transformation of the Kaplan-Meier curves, where the proportionality of hazards was easier to detect.

The idea was that the difference between the two curves was constant at each timepoint, i.e., time-independent. Let X1 be the specifications for individual 1 and X2 for individual 2. Then, the distance between the two curves involves the differences in predictor values and was independent of time, as follows:

$$-\ln(-\ln S(t, X_1)) = -\ln(-\ln S(t, X_2)) + \sum_{i=1}^{p} \beta_i (X_{2i} - X_{1i})$$

Appendix E: Subgroup analysis

All pre-specified subgroup analysis in ARCHES and ENZAMET were performed as discussed in Section B.2.7. The results are shown in Section B.2.7. In addition, post-hoc analyses were conducted for the flowing patient subgroups in ARCHES: newly diagnosed mHSPC, recurrent mHSPC, mHSPC patients previously treated with docetaxel, newly diagnosed high-risk mHSPC, high volume disease, low volume disease, high risk and low risk. The outcomes for these patient subgroups are provided in Table 24. Post-hoc analyses were also conducted for newly diagnosed high-risk mHSPC in ENZAMET (Table 25).

Appendix F: Adverse reactions

No studies providing additional safety information for enzalutamide in mHSPC were identified other than the ARCHES- and ENZAMET-related publications.

Appendix G: Published cost-effectiveness studies

A SLR was conducted in May 2019 to identify the available economic evidence in the mHSPC setting in terms of cost-effectiveness models, health resource utilisation and costs. No separate SLR was conducted to identify cost-effectiveness studies. The SLR was conducted in two stages: an initial one in September 2018 and an update in May 2019[26].

G1.1 Search strategy

The research questions for the cost-effectiveness SLR were[26]:

- What is the health resource utilisation (HRU) associated with the management of adult patients with mHSPC in terms of at least:
    - Hospitalisation (inpatient, outpatient, emergency room [ER])
    - General practitioner, specialists, nurse visits
    - Laboratory tests
    - Management of treatment toxicity and complications
- What direct and indirect costs are associated with the management of adult patients with mHSPC?

The databases searched and provider used to identify cost-effectiveness evidence are provided in Table 84. The timeframe was restricted to the last 10 years in the initial SLR (i.e., between January 2008 and September 2018). No additional limitations were applied.

Table 84 Databases searched and provider used to for cost-effectiveness SLR

Database / information source	Interface / URL
Medline and Medline in Process	OvidSP
EMBASE	OvidSP
EconLit	OvidSP
CDSR in the Cochrane Library	Cochrane Library/Wiley Interscience
HTA in the Cochrane Library	Cochrane Library/Wiley Interscience
NHS EED in the Cochrane Library	Cochrane Library/Wiley Interscience
HTA Accelerator	https://hta.quintiles.com/

Source: SLR report[26]
Abbreviations: CDRS: Cochrane Database of Systematic Reviews; HTA: Health Technology Assessment; NHS EED: NHS Economic Evaluation Database.

The complete search strategies used for Cochrane, Medline, Medline in Process, and Embase, including all the search terms: textwords (free text), subject index headings (for

example, MeSH), the relationship between the search terms (for example, Boolean) when applicable, and the number of hits for each search are given in Table 85, and Table 86.

Table 85 Search strategy in Cochrane for the cost-effectiveness review

Concept	ID	Search string	Hits - 03 Sept 2018[*1]	Hits – 22 May 2019[*2]
Disease	#1	"prostatic neoplasms"[MeSH Terms]	4,747	4,916
	#2	prostat*:ti,ab,kw	11,427	1,084
	#3	"cancer":ti,ab,kw OR carcinoma:ti,ab,kw OR malignant:ti,ab,kw OR malignancy:ti,ab,kw OR tumor:ti,ab,kw OR tumoral:ti,ab,kw OR tumour:ti,ab,kw OR adenocarcinoma:ti,ab,kw	102,812	10,824
	#4	#2 AND #3	7,912	742
	#5	#4 OR #1	8,088	751
	#6	"hormone-sensitive":ti,ab,kw OR "hormone-dependent":ti,ab,kw OR "androgen-sensitive":ti,ab,kw OR "androgen-dependent":ti,ab,kw OR "castration-naive":ti,ab,kw OR "castration-sensitive":ti,ab,kw OR HSPC:ti,ab,kw OR ADPC:ti,ab,kw	438	43
	#7	#5 AND #6	186	33
	#8	"metastatic":ti,ab,kw OR mHSPC:ti,ab,kw OR "metastasized":ti,ab,kw OR "metastasised":ti,ab,kw OR “advanced”:ti,ab,kw OR “disseminated”:ti,ab,kw	38,504	236
	#9	#7 AND #8	134	32
Outcomes	#10	"costs and cost analysis"[MeSH Terms]	9,580	9,811
	#11	"models, economic"[MeSH Terms]	299	317
	#12	productivity[MeSH Terms]	312	319
	#13	hospitalization[MeSH Terms]	326	12,958
	#14	budget[MeSH Terms]	34	29
	#15	expenditure[MeSH Terms]	181	197
	#16	"costs":ti,ab,kw OR "cost":ti,ab,kw OR "costing":ti,ab,kw OR "costly":ti,ab,kw OR "economic burden":ti,ab,kw OR economic*:ti,ab,kw OR pharmacoeconomic*:ti,ab,kw OR "budget":ti,ab,kw OR "healthcare cost":ti,ab,kw OR "healthcare costs":ti,ab,kw OR "expenditure":ti,ab,kw OR "hospital finance":ti,ab,kw	43,856	5,402
	#17	"model":ti,ab,kw AND ("economic":ti,ab,kw OR "cost-effectiveness":ti,ab,kw OR "cost-benefit":ti,ab,kw OR "cost-utility":ti,ab,kw OR "discrete event":ti,ab,kw)	3,232	434
	#18	"healthcare utilisation":ti,ab,kw OR "health care utilisation":ti,ab,kw OR “resource utilization”:ti,ab,kw OR “resource use”:ti,ab,kw OR "health care resource":ti,ab,kw OR "health care resources":ti,ab,kw	4,431	605
	#19	"productivity":ti,ab,kw OR "absenteeism":ti,ab,kw OR ("work":ti,ab,kw AND "loss":ti,ab,kw) OR ("work":ti,ab,kw AND "disability":ti,ab,kw)	4,796	622

Concept	ID	Search string	Hits - 03 Sept 2018[*1]	Hits – 22 May 2019[*2]
	#20	"hospitalisation":ti,ab,kw OR "hospitalization":ti,ab,kw OR "ICU":ti,ab,kw OR "intensive care":ti,ab,kw OR "urologist":ti,ab,kw OR "physician":ti,ab,kw OR "oncologist":ti,ab,kw OR "outpatient visit":ti,ab,kw OR "outpatient visits":ti,ab,kw OR "admission":ti,ab,kw OR "inpatient visit":ti,ab,kw OR "inpatient visits":ti,ab,kw	55,831	6,922
	#21	"QALY":ti,ab,kw OR "quality adjusted life year":ti,ab,kw OR "ICER":ti,ab,kw OR "incremental cost effectiveness ratio":ti,ab,kw	2,957	478
	#22	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23	97,723	12,012
All	#23	#9 AND #22	11	5

Source: SLR report[26]

*[1]The search was conducted on the 3rd of September 2018 with a timeframe restriction of the last 10 years.

*[2]Thsearch was conducted on the 22nd of May 2019 with a timeframe restriction of publications between 01 September 2018 and 22nd of May 2019.

Table 86 Search strategy in Medline, Medline in Process and Embase for the cost-effectiveness review

ID	Search string	Hits - 03 Sept 2018[*1]	Hits – 22 May 2019[*2]
1	exp prostate tumor/	199,871	224,326
2	exp Prostatic Neoplasms/	315,419	344,783
3	prostat*.ab,ti.	448,364	487,105
4	(cancer or carcinoma or malignant or malignancy or tumor or tumoral or tumour or adenocarcinoma).ti,ab.	5,869,622	6,426,673
5	1 or 2 or (3 and 4)	387,515	425,976
6	(hormone-sensitive or hormone-dependent or androgen-sensitive or androgen-dependent or castration-naive or castration-sensitive or HSPC or ADPC).ti,ab.	34,461	36,930
7	exp hormone sensitivity/	3,002	3,150
8	5 and (6 or 7)	10,089	11,058
9	(metastatic or mHSPC or metastasized or metastasised or advanced or disseminated).ab,ti.	1,375,049	1,522,493
10	exp metastasis/	694,769	770,097
11	exp Neoplasm Metastasis/	694,769	770,097
12	8 and (9 or 10 or 11)	3,178	3,725
13	exp economics/ or exp economic aspect/	1,976,009	2,127,945
14	exp Models, Economic/ or exp productivity/ or exp hospitalization/ or exp health expenditures/ or exp budget/	847,511	933,300
15	(costs or cost or costing or costly or burden or economic* or pharmacoeconomic* or budget or healthcare cost or healthcare costs or expenditure or hospital finance).mp.	2,581,181	2,846,716
16	(model and (economic or cost-effectiveness or cost-benefit or cost-utility or discrete event)).mp.	109,153	123,600
17	(healthcare utilisation or health care utilisation).mp.	2,461	2,948

ID	Search string	Hits - 03 Sept 2018*1	Hits – 22 May 2019*2
18	(resource utilization or resource or health care resource or health care resources).mp.	302,289	344,704
19	(hospitalisation or hospitalization or ICU or intensive care or urologist or physician or oncologist or outpatient visit or outpatient visits or admission or inpatient visit or inpatient visits).mp.	1,984,161	2,184,332
20	(QALY or quality adjusted life year or ICER or incremental cost effectiveness ratio).mp.	38,186	44,256
21	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	5,229,628	5,754,774
22	12 and 21	210	292
23	limit 22 to yr="2008 - 2018"	174	
	limit 22 to yr="2018 -Current"		80
24	remove duplicates from 23	135	64

Source: SLR report[26]

*[1]The search in Medline, Medline in Process and Embase for the economic component was conducted on 9th of August 2018. The timeframe covered was: Embase: 2008 to August 09, 2018; Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R): 2008 to August 09, 2018. *[2]The search in Medline, Medline in Process and Embase for the economic component was conducted on 22nd of May 2019. The timeframe covered was1974 to 2019 May 22; Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R): 1946 to May 22, 2019. However, only publications from 2018 onwards were identified.

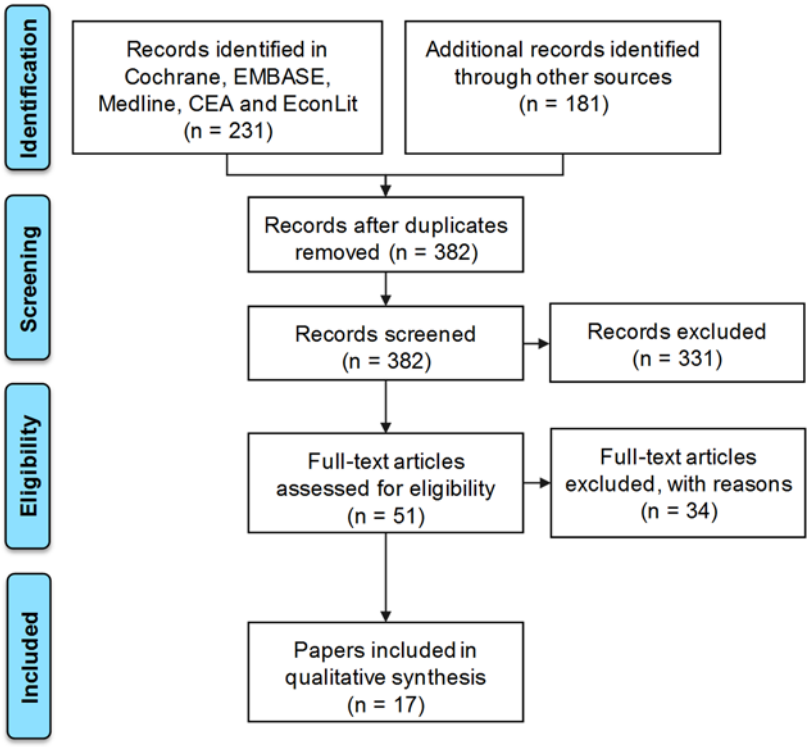
Searches were also conducted in:

- ISPOR website:
    - In the initial SLR, 3 studies were identified when searching for “Metastatic hormone sensitive prostate cancer” in title or abstract
    - In the SLR update, 62 presentations were identified with the keyword “prostate cancer”
- EconLit: The search for the initial SLR was conducted on the 10th of July 2018 and the SLR update on the 22nd of May 2019. The search strategy was:
    - S1: AB metastatic OR TI metastatic: 42 (initial SLR) and 0 (SLR update)
    - S2: AB prostate cancer OR TI prostate cancer: 99 (initial SLR) and 0 (SLR update)
    - S1 AND S2: 6 (initial SLR) and 0 (SLR update)
- HTA Accelerator (IQVIA proprietary database): Three HTA submissions were identified for mHSPC in the initial SLR and one additional submission (NICE appraisal for apalutamide in mHSPC) was identified in the SLR update. However, for the latter only the draft scope was available at the time of the SLR update.

G1.2 Results

The literature search for the economic burden identified 412 references of which 382 were unique (Figure 32). After the initial screening of titles and abstracts, 51 references were considered as potentially relevant. Following detailed examination of the full article, 17 were included for abstraction.

Figure 32 PRISMA flow diagram with the identified studies from cost-effectiveness SLR



Source: SLR report[26]

Of the 17 studies identified in the SLR, 13 were cost effectiveness studies in mHSPC. Of these, only 3 studies were specific to the UK. These studies are described in section B.3.1.

Appendix H: Health-related quality-of-life studies

A SLR was conducted in May 2019 to identify the humanistic burden of enzalutamide and standard of care in the management of mHSPC. The SLR was conducted in two stages: an initial one in September 2018 and an update in May 2019[26].

I1.1 Search strategy

The research questions for the HRQoL SLR were:

- What utility and disutility weights have been derived for patients with mHSPC?
- What is the impact of mHSPC and its treatment on the health related quality of life (HRQoL) of patients with mHSPC?

The databases searched and provider used to identify HRQoL evidence are provided in Table 87. No timeframe, country or language limit was applied to the clinical effectiveness searches

Table 87 Databases searched and provider used to for cost-effectiveness SLR

Database / information source	Interface / URL
PubMed*	http://www.ncbi.nlm.nih.gov/pubmed
Medline and Medline in Process	OvidSP
EMBASE	OvidSP
CDSR in the Cochrane Library	Cochrane Library/Wiley Interscience
CENTRAL in the Cochrane Library	Cochrane Library/Wiley Interscience
DARE in the in Cochrane Library	Cochrane Library/Wiley Interscience
CEA Registry	http://healtheconomics.tuftsmedicalcenter.org/cear4/home.aspx
HTA Accelerator	https://hta.quintiles.com/

Source: SLR report[26]
Abbreviations: CDRS: Cochrane Database of Systematic Reviews; CEA: cost-effectiveness analysis; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; HTA: Health Technology Assessment.

Only the search strategies used to identify health utilities are provided here. The complete search strategies used for Cochrane, and Medline, Medline in Process and Embase including all the search terms: textwords (free text), subject index headings (for example, MeSH), the relationship between the search terms (for example, Boolean) when applicable, and the number of hits for each search are given in Table 88, Table 89 and Table 90.

Table 88 Search strategy in Cochrane for humanistic review – utility weights

Concept	ID	Search string	Hits – 03 Sept 2018*[1]	Hits – 22 May 2019*[2]
Disease	#1	"prostatic neoplasms"[MeSH Terms]	4,747	4,916
	#2	prostat*:ti,ab,kw	15,762	1,084
	#3	"cancer":ti,ab,kw OR carcinoma:ti,ab,kw OR malignant:ti,ab,kw OR malignancy:ti,ab,kw OR tumor:ti,ab,kw OR tumoral:ti,ab,kw OR tumour:ti,ab,kw OR adenocarcinoma:ti,ab,kw	141,457	10,824
	#4	#2 AND #3	10,223	742
	#5	#4 OR #1	10,527	751
	#6	"hormone-sensitive":ti,ab,kw OR "hormone-dependent":ti,ab,kw OR "androgen-sensitive":ti,ab,kw OR "androgen-dependent":ti,ab,kw OR "castration-naive":ti,ab,kw OR "castration-sensitive":ti,ab,kw OR HSPC:ti,ab,kw OR ADPC:ti,ab,kw	656	43
	#7	#5 AND #6	242	33
	#8	"metastatic":ti,ab,kw OR mHSPC:ti,ab,kw OR "metastasized":ti,ab,kw OR "metastasised":ti,ab,kw OR “advanced”:ti,ab,kw OR “disseminated”:ti,ab,kw	52,584	236
	#9	#7 AND #8	169	32
Outcome	#10	"health status"[MeSH]	25,714	26,637
	#11	"health utility":ti,ab,kw OR "health utilities":ti,ab,kw OR disutility:ti,ab,kw OR disutilities:ti,ab,kw or "EQ-5D":ti,ab,kw OR EuroQoL:ti,ab,kw OR "SF6":ti,ab,kw OR "SF12":ti,ab,kw OR "SF36":ti,ab,kw OR "short form 6":ti,ab,kw OR "short form 12":ti,ab,kw OR "short form 36":ti,ab,kw OR “HUI”:ti,ab,kw OR “Health utilities index”:ti,ab,kw OR "QALY":ti,ab,kw OR "quality adjusted life year":ti,ab,kw	11,105	1,688
	#12	#10 OR #11	34,161	2,510
All	#13	#9 AND #12	12	4

Source: SLR report[26]

*[1]The search was conducted on the 3rd of September 2018 with a timeframe restriction of the last 10 years.

*[2]Thsearch was conducted on the 22nd of May 2019 with a timeframe restriction of publications between 01 September 2019 and 22nd of May 2019.

Table 89 Search strategy in Embase and Medline for the HRQoL review – utility weights

ID	Search string	Hits – 03 Sept 2018*[1]	Hits – 22 May 2019*[2]
1	exp prostate tumor/	199,871	224,326
2	exp Prostatic Neoplasms/	315,419	344,783
3	prostat*.ab,ti.	448,364	487,105
4	(cancer or carcinoma or malignant or malignancy or tumor or tumoral or tumour or adenocarcinoma).ti,ab.	5,869,622	6,426,673
5	1 or 2 or (3 and 4)	387,515	425,976

ID	Search string	Hits – 03 Sept 2018*[1]	Hits – 22 May 2019*[2]
6	(hormone-sensitive or hormone-dependent or androgen-sensitive or androgen-dependent or castration-naive or castration-sensitive or HSPC or ADPC).ti,ab.	34,461	36,930
7	exp hormone sensitivity/	3,002	3,150
8	5 and (6 or 7)	10,089	11,058
9	(metastatic or mHSPC or metastasized or metastasised or advanced or disseminated).ab,ti.	1,375,049	1,522,493
10	exp metastasis/	694,769	770,097
11	exp Neoplasm Metastasis/	694,769	770,097
12	8 and (9 or 10 or 11)	3,178	3,725
13	exp health status/ or exp health status indicator/ or exp health status indicators/	742,369	800,776
14	(utility or utilities or disutility or disutilities or EQ-5D or EuroQoL or SF6 or SF12 or SF36 or short form 6 or short form 12 or short form 36 or HUI or Health utilities index or QALY or quality adjusted life year).ab,ti.	457,282	514,179
15	13 or 14	1,165,621	1,277,726
16	12 and 15	108	133
17	limit 16 to yr="2018 -Current"		28
18	remove duplicates from 16	79	
	remove duplicates from 17		23

Source: SLR report[26]

*[1]The search in Medline, Medline in Process and Embase for the utility weights component was conducted on 9th of August 2018. The timeframe covered was: Embase: 1974 to August 09, 2018; Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R): 1946 to August 09, 2018. *[2]The search in Medline, Medline in Process and Embase for the utility weights component was conducted on 22nd of May 2019. The timeframe covered was1974 to 2019 May 22; Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R): 1946 to May 22, 2019. However, only publications from 2018 onwards were identified.

Table 90 Search strategy used in the CEA registry database for HRQoL review

	Initial SLR*[1]		SLR update*[2]	
Search terms	**Number of utility weights**	**Number of articles**	**Number of utility weights**	**Number of articles**
Metastatic hormone-sensitive prostate cancer	2	1	0	0
Metastatic hormone sensitive prostate cancer	0	0	0	0
Metastatic androgen-dependent prostate cancer	0	0	0	0
Metastatic androgen dependent prostate cancer	0	0	0	0

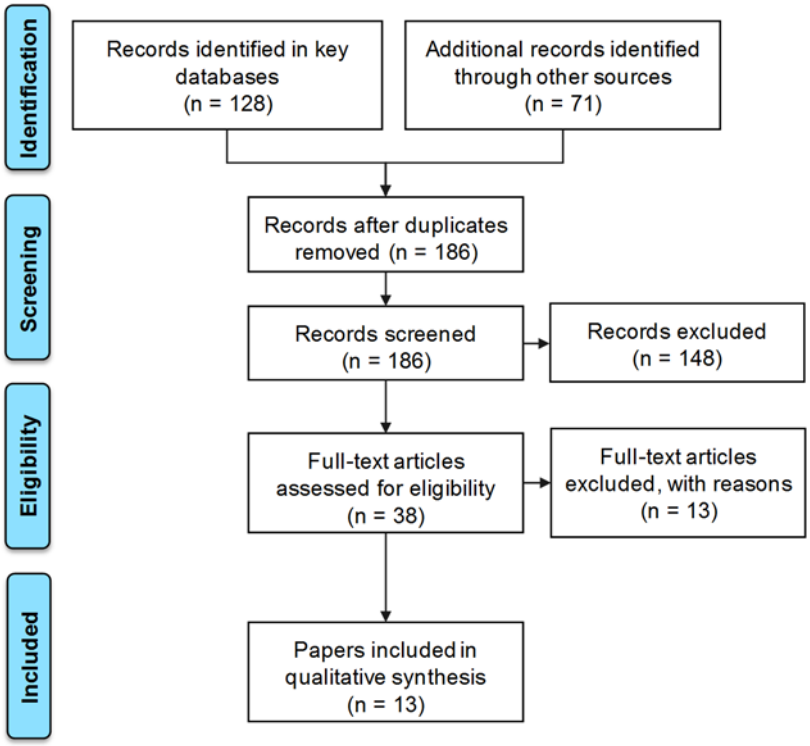
Source: SLR report[26]
*[1]The search was conducted on the 3rd of September 2018 with no timeframe restriction. *[2]Thsearch was conducted on the 22nd of May 2019 with a timeframe restriction of publications between 01 September 2019 and 22nd of May 2019.

I1.2 Results utility weights

The SLR identified 199 references of which 186 were unique (Figure 33).

After the initial screening of titles and abstracts, 38 references were considered as potentially relevant. Following detailed examination of the full article, 13 publications were included for abstraction.

Figure 33 PRISMA flow diagram with the utility studies identified through the predefined search strategy



Source: SLR report[26]
*Key databases included PubMed (n=87), Cochrane (n=7), Medline, Medline in Process and Embase (n=46).

An overview of the three studies identified by the SLR is provided in Table 91. Eight of these studies were cost-effectiveness models, of which three included advanced or metastatic prostate cancer[146],[112, 113], one metastatic and non-metastatic HSPC patients[92], one mHSPC patients exclusively[108, 111], one with HVD mHSPC patients[109], and one oligometastatic HSPC patients[110].

Table 91 Overview of selected studies providing health utilities

Reference	Study type	Patient population	Nationality	Utility derivation method
Aguiar 2019[108]	Cost-effectiveness	mHSPC	Brazil	From literature
ARCHES PRO report[33]	RCT, DB (ARCHES)	mHSPC (HVD/LVD; newly diagnosed / previously treated)	International	EQ-5D 5L
Bayoumi 2000[146]	CEA of androgen suppression	Advanced prostate cancer	Not specified	Estimation based on review of literature assessing PC-related QoL from perspective of patients and physicians
Beca 2019[109]	Cost-effectiveness	HVD mHSPC	Canada	From literature
Bennett 1996[113]	CEA of flutamide	Metastatic prostate carcinoma	US	Trade-off during physician focus group
Chi 2018[84]	RCT (LATITUDE)	Metastatic castration-naïve prostate cancer	International	EQ-5D-5L: EQ-VAS
Hall 2017[114]	Targeted LR, HCP and patient interviews	Metastatic hormone-sensitive prostate cancer	UK	EQ-5D-5L: EQ-VAS TTO
Hall 2019[115]	A literature review supplemented with patient and clinical expert interviews for patient experience Health state valuation with a sample of the UK general public	Interviews with mHSPC patients (n = 4), clinicians (n = 3), and specialist nurses (n = 2) Patients had to have mHSPC (ideally within the last 7 months), be on ADT alone or docetaxel plus ADT, aged 18 or over, a resident in the UK, able to speak English fluently, and able and willing to provide informed consent	UK	EQ-5D and TTO exercises
Ito 2018[116]	Two phase study with semi-structured qualitative interviews (phase 1) and online survey (phase 2)	mHSPC patients	EU5	EQ-5D 5L
NICE TA404[112]	CEA of degarelix	Locally advanced/metastatic prostate cancer	UK	Mapping SF-12 and EORTC QLQ-C30 (CS21 trial) to EQ-5D

Reference	Study type	Patient population	Nationality	Utility derivation method
Parikh 2019[110]	Cost-effectiveness	Oligometastatic HSPC patients	Assumed US	From literature
Woods 2018[92]	Cost-effectiveness	STAMPEDE patients (nmHSPC and mHSPC) treated with DOC+ADT or ADT alone	UK	EQ-5D 5L
Zheng 2017[111]	CEA of docetaxel plus ADT	Metastatic hormone-sensitive prostate cancer	China	Estimation based on literature

Source: SLR report[26]
Abbreviations: ADT: androgen deprivation therapy; CEA: cost-effectiveness analysis; DB: double-blinded; DOC: docetaxel; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – core 30 items; EQ-5D-5L: EuroQol – 5 dimensions – 5 levels; EQ-VAS: EuroQol Visual Analogue Scale; EU: European Union; HCP: healthcare practitioner; HVD: high-volume disease; LR: literature review; LVD: low-volume disease; mHSPC: metastatic Hormone-Sensitive Prostate Cancer; PC: prostate cancer; RCT: randomised controlled trial; SF: short form; TTO: time trade-off; UK: United Kingdom; US: United States of America.

Utility weights for stable disease

An overview of the utilities reported for mHSPC patients when they are in a stable state either before initiating therapy or when being on first-line therapy for mHSPC is provided in Table 92.

The utility weights reported for mHSPC patients ranged from 0.64 for mHSPC patients on docetaxel[114, 115] to 0.93 after 12 months of 1-month depot goserelin[112]. However, it should be noted that in the NICE manufacturer submission, the 0.93 utility weight referred to a mixed patient population with advanced or metastatic HSPC. This value was close to the median reported in the ARCHES PRO report[33] for mHSPC patients using the UK English set EQ-5D 5L (0.92). The large range of utility weights was due to different elicitation methods as well as differences in the patient subgroups.

In Hall et al[114, 115], addition of docetaxel to ADT was associated with a lower utility weight (0.64 ± 0.27 vs 0.71 ± 0.26 for mHSPC patients on ADT). Being on docetaxel also leads to a disutility in Beca 2019[109] (-0.13) and Woods 2018[92] (-0.02).

Table 92 Utility weights reported in mHSPC

Reference	Condition	Utility weight
Local metastases		
Bayoumi 2000[146]	Local recurrent/metastatic disease	0.92 (range: 0.8-1)
Stable disease		
Aguiar 2019[108]	PFS	0.844 [0.824; 0.864]
ARCHES PRO report[33]	mHSPC - EQ-5D 5L – UK mapping (all patients), Mean (SD)	ENZA: [redacted] PLA: [redacted]
	mHSPC - EQ-5D 5L – UK mapping (all patients) - Median (Min/Max)	ENZA: [redacted] PLA [redacted]

Reference	Condition	Utility weight
	mHSPC - EQ-5D 5L – UK English set (all patients) - Mean (SD)	ENZA: [redacted] PLA: [redacted]
	mHSPC - EQ-5D 5L – UK English set (all patients) - Median (Min/Max)	ENZA: [redacted] PLA: [redacted]
	mHSPC - EQ-5D 5L – France mapping (all patients) - Mean (SD)	ENZA: [redacted] PLA: [redacted]
	mHSPC - EQ-5D 5L – France mapping (all patients) - Median (Min/Max)	ENZA: [redacted] PLA: [redacted]
	mHSPC - EQ-5D (UK mapping; HVD) - Mean (SD)	ENZA: [redacted] PLA: [redacted]
	mHSPC - EQ-5D (UK mapping; HVD) - Median (Min/Max)	ENZA: [redacted] PLA: [redacted]
	mHSPC - EQ-5D (England value set; HVD) - Mean (SD)	ENZA: [redacted] PLA: [redacted]
	mHSPC - EQ-5D (England value set; HVD) - Median (Min/Max)	ENZA: [redacted] PLA: [redacted]
	mHSPC - EQ-5D (France mapping; HVD) - Mean (SD)	ENZA: [redacted] PLA: [redacted]
	mHSPC - EQ-5D (France mapping; HVD) - Median (Min/Max)	ENZA: [redacted] PLA: [redacted]
	mHSPC - EQ-5D (UK mapping; LVD) - Mean (SD)	ENZA: [redacted] PLA: [redacted]
	mHSPC - EQ-5D (UK mapping; LVD) - Median (Min/Max)	ENZA: [redacted] PLA: [redacted]
	mHSPC - EQ-5D (England value set; LVD) - Mean (SD)	ENZA: [redacted] PLA: [redacted]
	mHSPC - EQ-5D (England value set; LVD) - Median (Min/Max)	ENZA: [redacted] PLA: [redacted]
	mHSPC - EQ-5D (France mapping; LVD) - Mean (SD)	ENZA: [redacted] PLA: [redacted]
	mHSPC - EQ-5D (France mapping; LVD) - Median (Min/Max)	ENZA: [redacted] PLA: [redacted]
	All pre-progression assessments (UK mapping)	ENZA: [redacted] PLA: [redacted] ENZA+PLA: [redacted]
Beca 2019[109]	mHSPC	0.90 (Bayoumi 2000)
	Disutility for DOC	-0.13 (Collins 2007)
Bennett 1996[113]	Stable disease	0.92 (IQR: 0.88-0.96)
Bayoumi 2000[146]	Distant asymptomatic disease	0.9 (range: 0.8-1)
	Distant symptomatic disease, hormone responsive	0.8 (range: 0.4 – 0.9)
Chi 2018[84]	mHSPC	0.8 ± 0.2
Hall 2017[114]	mHSPC receiving ADT	0.71 ± 0.26
	mHSPC receiving DOC + ADT	0.64 ± 0.27
	mHSPC completed six cycles DOC + ADT, progression-free	0.68 ± 0.26
Hall 2019[115]	mHSPC on ADT (TTO)	0.71+/-0.26
	mHSPC on ADT (GEE model)	0.71+/-0.02

Reference	Condition	Utility weight
	mHSPC on DOC + ADT (TTO)	0.64+/-0.27
	mHSPC on DOC + ADT (GEE model)	−0.07+/-0.01; p<0.0001*
Ito 2018[116]	mHSPC - EQ-5D-5L, mean (SD)	0.70 (0.25)
NICE TA404[112]	Advanced prostate cancer: disseminated symptomatic or locally advanced	0.785 ± 0.201
	mHSPC first-line treatment	0.887 [95% CI: 0.879-0.894]
	mHSPC anti-androgen addition or withdrawal	0.753 [95% CI: 0.697-0.806]
	Baseline advanced prostate cancer, using 1-month depot goserelin	0.87 ± 0.2
	After 12 months of 1-month depot goserelin in advanced prostate cancer	0.93 ± 0.1
	Baseline advanced prostate cancer, using 3-month depot goserelin	0.83 ± 0.2
	First-line chemotherapy	0.689 [95% CI: 0.686-0.692]
	After 12 months of 3-month depot goserelin in advanced prostate cancer	0.88 ± 0.1
Parikh 2019[110]	mHSPC not on ADT	0.90
	mHSPC on ADT	0.82
Woods 2018[92]	Disutilities vs a nmHSPC patient WHO 0 in STAMPEDE mHSPC bone	-0.01 [-0.02; 0.00]
	Disutilities vs a nmHSPC patient WHO 0 in STAMPEDE First year on DOC+SOC	-0.02 [-0.03; -0.01]
Zheng 2017[111]	mHSPC with progression-free survival	0.8

Source: SLR report[26]
*Versus mHSPC on ADT (GEE model). Abbreviations: ADT: androgen deprivation therapy; CI: confidence interval; DOC: docetaxel; ENZA: enzalutamide; EQ-5D-5L: EuroQol – 5 dimensions – 5 levels; GEE: generalised estimating equation; HVD: high-volume disease; IQR: interquartile range; LVD: low-volume disease; mCNPC: metastatic Castration-Naïve Prostate Cancer; mHSPC: metastatic Hormone-Sensitive Prostate Cancer; SD: standard deviation; nmHSPC: non-metastatic hormone-sensitive prostate cancer; PLA: placebo; PFS: progression-free survival; TTO: time trade-off; UK: United Kingdom.

After disease progression

An overview of the utilities reported for mHSPC patients when disease progresses is provided in Table 93. The utility weight for patients when disease progresses markedly differed across studies. Bayoumi 2000[146] reported a utility weight of 0.4 for patients with mHSPC when disease no longer responds to hormone treatment. This value was similar to that reported by Bennett 1996[113] (0.42).

In the more recent studies, values ranged between 0.59 for patients with disease progressing to HRPC with bone metastases to 0.81 for patients with disease progressing to mHRPC and prior to chemotherapy for HRPC[112].

Aguiar 2019[108] reported different utility weights for mHSPC patients who had progressed after receiving abiraterone (0.658) or docetaxel (0.612). The utility for patients progressing after docetaxel estimated by Aguiar 2019[108] was lower than that in Hall 2019[115] (0.68). In the

latter, this value was elicited by a TTO method. No information on the elicitation method was given in Aguiar 2019[115].

In the ARCHES PRO report[33], two different progression-related values were reported:

- The utility weight in the first assessment after progression ([redacted])
- The average utility weight of all available assessments after disease progression in ARCHES ([redacted]).

Table 93 Utility weights reported for patients with mHSPC when disease progresses

Reference	Condition	Utility weight
Aguiar 2019[108]a	Post-progression survival with ABI	0.658 [0.618; 0.698]
	Post-progression survival with DOC	0.612 [0.572; 0.652]
ARCHES PRO report[33]a	First post-progression assessment (UK mapping)	[redacted]
	All progressed assessments (UK mapping)	[redacted]
Bayoumi 2000[146]	Distant symptomatic disease, hormone resistant	0.4 (range: 0.1-0.7)
Bennett 1996[113]	Early progressive disease	0.83 (IQR: 0.67-0.88)
	Late progressive disease	0.42 (IQR: 0.25-0.59)
Beca 2019[109]	mHRPC	0.77 (National Centre for Pharmacoeconomics 2012)
	Disutility for DOC	-0.13 (Collins 2007)
Hall 2019[115]	mHSPC after DOC (TTO)	0.68+/-0.26
	mHSPC after DOC (GEE model)	−0.04+/-0.01; p=0.0002*
NICE TA404[112]	mHRPC with progression during or after first-line docetaxel treatment	0.63 ± 0.26
	HRPC at high-risk for bone metastases	0.77
	HRPC with bone metastases	0.59
	mHRPC	0.635 ± 0.309
	mHRPC	0.72 ± 0.30
	mHRPC with no previous chemotherapy	0.81 ± 0.27
	mHRPC after chemotherapy	0.66 ± 0.30
	mHRPC on chemotherapy	0.64 ± 0.31
Parikh 2019[110]	No ADT	0.9
	With ADT	0.82
Woods 2018[92]	Disutilities vs a nmHSPC patient WHO 0 in STAMPEDE mHRPC bone	-0.06 [-0.08; -0.04]
	Disutilities vs a nmHSPC patient WHO 0 in STAMPEDE mHRPC bone + SRE	-0.13 [-0.16; -0.11]

	Disutilities vs a nmHSPC patient WHO 0 in STAMPEDE mCRPC visceral	-0.12 [-0.15; -0.09]
Zheng 2017[111]	mHSPC with progressed disease	0.6

Source: SLR report[26]
*Versus mHSPC on ADT (GEE model). Abbreviations: ADT: androgen deprivation therapy; HRPC: hormone-relapsed prostate cancer; DOC: docetaxel; ENZA: enzalutamide; GEE: generalised estimating equation; IRQ: interquartile range; mHRPC: metastatic hormone-relapsed prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; PLA: placebo; TTO: time trade-off; UK: United Kingdom; WHO: World Health Organisation.

Adverse events and SREs

An overview of the utilities reported for mHSPC patients who experience side effects or SREs is provided in Table 94. Bayoumi 2000[146] and Bennett 1996[113] provided utility weights for mHSPC patients with gastrointestinal or minor side effects. The impact on the utility weight was minimal. In contrast, SREs that compress spinal cord had an important impact on utility weights. Prior to treatment for the compression the utility weight was reported to be 0.39. This value improved to 0.55 six months after surgery.

In addition Hall 2019[115] provided utility weights for several adverse events. These weights were derived by two different approaches: using TTO method with 200 members of the UK general population and a GEE model to estimate disutility weights[115].

Utility weights for metastatic epidural spinal cord compression were reported in NICE TA404[112].

Table 94 Utility weights reported for side effects or SRE

Reference	Condition	Utility weight
Side effects		
Bennett 1996[113]	Stable disease with gastrointestinal toxicity	0.84 (IQR: 0.75-0.88)
Bayoumi 2000[146]	Adjustment for living with minor side effect	0.85 (Range: 0.5-1)
Hall 2019[115]	Fatigue (grade 3; TTO)	0.54+/-0.34
	Fatigue (grade 3; GEE)	−0.09+/-0.02; p<0.0001*
	Nausea and vomiting (grade 3-4; TTO)	0.41+/-0.36
	Nausea and vomiting (grade 3-4; GEE)	−0.21+/-0.02; p<0.0001*
	Reduced immunity (grade 3-4; TTO)	0.48+/-0.33
	Reduced immunity (grade 3-4; GEE)	−0.14+/-0.02; p<0.0001*
	Fluid retention (grade 3; TTO)	0.58+/-0.29
	Fluid retention (grade 3; GEE)	−0.07+/-0.01; p<0.0001*
	Alopecia (grade 2; TTO)	0.58+/-0.29
	Alopecia (grade 2; GEE)	−0.04+/-0.01; p=0.0017*
	Diarrhea (grade 3-4; TTO)	0.40+/-0.38
	Diarrhea (grade 3-4; GEE)	−0.18+/-0.02; p<0.0001*
Metastatic epidural spinal cord compression		
NICE TA404[112]	Baseline	0.39 ± 0.26
	6 months after surgery	0.55 ± 0.30

Source: SLR report[26]
*Versus mHSPC on ADT (GEE model). Abbreviations: GEE: generalised estimating equation; IR: interquartile range; SRE: skeletal-related event; TTO: time trade-off;.

For palliative care

An overview of the utilities reported for mHSPC patients on palliative care or at their last year of life is provided in Table 95. The utility weight applied in the degarelix NICE submission was 0.55 for patients on palliative care, and 0.54 - 0.56 for the last year of life[112].

Table 95 Utility weights reported for palliative care or last year

Reference	Last year before death	Utility weight
NICE TA404 MS[112]	Prostate cancer, year before death - Dead from prostate cancer	0.538 ± 0.077
	Prostate cancer, year before death - Dead from other cause	0.564 ± 0.067
NICE TA404 ERG[112]	Palliative care	0.551 [95% CI: 0.527-0.580]

Source: SLR report[26]
Abbreviations: CI: confidence interval.

Appendix I: Cost and healthcare resource identification, measurement and valuation

Cost and healthcare resource identification was also included in the cost-effectiveness SLR and is discussed in Appendix G.

Of the 17 economic studies identified in the SLR, six studies reported health resource utilisation and 13 costs.

An overview of the studies providing HRU and costs is provide in Table 96.

Table 96 Studies reporting health resource utilisation and/o costs

Country	Study ID	Patient population	Type of model	Intervention	Comparator	Health states	Perspective	Time horizon	Currency / discounting
Brazil	**Aguiar 2017**[147]	mHSPC	Analytical decision model	DOC + ADT	ADT	Diagnosis; 1L; 2L (post progression); Death	NR	NR	US$ (2016) Discount: NR
Brazil	**Aguiar 2019**[108]	mHSPC	Cost-effectiveness	ABI + ADT DOC + ADT	ADT alone	Three: • Alive and without progression • Alive and post-progression • Dead	Not provided	7 years	Discounting: not provided Brazilian Real (R$; 2017)
Canada	**Beca 2019**[109]	HVD mHSPC	Cost-effectiveness	• 6 cycles of DOC 75 mg/m2 every 3 weeks + ADT	• ADT alone (pharmacological)	• 3 health states: HSPC, HRPC and death	Government	15 years	1.5% Canadian dollars (2017)
China	**Zheng 2017**[111]	mHSPC	Markov	DOC + ADT	ADT	PFS; Progression; Death	Societal (China)	10 years	US$ (2015) 3% per year
China	**Hu 2018**[148]	HVD mHSPC	Cost study	DOC+ADT	ABI+ADT	Not applicable	Healthcare and the patient perspectives	Lifetime	Discounting: not provided Renminbi (RMB)
England	**NICE ID945**[97]	Newly diagnosed mHSPC	Markov	ABI + ADT	ADT + DOC ADT alone	mHSPC progression-free, mHSPC PD, mHRPC 1L, mHRPC 2L, mHRPC 3L	NHS UK	20 years	GBP 3.5% per year

Country	Study ID	Patient population	Type of model	Intervention	Comparator	Health states	Perspective	Time horizon	Currency / discounting
Global***	**Li 2019**[131]	Newly diagnose high-risk mHSPC (ECOG ≤2)	Clinical trial collecting HRU	ABI+PRED+ADT	ADT +PLAs	Not applicable	Not applicable	Total person-years • ABI+ADT: 1120 • ADT: 836	Not applicable
Italy	**Iannazzo 2011**[149]	mPC*	Markov	3-month LHRH agonist: LEU 11.25 mg, LEU 22.5 mg, TPT 11.25 mg, BUS 9.9 mg, GOS 10.8 mg	NR	Alive Biochemical relapse Death	Italian NHS	Lifetime	EUR 5%
Spain	**García 2017**[150]	mHSPC**	CEA not further specified	DOC + ADT	ADT	NR	NR	NR	EUR (2016) Discount: NR
UK	**James 2018**[91]	STAMPEDE patients (nmHSPC and mHSPC) treated with DOC+ADT or ADT alone	Cost-effectiveness	DOC + ADT	ADT	Five health states • Hormone-sensitive • HRPC M0 or M1 lymph node • HRPC M1 Bone • HRPC M1 Bone+SRE • HRPC M1 Visceral	UK NHS	Lifetime	Discounting: 3.5% GBP
UK	**Lu 2012**[90]	mHSPC	Decision analytic; with decision tree and Markov	DEG	TPT	Response; Progression; Death	Payer	10 years	GBP 3.5%

Country	Study ID	Patient population	Type of model	Intervention	Comparator	Health states	Perspective	Time horizon	Currency / discounting
US	**Parikh 2019**[110]	Oligometastatic	Cost-effectiveness	• Stereotactic body radiation therapy (SBRT) over 3 fractions	• ADT consisted of Lupron injections every 3 months	Not provided	Payor's perspective	1 and 3 years	Discounting: not provided US $
US	**Penson 2005**[151]	Newly identified mPC (stage D2)*	Decision Markov model	Combined AB (BIC) + LHRH agonist	LHRH agonist	Stable disease, progression, death	Health care payer	5 and 10 years	US$ Discount: not provided
US	**Ramsey 2005**[152]	mPC (stage D2)*	Decision Markov model	Combined AB (BIC) + LHRH agonist	Combined AB (FLU) + LHRH	Stable disease, progression, death	Health care payer	5 and 10 years	US $ 3%
US	**Wong 2018**[153]	mHRPC and mHSPC	Cost study	ABI + ADT ENZA + ADT		Not applicable	Not provided	Not provided	Discounting: not provided US $

Source: SLR report[26]

*The disease indication is referred to as metastatic prostate cancer but all patients were mHSPC. **Although the publication provides data for metastatic and non-metastatic patients, the economic information is for mHSPC patients only. ***33 countries in Europe, Asia-Pacific region, Latin America, Canada. Abbreviations: 1L: first line therapy; 2L: second line therapy; $: dollar; ABI: abiraterone; AB: androgen blockade; ADT: androgen-deprivation therapy; BIC: bicalutamide; BUS: buserelin; CEA: cost-effectiveness analysis; HRPC: hormone-relapsed prostate cancer; DEG: degarelix; DOC: docetaxel; ECOG: Eastern Cooperative Oncology Group performance status; ENZA: enzalutamide; EUR: euro; FLU: flutamide; GBP: Great British Pound; GOS: goserelin; HSPC: hormone-sensitive prostate cancer; HK: Hong Kong; HRU: health resource utilisation; HSPC: hormone-sensitive prostate cancer; HVD: high-volume disease; LEU: leuprorelin; LHRH: luteinizing hormone-releasing hormone; M0: non-metastatic; M1: metastatic; mHRPC: metastatic hormone-relapsed prostate cancer; mHNPC: metastatic hormone-naive prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; mPC: metastatic prostate cancer; NHS: National Health Services (UK); NR: not reported; PFS: progression-free survival; PSS: Personal Social Services (UK); PRED: prednisone; RMB: Renminbi; SBRT: Stereotactic body radiation therapy; TPT: triptorelin; UK: United Kingdom; US: the United States.

An overview of the HRU reported in the selected studies for mHSPC is provided in Table 97.

Overall six studies[90, 111, 131, 149, 151, 152]reported the type of HRU included in their analyses. However, only Iannazzo 2011[149]i, Li 2019[131] and Lu 2012[90] report the number of service units patients needed.

Table 97 HRU in the selected economic studies

Country [Study]	HRU	Number of items
China[111]	Hospitalisation	NR
Italy[149]	Medical examination plus DRE	Once every 6 months
	PSA and hematochemical examinations	Once every 6 months
	Bone densitometry	Once a year
	Cardiology evaluation (visit plus ECG)	Once a year
	Abdominal echography	Once every 6 months
	Bone scintigraphy (total body)	Once every 6 months
UK[90]	TURP	50% of patients with bladder outlet obstruction (treatment for 10 days)
	Catherisation	50% of patients with bladder outlet obstruction (treatment for 10 days)
	RT	50% of patients with spinal cord compression
	Surgery	50% of patients with spinal cord compression
	Nursing home	50% of patients with spinal cord compression
US[151]	Doctor visit	NR
US[152] [Ramsey 2005]	Doctor visit	NR
International[131]	Overnight hospitalisation, No (%)	• 0 visits: ABI: 463 (77.55); ADT: 475 (78.90) • 1 or 2 visits: ABI: 103 (17.25); ADT: 88 (14.62) • ≥3 visits: ABI: 31 (5.19); ADT: 39 (6.48) • HR ABI+ADT vs ADT: 0.76 [0.60; 0.97]
	Emergency room, No (%)	• 0 visits: ABI: 522 (87.44); ADT: 552 (91.69) • 1 or 2 visits: ABI: 62 (10.39); ADT: 42 (6.98) • ≥3 visits: ABI: 13 (2.17); ADT: 8 (1.33) • HR ABI+ADT vs ADT: 0.98 [0.66; 1.46]
	Imaging, No (%)	• 0 visits: ABI: 475 (79.57); ADT: 494 (82.06) • 1 or 2 visits: ABI: 88 (14.74); ADT: 73 (12.13) • ≥3 visits: ABI: 34 (5.69); ADT: 35 (5.81) • HR ABI+ADT vs ADT: 0.64 [0.49; 0.84]
	Radiotherapy, No (%)	• 0 visits: ABI: 580 (97.15); ADT: 580 (96.35) • 1 or 2 visits: ABI: 9 (1.51); ADT: 10 (1.66) • ≥3 visits: ABI: 8 (1.34); ADT: 12 (1.99) • HR ABI+ADT vs ADT: 0.50 [0.25; 1.00]
	Surgery, No (%)	• 0 visits: ABI: 546 (91.46); ADT: 551 (91.53) • 1 or 2 visits: ABI: 49 (8.21); ADT: 49 (8.14) • ≥3 visits: ABI: 2 (0.33); ADT: 2 (0.33) • HR ABI+ADT vs ADT: 0.81 [0.52; 1.25]

Country [Study]	HRU	Number of items
	Specialist, No (%)	• 0 visits: ABI: 519 (86.93); ADT: 531 (88.21) • 1 or 2 visits: ABI: 56 (9.38); ADT: 53 (8.80) • ≥3 visits: ABI: 22 (3.69); ADT: 18 (2.99) • HR ABI+ADT vs ADT: 0.80 [0.57; 1.12]
	General practitioner, No (%)	• 0 visits: ABI: 483 (80.70); ADT: 504 (83.72) • 1 or 2 visits: ABI: 64 (10.72); ADT: 53 (9.14) • ≥3 visits: ABI: 50 (8.38); ADT: 45 (7.14) • HR ABI+ADT vs ADT: 1.17 [0.90; 1.52] • HR GP (excl outlier) ABI+ADT vs ADT: 0.95 [0.73; 1.24]
	Conditions Listed for Hospitalisation	• Genitourinary symptoms/disorders: 273 (26.98) • Musculoskeletal symptoms/disorders: 165 (16.31) • Respiratory tract symptoms/disorders/infections: 113 (11.16) • Nervous system symptoms/disorders: 102 (10.1) • Vascular disorders/symptoms: 99 (9.78) • Other infections: 85 (8.4) • Cardiac disorders/symptoms: 56 (5.55) • Neoplasms: 34 (3.38) • Gastrointestinal tract symptoms/disorders: 33 (3.27) • Endocrine symptoms/disorders: 15 (1.49) • Skin symptoms/disorders: 13 (1.29) • Miscellaneous: 25 (2.49)
	Average LOS per hospitalisation in days	• ABI: 6.9 days [5.3-8.5 days] • ADT: 7.0 days [5.4-8.6 days]

Source: SLR report[26]
Abbreviations: ABI: abiraterone; ADT: androgen-deprivation therapy; ECG: electrocardiogram; GP: general practitioner; HR: Hazard Ratio; HRU: health resource utilisation; LOS: Length of hospital stay; NR: not reported; PSA: prostate specific antigen; RT: radiotherapy; TURP: Transurethral Resection of the Prostate; UK: United Kingdom; US: United States of America.

An overview of the costs reported in the selected studies is provided in Table 98.

Table 98 Costs reported in the selected studies

Country	Costs
US[110]	Total cost at 1 year: ADT upfront: $3,430; MDT + salvage ADT: $9,434 Total costs at 3 years: ADT upfront: $10,289; MDT + salvage ADT $13,806
Brazil[147]	Docetaxel + ADT arm: docetaxel: $4,733.90; ADT: $5,441.74; Post progression: $9,618.64; Adverse events: not included due to limited data available; Supportive care: none; Total: $19,794.28 ADT alone arm: Docetaxel: $0; ADT: $3,886.95; Post progression: $9,863.14; Adverse events: not included due to limited data available; Supportive care: none; Total: $13,750.09
Brazil[108]	Drug cost: ABI + ADT vs ADT: R$ 378.549,00; DOC + ADT vs ADT: R$ 54.336,00

Country	Costs
	Adverse events costs: ABI + ADT vs ADT: R$ 2.042,00; DOC + ADT vs ADT: R$ 3.526,00 Post progression drugs costs: ABI + ADT vs ADT: R$ 70.455,00; DOC + ADT vs ADT: R$ 103.446,00 End-of-life costs: ABI + ADT vs ADT: R$ 112,00; DOC + ADT vs ADT: R$ 172.00 Monitoring costs: ABI + ADT vs ADT: R$ 14.808,00; DOC + ADT: R$ 15.256,00 Total costs: ABI + ADT: R$ 465.966,00; DOC + ADT: R$ 176.738,00
Canada[109]	Costs – DOC+ADT: Total: $140,183; HSPC: $14,524; HRPC: $125,659 Costs –ADT: Total: $114,426; HSPC: $6,873; HRPC: $107,552 Incremental costs: Total: $25,757; HSPC: $7,651; HRPC: $18,106
China[111]	ADT + DOC vs ADT arms: • Costs for PFS per month: Docetaxel: $275.67 vs $0; Dexamethasone: $0.098 vs $0; Hospital: $4.54 vs $0; ADT: $310.92 vs $310.92; Test: $214.73 vs $152.39; AE: $0.40 vs $0; Calcium carbonate: $4.18 vs $ 4.18; Vitamin D: $66.63 vs $66.63; Total: $877.18 vs $ 534.12 • Costs for PD per month: $172.90 vs $216.54 • Costs for PFS state: $24 035.64 vs $9916.45 • Costs for PD state: $3051.13 vs $4353.40 • Total costs: $27 086.78 14 vs $269.85
China[148]	• DOC+ADT less costly than ABI+ADT with potential savings of up to RMB 246,137 and RMB 66,549 per patient from the healthcare perspective and patient perspective
England[97]	Disaggregated and total costs are marked as commercial in confidence ABI + ADT vs ADT alone (manufacturer) • Incremental costs: GBP19,066 ABI + ADT vs DOC + ADT (manufacturer) • Incremental costs: GBP10,618 ABI + ADT vs ADT ERG Rebuild • Incremental Costs: GBP27,185 ABI + ADT vs DOC + ABI ERG Rebuild • Incremental Costs: GBP19,195
Italy[149]	Total costs • LEU 22.5 mg: EUR 13,981 • LEU 11.25 mg: EUR 15,114 • GOS: EUR 16,579 • TPT: EUR 15,935 • BUS: EUR 14,546 The authors also provide disaggregated costs: • Hormone therapy (SD), €: LEU 122.5 mg: 4856.87 (2670.25): LEU 1125 mg: 5977.07 (3138.54); GOS: 7404.81 (3943.09): TPT: 6804.14 (3603.69); BUS: 5427.60 (2825.12) • Follow-up (SD), €: LEU 22.5 mg: 2809.05 (1521.93); LEU 11.25 mg: 2772.40 (1506.50); GOS: 2702.59 (1470.35); TPT: 2789.34 (1517.25); BUS: 2811.31 (1524.54) • Chemotherapy (SD), €: LEU 22.5 mg: 6315.29 (3115.62); LEU 11.25 mg: 6364.41 (3101.18); GOS: 6471.77 (3058.34); TPT: 6341.11 (3108.41); BUS: 6307.34 (3120.84
Spain[150]	DOC+ADT vs ADT alone:

Country	Costs
	• Advanced HSPC in whom ADT is indicated and who would be prescribed a LHRH agonist • Incremental costs EUR 3,196.98 No data are provided for disaggregated costs
UK[91]	• M1 overall: £2,787 • M0 overall: £-251 • Savings were much greater for M0 patients as patients allocated to docetaxel arm spend a much shorter period in HRPC (i.e. extensions to FFS do not fully translate to increased OS)
UK[92]	M1 Costs (UK pounds, discounted) • Docetaxel: SOC: –;DOC: 1761; Incremental: 1761 • Monitoring: SOC: 5471; DOC: 5641; Incremental: 170 • Management including toxicities: SOC: 14,415; DOC: 16,555; Incremental: 2139 • Life-extending therapies: SOC: 27,716; DOC: 26,611; Incremental: -1105 • End-of-life care: SOC: 4864; DOC: 4687; Incremental: -177 • Total: SOC: 52,466; DOC: 55.253; Incremental: 2787
UK[90]	DEG vs TPT • Incremental cost: GBP 758 (3,883 vs 3,125) • DEG costs 3,617 (93.2%) drugs + 266 (6.8%) administration • TPT costs 1,965 (62.9% drugs + 92 (2.9%) administration 57 (1.8%) spinal cord compression + 283 (9.0%) bladder outlet obstruction + 728 (23.3%) care for care resulting from spinal cord compression
US[153]	Monthly Drug Cost (USD) • Post-chemo mHRPC (COU-AA- 301): ABI+ADT: $11,657.83 • Post-chemo mHRPC (AFFIRM): ENZA+ADT: $12,769.06 • Pre-chemo mHRPC (COU-AA- 302): ABI: $11,657.83 • Pre-chemo mHRPC (PREVAIL): ENZA + ADT: $12,769.06 • mCSPC (LATITUDE): ABI+ADT: $12,830.15 • mCSPC (STAMPEDE): $12,830.15 Incremental Cancer Drug Cost • Post-chemo mHRPC (COU-AA- 301): ABI+ADT: $83,460.94 • Post-chemo mHRPC (AFFIRM): ENZA+ADT: $102,564.40 • Pre-chemo mHRPC (COU-AA- 302): ABI: $155,632.73 • Pre-chemo mHRPC (PREVAIL): ENZA + ADT: $205,128.85 • mCSPC (LATITUDE): ABI+ADT: $392,896.68 • mCSPC (STAMPEDE): $510,938.62

Source: SLR report[26]

Abbreviations: $: dollar; €: euro; AA: antiandrogen; AB: androgen blockade; ADT: androgen-deprivation therapy; AE: adverse event; BIC: bicalutamide; BUS: buserelin; CE: cost-effectiveness; HRPC: hormone-relapsed prostate cancer; DEG: degarelix; DOC: docetaxel; ERG: evidence review group; EUR: euro; FLU: flutamide; GBP: Great British Pound; GOS: goserelin; ICER: incremental cost-effectiveness ratio; LEU: leuprorelin; LHRH: luteinizing hormone releasing hormone; LY: life-year; LYG: life-year gained; mHRPC: metastatic hormone-relapsed prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; NICE: National Institute for Health and Care Excellence; nmHSPC: non-metastatic hormone-sensitive prostate cancer; OS: overall survival; PFS: progression-free survival; QALY: quality-adjusted life year; TPT: triptorelin; UK: United Kingdom; US: United States of America; vs: versus; WTP: willingness-to-pay threshold.

Appendix J: Clinical outcomes and disaggregated results from the model

J1.1 Clinical outcomes from the model

As part of the validation process, results from the model were compared with outcomes from the enzalutamide plus ADT clinical trial program, as discussed in section B.3.10. A recap of the summary of this comparison in terms of OS and PFS is presented in Table 99. The results show close alignment between model and outcomes.

Table 99 Comparison of base case model and trial outcomes

Outcome	Data source	3 months	6 months	12 months	18 months	24 months
Enzalutamide outcomes: model versus trials						
OS (Pooled Weibull)	ARCHES	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ENZAMET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS (ARCHES LogNormal)	ARCHES	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADT outcomes: model versus trials						
OS (Pooled Weibull)	ARCHES	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ENZAMET	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS (ARCHES LogNormal)	ARCHES	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median PFS*	ARCHES ADT median rPFS: 19.0 months			Modelled ADT median rPFS: 17.5 months		

*Medians of all other outcomes and comparators were not reached in the respective trials, and therefore not included in the overview
Abbreviations: ADT: androgen deprivation therapy; PFS: progression-free survival; OS: overall survival.

J1.2 Disaggregated results of the base case incremental cost effectiveness analysis

The QALY gain and costs disaggregated by health state is shown in Table 100 and Table 101. The predicted resource use by category of cost is shown in Table 102. The 'health state' category included all monitoring and administration costs and other direct medical costs not included by any of the other categories.

Table 100 Summary of QALY gain by health state

Health state	QALY ENZA	QALY ADT	QALY Doc	ADT Increment	ADT absolute increment	ADT % absolute increment	DOC Increment	DOC absolute increment	DOC % absolute increment
mHSPC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	68%	[redacted]	[redacted]	67%
PD1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17%	[redacted]	[redacted]	17%
PD2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2%	[redacted]	[redacted]	1%
PD3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13%	[redacted]	[redacted]	15%
End of life disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0%	[redacted]	[redacted]	0%
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	100%	[redacted]	[redacted]	100%
	Abbreviations: ADT: androgen deprivation therapy; DOC: docetaxel; ENZA: enzalutamide; mHSPC: metastatic hormone-sensitive prostate cancer; PD: progressed disease; QALY, quality-adjusted life year. Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee								

Table 101 Summary of costs by health state

Health state	Costs ENZA	Costs ADT	Costs Doc	ADT Increment	ADT absolute increment	ADT % absolute increment	DOC Increment	DOC absolute increment	DOC % absolute increment
mHSPC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	65%	[redacted]	[redacted]	69%
PD1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	24%	[redacted]	[redacted]	21%
PD2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3%	[redacted]	[redacted]	4%
PD3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7%	[redacted]	[redacted]	6%
Terminal care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0%	[redacted]	[redacted]	0%
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	100%	[redacted]	[redacted]	100%
	Abbreviations: ADT: androgen deprivation therapy; DOC: docetaxel; ENZA: enzalutamide; mHSPC: metastatic hormone-sensitive prostate cancer; PD: progressed disease. Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee								

Table 102 Summary of predicted resource use by category of cost

Health state	Costs ENZA	Costs ADT	Costs Doc	ADT Increment	ADT absolute increment	ADT % absolute increment	DOC Increment	DOC absolute increment	DOC % absolute increment
Active tx costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	74%	[redacted]	[redacted]	81%
Health state costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14%	[redacted]	[redacted]	10%
Conmed costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9%	[redacted]	[redacted]	7%
AE and SRE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2%	[redacted]	[redacted]	1%
Terminal care costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1%	[redacted]	[redacted]	1%
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	100%	[redacted]	[redacted]	100%
	Abbreviations: ADT: androgen deprivation therapy; DOC: docetaxel; ENZA: enzalutamide; mHSPC: metastatic hormone-sensitive prostate cancer; PD: progressed disease. Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee								

Appendix K: Checklist of confidential information

This appendix is provided separately.

Appendix L: Full model QC checklist and outcomes

An elaborate model QC was performed to check the functionality and consistency of the cost effectiveness model. An overview of the model QC is provided in Table 103

Table 103 Cost effectiveness model QC overview

Quality Check Tasks	Error?	Error description and solution
Accuracy		
Check the file properties to ensure information is correct.	Yes	Title and category missing, added missing info
Check that the name manager contains valid references.	Yes	Name manager contained unused values, in part informed by 'input parameter subheadings'. Unused parameters removed
Check that version number and date are correct.	No	-
Consistency		
Check latest version of model template used.	No	-
Consistent use of fonts, colours and logos.	No	-
Check that file uses appropriate and consistent naming convention.	No	-
Confirm that all worksheets have a consistent layout.	No	-
Check that variables use consistent naming conventions.	No	-
Functionality		
Check the model size; flag if too large.	No	-
Remove any links to external sources.	No	-
Check for general error messages in outputs	No	-
Clarity		
Check that all text is visible (not truncated).	Yes	PartSA and Markov results were hidden, tabs unhidden
All screens		
Verify navigation buttons contain valid links.	No	-
Verify navigation buttons have valid screen tips.	No	-
Check that navigation buttons are formatted (don't change size or move with cells).	No	-
Check spelling and grammar.	No	-
Check that all control forms work/refer to correct cells.	No	-
Check that all macros work/are required.	No	-
Reviewed naming conventions for consistency across screens.	No	-
Verified that named ranges and ‘look-ups’ have valid, accurate cell references.	Yes	Replaced mCRPC with mHRPC in model and named ranges

Check that cells have appropriate formatting (currency, same number of decimals where appropriate, etc).	Yes	Treatment efficacy sheets had 2 decimals in the 'Currently in use' parameters, updated to 3 decimals
Overview Screen		
Abbreviations are listed out.	Yes	Removed unused abbreviations and added missing ones
Model assumptions are detailed.	No	-
Information on model perspective, treatment and comparator arms and indication is provided.	Yes	Updated instructions sheet to remove unused content
Model conventions are included (cell colour description, etc).	No	-
Confirm that this screen clearly describes the model.	No	-
A model diagram has been included (if relevant).	No	-
Executive Summary		
Check that the outputs table is pulling in the correct data.	No	-
If applicable, check that the graph is pulling in the correct data.	No	-
Check that the time horizon is being applied correctly	No	-
Check that any other drop down selections are properly applied (analysis type, willingness to pay, etc).	No	-
Ensure that values are being pulled correctly from the results screen.	No	-
Ensure inclusion of "IF" statements for when ICERs are negative to ensure results are correctly labelled as "dominant" or "dominated".	No	-
Input sheets		
Test extreme high and low values to ensure data validation on all custom input cells.	No	-
Tested extreme low and high values to check for calculation errors.	No	-
Check model assumptions, if relevant.	No	-
Confirm that input parameters have been verified against source documentation.	No	-
Check that all proportions sum to 1 where appropriate.	No	-
Check that all abbreviations are included in list of abbreviations in the Overview.	Yes	Missing abbreviations added
Check that the "restore defaults" button works.	No	-
Calculation sheets		
Ensure that default calculations are pulling in default numbers.	No	-
Ensure that in use calculations are pulling in in use numbers.	No	-

Using Formulas | Formula Auditing | Show Formulas, check to ensure consist formulas are used, where necessary.	Yes	2 issues in end-of-life utility calculations: The range was wrong and some cells related to end of life utility were pulling numbers from the 'Markov Enza' sheet whereas they should pull from 'Markov Doce' and 'Markov ADT'. Updated the calculations on both accounts
Check that discount rates are being applied correctly.	No	-
Ensure all linked cells refer back to the original source (no spider webs)	No	-
Check that the cell names and descriptions make sense?	No	-
Check that cells have appropriate formatting (currency, same number of decimals where appropriate, etc)?	No	-
Markov/Survival analysis		
Are the discount rates for costs and outcomes correctly calculated?	No	-
Does the time spent in the health states (e.g. stable disease, PD and death) add up to 1?	No	-
Does the number of subjects remain constant over model cycles?	No	-
Check that time horizon/ cycles/ age are linked in correctly.	No	-
Confirm that the first row of the Markov Trace refers to the correct input.	No	-
Confirm that cost formulas in Markov Trace refer to the right cells.	No	-
Confirm that QALY and LY formulas in Markov Trace refer to the right cells.	No	-
Is the model type (Weibull, Exponential, Gompertz, etc) calculated correctly?	No	-
Is the model pulling in the correct survival model based on user selection?	No	-
Check that PFS is never greater than OS (check that they never cross).	No	-
Check that the choice of survival functions (e.g. for Weibull) has been justified (see log-likelihood, visual inspection, etc).	No	-
If hazard ratios have been used, check they have been applied correctly	No	-
Check that the hazard of death in the model doesn't fall below that of the general population.	No	-
OWSA Screen		
Check results for OWSA - do they make sense?	No	-
Are there any problems with the OWSA macro?	No	-
Check the graphs (example: tornado) - does the scale make sense? Are all axes labelled properly? Is there a legend for the graph? Does the base case	No	-

result clearly labelled on the graph? Is the diagram sorted?		
Does the graph handle correctly the situations where preference changes at low and high values of the parameter?	No	-
Does including/excluding a variable work?	No	-
Do the high and low values make sense?	No	-
For custom high/low values, is there data validation to ensure the range makes sense (ensure that the high range can't be lower than the low range; bounded appropriately)	No	-
PSA Screen		
Do the results of the PSA make sense?	No	-
Are there any problems with the PSA macro?	No	-
Check the scatterplot and CEAC graphs - do these make sense based on the base case results?	No	-
Check that the average cost and outcomes calculated from PSA array are close to their point estimate values.	No	-
Check distributions (appropriateness of types of distributions - normal, beta, gamma) and low and high estimates (95% CI and SE).	No	-
Check that the PFS and OS curves do not cross at any point (including during PSA!).	No	-
In the event of negative ICERs, was a net monetary benefit analysis included? Do the graph and results make sense?	No	-
Scenario testing - CEA		
Make treatment costs equal - sense check results.	No	-
Make treatment costs for each arm very high - sense check results.	No	-
Treatment Costs: Turn off all health state costs and set AE rates to 0. Total costs should now only include treatment costs; ensure that intervention treatment costs reflect expectations given inputs.	No	-

Abbreviations: AE: adverse events; CEA: cost effectiveness analysis; CEAC: cost effectiveness acceptability curve; CI: confidence interval; ICER: incremental cost effectiveness ratio; LY: life-year; OS: overall survival; OWSA: one-way sensitivity analysis; PD: progressed disease; PFS: progression-free survival; PSA: probabilistic sensitivity analysis QALY: quality-adjusted life year; QC: quality control; SE: standard error

Appendix M: Additional efficacy data from ARCHES and ENZAMET

M.1 ARCHES

Radiographic progression-free survival

The results of the protocol prespecified sensitivity analyses evaluating the effect of various censoring rules on rPFS are provided in Table 104.

Table 104 Summary of rPFS sensitivity analyses (ITT population)

Analyses	Enzalutamide + ADT	Placebo + ADT
Primary rPFS analysis†		
n¶	574	576
Events, n (%)	89 (15.51)	198 (34.38)
Kaplan-Meier median (95% CI)‡ (months)	NYR	19.4 (16.59, NYR)
Cox HR (95% CI)§	0.39 (0.30, 0.50)	
Log-rank p value§	< 0.0001	
Sensitivity 1 - modified rPFS events (inclusion of study drug discontinuation)		
n¶	[redacted]	[redacted]
Events, n (%)	[redacted]	[redacted]
Kaplan-Meier median (95% CI)‡ (months)	[redacted]	[redacted]
Cox HR (95% CI)§	[redacted]	
Log-rank p value§	[redacted]	
Sensitivity 2 - modified rPFS events (inclusion of new antineoplastic therapy and occurrence of an SSE)		
n¶	[redacted]	[redacted]
Events, n (%)	[redacted]	[redacted]
Kaplan-Meier median (95% CI)‡ (months)	[redacted]	[redacted]
Cox HR (95% CI)§	[redacted]	
Log-rank p value§	[redacted]	
Sensitivity 3 - inclusion of all deaths		
n¶	[redacted]	[redacted]
Events, n (%)	[redacted]	[redacted]
Kaplan-Meier median (95% CI)‡ (months)	[redacted]	[redacted]
Cox HR (95% CI)§	[redacted]	
Log-rank p value§	[redacted]	
Sensitivity 4 - impact of radiographic disease progression documented between visits		
n¶	[redacted]	[redacted]
Events, n (%)	[redacted]	[redacted]
Kaplan-Meier median (95% CI)‡ (months)	[redacted]	[redacted]
Cox HR (95% CI)§	[redacted]	
Log-rank p value§	[redacted]	
Sensitivity 5 – 'missing' data impact: censoring on date of last evaluable scan		
n¶	[redacted]	[redacted]
Events, n (%)	[redacted]	[redacted]

Analyses	Enzalutamide + ADT	Placebo + ADT
Kaplan-Meier median (95% CI)‡ (months)	[redacted]	[redacted]
Cox HR (95% CI)§	[redacted]	
Log-rank p value§	[redacted]	
Sensitivity 6 – 'missing' data impact: censoring prior to any period with 2 missing consecutive scans		
n¶	[redacted]	[redacted]
Events, n (%)	[redacted]	[redacted]
Kaplan-Meier median (95% CI)‡ (months)	[redacted]	[redacted]
Cox HR (95% CI)§	[redacted]	
Log-rank p value§	[redacted]	
Sensitivity 7 – censoring radiographic disease progression on new antineoplastic therapy and occurrence of an SSE		
n¶	[redacted]	[redacted]
Events, n (%)	[redacted]	[redacted]
Kaplan-Meier median (95% CI)‡ (months)	[redacted]	[redacted]
Cox HR (95% CI)§	[redacted]	
Log-rank p value§	[redacted]	
Sensitivity 8 – 'missing' data impact and censoring on new antineoplastic therapy, occurrence of an SSE and study drug discontinuation		
n¶	[redacted]	[redacted]
Events, n (%)	[redacted]	[redacted]
Kaplan-Meier median (95% CI)‡ (months)	[redacted]	[redacted]
Cox HR (95% CI)§	[redacted]	
Log-rank p value§	[redacted]	
Sensitivity 9 - rPFS in patients with ICR-assessed metastasis at baseline		
n¶	[redacted]	[redacted]
Events, n (%)	[redacted]	[redacted]
Kaplan-Meier median (95% CI)‡ (months)	[redacted]	[redacted]
Cox HR (95% CI)§	[redacted]	
Log-rank p value§	[redacted]	
Sensitivity 10 - rPFS based on investigator's assessment		
n¶	[redacted]	[redacted]
Events, n (%)	[redacted]	[redacted]
Kaplan-Meier median (95% CI)‡ (months)	[redacted]	[redacted]
Cox HR (95% CI)§	[redacted]	
Log-rank p value§	[redacted]	
Sensitivity 11 - rPFS based on PCWG2 criteria and investigator's assessment		
n¶	[redacted]	[redacted]
Events, n (%)	[redacted]	[redacted]
Kaplan-Meier median (95% CI)‡ (months)	[redacted]	[redacted]
Cox HR (95% CI)§	[redacted]	
Log-rank p value§	[redacted]	
Sensitivity 12 - rPFS based on PCWG2 criteria and ICR		
n¶	[redacted]	[redacted]
Events, n (%)	[redacted]	[redacted]
Kaplan-Meier median (95% CI)‡ (months)	[redacted]	[redacted]
Cox HR (95% CI)§	[redacted]	

Analyses	Enzalutamide + ADT	Placebo + ADT
Log-rank p value§	[redacted]	

Source: ARCHES Clinical Study Report[23]
Data cut-off date: 14 Oct 2018
† A progression event was defined as objective evidence of radiographic disease progression based on the assessments by ICR or death by any cause within 24 weeks from study drug discontinuation, whichever occurred first. The time to event was calculated from the date of randomisation to the date of occurrence of the first progression event. For patients with no documented progression event, rPFS was censored on the date of the last radiologic assessment performed before the cut-off date.
‡ Calculated by Brookmeyer and Crowley method
§ Stratified by volume of disease (low vs high) and prior docetaxel use (yes vs no)
¶ Analysis was conducted in patients with metastatic disease based on ICR assessments.
Abbreviations: ADT: androgen deprivation therapy; CI: confidence interval; HR: hazard ratio; ICR: independent central review; ITT: intent-to-treat; NYR: not yet reached; PCWG2: Prostate Cancer Clinical Trials Working Group 2; rPFS: radiographic progression-free survival; SSE: symptomatic skeletal event.

PSA undetectable rate

The proportion of patients with detectable/undetectable PSA at baseline were similar between both the treatment groups. In patients with a detectable PSA level at baseline, treatment with enzalutamide plus ADT significantly increased the chance of a PSA decline to an undetectable level (<0.2 ng/mL) compared to placebo plus ADT with an absolute difference of [redacted]; p<0.0001). Based on the lowest PSA level during the treatment period, the PSA undetectable rate was 68.1% (348/511) in the enzalutamide plus ADT group and 17.6% (89/506) in the placebo plus ADT group[23, 27] (Table 105).

Table 105 PSA undetectable rates (ITT population)

Category Parameter/Statistics	Enzalutamide + ADT (n=574)	Placebo + ADT (n=576)
Patients with PSA detectable at baseline, n	511	506
Patients with PSA undetectable at baseline, n	63	70
Lowest PSA value during the treatment period, n (%)		
Undetectable†	348/511 (68.1)	89/506 (17.6)
95% CI for rate‡	[redacted]	[redacted]
Difference in rate (95% CI)‡	[redacted]	
P value§	<0.0001	
Detectable	[redacted]	[redacted]
No post-baseline	[redacted]	[redacted]

Source: ARCHES CSR[23], Armstrong et al[27]
Data cut-off date: 14 Oct 2018
† The PSA undetectable rate was defined as the percentage of patients with undetectable (< 0.2 ng/mL) PSA values at any time during study treatment, of those patients with detectable (≥ 0.2 ng/mL) PSA values at baseline.
‡ 95% CI was computed using Clopper-Pearson method based on exact binomial distribution; the asymptotic one was provided on the difference.
§ Cochran-Mantel-Haenszel score test, stratified by volume of disease and previous docetaxel use.
Abbreviations: ADT: androgen deprivation therapy; ITT: intent-to-treat; PSA: prostate-specific antigen.

Combined response (soft tissue and bone lesions)

In the enzalutamide plus ADT group, the proportion of patients with complete and partial response as their best overall response as assessed by ICR was [redacted] and [redacted], respectively (Table 106). For both response categories, these proportions were greater with enzalutamide than with placebo (complete response: [redacted]; partial response: [redacted]). Consistent with these results, the proportion of patients with progressive disease as their best overall response was lower in the enzalutamide plus ADT group compared with the placebo plus ADT group ([redacted] vs [redacted], respectively). Investigator-based assessments showed similar results (Table 106). Regarding stable disease, a higher proportion of patients in the placebo plus ADT group achieved stable disease as the best overall response than in the enzalutamide plus ADT arm.

Table 106 Best overall response (ITT population)

Best overall response	ICR		Investigator	
	Enzalutamide + ADT (n=574)	Placebo + ADT (n=576)	Enzalutamide + ADT (n=574)	Placebo + ADT (n=576)
Categories, n (%)				
CR	[redacted]	[redacted]	[redacted]	[redacted]
PR	[redacted]	[redacted]	[redacted]	[redacted]
Stable disease	[redacted]	[redacted]	[redacted]	[redacted]
Non-CR/ Non-PD†	[redacted]	[redacted]	[redacted]	[redacted]
Unconfirmed PD	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]
NA‡	[redacted]	[redacted]	[redacted]	[redacted]
NE	[redacted]	[redacted]	[redacted]	[redacted]
No overall response assessment	[redacted]	[redacted]	[redacted]	[redacted]

Source: ARCHES CSR[23]
Data cut-off date: 14 Oct 2018
The best overall response corresponded to the best of the overall response assessments derived by ICR or calculated programmatically from investigator data at any time during the treatment period. For patients still on treatment by the data cut-off date, the best overall response corresponded to the best of the overall time point response reported up to the data cut-off date. Patients with no postbaseline assessment at any visit are reported in the NE category.
† In patients without measurable disease at baseline, Non-CR/Non-PD refers to assessments that were evaluable and were neither CR nor PD.
‡ The ICR reassessed the baseline tumour status of these patients during postbaseline time points.
Abbreviations: ADT: androgen deprivation therapy; CR: complete response; ICR: independent central review; ITT: intent-to-treat; NA: not applicable; NE: not evaluable; PD: progressive disease; PR: partial response.

PSA reduction from baseline

The median maximal PSA reduction was [redacted] in the enzalutamide plus ADT group and [redacted] in the placebo plus ADT group (Table 107). Nearly all patients in the enzalutamide plus ADT group had a PSA reduction from baseline of ≥50% ([redacted]) and the majority had a PSA reduction from baseline of ≥90% ([redacted]). In contrast, PSA reductions of ≥50% and ≥90% were reported in [redacted] and [redacted] of patients in the placebo plus ADT group, respectively.

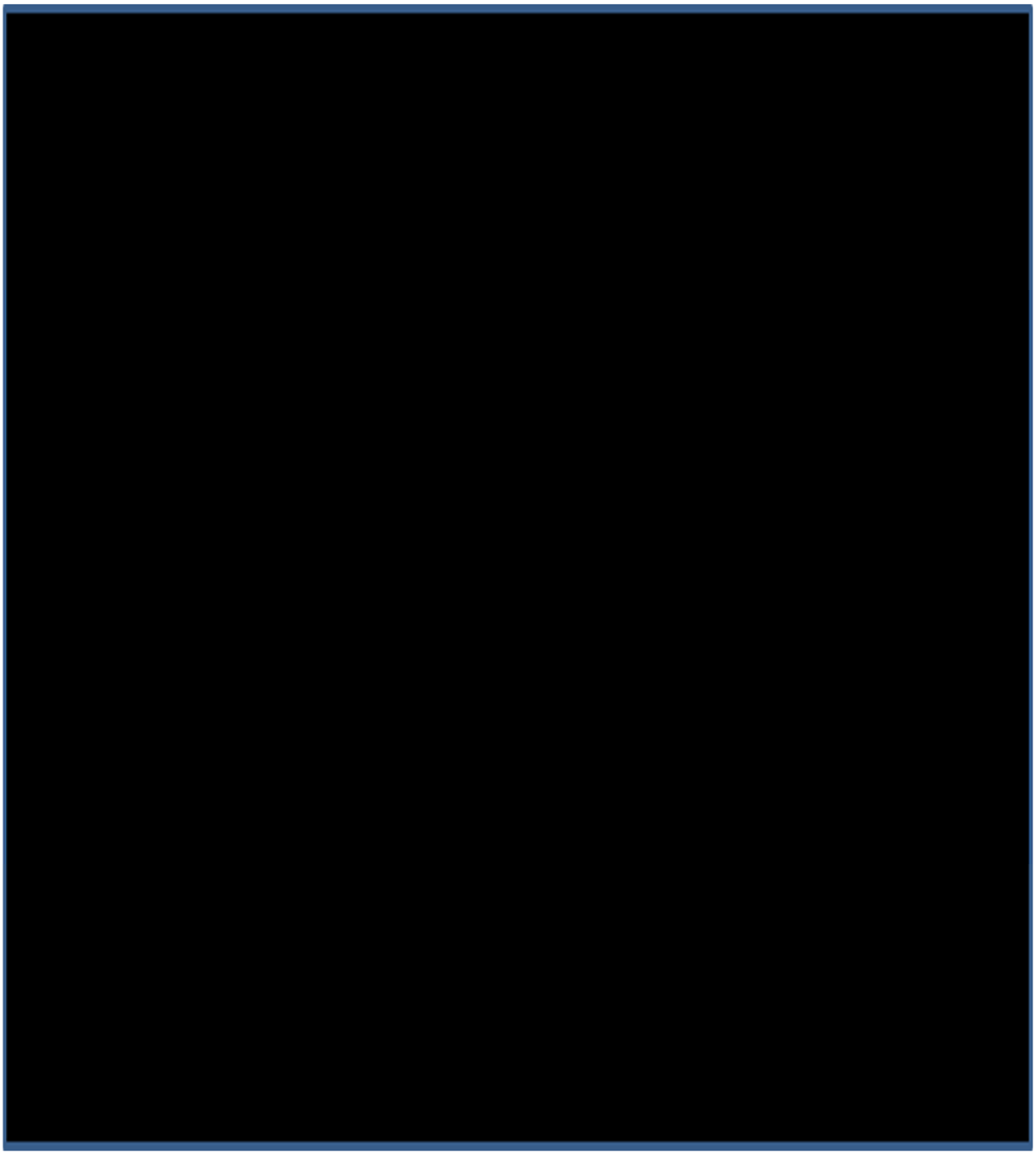
Table 107 PSA reductions from baseline (ITT population)

Parameter	Enzalutamide + ADT (n=574)	Placebo + ADT (n=576)
Maximal PSA reduction†, %		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Minimum, Maximum	[redacted]	[redacted]
PSA reduction ≥ 50%‡, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
PSA reduction ≥ 90%‡, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]

Source: ARCHES CSR[23]
Data cut-off date: 14 Oct 2018
†The maximal PSA reduction postbaseline was defined as the largest decrease from baseline in PSA that occurred at any point after the start of treatment, expressed as the percentage change of PSA from baseline. For patients with no decrease from baseline in PSA, the smallest increase from baseline in PSA was used. For patients with no postbaseline PSA values, the largest decrease from baseline in PSA was set to missing.
‡PSA reductions of ≥ 50% and ≥ 90% from baseline were defined as binary variables for achieving this criterion based on the lowest PSA value observed postbaseline. For patients with no postbaseline PSA value, the variable was set to missing (no).
Abbreviations: ADT: androgen deprivation therapy; ITT: intent-to-treat; PSA: prostate-specific antigen.

A waterfall plot of maximum decline in PSA for the evaluable ITT population is presented in Figure 34. The results showed that most patients treated with enzalutamide plus ADT had substantial decreases in PSA levels while this proportion was lower in the placebo plus ADT arm with more patients in the latter experiencing an increase in PSA levels.

Figure 34 Waterfall plot of maximum decline (%) in PSA (ITT population)



Source: ARCHES CSR[23]
Data cut-off date: 14 Oct 2018
Patients with increased percentage > 50% are shown as 50% and noted with star.
Abbreviations: ADT: androgen deprivation therapy; ITT: intent to treat; PSA: prostate-specific antigen.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Enzalutamide with ADT for treating metastatic hormone-sensitive prostate cancer [ID1605]

Clarification questions

November 2019

File name	Version	Contains confidential information	Date
ID1605_Enzalutamide Clarification Letter to PM for company ACIC_12DEC2019	1.0	Yes	12 December 2019

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

Identification and selection of relevant studies

A1 CS, Section B.2.1 Identification and selection of relevant studies. According to the company submission, 41 studies met the SLR criteria but only 18 studies were deemed relevant for inclusion. Please explain why each of the 23 excluded studies was deemed unsuitable.

The list of studies deemed not relevant for the company submission and reason for exclusion are provided in Table 1.

Table 1 Studies deemed not relevant for ID1605 and reason for exclusion from submission

Study	Reason for exclusion
ADRRAD [Turner 2019[1]]	This was a single arm study. The intervention (ADT, radium 223 plus concurrent whole pelvis radiotherapy) was not in scope
Alex 2016 [Alex 2016a[2], 2016b[3]]	This was a single arm study with ADT. Only congress abstracts were available with limited data
ARASENS; NCT02799602 [Smith 2017[4]; Tombal 2017[5]; Smith 2018[6]m]	This RCT compared darolutamide, ADT plus docetaxel vs placebo, ADT plus docetaxel. No data have yet been presented at congresses or published
CALGB 90202/NCT00079001 [Smith 2014[7]]	This RCT compared zoledronic acid vs placebo, both with ADT. Zoledronic acid was not in scope and the placebo arm would have not provided any additional data or enriched the evidence network
EORTC-1532-GUCG [Tombal 2018[8]]	This RCT compared darolutamide to placebo, both with ADT. Darolutamide was not in scope and the placebo arm would

Study	Reason for exclusion
	have not provided any additional data or enriched the evidence network
HORRAD [Boevé 2019[9]]	This RCT compared radiotherapy plus ADT to ADT alone. Radiotherapy was not in scope and the ADT alone arm would have not provided any additional data or enriched the evidence network
Kushnir 2019[10]	This single arm study assessed dose intensity docetaxel. Its retrospective nature and no details on the docetaxel dose administered to patients rendered the study not relevant. In addition, this study was available as a congress abstract only
LACOG 0415 [Maluf 2018[11]]	This RCT compared apalutamide, abiraterone plus ADT vs apalutamide plus ADT vs ADT alone. Apalutamide with or without abiraterone was not in scope and the ADT alone arm would have not provided any additional data or enriched the evidence network
Lavoie 2018[12]	This single arm study assessed docetaxel. Its retrospective nature rendered it not relevant for the network meta-analysis
NCT01751438 [Chapin 2019[13]]	The study intervention (radiotherapy plus standard of care) was not relevant for the submission
NCT02058706 [Vaishampayan 2018[14]]	This phase II study compared enzalutamide plus ADT vs bicalutamide plus ADT. It was terminated early. The only publication is a congress abstract providing data on patients achieving the PSA nadir <4 ng/ml after 7 months of therapy. This outcome is not relevant for the submission. In addition, it provided data for four adverse events
NCT00081159 [Bilen 2015[15]]	This RCT compared strontium plus ADT vs ADT alone. Strontium was not in scope and the ADT alone arm would have not provided any additional data or enriched the evidence network
NCT00817739 [Mottet 2012[16]]	This RCT compared two ADT modalities (intermittent vs continuous ADT). This study would have not provided any additional data or enrich the evidence network.
NTR130 [Verhagen 2014[17]]	This RCT compared two ADT modalities (intermittent vs continuous ADT). This study would have not provided any additional data or enriched the evidence network
Pathak 2019[18]	This study compared docetaxel plus ADT vs ADT alone. Its retrospective nature rendered it inappropriate for the network meta-analysis
Schweizer 2016[19]	This single arm study assessed docetaxel. Its retrospective nature rendered it inappropriate for the network meta-analysis
SensiCab / NCT01978873 [Andrén 2017[20]]	This RCT compared ADT alone to short-term complete androgen blockade followed by ADT alone. This study would have not provided any additional data or enriched the evidence network
Sonthwal 2019[21]	This prospective cohort study compared docetaxel plus ADT (n=31) vs abiraterone plus ADT (n=22) vs ADT alone (n=37). The non-randomised nature, small sample size and data being available as a congress abstract only rendered it inappropriate for the network meta-analysis
SWOG-9346 / NCT00002651 [Hussain 2013[22]]	This RCT compared two ADT modalities (intermittent vs continuous ADT). This study would have not provided any additional data or enriched the evidence network
Teoh 2019[23]	This prospective study compared docetaxel plus ADT vs a historical control treated with ADT alone. The non-randomised

Study	Reason for exclusion
	nature and use of a historical control group rendered it inappropriate for the network meta-analysis
TITAN / NCT02489318 [Chi 2016[24]; Chi 2019a[25]; Chi 2019b[26]]	This RCT compared apalutamide plus ADT vs ADT alone. Apalutamide was not in scope and the ADT alone arm would have not provided any additional data or enriched the evidence network
Tsai 2018[27]	This prospective cohort study compared docetaxel plus ADT (n=14) vs ADT alone (n=56). The non-randomised nature rendered it inappropriate for the network meta-analysis
ZABTON-PC [Ueno 2013[28]]	This RCT compared zoledronic acid to placebo, both with complete androgen blockade. Zoledronic acid was not in scope and the complete androgen blockade alone arm would have not provided any additional data or enriched the evidence network

Abbreviations: ADT: androgen deprivation therapy; RCT: randomised controlled trial

Methodology of the relevant clinical effectiveness evidence

A2. CS, Document B, page 28. The primary efficacy endpoint of the ARCHES study was rPFS based on central review in the ITT population and defined as objective evidence of rPD as assessed by ICR or death. Please provide further information on the ICR and on the process used.

An axial computed tomography (CT) / magnetic resonance imaging (MRI) of the chest, abdomen, pelvis and other areas of disease, if clinically indicated, a bone scan and a chest X-ray or chest CT/MRI were scheduled at screening, week 13 and every 12 weeks thereafter. For each assessment and patient, the blinded independent review was a staggered process with the radiology review by at least two radiologists first (Figure 1), and the bone scan review by at least two nuclear medicine physicians after (Figure 2).

The radiology review consisted of the following review steps in the given sequence[29]:

- Primary (timepoint by timepoint) radiology review during which each CT/MRI imaging timepoint for a subject was assessed by two independent radiologists who determined the overall tumour assessment at that timepoint according to RECIST 1.1.
- Global radiology review during which the same two independent radiologists each globally assessed all their previous assessments for the subject and confirmed or updated any of their previous timepoint overall tumour assessments according to RECIST 1.1.

- Adjudication radiology review if there was a disagreement during the global review between the primary radiologists. During the adjudication radiology review, a third board-certified radiologist who had not participated in the previous two steps reviewed the radiology review assessments and selected the radiologist whose global radiology review assessments were the most accurate as the final assessment and provided a corresponding rationale.

The bone scan review consisted of the following review steps in the given sequence[29]:

- Primary (timepoint by timepoint) bone scan review during which each bone scan imaging timepoint for a subject was assessed by two independent nuclear medicine physicians who recorded the bone lesion count at each timepoint and if applicable, any new bone lesion from the previous assessment.
- Global bone scan review during which the same two independent nuclear medicine physicians each globally assessed all their previous assessments for the subject and an assessment of progression. In addition, an assessment of whether there were ≥2 new lesions was provided.
- Adjudication bone scan review if there was a disagreement during the global review between the primary two nuclear medicine physicians. During adjudication bone scan review, a third board-certified nuclear medicine physician who had not participated in the previous two steps reviewed the bone scan review assessments and selected the physician whose global bone scan review assessments were the most accurate as the final assessment and provided a corresponding rationale.

In addition to the steps described above, a secondary radiology review was conducted to determine the intra- and/or inter-observer disagreement or variability for a sample of subjects (n=10). During secondary radiology review, the primary and global radiology and bone scan reviews for the sample of subjects were repeated by the same reviewers who had performed the primary radiology and bone scan reviews.

Further details on the ICR review of all imaging and the process that was followed is provided in the Independent Review Carter which is provided as a reference[29].

Figure 1 Independent Review Workflow for a Radiology Review Period (double reads)

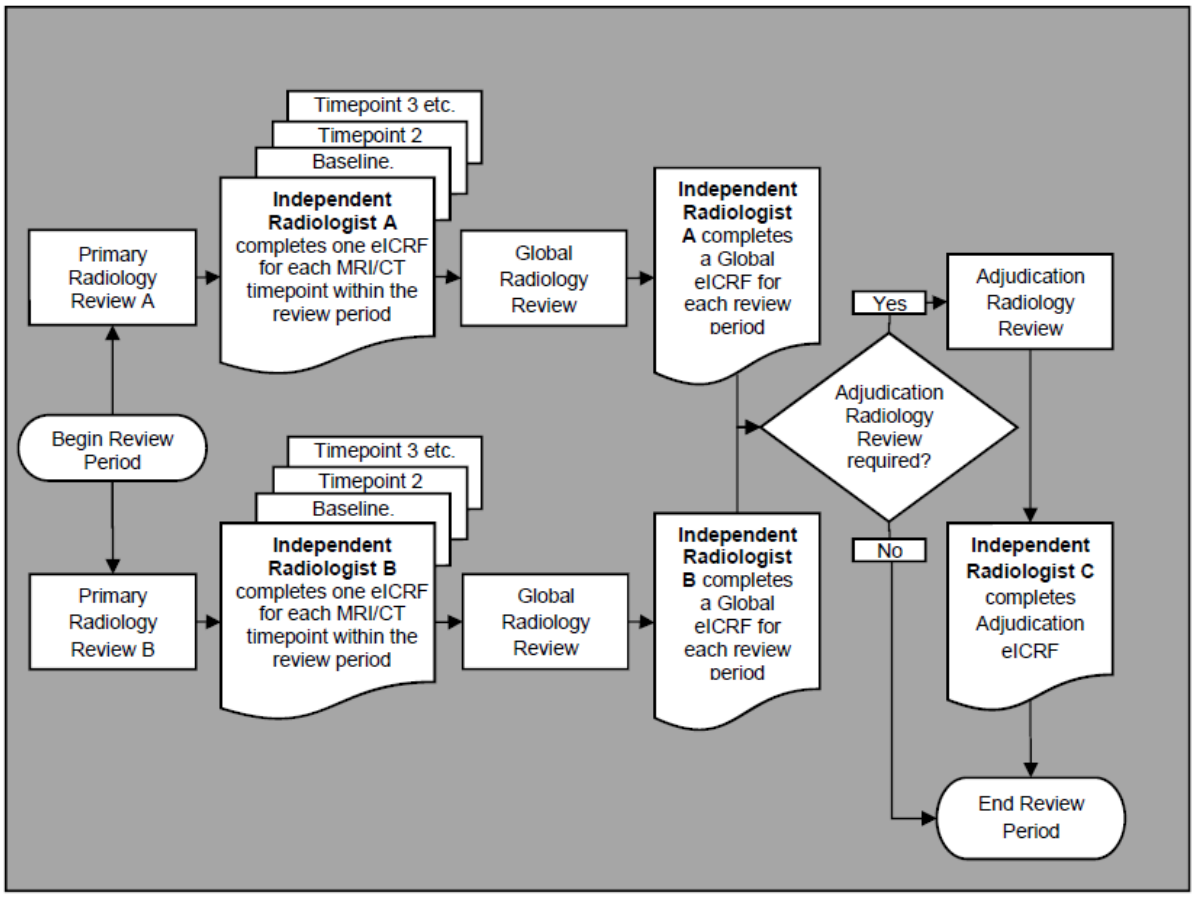
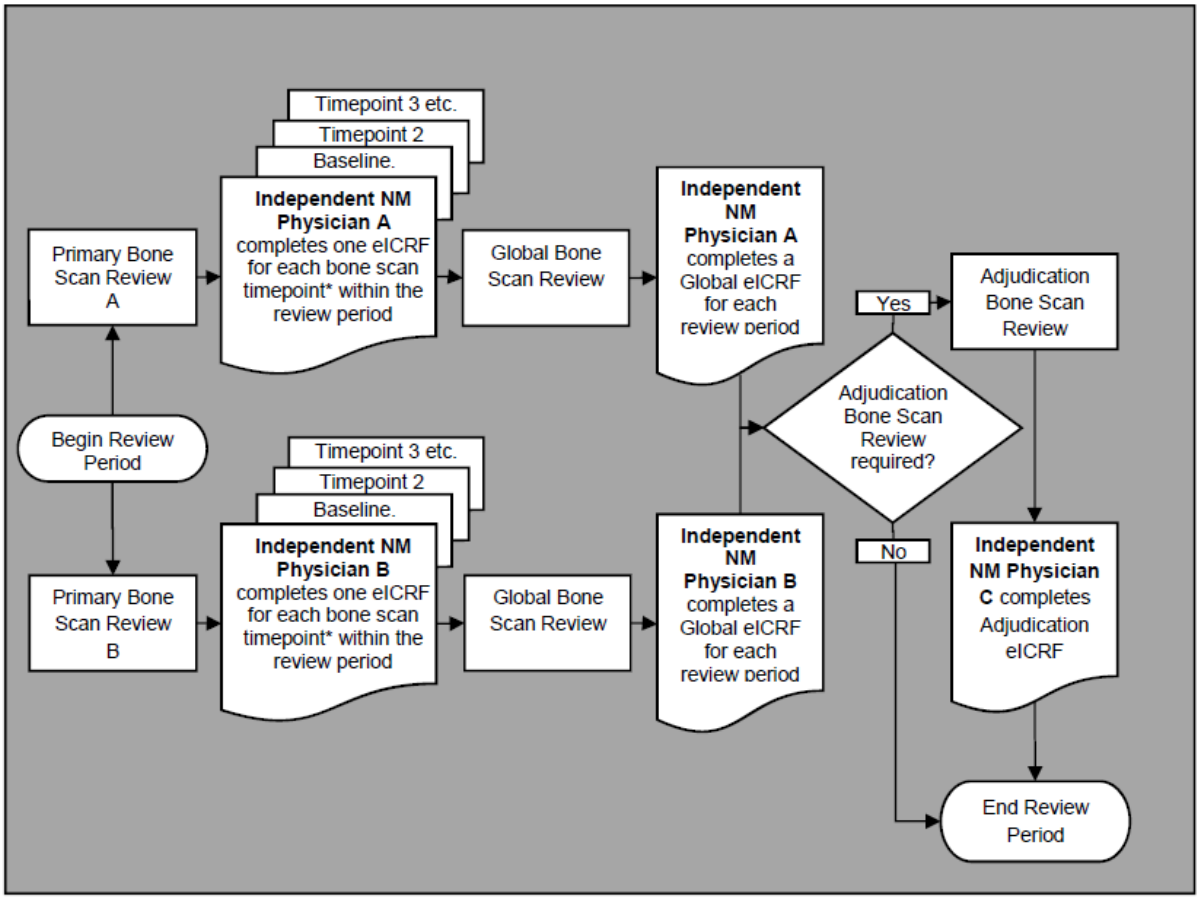


Figure 2 Independent Review Workflow for a Bone Scan Review Period (double reads)



A3. CS, Document B, Table 6, ARCHES and ENZAMET methodology, page 27. The table shows that the ARCHES study was conducted at 204 study sites and ENZAMET was conducted at 79 sites. However, in the published papers, it is stated that ARCHES was conducted in 202 sites and ENZAMET was conducted in 83 sites. Please clarify the total number of sites and number of patients for all relevant studies.

The data included in Table 6 is based on the clinical study report (CSR) of the two trials. Regarding ARCHES, 204 sites participated in the study but in line with the information reported in Armstrong et al[30], only 202 sites recruited patients.

In ENZAMET, there were 83 sites of which 79 randomised patients.

A4. CS, Document B, page 39. The submission states that 685 patients were recruited in Europe, but only ▌ patients were recruited from UK centres. Please

confirm that these ▌ patients were excluded and not included in the EUROPE region group in Table 8.

The ▌ patients recruited from UK sites were considered part of the Europe region group; they were not excluded from the EUROPE region group.

A5. CS, Document B, Section 2.3.1.1, page 32. The submission states that the ARCHES study consisted of a double-blind treatment period followed by an open label period after study unblinding. Please clarify whether the patients were followed-up into the transition to an optional open-label extension.

The ARCHES study is still ongoing for overall survival (OS) data collection. Patients still on study treatment after study unblinding are followed-up for OS until death regardless of whether they participate in the open-label extension phase or not. Patients who discontinued the ARCHES study treatment before the study unblinding were also followed up until death. For those patients who signed the informed consent to participate in the open-label extension phase, once in the extension phase they are regularly monitored as per protocol. To note, patients who had been randomised to placebo during the double-blind treatment period and had taken commercially available enzalutamide after study unblinding were not eligible to enter the open-label extension period. No data are yet available for the open-label extension phase. Patients not entering the open-label extension phase are also being followed up for OS.

Clinical effectiveness results of the relevant trials

A6. PRIORITY QUESTION. CS, Document B, Section 2.6. Please supply the time to event data for all outcomes from the ARCHES and ENZAMET studies.

The following time to event data are provided as a separate excel file:

- For the ENZAMET trial:
    - OS
    - Clinical progression-free survival (cPFS)
- For the ARCHES trial:
    - OS
    - Radiographic progression-free survival (rPFS)
    - Time to first symptomatic skeletal event (SSE)

- Time to castration resistance
- Time to start of new antineoplastic therapy
- Time to PSA progression
- Time to deterioration of HRQoL based on FACT-P total score
- Time to deterioration in urinary symptoms
- Time to pain progression.

In addition, the excel file also includes the data on file for PFS (ARCHES) and OS (ARCHES, ENZAMET and pooled analysis) with the ERG preferred censoring rules.

A7. CS, Document B, Table 22, page 65. Please explain the UK value set reported in the table. Does this refer to all participants based on the UK EQ-5D?

The utility values reported in Table 22 for the UK value set (i.e., [redacted] and [redacted] for enzalutamide and placebo, respectively) were derived using data of the overall ARCHES population (enzalutamide: n=539; placebo: n=545) and applying the UK tariff (see Table 6.2.3 of reference number B33 in the manufacturer submission).

Subgroup analysis

A8. CS, Document B, Section 2.7.2, page 78, Table 25. For the ENZAMET subgroup population, analyses based on disease volume are reported for TTD. However, ENZAMET TTD results are not reported in Table 32, page 95 of the submission. Please explain why.

Omission of TTD results in Table 32 was an error. ENZAMET TTD was not available at the time of the network meta-analysis (NMA) but it was subsequently calculated for the NICE submission. Table 32 (page 95 of the submission) was copied from the NMA report (reference 44 of the initial manufacturer submission). This should have been clarified in the legend of Table 32. The TTD hazard ratio for the ENZAMET population who did not receive concomitant docetaxel was [redacted] (see section B.2.6.2.2.4 of the manufacturer submission).

Meta-analysis

A9. CS, Document B, Section B.2.8, page 78. The submission indicates that the definition of PFS in the ARCHES study does not match that in the ENZAMET study. Please clarify how the pooled analysis of ARCHES and ENZAMET (given in table 26, page 79) was conducted for PFS and provide the hazard ratios for each study separately.

As reported in Table 6 of the manufacturer submission (pages 27 – 31) and in Table 2 below, the PFS definition differed between the ARCHES and ENZAMET trials.

The PFS estimated in the pooled analysis was based on:

- Clinical PFS data from ENZAMET patients who did not receive concomitant docetaxel
- Data from ARCHES patients using a modified PFS definition. The PFS definition was modified to render it as close as possible to the ENZAMET cPFS definition. Accordingly, for the pooled analysis, time to start of new antineoplastic treatment was also included in the PFS definition for ARCHES patients. However, no data on the development of symptoms attributable to cancer progression were available for ARCHES patients and therefore, the modified PFS definition used for the pooled analysis for ARCHES patients could not be matched to that for ENZAMET patients.

Table 2 PFS definition used in the ARCHES and ENZAMET trials and in the pooled analysis

	ARCHES	ENZAMET
Definition used in Trial	Radiographic PFS was defined as time to objective evidence of rPD as assessed by ICR or death, as follows: • Death from any cause within 24 weeks (2 scan cycles) from study drug discontinuation • rPD defined by RECIST 1.1 for soft tissue disease or the appearance of 2 or more new bone lesions on bone scan. The date of rPD was the date when the first objective evidence of rPD was documented. Unconfirmed disease progression on bone scan at week 13 was not considered as an event.	Clinical PFS was defined as the interval from the date of randomisation to the date of first clinical evidence of disease progression or death from any cause, whichever occurs first, or the date of last known follow-up without clinical progression. Clinical progression was defined by progression on imaging (PCWG2 criteria for bone lesions and RECIST 1.1 for soft tissue lesions), development of symptoms attributable to cancer progression or initiation of other anticancer treatment for prostate cancer.
Definition used in pooled analysis	Time to death, rPFS (as in ARCHES) or start of new antineoplastic treatment. No data on the development of symptoms attributable to cancer	Same as in the trial

	progression were available for ARCHES.	

Abbreviations: ICR: independent central review; PFS: progression-fee survival; rPD: radiographic disease progression; rPFS: radiographic progression-fee survival.

The PFS hazard ratio (HR) for enzalutamide over ADT alone or with a non-steroidal anti-androgen (NSAA) from the trials and the pooled analyses were:

- Radiographic PFS in ARCHES: 0.39 (95% CI [0.30, 0.50])
- Clinical (modified) PFS in ARCHES: [redacted])
- Clinical PFS in ENZAMET: 0.40 (95% CI [0.33, 0.49])
- PFS in the pooled analysis (i.e., clinical PFS for ENZAMET patients and modified PFS for ARCHES patients): [redacted].

Indirect and mixed treatment comparisons

A10. PRIORITY QUESTION. CS, Document B, Section B2.9. Please provide a table with the list of studies that were included in the NMA or excluded from it, for each relevant outcome, along with a rationale for their exclusion. Table 32 only partially does this (see also A8 question above).

The list of studies included and excluded from the evidence network for each endpoint and where applicable, the reason for exclusion is provided in Table 3.

Table 3 Studies included and excluded from the NMA and reason for exclusion

Study	Analysis in which it was included	Analysis in which it was excluded	Reason for exclusion
ARASENS[6]		All endpoints	No data had been yet published or presented at any congress
ARCHES[31]	rPFS, OS, TSEE, TCR, TPSA	-	Not applicable
Beland 1988[32]		All endpoints	Only median OS was provided. The authors did not report the HR or provided the KM curve
Beland 1991[33, 34]		All endpoints	No demographics or patient characteristics were available and thus, no heterogeneity assessment could be conducted In addition, the authors stated that patients on placebo switched to nilutamide when they progressed, thus this KM-curve was excluded as treatment

Study	Analysis in which it was included	Analysis in which it was excluded	Reason for exclusion
			switching would potentially have confounded any treatment effect
CHAARTED[35, 36]	OS, TCR	rPFS, TSEE	CHAARTED assessed clinical PFS[35]. The PFS definition was considered different from that used in other studies TSEE was not assessed in CHAARTED
DAPROC[37]i	OS	rPFS, TSEE, TCR, TPSA	Studies comparing ADT plus a NSAA to ADT alone were included in the evidence network to allow linking of ENZAMET to the network. ENZAMET only provided OS data. Thus, DAPROC was included for OS only
ENZAMET[38]	OS	rPFS, TSEE, TCR, TPSA	The definition of PFS in ENZAMET (i.e., clinical PFS) was considered different from that in the other studies TSEE, TCR and TPSA were not assessed in ENZAMET
EORTC 30852[39, 40]	OS	rPFS, TSEE, TCR, TPSA	Studies comparing ADT plus a NSAA to ADT alone were included in the evidence network to allow linking of ENZAMET to the network. ENZAMET only provided OS data. Thus, the EORTC 30852 study was included for OS only
GETUG-AFU 15[41, 42]	rPFS, OS, TPSA	TSEE, TCR	TSEE and TCR were not assessed in the GETUG-AFU 15 trial
HORRAD[9]		All endpoints	The study treatment (i.e., radiotherapy) was not relevant for this submission
INTERGROUP STUDY 0036[43]	OS	rPFS, TSEE, TCR, TPSA	Studies comparing ADT plus a NSAA to ADT alone were included in the evidence network to allow linking of ENZAMET to the network. ENZAMET only provided OS data. Thus, the Intergroup study 0036 was included for OS only
IPCSG[44]		All endpoints	The sample size was 11 patients per arm in the metastatic population, thus the KM curves were highly uncertain
Janknegt 1993[45]	OS	rPFS, TSEE, TCR, TPSA	Studies comparing ADT plus a NSAA to ADT alone were included in the evidence network to allow linking of ENZAMET to the network. ENZAMET only provided OS data. Thus, Janknegt 1993 was included for OS only
LATITUDE[46, 47]		All endpoints	The study included newly diagnosed, high-risk mHSPC patients only. The study population was considered different than in the other studies
Namer 1990/1988[48, 49]		All endpoints	Neither the number at risk, nor the total number of events was reported. Thus, estimations using the algorithm published by Guyot et al 2012[50] would have provided highly uncertain results, as the authors state

Study	Analysis in which it was included	Analysis in which it was excluded	Reason for exclusion
Navratil 1987[51]		All endpoints	This study would have been needed for OS only. However, the authors did not report any OS data
NTR130[17]		All endpoints	This study would have been needed for OS only. However, the authors did not report any OS data
STAMPEDE-1[52]	OS	rPFS, TSEE, TCR, TPSA	James 2016 do not provide any data for rPFS, TSEE, TCR, TPSA
STAMPEDE-2[53, 54]	OS, TSEE	rPFS, TCR, TPSA	Neither James 2017 nor Hoyle 2018 provide any data for rPFS, TCR, TPSA
STAMPEDE-3[55]	rPFS, OS, TSEE	TCR, TPSA	Sydes 2018 do not provide any data for TCR or TPSA
STAMPEDE-4[56]		All endpoints	The study treatment in Parker 2018 (i.e., radiotherapy) was not relevant for this submission
SWOG-8894[57]	OS	rPFS, TSEE, TCR, TPSA	Studies comparing ADT plus a NSAA to ADT alone were included in the evidence network to allow linking of ENZAMET to the network. ENZAMET only provided OS data. Thus, SWOG-8894 was included for OS only
TITAN[25]	rPFS, OS, TSSE, TPSA	TCR	TCR was not assessed in TITAN
Tyrrell 1991[58]		All endpoints	Neither the number at risk, nor the total number of events was reported. Thus, estimations using the algorithm published by Guyot et al 2012[50] would have provided highly uncertain results, as the authors state
Zalcberg 1996[59]	OS	rPFS, TSEE, TCR, TPSA	Studies comparing ADT plus a NSAA to ADT alone were included in the evidence network to allow linking of ENZAMET to the network. ENZAMET only provided OS data. Thus, Zalcberg 1996 was included for OS only

Abbreviations: ADT: androgen deprivation therapy; HR: hazard ratio; KM: Kaplan-Meier; NSAA: non-steroidal anti-androgen; OS: overall survival; rPFS: radiographic progression-free survival; TCR: time to castration resistance; TPSA: time to prostate specific antigen progression; TSEE: time to symptomatic skeletal-related event.

A11. PRIORITY QUESTION. CS, Document B, Section 2.9.1, page 82. The submission states that studies comparing abiraterone plus ADT vs ADT alone were included in the evidence network to "enrich" it; however, abiraterone is not considered a relevant comparator for this submission. Please clarify why these studies were included in the evidence network when abiraterone was not

considered a relevant comparator. Please re-run the NMA excluding these studies.

As mentioned in section B2.1 of the manufacturer submission, the systematic literature review (SLR) was conducted as part of due diligence to prepare for health technology assessments (HTA) submissions including the NICE one. Similarly, the NMA was conducted to inform the different European HTA submissions. The NMA included all therapies with EMA approval for mHSPC.

For the NICE submission, the manufacturer considered that the inclusion of the abiraterone studies in the evidence network would not be a caveat. Studies comparing abiraterone plus ADT to ADT alone would only have an impact to the NMA HRs for enzalutamide vs docetaxel if studies comparing abiraterone plus ADT vs docetaxel plus ADT were available. The manufacturer considered that the latter (i.e., studies comparing abiraterone to docetaxel) provides additional information relevant to the submission.

The results of the NMA when excluding the abiraterone studies are provided in Table 4. The updated NMA excluding abiraterone includes only two endpoints: OS and PFS. None of the abiraterone studies provided data on time to castration-resistance, time to initiation of new antineoplastic treatment or time to PSA progression. In addition, if abiraterone is removed, the comparison enzalutamide vs docetaxel cannot be conducted for time to symptomatic skeletal event as there is no study comparing docetaxel vs ADT alone that assessed this endpoint. Since the time of conducting the NMA reported in the manufacturer submission, a new analysis cut-off has been published for the STAMPEDE comparison of docetaxel plus ADT vs ADT alone (referred to as STAMPEDE-1 in the manufacturer submission). This new data analysis is captured in the updated NMA. The company provides two NMA updates excluding abiraterone:

- One using the previous STAMPEDE data for docetaxel (i.e., data reported in James et al 2016 [reference 48 of the manufacturer submission]). It should be noted that James et al 2016 do not report PFS and no abiraterone study informed the initial PFS NMA.
- One using the latest STAMPEDE data for docetaxel (i.e., data reported in Clarke et al 2019[*]).

[*] Clarke NW, Ali A, Ingleby FC, et al. Addition of docetaxel to hormonal therapy in low- and high-burden metastatic hormone sensitive prostate cancer: long-term survival results from the STAMPEDE trial. Ann Oncol. 2019 Sep 27. pii: mdz396. doi: 10.1093/annonc/mdz396. [Epub ahead of print]

For the NMA updates, the apalutamide studies were also excluded as apalutamide is not a relevant comparator.

Table 4 Initial and updated NMA results

Endpoint	Input parameters		Analysis	NMA, HR [95% CrI]				
	ENZA+ADT vs ADT HR [95% CI]	DOC+ADT vs ADT HR [95% CI]		Model	ENZA vs DOC	ENZA vs NSAA+ADT	ENZA vs ADT	DOC vs ADT
PFS	ARCHES[a]: 0.39 [0.30, 0.50]	GETUG-AFU15[c]: 0.69 [0.55, 0.87]	Initial NMA	FE	[redacted]	[redacted]	[redacted]	[redacted]
		GETUG-AFU15[c]: 0.69 (0.55,0.87) STAMPEDE-1[d]: 0.72 [0.62; 0.84][g]	Updated NMA[h] (new STAMPEDE-1 data[d])	FE	[redacted]	[redacted]	[redacted]	[redacted]
OS	ARCHES[a]: 0.81 [0.53, 1.25] ENZAMET[b]: 0.53 [0.37, 0.74]	GETUG-AFU15[c]: 0.88 [0.68, 1.14] CHAARTED[e]: 0.72 [0.59, 0.89] STAMPEDE-1[f]: 0.76 [0.62, 0.92]	Initial NMA	RE	[redacted]	[redacted]	[redacted]	[redacted]
				FE	[redacted]	[redacted]	[redacted]	[redacted]
			Updated NMA[h] (same STAMPEDE-1 as in submission[f])	RE	[redacted]	[redacted]	[redacted]	[redacted]
				FE	[redacted]	[redacted]	[redacted]	[redacted]
		GETUG-AFU15[c]: 0.88 [0.68, 1.14] CHAARTED[e]: 0.72 [0.59, 0.89] STAMPEDE-1[d]: 0.81 [0.69; 0.95]	Updated NMA[h] (new STAMPEDE-1 data[d])	RE	[redacted]	[redacted]	[redacted]	[redacted]
				FE	[redacted]	[redacted]	[redacted]	[redacted]

[a]Armstrong et al 2019 (reference B21 in submission). [b]Davis et al 2019 (reference B28 in submission). [c]Gravis et al 2016 (reference B47 in submission). [d]Clarke et al 2019 (submitted as an additional reference). [e]Sweeney et al 2015 (reference B17 in submission). [f]James et al 2016 (reference B48 in submission). [g]Metastatic progression-free survival was used because the definition was closer to the radiographic progression-free survival definition used in ARCHES. [h]Excluding the abiraterone and apalutamide studies.

Abbreviations: ADT: androgen deprivation therapy; CI: confidence interval; CrI: credible interval; DOC: docetaxel; ENZA: enzalutamide; FE: fixed effects; HR: hazard ratio; NMA: network meta-analysis; NSAA: non-steroidal antiandrogen; RE: random effects.

A12. CS, Document B, Section B.2.9.2, page 89. In the methodological heterogeneity section, the submission indicates that the clinical progression results from CHAARTED study were not used in the NMA because the clinical PFS definition could not be considered equivalent to the rPFS used in other studies. However, Table 30 shows that CHAARTED study was included in the NMA. The same issue applies to the ENZAMET study, where PFS results were not used in NMA because of the different definition; however, Table 30 shows otherwise. Please clarify.

Table 30 (page 89) provides the definition of PFS used in the studies included in the master evidence network. The PFS definition used in CHAARTED and ENZAMET was provided in Table 30 to highlight the differences between the PFS definition used in these two studies and the definition in the other studies. Both CHAARTED and ENZAMET were included in the NMA for OS only.

A13. PRIORITY QUESTION. CS, Document B, Section 2.9.5, Table 34, page 97. The results of the sensitivity analyses reported in Table 34 are identical or very similar to those of the base case. Please check that these results have been reported correctly.

The base case and sensitivity results reported in Table 34 of the manufacturer submission are correct. The assumptions for the base case and sensitivity analyses (SA) are summarised in Table 5 below.

The reason for lack of differences between base case and SAs are:

- For PFS, the results for the SA2 are identical to those for the base case and the results for the SA3 identical to those for SA1 given that none of the studies with an NSAA plus ADT arm provided PFS. In addition, inclusion or exclusion of the GETUG-AFU 15 (docetaxel vs ADT) trial is expected to have no impact on the PFS HR of enzalutamide over ADT because it does not inform this comparison
- For OS:
    - The HR for the enzalutamide vs ADT comparator is identical between the base case and SA1 and between SA2 and SA3 because the GETUG-AFU 15 study does not inform the enzalutamide vs ADT comparison. However, as expected the HR is different between base case/SA2 and SA1/SA3 because

the studies comparing NSAA plus ADT to ADT alone inform the comparison enzalutamide vs ADT

- The HR for the enzalutamide vs docetaxel comparison differs across the four analyses given that the GETUG-AFU 15 trial and the studies comparing NSAA plus ADT to ADT alone inform the enzalutamide vs docetaxel comparison.

Table 5 Assumptions taken in the NMA base case and sensitivity analyses

	Assumptions	**Endpoints affected by the assumptions**
Base case	Inclusion of the GETUG-AFU 15 trial	All endpoints
SA1	Exclusion of GETUG-AFU 15	PFS, OS
SA2	Inclusion of GETUG-AFU 15 and considering that the efficacy of ADT alone or with placebo is the same as for ADT plus a NSAA	OS For PFS the results of SA2 are the same as those for the base case
SA3	Exclusion of GETUG-AFU 15 and considering that the efficacy of ADT alone or with placebo is the same as for ADT plus a NSAA	OS For PFS the results of SA3 are the same as those for SA1

Abbreviations: SA: sensitivity analysis.

A14. CS, Document B, Section 2.9.5, page 97. The outcomes reported in the results section differ from those reported in Table 1 (The decision problem), page 13. In Table 1, PSA, PFS, OS, TTD, TINAT and HRQoL were listed as relevant outcomes. However, Table 34 on page 97 presents the NMA results for rPFS, OS, TSSE, TCR and TPSA. Please explain this discrepancy and provide a rationale for not reporting certain outcomes.

The NMA prespecified rPFS, OS, TSSE, TCR, TINAT, and TPSA. The NMA did not prespecify TTD or time to HRQoL deterioration because data for these endpoints were not available for any of the comparators included in the NMA. In addition, the NMA did not prespecify the PSA response either, because the definition of this endpoint differs across studies (see Table 6-28 of reference B28). In ARCHES, the PSA response was defined as PSA reduction by ≥50% or ≥90% whereas in CHAARTED (i.e., the only RCT trial assessing docetaxel which reported the PSA response), it was defined as PSA level lower than 0.2 ng/ml at 6 and 12 months[36].

Of the prespecified outcomes, the NMA was feasible only for rPFS, OS, TSSE, TCR and TPSA. The NMA could not be performed for TINAT given that data for this outcome was only available for the comparison enzalutamide vs ADT (data from ARCHES).

Adverse events

A15. Appendix F, page195, states: "No studies providing additional safety information for enzalutamide in mHSPC were identified other than the ARCHES- and ENZAMET-related publications." Please clarify whether this refers to the RCTs alone or whether safety data from non-randomised studies are also available.

The statement related to both randomised and non-randomised studies. The only additional study providing some data for enzalutamide was NCT02058706 [Vaishampayan 2018[14]] (see Table 1). This investigator-sponsored RCT compared enzalutamide plus ADT vs bicalutamide plus ADT. However, the study was terminated early and the data at the time of study termination has been published only as a congress abstract with limited information. The safety-related data provided in the abstract is summarised in Table 6.

Table 6 Safety-related data reported in Vaishampayan 2018

	Enzalutamide +ADT	**Bicalutamide `+ ADT**
Seizures	0	No mention in the abstract
Grade 3+ adverse events	Hypertension (13%) Infection (7%) Syncope (7%)	Hypertension (21%) Fatigue (7%) Haematuria (7%)

Network meta-analysis (NMA)

A16. CS, Appendix C, page 192. Table 83 reports the quality appraisal results of the 11 studies included in the NMA. The caption of the table is: 'Quality assessment results for PROSPER and STRIVE'. However, these two trials do not appear within the list of trials presented in the table. Please clarify.

This was an error. The caption of Table 83 should have read: "Quality assessment results for the studies included in the NMA".

Section B: Clarification on cost-effectiveness data

Features of the Economic Analysis

B1. PRIORITY QUESTION. CS, Document B, Table 47, page 119. Please clarify the justification for choosing a time horizon (30 years) that is ten years longer than the time horizon used within the company submissions for Abiraterone in mHSPC (ID945).

NICE guidance dictates that the time horizon in an economic evaluation should be sufficiently long to reflect all important differences in costs or outcomes between the technologies that are being compared[60]. At 20 years, the model predicted [redacted] of patients on enzalutamide plus ADT to still be alive, which decreased to [redacted] after 30 years. In line with NICE guidance therefore a 30-year time horizon was adopted. However, as shown by the sensitivity analysis 12.1 on page 162 of the submission, the impact of choosing a 30-year or a 20-year time horizon has little impact on the results with the ICER vs ADT increasing from £19,911 to £20,804 and the ICER vs docetaxel increasing from £22,877 to £24,325 if a 20-year time horizon was used.

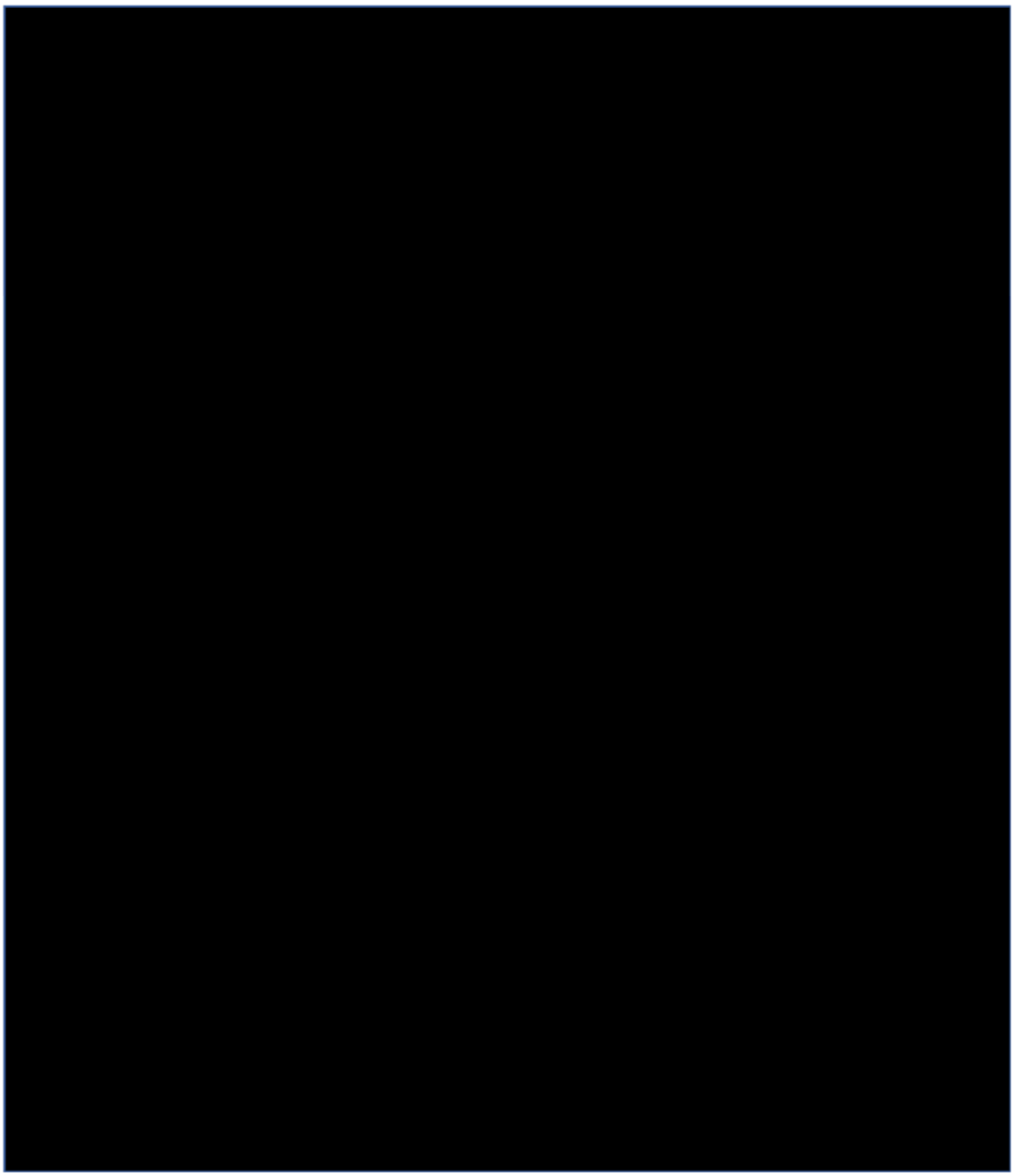
Furthermore, a longer time horizon than the abiraterone model is appropriate because survival is likely to be longer than the abiraterone model. This is due to the fact that the abiraterone model simulates the subgroup of mHSPC patients (newly diagnosed high-risk) who are at high risk of progression and may have a lower expected survival. A longer time horizon in the enzalutamide model is needed to capture all relevant differences, as shown by the results above.

B2. Document B, Figures 20 to 23 on pages 123 to 126 are helpful but are drawn over a time horizon of 20 years. As stated in Document B, Table 47, page 119 and elsewhere, the time horizon for the economics model is 30 years. Please can you:

A) redraw these Figures over 30 years?

The updated figures with the 30-year time frame are presented below (Figure 3 - Figure 6). In addition, Figure 6 has been corrected for the exponential, log-normal and generalised gamma curve fits as the general population mortality was applied incorrectly for these curves in Figure 23, page 126 of the submission. This correction only affects the curves above the log-logistic curve in Figure 23. However, none of the model results with any of the curves fits are affected by this adjustment.

Figure 3 ARCHES PFS extrapolated by the 6 standard parametric models



Abbreviations: ADT: androgen deprivation therapy; K-M Kaplan Meier; PFS: progression-free survival.

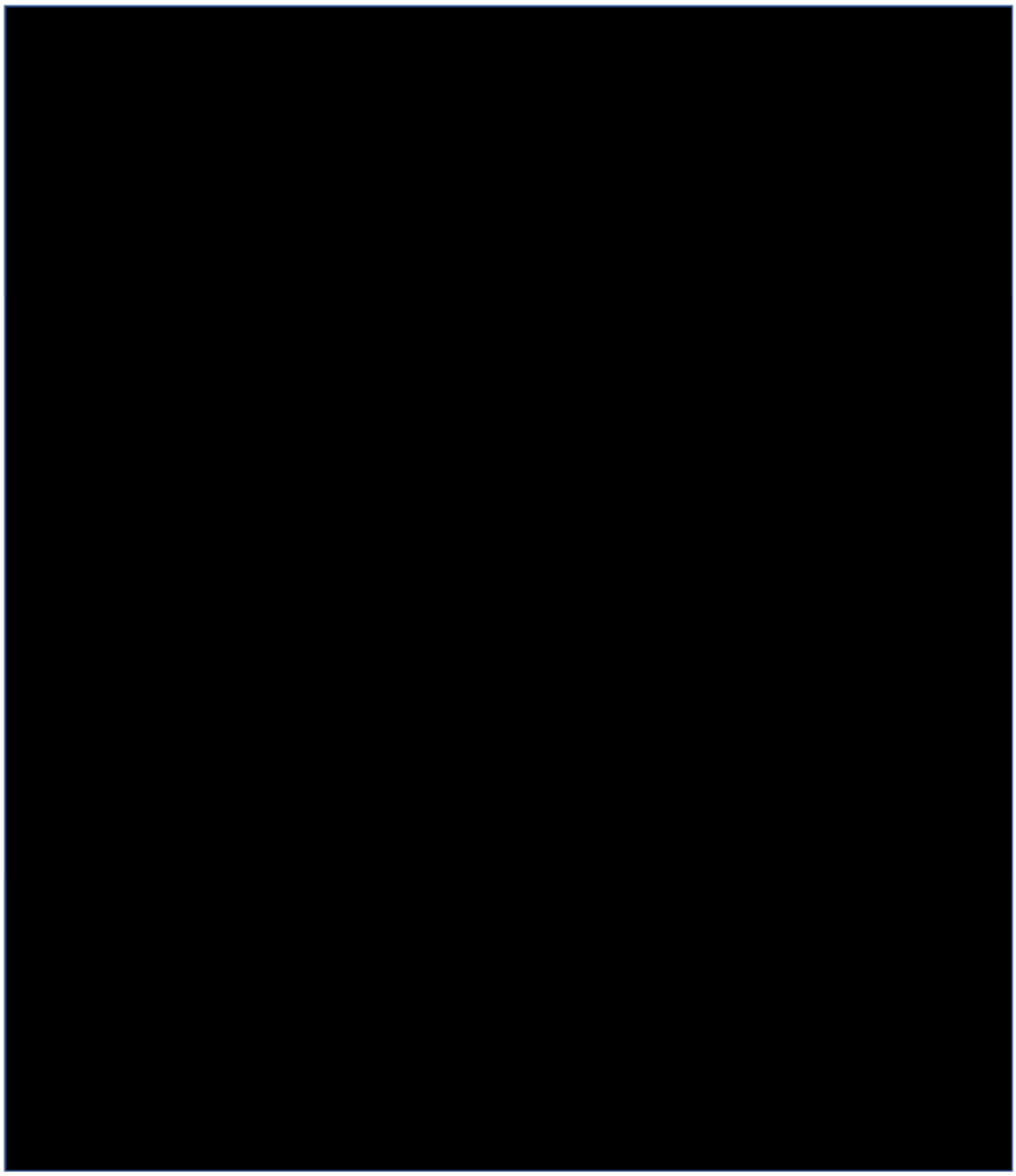
Figure 4 ARCHES enzalutamide plus ADT TTD extrapolated by the 6 standard parametric models

Abbreviations: ADT: androgen deprivation therapy; K-M Kaplan Meier; TTD: time to treatment discontinuation.

Figure 5 Modelled ARCHES TTD extrapolations relative to the base case rPFS OS curves

Abbreviations: ADT: androgen deprivation therapy; K-M Kaplan Meier; TTD: time to treatment discontinuation.

Figure 6 Pooled OS extrapolated by the 6 standard parametric models



Abbreviations: ADT: androgen deprivation therapy; K-M Kaplan Meier; OS: overall survival.

B) provide new tables presenting the data in Figures 20 to 23 as follows:

- **Table 1: For PFS treated with enzalutamide plus ADT, the predicted PFS at 5 years, 10 years, 20 years and 30 years for each of the six parametric fits**
- **Table 2: as for Table 1 but for ADT alone**

- **Table 3: as for Table 1 but for OS**
- **Table 4: as for Table 1 but for OS for ADT alone**
- **Table 5: as for Table 1 but for TTD**
- **Table 6: as for Table 1 but for TTD for ADT alone**

The event-free percentages for PFS, OS and TTD for the six parametric curves are shown in Table 7 to Table 11. The final table requested by the ERG (i.e. TTD extrapolated for ADT alone) was not provided, since TTD is not used in the model for ADT alone. ADT alone is never discontinued, so there is no point in including TTD for ADT alone.

Table 7 Predicted PFS % at 5 years, 10 years, 20 years and 30 years for each of the six parametric fits for enzalutamide plus ADT

	Exponential	Weibull	Log-normal	Log-logistic	Gamma	Gompertz
Year 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADT: androgen deprivation therapy; PFS: progression free survival.

Table 8 Predicted PFS % at 5 years, 10 years, 20 years and 30 years for each of the six parametric fits for ADT alone

	Exponential	Weibull	Log-normal	Log-logistic	Gamma	Gompertz
Year 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADT: androgen deprivation therapy; PFS: progression free survival.

Table 9 Predicted OS % at 5 years, 10 years, 20 years and 30 years for each of the six parametric fits for enzalutamide plus ADT

	Exponential	Weibull	Log-normal	Log-logistic	Gamma	Gompertz
Year 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADT: androgen deprivation therapy; OS: overall survival.

Table 10 Predicted OS % at 5 years, 10 years, 20 years and 30 years for each of the six parametric fits for ADT alone

	Exponential	Weibull	Log-normal	Log-logistic	Gamma	Gompertz
Year 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADT: androgen deprivation therapy; OS: overall survival.

Table 11 Predicted TTD % at 5 years, 10 years, 20 years and 30 years for each of the six parametric fits for enzalutamide plus ADT

	Exponential	Weibull	Log-normal	Log-logistic	Gamma	Gompertz
Year 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 30	*.*%	*.*%	**.*%	*.*%	*.*%	*.*%

Abbreviations: ADT: androgen deprivation therapy; TTD: time to treatment discontinuation.

B3. CS, Document B, Section 3.3.1.1, page 122. The submission states that the PFS curves for Enzalutamide plus ADT or ADT alone have been selected "In line with best modelling practices". Please summarise and discuss the evidence for the clinical plausibility of the selected extrapolations.

The PFS extrapolations were selected based on statistical fit and clinical plausibility of the extrapolated values. Based on the Akaike information criterion (AiC) and Bayesian information criterion (BiC) values in both ADT alone and enzalutamide plus ADT the log-normal provided the best statistical fit, followed by gamma (Table 12).

Table 12 AIC/BIC values for the 6 parametric PFS extrapolations

	Exponential	Weibull	Log-normal	Log-logistic	Gamma	Gompertz
ADT alone						
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide plus ADT						
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; ADT: androgen deprivation therapy; BIC: Bayesian information criterion; PFS: progression-free survival

The clinical plausibility of the PFS extrapolations for ADT alone was validated against long-term PFS outcomes of external reference studies. Subsequently, the plausibility of the extrapolations for both enzalutamide plus ADT and ADT alone were validated by a clinical expert.

As stated on page 125 of the submission, several external sources were examined to assess the face validity of the extrapolation predictions:

- STAMPEDE trial comparing several interventions to standard of care (SOC) in metastatic or high-risk non-metastatic prostate cancer[52, 53]. The authors provide the results for the whole patient population (i.e., metastatic and non-metastatic HSPC) but report OS data for the metastatic patient cohort separately in[52]. In addition, the results for the abiraterone arm are provided in James et al[53]. The authors also provide the results for the mHSPC subgroup separately.
- CHAARTED trial[36] comparing docetaxel with SOC in patients with newly diagnosed mHSPC
- GETUG trial[42] comparing docetaxel with SOC in patients newly diagnosed or previously treated mHSPC.

The proportion of patients alive at various timepoints is provided in Table 13. These values were obtained after the Kaplan Meier plots in the corresponding papers were digitised and the survival probabilities at the specific timepoints were extracted.

Table 13 Percentages of patients PFS free at different timepoints from external data sources

		Proportion of patients without progression at				
Study [reference]	**Treatment Arms**	**3-years**	**4-years**	**5-years**	**6-years**	**7-years**
STAMPEDE [James 2016[52]]	ADT	38%	NA	28%	NA	22%
STAMPEDE [James 2017[53]]	ADT	23%	NA	54 months: 21%	NA	NA
CHAARTED [Sweeney 2015[36]]	ADT	34%	25%	NA	25%	NA
GETUG [Gravis 2016[42]]	ADT	26%	NA	19%	13%	NA
Range	ADT	23%-38%	25%	19%-28%	13%-25%	22%

Abbreviations: NA: not available; PFS: progression free survival; ADT; androgen deprivation therapy.

The gamma, exponential and log-normal curves were best in line with these clinical data. However, as shown in Table 7, the enzalutamide gamma extrapolation resulted in long term PFS extrapolations that were not considered to be clinically plausible; this was confirmed by

the consulted clinical expert[61]. As shown in Table 13, the exponential curve did not provide a good statistical fit. Therefore log-normal was chosen to inform PFS in the model.

B4. PRIORITY QUESTION. CS, Document B, Section 3.3.1.1, page 122. Please clarify any adjustments made to the ARCHES PFS extrapolation for enzalutamide plus ADT. Are adjustments made for mortality to ensure PFS does not cross OS? If so, at what time point does this adjustment occur? Is there any evidence available to indicate that OS is an appropriate indicator of PFS within this time range?

The PFS curve in the model was indeed adjusted to ensure that it does not cross with the OS curve. Health state membership in a partitioned survival model is informed by the area between the curves of the different efficacy inputs. The PD1-3 health state, for example, is informed by the area between the PFS and OS curves. However, if the OS and PFS curves cross, this would result in a negative number of patients in PD1-3, which is not realistic. PFS curve was therefore adjusted to become equal to OS, if the curves cross, reducing the making the PD1-3 health state membership to 0 from that point forward. Small PFS adjustments are therefore required to prevent this from happening.

However, the PFS corrections due to the OS only occurred late in the simulation when only a small proportion of patients was still alive (Figure 7). More specifically, the enzalutamide curve was adjusted [redacted]. Considering that the median age was 84-89.5 when these corrections start to occur, it is plausible that patients indeed do not progress to PD1-3, but already die within the mHSPC health state from natural causes.

Figure 7 Overlay of the unadjusted efficacy curves informing ADT alone, enzalutamide plus ADT and docetaxel plus ADT

Abbreviations: ADT: androgen deprivation therapy; OS: overall survival; rPFS: radiographic progression-free survival; TTD: time to treatment discontinuation.

B5. PRIORITY QUESTION. CS, Document B, Section 3.3.2, page 125. Please provide justification for the adjustments required to prevent extrapolated mortality rates being lower than age matched general population mortality. In particular, with reference to any supporting evidence, please comment on the plausibility of mortality becoming equal to general population mortality for men with metastatic prostate cancer. Please also comment on the reasons why so many of the parametric curves in Figures 23, Document B, end up following general population mortality.

As stated in dossier section B.3.3, page 121, the efficacy data had to be extrapolated to match the 30-year time horizon of the model. It is common practice for extrapolated survival data extrapolations to be corrected for the general population mortality to ensure that the extrapolated mortality would never be lower than that of an age-matched individual. A similar approach has been applied in various previous technology appraisals[62-65]. The reasoning

behind this is that a patient with prostate cancer is not likely to have better survival than the age matched general population.

Figure 8 illustrates the general population mortality versus the enzalutamide OS extrapolations. As explained in response B2 the exponential, log-normal, and gamma curves were not plotted correctly in Figure 23, but Figure 8 shows that at the extrapolated curves are all below the general population mortality.

Figure 8 Pooled enzalutamide OS extrapolations compared to the general population mortality

Abbreviations: ADT: androgen deprivation therapy; OS: overall survival.

Furthermore, although correcting for the general population mortality is standard practice, a case could be made that it represents a conservative approach. In line with most clinical trials, selection criteria in the enzalutamide trials were biased as they exclude patients with significant cardiovascular disorders that themselves reduce survival. Life threatening cardiovascular diseases are common in men aged 70 or older. By excluding this comorbidity from the enzalutamide trials, a case can be made that patients in the enzalutamide trials may be healthier than the age-matched general population, as long as prostate cancer does not rapidly progress. However, since this is only speculative, an age-matched adjusted mortality represents the safest approach.

B6. CS, Document B, Section 3.3.2, page 125. Please provide further justification for the decision to pool data from ARCHES and ENZAMET for OS. Please refer to any differences in patient characteristics that might influence

overall survival and/or the relative treatment effect of enzalutamide versus ADT.

As stated in B.3.3.2 on page 125 of the submission, the pooled ARCHES and ENZAMET data was considered the most appropriate data source to inform survival in the model as it makes the best use of all available enzalutamide data and because OS is a hard endpoint, not prone to differences in endpoint definition.

Furthermore, the patient populations in both trials were considered sufficiently homogeneous to facilitate pooling [61]. Both trials included patients of comparable mean age (69.5 for ACHES vs. 70.2 for ENZAMET), ECOG score (77.5% <1 for ARCHES vs 72.7% for ENZAMET), Gleason score (31.1% <8 for ARCHES vs 34.0% <8 for ENZAMET), and prior use of docetaxel (82.2% no docetaxel in ARCHES vs 86.1% in ENZAMET). The only inconsistency between patient characteristics that could have an effect on OS was the difference in high vs. low volume patients, with 36.8% of patients being low-volume at baseline in ARCHES versus 62.8% in ENZAMET. However, based on the available clinical data, this did not result in an OS difference, with both trials showing comparable OS results for the duration where data for both trials are available. At median follow-up for ARCHES, the survival in ENZAMET was comparable to that observed in ARCHES with an OS at 14.4 months of 92.9% and 94.5% for enzalutamide vs 91.4% and 93.6% for ADT and/or NSAA in ARCHES and ENZAMET.

B7. CS, Document B, Section 3.2.2, page 118. The submission states that "TTD appears to be slightly shorter than rPFS and cPFS". Please specify the evidence provided by ARCHES and ENZAMET to support this statement, outline the likely mechanism by which this result occurs, and comment on the generalisability of this result to a real-world clinical setting.

The shorter duration of TTD compared with PFS was based on the median PFS and TTD for the comparator arms of ARCHES and ENZAMET. ADT alone in ARCHES reported a median TTD of [redacted] months compared to a median rPFS of 19.0 months, and NSAA plus ADT in ENZAMET reported a median TTD of [redacted] months compared to a median cPFS of [redacted] months. Furthermore, although median PFS was not reached for enzalutamide plus ADT in both studies, ARCHES also showed a lower number of PFS than TTD events at data cut-off, with 15.8% of patients having a PFS event, compared to 23.8% having a TTD event.

The reasons for drug discontinuation in ARCHES are shown in Table 14. Based on these data, only about half the patients receiving enzalutamide discontinued the study drug due to disease progressions (65 out of 135). Other common reasons for discontinuation included

adverse events (25 out of 135) and withdrawal by subject (25 out of 135). These data make it plausible that TTD would indeed happen before disease progression in clinical practice.

Table 14 Reasons for drug discontinuation reported in ARCHES

Category	ENZA + ADT (N=574)	Placebo + ADT (N=576)
Total drug discontinuations	135 (23.5%)	242 (42.0%)
Adverse Event	28 (4.9%)	21 (3.6%)
Death	9 (1.6%)	7 (1.2%)
Lost to Follow-Up	0	1 (0.2%)
Progressive Disease	65 (11.3%)	171 (29.7%)
Protocol Deviation	2 (0.3%)	1 (0.2%)
Withdrawal by Subject	25 (4.4%)	30 (5.2%)
Other	6 (1.0%)	11 (1.9%)

Abbreviations: ADT: androgen deprivation therapy; ENZA: enzalutamide; N: number.

B8. In Figure 21, the TTD Kaplan-Meier plot for ADT alone drops sharply in the last few months of observed data from the clinical study. All parametric curves seem a poor fit for these final months of observed data – is there any explanation for the drop observed in the RCT and can you propose a better way to fit a curve?

As a prelude to our answer, the manufacturer would like to clarify that the figure discussed in question B8 describes the extrapolated TTD data for enzalutamide plus ADT, not ADT alone. The extrapolated TTD alone data were not used in the model, so this curve is also not described in the dossier.

The last few months of a Kaplan-Meier curve are inherently unreliable due to the low number of patients that informs this part of the curve. For the ARCHES TTD curve specifically, the patients at risk at the time the TTD curve drops were between [redacted] and [redacted] patients for enzalutamide plus ADT. Discontinuation of only one patient could therefore already have a big impact on the shape of the curve at this point. However, it is unlikely that this drop is representative for the entire ARCHES population. The statistical methods that determine curve fit therefore also consider the number of patients at risk and generally assign less weight on the final few months of a KM curve. This can result in a poorer fit towards the end of the KM curve (Figure 9)

Figure 9 Overlay of the digitised ARCHES TTD KM curve of enzalutamide plus ADT and the exponential TTD extrapolation used in the model

Abbreviations: ADT: androgen deprivation therapy; KM: Kaplan Meier; TTD: time to treatment discontinuation.

It may be possible to use a different method of curve fitting; a piecewise model may for example be better suited to more precisely follow the observed KM curve. However, this introduces the risk of overfitting the data, since only a few TTD cases could in that case lead to a big underestimation of the actual TTD. Furthermore, when patients on enzalutamide discontinue treatment, it is assumed that they continue on ADT alone. A lower TTD estimate would therefore lower the mHSPC costs of the enzalutamide arm leading to a lower ICER. Any overestimation of TTD due to the method of fitting could therefore be considered a conservative approach.

Selection of clinical data sources

B9. The submission explains the choice between using the clinical studies ARCHES, ENZAMET and the pooled data in the base case. Please summarise the case against using ENZAMET in the base case for PFS as opposed to ARCHES? Please also summarise the strengths and weaknesses of using the pooled data for OS rather than either of the individual studies?

Several reasons against using ENZAMET cPFS in the base case are stated in section B.3.3.1 of the dossier, pages 121 and 122. The most important reason mentioned in the dossier is because the ARCHES rPFS definition is more aligned with what is commonly used

in clinical trials, including most available docetaxel plus ADT studies. This makes the comparison vs docetaxel much more robust when ARCHES rPFS is used and makes the results more comparable to other prostate cancer submissions.

In addition to the points already highlighted in the dossier, it should be noted that ENZAMET has an open label design. This is not likely to affect hard endpoints, like OS, but cPFS is much more subjective because it is in part informed by the development of symptoms reported by patients and assessed by the investigator. It cannot be ruled out that physicians and patients knowing what treatment they administer or receive may have biased the reporting of symptoms and/or need to start a new antineoplastic. This renders ARCHES rPFS a more reliable PFS input for the model.

Regarding the pooled OS data; the main strengths are stated above: more data increases the reliability of the OS input and it makes use of all available enzalutamide OS data. There are some differences in trial design and patient characteristics, with ARCHES comparing against ADT alone rather than ADT plus NSAA and containing fewer low volume patients. However, NSAA is not expected to influence survival, based on the NMA results and expert opinion[61, 66] and the difference in low volume patients did not lead to a difference in OS results in the overlapping trial period (see question B6).

B10. Please provide a summary of the curve selection for scenarios that used data only from ENZAMET and only from ARCHES. Please clarify which curves were preferred for PFS (ENZAMET only) and OS (ARCHES only and ENZAMET only) and why?

The ENZAMET OS and PFS curves and ARCHES OS curve were selected following the same approach as for all other curves; i.e., the best curve was selected based on statistical fit (AIC/BIC values), clinical plausibility of the predictions and expert validation. The respective AIC/BIC values for ENZAMET PFS, ENZAMET OS, and ARCHES OS are given in Table 15 to Table 17. Based on these data, the best statistical fits were Weibull/Gomperz/log-normal for ENZAMET PFS, log-logistic for ENZAMET OS, and Weibull/log-normal/log-logistic for ARCHES OS.

Table 15 AIC/BIC values for the 6 parametric ENZAMET PFS extrapolations

	Exponential	Weibull	Log-normal	Log-logistic	Gamma	Gompertz
ADT alone						
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Exponential	Weibull	Log-normal	Log-logistic	Gamma	Gompertz
Enzalutamide plus ADT						
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; ADT: androgen deprivation therapy; BIC: Bayesian information criterion; PFS: progression-free survival

Table 16 AIC/BIC values for the 6 parametric ENZAMET OS extrapolations

	Exponential	Weibull	Log-normal	Log-logistic	Gamma	Gompertz
ADT alone						
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide plus ADT						
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; ADT: androgen deprivation therapy; BIC: Bayesian information criterion; OS: overall survival

Table 17 AIC/BIC values for the 6 parametric ARCHES OS extrapolations

	Exponential	Weibull	Log-normal	Log-logistic	Gamma	Gompertz
ADT alone						
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide plus ADT						
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; ADT: androgen deprivation therapy; BIC: Bayesian information criterion; OS: overall survival

The 3, 5, 6, and 7 year OS and PFS free predictions were again compared against external reference data for ADT from STAMPEDE[52, 53], CHAARTED[36], and GETUG[42]. The values used to asses PFS and OS are listed in Table 13 and Table 18. Based on these data and clinical expert input (reference B33 of the manufacturer submission), the most statistically and clinically plausible curves were Weibull for ENZAMET PFS, log-logistic for ENZAMET OS, and log-logistic for ARCHES OS[61]. These were used in the respective sensitivity analyses.

Table 18 Percentages alive at different timepoints from external data sources

		Proportion of patients alive at			
Study [reference]	**Treatment Arms**	**3-years**	**5-years**	**6-years**	**7-years**
STAMPEDE [James 2016[52]]	ADT	59%	36%	NA	30%
STAMPEDE [James 2016[52]]	ADT	62%	54 mo: 45%	NA	NA
CHAARTED [Kyriakopoulos 2018[35]]	ADT	58%	39%	33%	27%
GETUG [Gravis 2016[42]]	ADT	61%	43%	NA	34%
Range	ADT	58%-62%	39%-45%	33%	27%-34%

Abbreviations: ADT: androgen deprivation therapy; mo: months; NA: not available; OS: overall survival.

Valuation of Health Effects

B10. Given that patients have metastatic cancer, the utility values used in the base case seem quite high, but the pre-progression values do not appear to be tested in the sensitivity analyses. Please compare the utility values in Table 49 with those used in the NICE review of docetaxel in people with hormone sensitive prostate cancer [NGG131] and provide further sensitivity analysis on:

a) **Utilities applied in the pre-progression state alone (Document B, Table 49, page 128, first row)**

b) **All utility values (all rows in Table 49 other than death)**

The one-way sensitivity analysis varied all values that had a level of uncertainty, within their 95% confidence interval. This included the mHSPC utility. However, the mHSPC utility does not appear in Figures 24 or 25, and Tables 70 or 71 in the manufacturer submission because it is not one of the top 15 most influential parameters for the comparison against ADT alone or the comparison against docetaxel plus ADT. This is because the large number of observations that informed the mHSPC utility value results in a very low level of uncertainty and a small standard error and 95% confidence interval (Table 19).

Table 19 Health state utility values included in the model and their associated standard errors

Health state	N	Utility	Standard Error
mHSPC	[redacted]	[redacted]	0.0026
PD1	[redacted]	[redacted]	0.0118

Health state	N	Utility	Standard Error
PD2	[redacted]	[redacted]	N/A
PD3	[redacted]	[redacted]	0.0195

The utility values in Table 49 could not be compared with those used in the NICE review of docetaxel in people with hormone sensitive prostate cancer [NG131] as only disutilities, and no baseline values are reported in NG131 or in Woods et al[67].

Subsequent treatments for progressed disease

B11. Document B, Table 48. For treatment duration periods after progression, data from clinical studies at that place in the treatment pathway is used. Please comment on how previous treatment with enzalutamide (for hormone sensitive metastatic prostate cancer) might be expected to have affected the results of those studies? Please also compare the characteristics of patients who progressed in ARCHES (the company's preferred clinical study) with the baseline characteristics of patients in the clinical study used for data for PD1 (post-progression treatment 1).

The most impactful baseline characteristics of ARCHES are compared to PREVAIL in Table 20. All other PD1 studies do not provide enough overlapping meaningful baseline characteristics to make a proper comparison to ARCHES. Based on the baseline characteristics, both studies are very comparable in terms of ECOG score, and disease localisation at baseline. However, ARCHES did contain more patients with a high Gleason score, indicating that ARCHES patients represent a more high-risk cohort. Furthermore, patients in PREVAIL were 1.7 years older than patients in ARCHES. Considering the expected time before ARCHES patients reach mHRPC (median rPFS of 19.0 months for ADT and not reached for enzalutamide), it is likely that PREVAIL patients are the same age a patient who progressed on ADT, but younger than patients who progressed on enzalutamide. Although PREVAIL patients represent a slightly lower risk-group, the studies are considered similarly comparable to inform the PD1 treatment duration.

Table 20 Most impactful baseline patient characteristics from PREVAIL and ARCHES

	PREVAIL	ARCHES
Median age	71.2	69.5
Gleason score at diagnosis <8	48.5%	31.1%

	PREVAIL	ARCHES
Gleason score at diagnosis ≥8	51.5%	65.9%
ECOG 0	68.1%	77.5%
ECOG 1	31.9%	22.5%
ECOG 2	0%	0%
Disease localisation at screening		
Bone only	39.8%	44.6%
Soft tissue only	15.9%	11.8%
Both bone and soft tissue	43.6%	44.5%
Not available	0.8%	-

To the manufacturer's knowledge no data are available informing the effect of enzalutamide on later line treatments. It is likely that treatment with enzalutamide would either have no effect on the PFS durations or would reduce the PFS duration of later line studies. However, this would have limited effect on the model outcomes, as the duration of the mHRPC health state as a whole is informed by OS rather than the respective durations of each PD1-3 health states. The treatment durations are used to inform health state membership for each of the PD1-3 states, but this only influences costs and utility, not the survival in the model. Furthermore, an overestimation of these durations has a negative effect on the costs in the enzalutamide arm, as patients who start on enzalutamide spend a longer time in mHRPC. This statement is further explored in the answer to question B13, but in general longer PD1 durations represent a conservative approach.

B12. Document B, Table 48. Please clarify if the reported durations in column two are all median durations as the column heading implies, or if some are mean durations as the Table heading implies?

The durations used in the cost-effectiveness model are all medians. The table heading should indeed state 'median' instead of 'mean'.

B13. Document B, Table 48. Since some of the subsequent treatments are fixed duration/cycle treatments (e.g. R-223), please comment on the suitability of selected sources for modelling expected time in the progressed disease states (before going on to subsequent therapies).

The ERG is correct in observing that a fixed number of cycles was used to inform the time on docetaxel, cabazitaxel and radium-223 in the PD1-3 health states rather than time to

progression. However, the respective trials informing treatment duration in mHRPC did not always include PFS, making it difficult to get a reliable progression measure. Furthermore, the fixed durations measures used in the model all closely matched the progression measure in those trials that report PFS (Table 21). It could even be stated that the model provides a conservative approach as the durations in the model were generally longer than what was reported in the trials. These longer treatment durations in mHRPC have a bigger effect on the enzalutamide arm of the model, as patients who start on enzalutamide spend a longer time in mHRPC. In fact, when you change the durations in the model to the reported PFS measures in Table 21 the ICER decreases both vs ADT (£19,911 to £18,781) and vs docetaxel (£22,877 to £22,741).

Table 21 Reported PFS measures in the respective mHRPC trials compared to the cycle-based input in the model

PD treatment	Duration in model	Reported PFS or closest measure
Docetaxel	6.58 months	6 months
Cabazitaxel	4.15 months	2.8 months
Radium-223	5.54 months	Not reported in ALSYMPCA (time to PSA increase: 3.6 months)

Abbreviations: mHRPC: metastatic hormone-relapsed prostate cancer; PFS: progression-free survival; PSA: prostate-specific antigen; TTD: time to treatment discontinuation.

B14. Document B, Table 61. Please summarise the reasoning and logic given by experts to support their choice of subsequent treatment distributions used to inform the distributions in the model.

To inform the post-progression treatment distribution in the model, the clinical expert was asked to provide his view on the treatment sequence, based on what he currently saw in UK clinical practice.

Use of NMA hazard ratios

B15. The submission explains that pooled RCT data was favoured over ARCHES or ENZAMET because it was better to use all the evidence. A similar explanation would surely make the NMA the best option for the comparative

effectiveness of all three treatment options. Therefore, please explain why the hazard ratios for PFS and OS from the NMA were not used in the base case to model enzalutamide.

There are several reasons for not using the NMA HRs for PFS and OS to model enzalutamide. The most important reasons include:

- Patient level data were available to model efficacy of enzalutamide and ADT alone.
- Applying the NMA HR to the ADT arm to model enzalutamide causes the OS and PFS curves to cross much sooner and much more drastically. Because the NMA adjusted curves do not represent the actual PFS and OS, the shapes of the curves are not fine-tuned to each other, which may cause implausible curve crossing. In this scenario the OS and PFS curves already cross after [redacted] (Figure 10). Although PFS is adjusted to prevent negative transition rates when the OS and PFS curves cross, crossing of curves this early in the simulation leads to implausible model outcomes, since it is not realistic that OS and PFS would already be the same [redacted].

Figure 10 OS and PFS curves in the scenario where the NMA HRs are used to model enzalutamide

Abbreviations: OS: overall survival; HR: hazard ratio; NMA: network meta-analysis; PartSA: partitioned survival analysis; rPFS: radiographic progression-free survival

Furthermore, the statement that the NMA is more reliable, because it makes use of all available evidence is also not entirely accurate. It is true that the NMA includes more studies than the pooled enzalutamide data, however, the additional studies that inform the comparison enzalutamide vs ADT were used only for OS so that the ENZAMET trial could be linked to the evidence network. These additional studies however were old and provided

limited information. In addition, judging from the NMA OS HR (0.610) and the Pooled OS HR (0.626), the additional studies only had a minor impact on enzalutamide's efficacy. The benefit of including these additional data do not outweigh the drawbacks of using the NMA HR (and the old studies) to model enzalutamide.

B16. Scenario 8 in Table 74 uses the NMA hazard ratios for enzalutamide applied to the reference curves of ADT alone. Please provide an additional scenario where PFS and OS for ADT alone and docetaxel + ADT are modelled by applying NMA hazard ratios to the reference curves of enzalutamide.

The NMA HRs of docetaxel and ADT versus enzalutamide used for scenario 8 are shown in Table 22. Applying these HRs to the enzalutamide curve increases the modelled efficacy of both ADT alone and docetaxel plus ADT relative to the base case, with the resulting QALYs increasing from [redacted] to [redacted] for ADT alone and from [redacted] to [redacted] for docetaxel. However, this greater efficacy resulted in an increase in total costs from £[redacted] to £[redacted] for ADT alone and from £[redacted] to £[redacted] for docetaxel plus ADT. The results for enzalutamide remained unchanged at [redacted] total QALYs and £[redacted] total costs. This resulted in slightly higher ICERs in this scenario of £21,199 versus ADT alone and £27,903 versus docetaxel plus ADT.

Table 22 PFS and OS hazard ratios of enzalutamide vs docetaxel and ADT

	PFS	OS
Enzalutamide vs. docetaxel HR	0.56	0.81
Enzalutamide vs ADT HR	0.39	0.61

Abbreviations: ADT: androgen deprivation therapy; OS: overall survival; HR: hazard ratio; PFS: progression-free survival; vs.: versus.

Validation

B17. Document B, Section 3.10.3, page 166. The submission states that the model fits and predictions were in line with UK health economics and clinical experts. Please explain this statement? For example, how many clinical experts were involved? Were they asked for estimates of 5-year PFS and OS on ADT alone before they saw the model predictions? What variation was there between the clinical experts or did they agree on a single set of results for usual care?

The model input and results were validated by one health economic expert and one clinical expert in two meetings (reference B83 in the manufacturer submission). Both experts were

simultaneously present during both meetings to provide feedback on the other's input. Model fits were validated by first asking the experts about their preferred long-term OS and PFS estimates, without showing the parametric curves. Subsequently, the curves were shown and experts were asked to provide input on which curve best suited their expected long-term PFS and OS values.

B18. Please provide a full incremental cost-effectiveness analysis, comparing each alternative to the next less effective option, and indicate the probability of each treatment being preferred at the thresholds of £20,000 and £30,000 per QALY.

The comparators in the model from greatest to lowest efficacy are enzalutamide plus ADT (base case QALYs: [redacted]), docetaxel plus ADT (base case QALYs: [redacted]), and ADT alone (base case QALYs: [redacted]). The incremental cost effectiveness results of enzalutamide compared to docetaxel plus ADT and from docetaxel plus ADT versus ADT alone are provided in Table 23, and the corresponding efficiency frontier in Figure 11. Based on these data, there is no extensive dominance of enzalutamide over docetaxel, and both treatments should be considered cost-effective treatment options for mHSPC.

Table 23 incremental cost-effectiveness analysis, comparing each alternative to the next less effective option

Treatment	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER vs baseline (£/QALY)	Incr. ICER (£/QALY)
ADT	[redacted]	[redacted]	-	-	-	-
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	-	£12,314
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	£19,911	£22,877

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; incr: incremental; QALY: quality-adjusted life year

Figure 11 Efficiency frontier of the comparison between ADT alone, docetaxel and enzalutamide

To assess the probability of being cost effective against the next effective treatment, a probabilistic analysis of the cost effectiveness of docetaxel vs. ADT and of enzalutamide vs. docetaxel was performed. The probability of docetaxel plus ADT being cost-effective vs. ADT alone is [redacted]% and [redacted]% at a WTP threshold of £20,000 and £30,000 per QALY respectively. The probability of enzalutamide plus ADT being cost-effective vs. docetaxel plus ADT is [redacted]% and [redacted]% at a WTP threshold of £20,000 and £30,000 per QALY respectively.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Enzalutamide with androgen deprivation therapy for treating metastatic hormone-sensitive prostate cancer [ID1605]

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.

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	TACKLE Prostate Cancer
3. Job title or position	Tackle Patient Representative
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 also support local prostate cancer support groups around the UK. We represent 91 support groups in England and Wales and through them have 15,000 members - men and their families whose lives have been affected by prostate cancer.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	Astellas £35,000 General unrestricted funding to assist in all patient support activities undertaken by Tackle Prostate Cancer Janssen £10,000 General unrestricted funding to assist in all patient support activities undertaken by Tackle Prostate Cancer

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 Enzalutamide but have spoken with men who have. The clinical indication under discussion is a potentially new indication for use of the drug and thus no patient has direct experience of using it at this point in their treatment pathway. However, I have spoken with patients who are faced with the clinical scenario of newly diagnosed high risk metastatic disease and thus know of the problems that they face. I have spoken with men who have been treated with the comparator drug, Docetaxel, currently used in this situation.
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?	A man newly diagnosed with high risk metastatic hormone sensitive prostate cancer (ndhrHSPC) is given a total 'bombshell' of a diagnosis. Not only is he told he has a cancer but also the possibility that he only has a very 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 may 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, my experience of talking with men from support groups suggests that an increasing number of younger men are being diagnosed with ndhrHSPC as men become more aware of the need for PSA testing at an earlier age.

	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 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 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 if such treatment is appropriate. Where the patient lives and his ability to travel for treatment may be an added burden on the life not only of the patient but those who care for him at home. Side effects of treatment such as chemotherapy can be not only reflected physiologically in blood test 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’. *Quotations from patients:* *“Fatigue not just tiredness is often a real problem – as is ‘Chemo-Fog’…..”*

	"There is always the knowledge that your current treatment will fail…" *"How will I cope with the ever-stronger therapies and will they be successful…"*
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	The initial choice is standard ADT - normally intermittent injectable hormone therapy as a stand-alone treatment. This may initially work well but very many will go on to have progression of their metastases and require further treatment - currently chemotherapy with Docetaxel or additional ADT with abiraterone or enzalutamide. Because of the very positive results from trials of the use of a combination of ADT and chemotherapy, some men with ndhrHSPC are now offered this combination as first line therapy – although there is no actual specific licence for the use of docetaxel in this context. This has been shown to significantly increase survival time. For many men this is a very appropriate treatment option. However, recent data from the National Prostate Cancer Audit show that the uptake / use of this adjuvant therapy is not as high as it could be. For those men unable or unwilling to have chemotherapy, or those who experience considerable early side effects from chemotherapy, there is currently no alternative approved additional drug therapy that can be combined with standard ADT. Abiraterone or enzalutamide are restricted to use once ADT is shown to failing to control the cancer.
8. Is there an unmet need for patients with this condition?	Adjuvant therapy (i.e. Docetaxel) has been shown to delay the progression of prostate cancer, extend survival and increase quality of life for the patient. There are patients who are unable to have docetaxel because of age, pre-existing medical conditions or have been unable to continue Docetaxel because of adverse effects. Currently there is no other adjuvant therapy available to them.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Slowing 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. It allows patients time to plan the future of not only their own lives but that of those around them. However, this must be considered along with the downsides and side effects of treatment which can decrease quality of life. It can be a difficult balancing act. Many men have struggled with chemotherapy when it has been used as an additional therapy in men with progressive disease. Enzalutamide has been well tolerated by many men when used similarly as additional therapy. The ability to choose which drug to combine with standard ADT as early combined therapy would be of undoubted benefit to patients. Currently they, and the healthcare professionals responsible for their care, just simply do not have the ability to choose. It is a great unmet need and one which, if fulfilled, would certainly enhance the potential treatment of many men with ndhrHSPC. It is not the remit of a patient representative to be able to make a detailed study of research and statistics supporting an application. However, it would appear that the early use of standard ADT in combination with Enzalutamide is effective in slowing progression and extending life in this clinical scenario.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The ultimate aim for the patient in this clinical scenario is to provide the maximum benefit but with minimal additional side effects. Advantages of clinical benefit must be very similar to those drugs used in a similar fashion. The combined use of docetaxel and ADT is the main comparator. Enzalutamide is not without side effects such as headache, back pain hot flushes. It is also contra-indicated in patients with raised blood pressure or heart disease and patients with a history of seizures. However, it has been well

	tolerated by appropriate patients when used in its more common setting of end-stage relapsing metastatic disease. The potential side effects for Docetaxel are well recorded. A disadvantage could be the need for ongoing regular therapy for a prolonged period. Chemotherapy is only used intermittently and for a maximum number of sessions. However, regular daily oral medication is not a huge burden. There will be an increased need for regular monitoring of adverse events with blood tests and consultations with healthcare professionals Cost of therapy may be an issue and could put an additional financial burden on healthcare providers. This, however, is not the responsibility / concern of the patient and there may well be a P.A.S. in operation of which I obviously have no information. There is always the fear for patients that the provision of a treatment may be withheld because of cost issues - despite that therapy being approved by regulatory bodies.
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.	The group of patients that would benefit the most are those patients who currently are unable to be given adjuvant treatment with Docetaxel: • Direct drug contraindications / interaction with current medication / abreaction to this drug group • Patients medical unfit because of age / stage of disease / general health issues etc • Patient who have ceased initial treatment with Docetaxel because of adverse effects Currently there is no other choice of adjuvant drug – it is basically Docetaxel or nothing. In addition, there is always the possibility for prescribing to be on a ‘postcode lottery’ basis. Even when a drug is approved it may not be funded by every Commissioning Group.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**NO**
Other issues	
13. Are there any other issues that you would like the committee to consider?	The current approach to the treatment of prostate cancer could be criticised for being one that is 're-active' rather than being 'pro-active'. In general, single treatments are used until they become ineffective and then a further single treatment is added or substituted. Treatments for other cancers such as leukaemia, breast cancer, testicular cancer etc. are now very often based on combinations of treatments being used immediately after diagnosis since research and clinical experience have shown better eventual outcome with such a 'multi-modal' approach. Men with prostate cancer are often now aware of such a change in treatment schedules and may question a treatment regime that relies of a series of single therapies only. Some would certainly highlight the potential for multi-modal therapy being used more often in the treatment of prostate cancer. Docetaxel is currently used in combination with ADT as initial therapy despite being outside the product licence for such a use. It is now available as a generic product and costs are comparatively low. Patients will question the reasons for why drugs capable of being similarly effective are also not approved for use. They may well just assume that costs are the only reason.

	Quotes from patients: *"Why are we so far behind in our thinking when dealing with prostate cancer? Breast cancer treatment seems so much more advanced"* *"I just want whatever it takes to control my cancer…."* *"It seems I have a very limited choice to add to my hormone treatment – chemotherapy or nothing"* *"I can't have Docetaxel – so it looks as though I am basically now stuffed…."*

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- The diagnosis of any cancer is always a significant shock to the patient. To hear that the cancer has already spread is a further bitter blow. The distress caused cannot be under-estimated.
- A man with newly diagnosed high risk metastatic hormone sensitive prostate cancer will wish for (and not unreasonably expect) the most effective treatment regime to be available and offered to him. Current hormone therapy (ADT) when used as a 'stand alone' initial therapy is less effective in slowing progression of disease and extending life-span than when combined with an appropriate additional therapy.
- Treatments offered should have the maximum efficacy and the minimum of side effects. This can be a difficult balancing act as there is a wide variety in the degree of side effects experienced by individual patients. Patients who are medically unsuitable for Docetaxel therapy currently have no other alternative for adjuvant therapy.

• There is an unmet need for additional therapies that may be used similarly to the current regime of ADT and docetaxel. The choice of which adjuvant therapy to use should be one made as a joint decision between clinician and patient. Currently the only choice available is Docetaxel or nothing. • Enzalutamide would appear to fulfil this unmet need and add an extra dimension to adjuvant therapy available.

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Enzalutamide with ADT for treating metastatic hormone-sensitive prostate cancer [ID1605]

Produced by Aberdeen HTA Group

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Daniel Kopasker, Andrew Walker and Graham Scotland, acted as health economists for this appraisal: critiqued the cost-effectiveness evidence and checked the economic model submitted by the company, and conducted further sensitivity analyses. Clare Robertson and Mari Imamura acted as systematic reviewers: critiqued the company's definition of the decision problem and the clinical effectiveness evidence reported in the company submission. Lorna Aucott with help from Thenmalar Vadiveloo acted as lead statistician for this appraisal: critiqued the statistical methods presented in the company submission, checked the numerical results, analyses, tables, and figures related to the review of the clinical effectiveness evidence and conducted additional analyses. Paul Mason acted as information scientist: critiqued the methods used for identifying relevant studies and checked the search strategies presented in the

company submission. Gordon Urquhart acted as clinical advisor: provided clinical advice and general guidance during the appraisal. Miriam Brazzelli acted as lead for the clinical effectiveness side of the appraisal. Graham Scotland acted as lead on the cost-effectiveness side of the appraisal. All authors contributed to the writing of this report and approved its final version.

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List of abbreviations

ADT	Androgen deprivation therapy
AR	Androgen receptor
CAB	Combined androgen blockade
CS	Company submission
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EMA	European Medicines Agency
ERG	Evidence review group
FACT-P	Functional Assessment of Cancer Therapy – Prostate
FDA	Food and Drug Administration
HNPC	Hormone-naïve
HRQOL	Health-related quality of life
HVD	High volume disease
ICR	Independent central review
ITT	Intention to treat
LHRH	Luteinizing hormone-releasing hormone
LVD	Low volume disease
MAB	Maximum androgen blockade
mHRPC	Metastatic hormone-relapsed prostate cancer
mHSPC	Metastatic hormone-sensitive prostate cancer
nmHSPC	Non-metastatic hormone-sensitive prostate cancer
OS	Overall survival
PFS	Progression-free survival
PSA	Prostate-specific antigen
SAE	Serious adverse event
SRE	Skeletal-related event
TEAEs	Treatment-emergent adverse events
TINAT	Time to new antineoplastic therapy
TTD	Time to treatment discontinuation

1 Summary

1.1 Critique of the decision problem in the company submission

The company, Astellas, provide clinical and cost-effectiveness evidence for enzalutamide (XTANDI®) with ADT for treating metastatic hormone-sensitive prostate cancer (mHSPC). As highlighted in Chapter 2 of this report, the decision problem addressed by the company is aligned with the final scope issued by NICE, with a few minor differences in the choice of comparators and outcomes. In particular, the company were unable to consider the subgroups of interest due to a paucity of evidence. These differences are outlined in Table 1 below.

Table 1 Differences in the company decision problem and final scope issued by NICE

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comments
Comparator(s)	• Androgen deprivation therapy alone (including orchidectomy, luteinising hormone-releasing hormone agonist therapy) or monotherapy with bicalutamide • Docetaxel with androgen deprivation therapy For people with newly diagnosed high-risk disease: Abiraterone with prednisone or prednisolone and androgen deprivation therapy (subject to ongoing NICE appraisal)	• Androgen deprivation therapy alone (including orchidectomy, luteinising hormone-releasing hormone agonist therapy) or monotherapy with bicalutamide Docetaxel with androgen deprivation therapy	At the time of this submission, NICE was still assessing the abiraterone submission in patients with newly diagnosed high-risk. Abiraterone is not standard of care or recommended in the NICE guidance in England or Wales and therefore, the Company does not consider abiraterone a relevant comparator for enzalutamide.	The ERG agrees with the company's choice of comparators A NMA was conducted to assess the clinical effectiveness of enzalutamide versus docetaxel.
Outcomes	The outcome measures to be considered include: • Time to prostate-specific antigen (PSA) progression • Progression-free survival (PFS) • Overall survival (OS) • Adverse effects of treatment • Health-related quality of life (HRQoL).	The list of outcomes presented in this submission is as follows: • Time to prostate-specific antigen (PSA) progression • Progression-free survival (PFS) • Overall survival (OS) • Time to treatment discontinuation (TTD)	The list of outcomes in the final scope is not exhaustive. Given the disease evolution of patients with mHSPC and proposed positioning of enzalutamide in this setting, additional outcomes such as time to discontinuation or time to next therapy for prostate cancer are relevant for the enzalutamide health economic model	The company's submission addresses the outcomes listed in the final scope as well as additional outcomes. The outcomes considered in the economic model are PFS, OS and TTD.

		• Time to new antineoplastic therapy (TINAT) • Adverse effects of treatment • Health-related quality of life (HRQoL).		
Subgroups	If the evidence allows, the following subgroups of people could be considered: • People with newly diagnosed metastatic prostate cancer • People with high-risk metastatic prostate cancer	None	Lack of evidence for the efficacy of docetaxel in the subgroups of high risk mHSPC patients and newly diagnosed mHSPC patients. Docetaxel studies provide efficacy data per patients based on disease volume but not level of risk. In addition, docetaxel studies include both patients with de novo and relapsed mHSPC.	The ERG agrees with the rationale provided by the company.

1.2 Summary of the key issues in the clinical effectiveness evidence

Overall, the ERG considers that the methods used by the company to conduct their systematic review are robust and in line with current methodological standards. The key clinical effectiveness evidence provided by the company consists of two enzalutamide Phase III randomised controlled trials: ARCHES and ENZAMET. ARCHES compared enzalutamide plus ADT with ADT plus placebo in 1,150 patients with mHSPC (median follow up 14.4 months) while ENZAMET compared enzalutamide plus ADT with conventional non-steroidal anti-androgen (NSAA) plus ADT in 1,125 patients with mHSPC (median follow up 33.8 months). Only the data for the ENZAMET patient subgroup (622 patients) with no concomitant docetaxel match the patient population specified in the NICE final scope, therefore the company limited presentation of results to this subgroup in the CS. The ERG agrees with this rationale. Data for the entire ARCHES population were considered relevant and most representative of patients seen in UK clinical practice. The ERG considers both trials of good methodological quality; however, the clinical characteristics of the enrolled patients differed between the two studies. While the two trial populations were similar in terms of mainly favourable ECOG status at baseline, compared with ENZAMET, ARCHES included a higher proportion of participants with a Gleason score $\geq$8 at time of diagnosis and a higher proportion of high-volume disease patients. The trials also differed in their definitions of progression-free survival (PFS). Radiographic PFS (rPFS) was the primary endpoint in ARCHES, while clinical PFS (cPFS) was assessed in ENZAMET. The company recognised also that the median follow-up in ARCHES was too short to demonstrate benefit in terms of overall survival (OS).

Results of the ARCHES trial indicate that in the overall population enzalutamide plus ADT reduced the risk of radiographic disease progression by 61% compared with placebo plus ADT but did not show a significant improvement in OS. With regard to the secondary endpoints, enzalutamide plus ADT demonstrated significant benefits compared with placebo plus ADT in TTD, TINAT ORR, time to first SSE, and time to castration resistance and a non-significant trend towards a delay in time to deterioration in urinary symptoms and time to pain progression. The benefit of enzalutamide plus ADT versus placebo plus ADT for all relevant endpoints was consistent across pre-specified subgroups with the exception of OS.

The results of the ENZAMET trial indicate that, compared with NSAA plus ADT, enzalutamide plus ADT reduced the risk of death in patients receiving no concomitant docetaxel by 47.2%, the risk of PSA by 76% and the risk of cPFS by 66%. Enzalutamide plus ADT was also associated with a reduction in the risk of treatment discontinuation and longer time to HRQOL deterioration. The benefit of enzalutamide plus ADT versus NSAA plus ADT for all relevant endpoints was consistent across subgroups.

The company did not perform a meta-analysis of the two trials, choosing to conduct a 'pooled analysis' for the total population in ARCHES and the ENZAMET patient subgroup with no concomitant docetaxel for OS and time to treatment discontinuation (TTD) to inform the economic model. The methods used for the pooled analysis were not provided in the CS and it is unclear whether it was the aggregated results or individual patient data from each trial that were combined, and if and how trial results were weighted. The company was unable to adjust the ARCHES rPFS definition to match the ENZAMET cPFS definition due to lack of available data and therefore did not used the pooled PFS results in the economic model. For the pooling the company assumed that efficacy of ADT plus placebo in ARCHES was comparable to that of NSAA plus ADT IN ENZAMET.

The ERG agrees with the company's that differences across trials in terms of comparator treatment (placebo plus ADT in ARCHES and NSAA plus ADT in ENZAMET) and distribution of high and low volume disease patients (lower proportion of high-volume disease patients in ENZAMET than in ARCHES) limited the possibility to conduct meaningful meta-analyses. The results of the pooled analyses indicate statistically significant benefits of enzalutamide plus ADT compared with ADT plus NSAA for OS and TTD. However, the ERG is of the opinion that in view of the differences across the two trials the pooled results should be interpreted with caution.

The company conducted NMAs to assess the relative effectiveness of enzalutamide plus ADT versus docetaxel for patients with mHSPC. Thirteen studies were included in the evidence network (counting the 3-arms in the STAMPEDE trial as three separate studies). The heterogeneity across studies in terms of study population and

patient characteristics casts some doubts about the validity and robustness of the NMA results. The ERG replicated the NMA results using the data provided initially in the CS and the updated data provided at clarification and conducted additional analyses. The ERG confirms that for OS there is some evidence that enzalutamide plus ADT compared with ADT alone is beneficial when studies with longer follow up are included in the network (i.e., ENZAMET, new STAMPEDE 1). When only the enzalutamide ARCHES trial (and not ENZAMET) is included in the NMA, this evidence becomes non-significant. However, for the comparison between enzalutamide and docetaxel while the point estimate favour enzalutamide plus ADT this benefit does not reach statistical significance in any of the models.

[redacted]

For OS and PFS, the NMA results preferred by the ERG are those of the base cases using the updated information provided by the company at clarification (new data from STAMPEDE 1 and exclusion of abiraterone and apalutamide data).

1.3 Summary of the key issues in the cost effectiveness evidence

The company submitted a partitioned survival model comparing enzalutamide plus ADT with ADT alone and with docetaxel plus ADT for people with mHSPC. The pre-progressed state (mHSPC) was divided into time on and time off treatment to allow for discontinuation of treatment prior to progression. For enzalutamide plus ADT and ADT alone, the company base case used extrapolations of rPFS data from ARCHES and pooled OS data from ARCHES and ENZAMET to partition the cohort between progression free, progressed and dead over a 30-year time horizon. A monthly cycle was used. The TTD data for enzalutamide from ARCHES was extrapolated and used to divide patients between the on and off-treatment mHSPC sub-states. For docetaxel plus ADT, the rPFS and OS curves were derived by applying hazard ratios from the NMA to the 'ADT alone' reference curves. The company also

provided a scenario where enzalutamide plus ADT was modelled using HRs versus 'ADT alone' derived from the NMA.

The progressed disease state (mHRPC) was further divided into three states PD1-PD3, reflecting subsequent treatment lines available to patients upon progression. Data from relevant trials in mHRPC were used to inform expected times in the progressive disease states, which were used within an accompanying Markov implementation of the same model to determine the distributions of patients across each of the three progressive disease states over each cycle of the model. These proportional distributions were fed into the PartSA model. The assumptions in the company base case give a deterministic ICER for enzalutamide plus ADT of £19,911 versus ADT alone and £22,877 versus docetaxel plus ADT.

The ERG believes the following to the be the key issues and uncertainties in the cost-effectiveness evidence:

1. The PFS and OS data from ARCHES and ENZAMET are immature (i.e. median survival not reached for enzalutamide), which leads to a high degree of uncertainty around the lifetime extrapolations which inform the model (see 4.2.6).
2. Based on clinical expert opinion and uncertainties reflected in the output of the NMA, the ERG believes the company may have substantially overestimated the PFS and OS benefits for enzalutamide plus ADT. In particular, it is the ERG's opinion that the company's estimated life year and QALY gains compared to docetaxel plus ADT lack face validity when considered in the context of the estimated effect of enzalutamide versus docetaxel on OS that emerges from the NMA; i.e. the estimated HR from the NMA is modest (Company revised estimate: [redacted] in comparison to the relative benefits implied by the company base case (which estimated a gain of [redacted] life-years and [redacted] QALYs) (see 4.2.6).
3. Related to point 2, the company base case reliance on independently fitted curves for enzalutamide results in the hazards of mortality diverging across the treatment arms for the majority of the model time horizon; i.e. the proportional reduction in the hazard of mortality with enzalutamide versus the comparators

increases out to 21 years before reducing slightly when general population mortality overrides the extrapolated mortality rate in the enzalutamide arm.

4. Based on available external sources to validate the rPFS and OS extrapolations for docetaxel plus ADT and ADT alone, the ERG believes that the company have underestimated PFS and to a lesser extent OS for the comparator arms of the model.
5. The company's base case extrapolation of TTD for enzalutamide diverges quite substantially from rPFS, resulting in a substantial proportion of patients in the enzalutamide plus ADT arm being off-treatment (no costs of enzalutamide) and progression free.
6. The utility values for progressive disease appear to remain too high across the progressive disease sub-states compared to the values applied in previous TAs in the mHRPC setting.

1.4 Summary of the ERG's preferred assumptions and resulting ICER

The ERG's preferred assumptions are as follows:

- On balance, given the immaturity of the OS data from the enzalutamide trials, the ERG prefers to rely on the HRs from the NMA to model PFS and OS for both docetaxel plus ADT and enzalutamide plus ADT (relative to the ADT reference curves).
- This also assumes that treatment with enzalutamide continues until progression.
- Based on comparison with external long-term survival data, the ERG prefers to use the company's fitted exponential curve for PFS on ADT alone, and to retain the company's base case Weibull curve for OS.
- In addition, the ERG prefers revised utilities for the progressive disease states that are more in keeping with the previous appraisal of enzalutamide for mHRPC prior to chemotherapy.
- Finally, the ERG base case makes a correction for what it believes may be a bug in the company model around the application of adverse event QALY decrements.

With these combined changes, the deterministic ICER for enzalutamide comes to £33,719 per QALY gained versus ADT alone and £47,972 per QALY gained versus docetaxel plus ADT (Table 1). These results include the PAS discount for enzalutamide, but do not include available discounts for subsequent therapies.

Table 1 Incremental cost-effectiveness results with ERGs preferred base case assumptions

Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER* (QALYs)	ICER vs baseline (QALY)
ADT alone	[redacted]	[redacted]	[redacted]				-	-
Docetaxel plus ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£9,850	£9,850
Enzalutamide plus ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,972	£33,719

*ICER versus next less costly non-dominated alternative.

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

As a result of the issues identified above, the ERG explored scenarios with alternative curve extrapolations; scenarios that equalised hazards of progression and OS between the treatment arms from set points in time; and further scenarios that also utilised the hazard ratios for enzalutamide versus ADT alone from the company NMA (rather than independently fitted curves). The ERG has also explored the application of utility values in the progressed disease state that are more in line with those used in previous appraisals of enzalutamide in mHRPC, and alternative costing assumptions. These scenarios indicate that the model results are most sensitive to alternative extrapolation assumptions that reduce the OS benefits of enzalutamide versus ADT alone and docetaxel plus ADT. These include the application of the NMA HRs for enzalutamide, and the equalisation of hazards of mortality from specified points in time. A further scenario illustrates the importance of the selected curve for time on treatment with enzalutamide when using independently fitted curves to model PFS.

2 Background

2.1 Critique of company's description of underlying health problems

The relevant health condition for this submission is metastatic hormone-sensitive prostate cancer (mHSPC). The company's description of mHSPC in terms of prevalence, symptoms and complications appears accurate to the decision problem.

Prostate cancer is classified based on its responsiveness to hormonal therapy (i.e. responsiveness to androgen deprivation therapy [ADT] or surgical castration) and the extent of the disease as localised, locally advanced or metastatic. In a UK study of 1,643 patients with localised prostate cancer, 3.8% (n = 62) developed metastases within 10 years.[2] The rate of progression to metastases was 6.3 per 1,000 person-years in patients who underwent active surveillance for their disease, 3.0 per 1,000 person-years in patients who underwent radiotherapy, and 2.4 per 1,000 person-years in patients who underwent surgery. On average, within 12 months of developing mHSPC, most patients progress toward metastatic hormone-relapsed prostate cancer (mHRPC) on ADT alone.[3-5]

Metastatic disease is associated with potentially serious complications and deterioration in health-related quality of life (HRQOL). Patients with bone metastases are at high risk of skeletal-related events (SREs) and visceral disease, commonly including liver and lung metastases, is a negative prognostic factor associated with reduced survival.[6, 7] mHSPC can be classified as high or low volume disease (HVD or LVD) depending on the number and site of metastases, although definitions vary between studies and there is no consensus on criteria for determining HVD or LVD. mHSPC can also be classified as high or low risk. High risk factors are associated with poor prognosis. Patients with newly diagnosed mHSPC also have worse median overall survival (OS) compared with recurrent disease. The company present data from a cohort of 192 recurrent and 215 newly diagnosed mHSPC patients treated with ADT between 1990 and 2013[8] in Table 3, Document B. The median OS was longest for recurrent LVD patients (92.4 [95% CI 80.4, 127.2] months) and shortest for newly diagnosed HVD patients (43.2 [95% CI 37.5, 56.4] months).

2.2 Critique of company's overview of current service provision

The company's description of current service provision is accurate. The ERG agrees with the company that treatment options are informed by on a mixture of symptomatic, tumour burden, pathology and biochemical criteria allied to patient performance status and preference.[9]

NICE guideline NG131 recommends docetaxel plus ADT for people with newly diagnosed mHSPC without significant comorbidities[10]. All other patients should be treated with ADT alone, either surgically or with a luteinizing hormone-releasing hormone (LHRH) agonist. Docetaxel treatment should start within 12 weeks of starting ADT. NICE does not recommend combined/maximum androgen blockade (CAB/MAB) as a first-line treatment for people with mHSPC; however, patients should be offered monotherapy with bicalutamide (150 mg), if the patient is willing to accept the high risk of gynaecomastia, with the aim of retaining sexual function. Monotherapy with bicalutamide has not shown a survival benefit.[10]

The company state that they expect enzalutamide will be administered to all mHSPC patients regardless of whether they are newly diagnosed or recurrent and independent of the metastatic disease volume or risk level.

2.3 Critique of company's definition of the decision problem

The text and Table 3 below summarise the decision problem in relation to the NICE final scope. A critique of how the company's economic modelling adheres to the NICE reference case is provided in Chapter 4.

2.3.1 Population

The population addressed in the NICE final scope and the company submission (CS) is adults with mHSPC. This population includes patients who are newly diagnosed at the metastatic stage (de novo mHSPC) and patients with a previous history of non-metastatic hormone-sensitive prostate cancer (nmHSPC) who have progressed (i.e. recurrent mHSPC). Newly diagnosed patients include those who have not received ADT or any other hormonal therapy (hormone-naïve [HNPC]) and patients who have initiated ADT and are still responsive.

2.3.2 Intervention

The intervention in both the NICE final scope and the CS is enzalutamide in combination with ADT. The company provides details of the technology in Table 2, Document B, and in the summary of product characteristics and European public assessment report in Appendix C of the CS. Briefly, prostate cancer is androgen-sensitive and responds to inhibition of androgen receptor (AR) signalling. Enzalutamide is an AR signalling inhibitor that targets the AR signalling pathway by blocking androgen binding, inhibiting nuclear translocation and impairing DNA binding, which inhibits gene transcription.[11-13] The licenced application for enzalutamide for mHSPC is one daily oral dose of 160 mg, taken as four 40 mg tablets.[11] No additional tests are required for the administration of enzalutamide or identification of patients that are suitable to receive enzalutamide. Enzalutamide should be used with caution in people with severe renal impairment.[14] Patients engaged in sexual activity with a pregnant partner or partner of childbearing potential should use condoms in combination with another contraceptive during, and for 3 months following, enzalutamide treatment.[14] The company state they are conducting active pharmacovigilance for the following safety concerns: seizures, falls, non-pathological fractures and ischemic heart disease.

The U.S. Food and Drug Administration (FDA) approved enzalutamide for mHSPC on 16th December 2019.[15] The company state that they expect the European Medicines Agency (EMA) to authorise enzalutamide for mHSPC by June or July 2020. At the time of submission, enzalutamide has European market authorisation for the following indications:

- "Treatment of adult men with mCRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated"
- "Treatment of adult men with mCRPC whose disease has progressed on or after docetaxel therapy"
- "Treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (nmCRPC

2.3.3 Comparators

Both the NICE final scope and the CS address the following comparators:

- Androgen deprivation therapy alone (including orchidectomy, luteinising hormone-releasing hormone agonist therapy) or monotherapy with bicalutamide
- Docetaxel with androgen deprivation therapy

The NICE final scope also includes abiraterone with prednisone or prednisolone and ADT for people with newly diagnosed high-risk disease, subject to ongoing NICE appraisal. The company have not addressed this comparator in the CS as, at the time of submission, abiraterone use in patients with newly diagnosed, high-risk mHSPC was still under assessment by NICE and is not currently recommended treatment in England and Wales. The ERG agrees with the company that abiraterone is not a relevant comparator for this submission.

2.3.4 Outcomes

The outcomes considered in the NICE final scope and the CS include: time to prostate-specific antigen (PSA) progression, progression-free survival (PFS), overall survival (OS), adverse effects of treatment and HRQOL. In addition, the CS addresses the following outcomes: time to treatment discontinuation (TTD) and time to new antineoplastic therapy (TINAT). The ERG notes that the two pivotal trials presented in the CS included different PFS definitions: defined as radiographic PFS in ARCHES[1] and clinical PFS in ENZAMET[16]. The company report that their pooled analysis of PFS was based on a modified definition of PFS in ARCHES to more closely match the ENZAMET definition; however, no data on the development of symptoms attributable to cancer progression were available for ARCHES patients and the modified definition could not be matched to ENZAMET. Details of the PFS definitions used in the trials and the company's pooled analysis are presented in Table 2.

Table 2 PFS definition used in the ARCHES and ENZAMET trial and in the pooled analysis (reproduced from Table 6 of Document B, CS)

	ARCHES[1]	ENZAMET[16]
Definition used in Trial	Radiographic PFS was defined as time to objective evidence of rPD as assessed by ICR or death, as follows: • Death from any cause within 24 weeks (2 scan cycles) from study drug discontinuation • rPD defined by RECIST 1.1 for soft tissue disease or the appearance of 2 or more new bone lesions on bone scan. The date of rPD was the date when the first objective evidence of rPD was documented. Unconfirmed disease progression on bone scan at week 13 was not considered as an event.	Clinical PFS was defined as the interval from the date of randomisation to the date of first clinical evidence of disease progression or death from any cause, whichever occurs first, or the date of last known follow-up without clinical progression. Clinical progression was defined by progression on imaging (PCWG2 criteria for bone lesions and RECIST 1.1 for soft tissue lesions), development of symptoms attributable to cancer progression or initiation of other anticancer treatment for prostate cancer.
Definition used in pooled analysis	Time to death, rPFS (as in ARCHES) or start of new antineoplastic treatment. No data on the development of symptoms attributable to cancer progression were available for ARCHES.	Same as in the trial

2.3.5 Other relevant factors

The ERG agrees that that there are no known equality issues for this submission.

A summary of the decision problem is presented in Table 3.

Table 3 Summary of the decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comments
Population	People with metastatic hormone-sensitive prostate cancer (mHSPC)	As per final scope	NA	The clinical evidence submitted by the company matches the patient population described in the NICE final scope and is comparable with the characteristics of the patient population eligible for this treatment in clinical practice.
Intervention	Enzalutamide in combination with androgen deprivation therapy (ADT)	As per final scope	NA	The intervention described in the company's submission matches the NICE final scope. The U.S. Food and Drug Administration (FDA) approved enzalutamide for mHSPC on 16th December 2019.[15] EMA authorisation is expected by June or July 2020. At the time of submission, enzalutamide has European market authorisation for the following indications: • "Treatment of adult men with mCRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy

				in whom chemotherapy is not yet clinically indicated" • "Treatment of adult men with mCRPC whose disease has progressed on or after docetaxel therapy" • "Treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (nmCRPC)"
Comparator(s)	• Androgen deprivation therapy alone (including orchidectomy, luteinising hormone-releasing hormone agonist therapy) or monotherapy with bicalutamide • Docetaxel with androgen deprivation therapy For people with newly diagnosed high-risk disease: Abiraterone with prednisone or prednisolone and androgen deprivation therapy (subject to ongoing NICE appraisal)	• Androgen deprivation therapy alone (including orchidectomy, luteinising hormone-releasing hormone agonist therapy) or monotherapy with bicalutamide Docetaxel with androgen deprivation therapy	At the time of this submission, NICE was still assessing the abiraterone submission in patients with newly diagnosed high-risk. Abiraterone is not standard of care or recommended in the NICE guidance[17] in England or Wales and therefore, the Company does not consider abiraterone a relevant comparator for enzalutamide.	The ERG agrees with the company's choice of comparators A NMA was conducted to assess the clinical effectiveness of enzalutamide versus docetaxel.
Outcomes	The outcome measures to be considered include: • Time to prostate-specific antigen (PSA) progression • Progression-free survival (PFS) • Overall survival (OS)	The list of outcomes presented in this submission is as follows: • Time to prostate-specific antigen (PSA) progression	The list of outcomes in the final scope is not exhaustive. Given the disease evolution of patients with mHSPC and proposed positioning of enzalutamide in this setting, additional outcomes such as time to discontinuation or	The company's submission addresses the outcomes listed in the final scope as well as additional outcomes. The outcomes considered in the economic model are PFS, OS and TTD.

	• Adverse effects of treatment • Health-related quality of life (HRQoL).	• Progression-free survival (PFS) • Overall survival (OS) • Time to treatment discontinuation (TTD) • Time to new antineoplastic therapy (TINAT) • Adverse effects of treatment • Health-related quality of life (HRQoL).	time to next therapy for prostate cancer are relevant for the enzalutamide health economic model	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.	As per final scope	NA	Outcomes were assessed over a time horizon of 30 years.
Subgroups	If the evidence allows, the following subgroups of people could be considered: • People with newly diagnosed metastatic prostate cancer • People with high-risk metastatic prostate cancer	None	Lack of evidence for the efficacy of docetaxel in the subgroups of high risk mHSPC patients and newly diagnosed mHSPC patients. Docetaxel studies provide efficacy data per patients based on disease volume but not level of risk. In addition, docetaxel studies include	The ERG agrees with the rationale provided by the company.

			both patients with de novo and relapsed mHSPC.	
Special considerations including issues related to equity or equality	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	As per final scope	NA	No special considerations related to equity or equality.

3 Clinical effectiveness

3.1 Critique of the methods of review(s)

Full details of the methods used to identify and select the relevant clinical evidence are reported in section B.2.1 and Appendix D of the CS. The ERG appraisal of the company's systematic review methods is summarised in Table 4 below.

Table 4 ERG appraisal of the systematic review methods presented in the CS

Review process ERG	ERG response	Comments
Were appropriate searches (e.g., search terms, search dates) performed to identify all relevant clinical and safety studies?	Yes	The searches included appropriate index terms relevant to each electronic database and extensive text terms. The search terms and combinations used are clearly documented in Appendix D of the CS and are fully reproducible.
Were appropriate bibliographic databases/sources searched?	Yes	Sources included PubMed, Ovid Medline (including In-Process), Ovid Embase, and Cochrane CENTRAL. See CS, Appendix D1.1.1, Table 78
Were eligibility criteria consistent with the decision problem outlined in the NICE final scope?	Yes	The company's systematic review had a wider scope than the NICE final scope, therefore, only the comparator treatments relevant to the decision problem were presented in the CS. See CS, section B.2.1, Table 4.
Was study selection conducted by two or more reviewers independently?	Unclear	The search presented in the CS is a subset of a broader search conducted for a systematic literature review of enzalutamide and all current treatments for mHSPC. Search results were rapidly assessed by two reviewers to remove obviously irrelevant records, although it is not clear whether the two reviewers worked independently of each other. The remaining records were assessed further by one reviewer with 'quality checking' (no further detail) provided by a second reviewer. Based on the searches conducted in May 2019, the company identified 41 eligible studies (from 71 articles), of which 18 studies were deemed relevant for the submission (Note that this includes one 3-arm trial, STAMPEDE[18]; when considering each of the STAMPEDE arm comparison as a single study, the number of included studies totalled to 20). At clarification the company provided specific reasons for reducing the number from 41 to 18; the ERG considers these reasons for exclusion to be

		reasonable. The company identified two randomised Phase III trials, ARCHES and ENZAMET, as the main source of evidence for the efficacy and safety of enzalutamide plus ADT for adults with mHSPC. With respect to the NMA, 20 of the 41 eligible studies (counting the 3-arm STAMPEDE trial as 3 studies) met the selection criteria. Thirteen of these studies were included in the NMA, while seven were excluded due to limited information available in the published articles (Section B.2.9 of the CS). An overview of the 20 studies eligible for the NMA is shown in Table 28, Section B.2.9.2, and a summary characteristics of the 13 studies included in the NMA are provided in Table 82, Appendix D1.1.2, of the CS.
Was data extraction conducted by two or more reviewers independently?	Yes	Data were extracted from study reports by one reviewer and 25% of records were checked by a second reviewer. A third reviewer resolved any discordant data extraction.
Were appropriate criteria used to assess the risk of bias of identified studies?	Yes	The risk of bias assessment of the two relevant RCTs was based on the ten-item list suggested in the NICE STA guidance. See CS, Section B.2.5, and Appendix D.1.3, Table 83.
Was risk of bias assessment conducted by two or more reviewers independently?	Unclear	The assessment was conducted by one reviewer, with a sample of records (no further detail provided) checked by a second reviewer, and a third reviewer resolved any discordance. It is unclear whether reviewers worked independently.
Was identified evidence synthesised using appropriate methods?	Unclear	The results of the two RCTs, ARCHES and ENZAMET, were not combined in a meta-analysis. Instead, the company carried out a 'pooled analysis' for the total population of ARCHES and the patient subgroup with no concomitant docetaxel in ENZAMET. The methods used for the pooled analysis were not provided in the CS. It is unclear whether aggregate data or individual patient data from each trial were combined, and whether and how the trials were weighted. See section B.2.8 of the CS. To assess the comparative clinical effectiveness of enzalutamide versus docetaxel the company conducted a NMA. See section B.2.9 of the CS.

Overall, The ERG considers the methods used by the company to conduct the systematic review of clinical effectiveness evidence to be acceptable according to

current methodological standards. In particular, it is unlikely that other relevant enzalutamide trials have been omitted from the submission.

The ERG conducted a quality assessment of the methods used by the company for the systematic review of clinical evidence using the Centre for Review and Dissemination (CRD) criteria; results are presented in Table 5.

Table 5 Quality assessment of the company's systematic review of clinical effectiveness evidence

CRD quality item	Yes/No/Unclear
1. Are any inclusion/exclusion criteria reported relating to the primary studies, which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all of the relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Are sufficient details of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

3.1.1 Evidence synthesis

The main source of evidence submitted by the company consists of two Phase III randomised controlled trials, ARCHES and ENZAMET. The two trials, sponsored by the company, assessed the efficacy of enzalutamide for people with metastatic hormone sensitive prostate cancer (mHSPC). The trial methods are summarised in Section B.2.3 and the participant flow of each trial is presented in Figures 30-31, Appendix D1.2, of the CS.

ARCHES[1] was a multi-centre, double-blind, placebo-controlled trial with a median follow-up of **14.4 months** in which enzalutamide (160 mg daily) was compared with matched placebo. The study population comprised a total of **1,150 participants** with mHSPC and ECOG performance score of 0-1, randomised in a 1:1 ratio to receive either **enzalutamide plus androgen deprivation therapy (ADT) or placebo plus ADT**. Patients could have received up to six cycles of docetaxel prior to randomisation. Randomisation was stratified by volume disease (low vs high) and previous docetaxel therapy (no docetaxel, 1 to 5 cycles, 6 cycles). Patients remained

on study treatment until radiographic progression was documented by independent central imaging review or until the initiation of new therapy for prostate cancer or until other discontinuation criteria were met. Patients who discontinued study treatment without radiographic disease progression were followed until confirmed radiographic progression by central imaging review or until the target number of radiographic progression events was reached. Some patients were eligible for transition to an optional open-label extension after study unblinding, which was not included in the CS.

ENZAMET[16] was a multi-centre, open-label randomized trial with a median follow-up of **33.8 months** in which enzalutamide (160 mg daily) was compared with conventional non-steroidal anti-androgen (NSAA). The study population comprised a total of **1,125 participants** with mHSPC and ECOG performance score of 0-2, randomised in a 1:1 ratio to receive either **enzalutamide plus ADT or NSAA plus ADT**. NSAA was either bicalutamide 50 mg daily, nilutamide 150 mg daily or flutamide 250 mg twice daily. Patients could have received up to two cycles of docetaxel prior to randomisation, as well as up to 6 cycles of concomitant docetaxel. Randomisation was stratified by volume disease (low vs high), study site, comorbidities, use of anti-resorptive therapy and planned use of docetaxel. Patients remained on study treatment until clinical evidence of disease progression or prohibitive toxicity. Only data for the patient subgroup with no concomitant docetaxel (N = 622), which meet the remit of the NICE final scope, were presented in the CS.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

3.2.1 ARCHES and ENZAMET trials

Based on the ten-item NICE checklist, the methodological quality was judged to be 'high' in both trials (Section B.5; Table 83 in Appendix D1.3). In general, the ERG agrees with the assessment made by the company

The two trials enrolled people with mHSPC. Demographic and baseline disease characteristics appear in Tables 8 and 9, Section B.2.3.2 of the CS and are

summarised in Table 6 below. The majority of ARCHES participants were recruited in Europe (60%), while the majority of the ENZAMET subgroup with no concomitant docetaxel came from Australia and New Zealand (around 65%). [redacted] of the 1150 participants in ARCHES and [redacted] of the 622 participants in the ENZAMET relevant subgroup were recruited from UK centres.

In both trials, baseline characteristics were well-balanced between study arms. At randomisation, the median age was around 70 years in both arms of both trials. The majority of participants had an ECOG performance status score of 0 at study entry (78.0% vs. 76.9% in ARCHES and [redacted] vs. [redacted] in ENZAMET) and no prior docetaxel chemotherapy (82.1% vs. 82.3% in ARCHES and [redacted] vs. [redacted] in ENZAMET). The ERG clinical expert is of the opinion that the patients enrolled in the two trials are not clinically dissimilar to the broader patient population with mHSPC to which enzalutamide + ADT would be offered.

Nevertheless, clinical characteristics of enrolled patients differed across the two studies. Compared with ENZAMET, ARCHES included a higher proportion of participants with a Gleason score of ≥8 at the time of diagnosis (67.2% vs. 64.8% in ARCHES and [redacted] vs. [redacted] in ENZAMET), high-volume disease (defined as ≥4 bone metastases, at least one of which was outside the spine or pelvis, and/or visceral metastases) (61.7% vs. 64.8% in ARCHES and [redacted] vs. [redacted] in ENZAMET) and prior ADT (73.2% vs. 89.2% in ARCHES and [redacted] vs. [redacted] in ENZAMET). Because of these characteristics, the company suggested that ARCHES participants were more similar to those seen in clinical practice than ENZAMET participants.[9]

Table 6 Selected demographic and baseline disease characteristics in ARCHES and ENZAMET (adapted from Tables 8 and 9 of the CS)

	ARCHES		ENZAMET (no concomitant docetaxel)	
	ENZA+ADT (n=574)	**PLA+ADT (n=576)**	**ENZA+ADT (n=309)**	**NSAA+ADT (n=313)**
Age (years)				
Median	70.0	70.0	[redacted]	[redacted]
Geographic region, n (%)				
Europe	341 (59.4)	344 (59.7)	[redacted]	[redacted]
North America	86 (15.0)	77 (13.4)	[redacted]	[redacted]
South America	32 (5.6)	30 (5.2)	-	-
Asia-Pacific	104 (18.1)	113 (19.6)	-	-
Australia/New Zealand	-	-	[redacted]	[redacted]
Other	11 (1.9)	12 (2.1)	-	-
Body mass index (kg/m^2)				
Mean (SD)	27.20 (4.44), N=567	27.21 (4.61), N=570	[redacted]	[redacted]
ECOG performance status at study entry, n (%)				
0	448 (78.0)	443 (76.9)	[redacted]	[redacted]
1	125 (21.8)	133 (23.1)	[redacted]	[redacted]
2	-	-	[redacted]	[redacted]
Total Gleason score at initial diagnosis, n (%)				
<8	171 (29.8)	187 (32.5)	[redacted]	[redacted]
≥8	386 (67.2)	373 (64.8)	[redacted]	[redacted]
Unknown or missing	-	-	[redacted]	[redacted]
Volume of disease, n (%)				
Low	220 (38.3)	203 (35.2)	[redacted]	[redacted]
High	354 (61.7)	373 (64.8)	[redacted]	[redacted]
Prior docetaxel therapy use, n (%)				
No	471 (82.1)	474 (82.3)	[redacted]	[redacted]
Yes	103 (17.9)	102 (17.7)	[redacted]	[redacted]
Missing	-	-	[redacted]	[redacted]
Previous use of ADT, n (%)				
No	39 (6.8)	61 (10.6)	[redacted]	[redacted]
Yes	535 (73.2)	514 (89.2)	[redacted]	[redacted]
Unknown	0	1 (0.2)	-	-
Total number of bone lesions based on ICR, n (%)				
1	83 (14.5)	70 (12.2)	NR	NR
2 to 4	151 (26.3)	142 (24.7)	NR	NR
5 to 9	95 (16.6)	106 (18.4)	NR	NR
10 to 19	111 (19.3)	114 (19.8)	NR	NR
≥20 (including TNC)	45 (7.8)	54 (9.4)	NR	NR
Total number of bone lesions based on investigator assessment, n (%)				
1	72 (12.5)	59 (10.2)	NR	NR
2 to 4	124 (21.6)	126 (21.9)	NR	NR
5 to 9	77 (13.4)	74 (12.8)	NR	NR

	ARCHES		ENZAMET (no concomitant docetaxel)	
	ENZA+ADT (n=574)	**PLA+ADT (n=576)**	**ENZA+ADT (n=309)**	**NSAA+ADT (n=313)**
10 to 19	26 (4.5)	28 (4.9)	NR	NR
≥20	23 (4.0)	23 (4.0)	NR	NR
TNC	181 (31.5)	189 (32.8)	NR	NR
Number of bone metastases				
None	NR	NR	[redacted]	[redacted]
1 to 3	NR	NR	[redacted]	[redacted]
≥4	NR	NR	[redacted]	[redacted]
Total	268 (46.7%)	245 (42.5%)	NR	NR

Abbreviations: ADT: androgen deprivation therapy; ECOG: Eastern Cooperative Oncology Group; ENZA: enzalutamide; NSAA: nonsteroidal antiandrogen; PLA: placebo; SD: standard deviation; ICR, independent central review; TNC, too numerous to count.

The main results of the ARCHES and ENZAMET trials are shown in Table 7 below.

3.2.2 Progression-free survival (PFS)

Radiographic progression-free survival (rPFS) was the primary endpoint in ARCHES and data are reported in section B.2.6.1.1 of the CS. Radiographic progression events were confirmed by the central imaging independent reviewer or until the target number of progression events was reached, as assessed by independent central review (ICR).[19] At the data cut-off, 292 patients had a progression event: with 91 patients (15.8%) in the enzalutamide plus ADT group and 201 patients (34.9%) in the placebo plus ADT group.[20] Enzalutamide plus ADT demonstrated a statistically significant reduction (61%) in the risk of a patient experiencing a rPFS event compared with placebo plus ADT (HR 0.39, 95% CI 0.30, 0.50; p<0.0001). The median time to a rPFS event was not reached in the enzalutamide plus ADT group. The median time to rPFS event was 19.0 months (95% CI 16.59, 22.24) in the placebo plus ADT group. The Kaplan-Meier event-free rate at 12 months was greater for patients in the enzalutamide plus ADT group compared with patients in the placebo plus ADT group (84.16% vs 63.18%). The company report that sensitivity analyses were consistent with the primary analyses.

Clinical progression-free survival data for ENZAMET are presented in Figure 13, Document B, of the CS. Clinical PFS events were reduced by 66% (HR 0.34, 95% CI 0.26, 0.44) for enzalutamide plus ADT (no docetaxel) versus NSAA plus ADT (no docetaxel). The company note that the estimation of the p-value for the non-concomitant docetaxel group was not pre-planned. The risk reduction in the overall population was 60% (HR 0.40, 95% CI 0.33, 0.49; p<0.001) in favour of enzalutamide.

3.2.3 Overall survival

The company presents the interim analysis of OS in ARCHES. The interim analysis was based on a median follow-up of 14.4 months and 84 deaths; 39 (6.8%) in the enzalutamide plus ADT group and 45 (7.8%) in the placebo plus ADT group. Enzalutamide plus ADT was associated with a 19% risk reduction of death compared with placebo, although this was not statistically significant (HR 0.81, 95% CI 0.53, 1.25; p=0.3361).[1, 19] The company note that the OS data are immature and the trial was not powered to detect significant differences in OS at the interim analysis. OS data for the ITT population are presented in Table 17 and Figure 9, Document B, of the CS.

OS data for ENZAMET are presented in section B.2.6.2.1 of the CS. At the time of the data-cut off (28 February 2019), 50 (16.2%) deaths had occurred in the enzalutamide plus ADT (no concomitant docetaxel) group compared with 88 (28.1%) deaths in the NSAA plus ADT (no concomitant docetaxel) group. Median follow-up time was 37.3 months. A statistically significant 47.2% reduction in risk of death was observed for enzalutamide plus ADT versus NSAA plus ADT (HR 0.528, 95% CI 0.370, 0.743, unstratified p=0.0002). Similar results were observed for the overall population, where the reduction in risk was 33% (HR 0.67, 95% CI 0.52, 0.86; p=0.002). Median OS was not reached in any trial group.

3.2.4 Time to prostate-specific antigen (PSA) progression

Time to PSA progression was a secondary endpoint in ARCHES. PSA progression was defined in ARCHES as "calculated as the time from randomisation to the date of first observation of PSA progression where PSA progression is defined as a ≥25% increase and an absolute increase of ≥2 ng/mL above the nadir (i.e., lowest PSA value

observed post-baseline or at baseline), which was confirmed by a second consecutive value at least 3 weeks later." while in ENZAMET it was defined as "the interval from the date of randomisation to the date of first evidence of PSA progression, clinical progression, or death from any cause, whichever occurs first, or the date of last known follow-up without PSA progression."

The company present PSA progression data for the ARCHES ITT population in section B.2.6.1.2.1 of the CS. Treatment with enzalutamide plus ADT was associated with a statistically significant reduction (81%) in the risk of PSA progression compared with placebo plus ADT (HR 0.19, 95% CI 0.13, 0.26; p<0.0001).[1,19] The company report that median time to PSA progression was not reached for either treatment group. The 12-month Kaplan-Meier event-free rate was greater in the enzalutamide plus ADT patients ([redacted]) compared with patients in the placebo plus ADT group ([redacted]). The company also report that, among patients with a detectable PSA level at baseline, a significantly higher percentage enzalutamide plus ADT patients had PSA decline to an undetectable level (<0.2 ng/mL) compared with patients in the placebo plus ADT group (treatment difference: 50.5%, 95% CI 45.3, 55.7; p<0.0001).

Kaplan-Meier data for PSA progression-free survival (PSA PFS) in ENZAMET are reported in Figure 12, Document B, of the CS. The risk of PSA PFS events was significantly reduced by 76% in the no docetaxel enzalutamide plus ADT group compared with the no docetaxel NSAA plus ADT group (HR 0.34, 95% CI 0.26, 0.44). The company notes that the estimation of the p-value for the non-concomitant docetaxel group was not pre-planned. In the overall population, the risk reduction was 61% (HR: 0.39, 95% CI 0.33, 0.47; p<0.001) in favour of enzalutamide.

3.2.5 Adverse effects of treatment

Data for treatment-emergent adverse events (TEAEs) in the ARCHES safety population are presented in Table 35, section B.2.10.1 of the CS. The median duration of treatment was 12.8 months for the enzalutamide plus ADT group and 11.6 months for placebo plus ADT group. The percentage of overall TEAEs were similar between

groups, although the percentage of drug-related TEAEs and TEAEs leading to death were slightly higher in the enzalutamide plus ADT arm compared with the placebo arm (53.0% versus 46.7% and 2.4% versus 1.7%, respectively); however, the percentage of total deaths was higher in the placebo arm (6.8% versus 7.8%). The most common TEAEs leading to death (presented in Table 38 of the CS) were [redacted] and [redacted] in the enzalutamide plus ADT arm and [redacted] in the placebo plus ADT arm. TEAEs leading to study drug discontinuation or dose reduction were higher in the enzalutamide plus ADT arm (data are presented in Tables 39 and 40 of the CS). Adverse events of special interest occurring at an event rate >2% higher in the enzalutamide plus ADT included hypertension (8.6% versus 6.3%), cognitive/memory impairment (4.5% versus 2.1%), fatigue (24.1% versus 19.5%), and fractures (6.5% versus 4.2%).[1]

The company state that there is limited safety data for the ENZAMET no concomitant docetaxel patients. Data are presented in section B.2.10.2 of the CS. Serious adverse events (SAEs) were assessed for their relatedness to the study drugs by investigator assessment. Study drug-related SAEs were [redacted] in the enzalutamide plus ADT arm than the NSAA plus ADT arm [redacted]). SAEs leading to study drug discontinuation were also [redacted] in the enzalutamide plus ADT arm ([redacted]. There were [redacted]. The number of fatal SAEs and deaths were [redacted] in the NSAA plus ADT arm than the enzalutamide plus ADT arm ([redacted]). SAEs occurring more frequently in the enzalutamide plus ADT arm than in the NSAA plus ADT arm included: [redacted].

The company note that only one additional RCT, comparing enzalutamide plus ADT versus bicalutamide plus ADT, provides further safety day for enzalutamide in the mHSPC population[21]. This trial reported a slightly higher number of hypertension, infection and syncope events in the enzalutamide arm than in ARCHES and ENZAMET. Comparisons with ARCHES and ENZAMET are, however, limited as

data are only available as a congress abstract. The investigators decided to stop the trial when the use of early abiraterone demonstrated OS benefit in mHSPC.

3.2.6 Health-related quality of life (HRQOL)

Data for time to deterioration of HRQOL in ARCHES is presented in Table 20, Document B of the CS. Time to deterioration was based on FACT-P (Functional Assessment of Cancer Therapy- Prostate) total score. Similar numbers of patients experienced at least a 10-point decrease from their baseline score (48.78% of patients in the enzalutamide plus ADT group and 47.57% of patients in the placebo plus ADT group). Median time to deterioration was also not significantly different between the two groups (11.3 months and 11.1 months for enzalutamide plus ADT and placebo plus ADT, respectively). Data for EQ-5D-5L are presented in section B.2.6.1.4.1. The company notes that the baseline scores indicate that patients in ARCHES had relatively good quality of life, which was maintained throughout the ARCHES trial. Most patients (approximately [redacted]) groups did not show any change in score during the first 73 weeks in both treatment groups[22]. Enzalutamide plus ADT was associated with a [redacted] delayed median time to first clinically meaningful deterioration based on EQ-5D-5L VAS compared to the placebo plus ADT group (median time [redacted] vs. [redacted] months; HR: [redacted])[22]; [redacted].[22]

Time to deterioration in HRQOL, data for ENZAMET are presented in Figure 14, section B.2.6.2.2.3 of the CS. The company report time to deterioration favoured enzalutamide plus ADT versus NSAA plus ADT for EORTC QLQ-C30 domains of physical function, cognitive function, fatigue and global health and quality of life. The company present these data for the non-concomitant docetaxel subgroup in graph format in the CS. The company provide a reference to an abstract (by Stockler et al 2019)[23] but this abstract reports HRQOL data for the whole trial population and does not provide separate data for the non-concomitant docetaxel group.

Table 7 Results of the ARCHES and ENZAMET trials for the outcomes listed in the NICE final scope

Outcome	Summary statistic	ARCHES		ENZAMET	
		ENZA+ADT ITT n=574 Safety n=572	PLA+ADT ITT n=576 Safety n=574	ENZA+ADT (no concomitant DOC) n=309	Conventional NSAA+ADT n=313
Radiographic/clinical Progression-free survival [1]	Events, n (%)	91 (15.85)	201 (34.90)		
	Kaplan-Meier event free rate at 12 months	84.16%	63.18%	NR	NR
	% risk reduction of progression	61		66	
	HR (95% CI)	0.39 (0.30, 0.50) p<0.0001		0.34 (0.26, 0.44) p value not reported	
Overall survival	Number of deaths, n (%)	39 (6.79)	45 (7.81)	50 (16.2)	88 (28.1)
	Median follow-up time, months	14.4		37.3	
	Kaplan-Meier event free rate at 12 months	[redacted]	[redacted]		
	% risk reduction of death	19		47.2	
	HR (95% CI)	0.81 (0.53, 1.25) p=0.3361		0.528 (0.37, 0.74) p=0.0002	
Time to PSA progression	Events, n (%)	[redacted]	[redacted]	NR	NR
	Kaplan-Meier event free rate at 12 months	[redacted]	[redacted]	NR	NR

	% risk reduction of progression	81		76	
	HR (95% CI)	0.19 (0.13, 0.26) p<0.0001		0.34 (0.26, 0.44) p value not reported	
Adverse effects of treatment	Serious study drug-related TEAE/AE, n (%)	22 (3.8)	16 (2.8)	[redacted]	[redacted]
	Study drug-related fatal AE, n (%)	0	1 (0.2)	[redacted]	[redacted]
	Drug-related TEAE/SAE leading to discontinuation of study drug, n (%)	16 (2.8)	12 (2.1)	[redacted]	[redacted]
	TEAE/SAE leading to dose reduction, n (%)	25 (4.4)	11 (1.9)	[redacted]	[redacted]
Time to deterioration in HRQOL [2]	Patients with deterioration	280 (48.78)	274 (47.57)	Reported in graph format in the CS	Reported in graph format in the CS
	Kaplan-Meier event free rate at 12 months	46.87%	47.30%		
	HR (95% CI)	0.96 (0.81, 1.14) p=0.6548			

CI, confidence interval; DOC, docetaxel; HR, hazard ratio; HRQOL, health-related quality of life; ITT, intention to treat; SAE, serious adverse event; TEAE, treatment-emergent adverse event

1. Defined as radiographic progression-free survival in ARCHES and clinical progression-free survival in ENZAMET
2. Time to deterioration in HRQOL based on Functional Assessment of Cancer Therapy-Prostate (FACT-P) total scores in ARCHES

3.2.7 Additional outcomes considered by the company in the decision problem

Time to treatment discontinuation (TTD)

In addition to the outcomes specified in the NICE final scope, the company included TTD as an outcome in their decision problem. The company state that both ARCHES and ENZAMET used the same assumptions to calculate TTD: "treatment end date" - "treatment start date" + 1. All patients were considered to have an event (discontinuation), unless their treatment was ongoing at the time of data cut-off. Patients with ongoing treatment at this time were censored.

The company report that [redacted] of patients in the enzalutamide plus ADT group and [redacted] of patients in the placebo plus ADT group in ARCHES had discontinued their allocated study treatment at the time of the data analysis cut-off date (14th October 2018). TTD was statistically longer in the enzalutamide plus ADT group (HR [redacted]) with median time to TTD [redacted] in this group compared with [redacted] months (95% [redacted]) in the placebo plus ADT arm. Kaplan-Meier data for TTD in the ARCHES ITT population are presented in Figure 10, Document B, of the CS.

The company report that TTD was also statistically significantly longer for enzalutamide plus ADT compared with NSAA plus ADT in ENZAMET (HR [redacted]). Median time to study drug discontinuation was [redacted] in the enzalutamide plus ADT arm versus [redacted] months (95% CI: [redacted]) in the NSAA plus ADT arm. At the data analysis cut-off date (28 February 2019), [redacted]) enzalutamide plus ADT patients and [redacted]) NSAA plus ADT patients had discontinued the randomised treatment.

Time to new antineoplastic therapy (TINAT)

The company present TINAT data for ARCHES in Table 13, section B.2.6.1.2.2 of the CS. More patients in the placebo plus ADT group (23.09%) received a new antineoplastic therapy compared with patients in the enzalutamide plus ADT group (8.01%). Enzalutamide plus ADT was associated with a statistically significant 72% reduction in the risk of initiation of a new antineoplastic therapy for prostate cancer compared with placebo plus ADT (HR 0.28, 95% CI 0.20, 0.40; p<0.0001). The Kaplan-Meier event-free rate at 12 months was greater for patients in the

enzalutamide plus ADT group compared with patients in the placebo plus ADT group ([redacted] vs [redacted], respectively).[1, 19] Data for subsequent therapies are presented in Table 14 of the CS. The most frequently used subsequent antineoplastic therapies in the enzalutamide plus ADT group were abiraterone acetate (2.3%), docetaxel (1.9%) and other therapies (2.4%). The most frequently used subsequent therapies in the placebo plus ADT group were docetaxel (9.0%), abiraterone acetate (4.9%) and enzalutamide (4.9%).

3.2.8 Other secondary endpoints

The company report data for several additional secondary endpoints in the CS, Document B, section 2.6. For ARCHES, the company report the following data favouring enzalutamide plus ADT over the placebo plus ADT group:

- Objective response rate assessed by ICR: significantly higher in patients with measurable disease (absolute difference: [redacted])
- Time to first SSE: a 48% risk reduction of experiencing a SSE (HR: 0.52, 95% CI: 0.33, 0.80; nominal p=0.0026)
- Time to castration resistance: a 72% reduction in the risk of a patient experiencing a castration-resistance event (HR: 0.28, 95% CI: 0.22, 0.36; nominal p<0.0001)
- Time to deterioration in urinary symptoms: statistically non-significant trend towards a delay in time to deterioration in urinary symptoms (HR: 0.88, 95% CI: 0.72, 1.08; p=0.2162)
- Time to pain progression: statistically non-significant trend towards delaying time to pain progression based on BPI-SF worst pain (HR: 0.92, 95% CI: 0.78, 1.07; nominal p=0.2715).

3.2.9 Subgroup analyses

Several subgroup analyses are presented for ARCHES. Data are presented in Figure 16 and Table 24 in section B.2.7.1 of the CS. Subgroup analyses favoured enzalutamide plus ADT. Results were mainly statistically significant except for:

- OS in any subgroup (the company acknowledge that the data for OS are immature);

- Time to SSE in patients with recurrent disease, patients previously treated with docetaxel and newly diagnosed high-risk patients;
- Objective response rate in low risk patients;
- Time to pain progression in all subgroups except high-risk patients.

Post hoc subgroup analyses were conducted for the no concomitant docetaxel HVD (n=232) and LVD mHSPC patients (n=390) in ENZAMET for OS, clinical PFS and TTD. Enzalutamide plus ADT was associated with a significantly reduced risk of mortality and risk of clinical disease progression in both HVD and LVD patients. TTD was [redacted]. Data are presented as HR and 95% CI in Table 25, section B.2.7.2 of the CS (unstratified p-value are reported for OS and clinical PFS).

3.2.10 Meta-analyses

The company stated that the results of the two trials, ARCHES and ENZAMET, were not combined in a meta-analysis. Instead, the company carried out a 'pooled analysis' for the total population of ARCHES and the patient subgroup with no concomitant docetaxel in ENZAMET (section B.2.8) to inform the economic model. Pooled analyses were conducted for OS, TTD and clinical PFS and reported in Table 26, Document B, section B.2.8 of the CS. Methods used for the pooled analysis were not provided in the CS. It is not clear to the ERG whether it was the aggregated results or individual patient data from each trial that were combined, and if and how trial results were weighted. For the pooling the company assumed that efficacy of ADT plus placebo in ARCHES was comparable to that of NSAA plus ADT IN ENZAMET.

The ERG agrees with the company's that differences across trials in terms of comparator treatment (placebo plus ADT in ARCHES and NSAA plus ADT in ENZAMET) and distribution of high and low volume disease patients (lower proportion of high-volume disease patients in ENZAMET than in ARCHES) limited the possibility to conduct meaningful meta-analyses.[9]

The ERG agrees that in view of the characteristics of the two enzalutamide trials, this was probably a reasonable approach even though the pooled analyses may encounter

the same issues identified by the company for not conducting meta-analyses. In particular, the ERG notes that the decision to pool results across the two enzalutamide trials could have increased the effect size in favour of enzalutamide. The lower baseline proportion of high-volume disease in ENZAMET could indicate a better prognosis or outcomes for ENZAMET patients than for ARCHES patients. While the company state to have stratified patients by disease volume (amongst other covariates) and acknowledge that the ENZAMET study has more data maturity and, therefore, more time to show possible benefits, the ERG has some concern that this would not account for the much reduced HR estimate for OS observed in ENZAMET compared to that observed in ARCHES. Note that ARCHES patients are said to have clinical characteristics more similar to those likely to be treated in clinical practice than ENZAMET patients. NSAA could also have delayed disease progression and improved clinical PFS in ENZAMET patients and this could explain, among other reasons, why the company did not use the pooled PFS in the economic model. Taking into account the above considerations, the ERG is of the opinion that the pooled analyses should be interpreted with caution.[9]

The company conducted pooled analysis for three endpoints: OS, clinical PFS and TTD. Justification for selecting these outcomes was not clearly provided in the CS. Outcome definitions used for PFS in the two trials differed: rPFS was used in ARCHES and cPFS in ENZAMET. An attempt to adjust the ARCHES rPFS definition to match the ENZAMET cPFS was conducted by the company by defining PFS in ARCHES as death, rPFS or initiation of new antineoplastic treatment. However, it is stated in the CS (Document B, section B.2.8) that the definition could not be fully matched to that in ENZAMET because of lack of data available and the company decided not to use the pooled PFS results in the economic model.

The company provide the results of the pooled analyses in Document B, section B.2.8 of the CS. Median clinical PFS was [redacted] and median TTD was [redacted] in the enzalutamide plus ADT arm. The results indicate statistically significant benefits for the enzalutamide plus ADT arm compared with the ADT plus NSAA arm: OS HR [redacted]; clinical PFS HR [redacted]; TTD HR [redacted].

It is worth noting that the OS and TTD pooled analyses are used in scenario analyses in the economic model. The ERG has investigated the pooled data using the data provided by the company at clarification – see text below.

Table 8 Pooled analyses of ARCHES and ENZAMET data for OS, cPFS and TTD

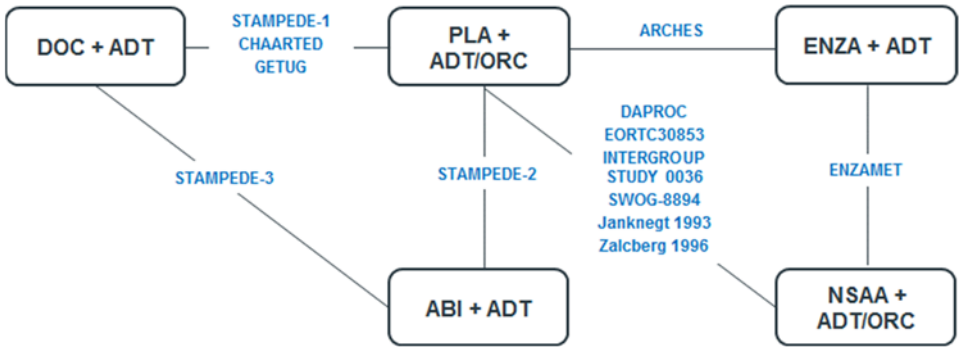
	N of events/N in group		HR (95% CI) p-value	Median follow-up (months)	Data source
	ENZA + ADT	ADT+PLA (ARCHES) or ADT+NSAA (ENZAMET, no concomitant DOC)			
Overall survival (OS)					
ARCHES	39/574	45/576	0.81 (0.53;1.25)	NYR (14.4)	Table 17
ENZAMET	50/309	88/313	0.53 (0.37;0.74)	NYR (37.3)	Table 23
Pooled	[redacted]	[redacted]	[redacted]	[redacted]	Table 26
Clinical progression-free survival (cPFS)					
ARCHES					
cPFS	NR	NR	NR	NR	NR
rPFS	46/574	133/576	NR	NR	Company clarification (Excel file)
TINAT	91/574	201/576	NR	NR	Company clarification (Excel file)
ENZAMET					
cPFS	NR/309	NR/313	0.34 (0.26;0.44)	NR	B.2.6.2.2.2
Pooled	[redacted]	[redacted]	[redacted]	[redacted]	Table 26
Time to treatment discontinuation (TTD)					
ARCHES	[redacted]	[redacted]	[redacted]	[redacted]	B.2.6.1.4.2
ENZAMET	[redacted]	[redacted]	[redacted]	[redacted]	B.2.6.2.2.4
Pooled	[redacted]	[redacted]	[redacted]	[redacted]	Table 26

Abbreviations: ADT: androgen deprivation therapy; CI: confidential interval; cPFS: clinical progression-free survival; DOC: docetaxel; ENZA: enzalutamide; HR: hazard ratio; NSAA: non-steroidal anti-androgen; NR: not reported; NYR: not yet reached; PLA: placebo; OS: overall survival; rPFS: radiographic progression-free survival; TINAT: time to initiation of new antineoplastic treatment.

3.3 Critique of trials identified and included in the indirect comparison and/ or multiple treatment comparison

In the absence of direct clinical evidence, the company conducted network meta-analyses (NMAs) to assess the relative effectiveness of enzalutamide plus ADT versus docetaxel for the treatment of adults with mHSPC. Relevant interventions considered

by the company were ADT alone (including orchiectomy), monotherapy with bicalutamide, and docetaxel. Abiraterone, which was not considered by the company a relevant comparator (no standard care at the time of the submission) was included in the evidence network with the justification 'to enrich it'. Thirteen studies were included in the evidence network. (counting the 3-arms in the STAMPEDE trial as three separate studies). An evidence network diagram is presented in Figure 8, Document B of the CS and reproduced below.



Abbreviations: ABI: abiraterone; ADT: androgen deprivation therapy; DOC: docetaxel; ENZA: enzalutamide; NSAA: non-steroidal antiandrogen; ORC: orchiectomy; PLA: placebo.

Figure 1 Evidence network for the overall mHSPC population (reproduced from Figure 18, section B.2.9.1 of the CS)

The company assessed the methodological quality of studies included in the NMA in accordance with the ten-item checklist suggested in the NICE STA guidance.[24] Although there are some differences between the ERG and the company (Table 83 in Appendix D1.3 of the CS) in assessment of the quality of the included studies, the ERG considers that the methodological quality of the included trials was reasonable. We note, however, that in the majority of the included studies methods of randomisation and allocation concealment are unclear and therefore a potential high-risk of selection bias cannot be eliminated. Moreover, information on blinding is either lacking or unreported in all studies.

Baseline characteristics of the 13 studies included in the NMA (11 studies if counting the 3-arm STAMPEDE trial as a single study) are summarised in Table 9 below.

Table 9 Characteristics of studies included in the NMA (adapted from Tables 28 and 29 of the CS, supplemented with reports of individual trials)

Study name [Key reference] Country	Patient eligibility for prostate cancer (PCa) & Primary endpoint	Intervention and comparator	Sample size	ECOG=0	Gleason score ≥8	High volume disease	Previous local therapy	Previous docetaxel use
ARCHES[1] [CS] Europe, North/South America	mHSPC **Primary endpoint** rPFS	ENZA + ADT	574	78%	67%	62%	21%	18%
		PLA + ADT	576	77%	65%	65%	22%	18%
ENZAMET[16] [CS] Subgroup with no concomitant docetaxel Europe, North America, Australia, New Zealand	mHSPC **Primary endpoint** OS	ENZA + ADT	309	[redacted]	[redacted]	[redacted]	[redacted]	Patients who had already commenced docetaxel prior to study entry were eligible if they were tolerating full doses of docetaxel (75 mg/m^2) with ADT and met all eligibility criteria for the study while receiving docetaxel and had no more than 2 cycles prior to randomisation. However, data on patients taking concurrent docetaxel were excluded from the NMA.
		NSAA + ADT	313	[redacted]	[redacted]	[redacted]	[redacted]	
CHAARTED[5] / E3805 [Sweeney 2015, B17] Various in ECOG	mHSPC **Primary endpoint** OS	ADT+DOC	397	70%	61%	66%	27%	**Exclusion criteria:** Prior chemotherapy in adjuvant or neoadjuvant setting.
		ADT	393	69%	62%	64%	27%	

Study name [Key reference] Country	Patient eligibility for prostate cancer (PCa) & Primary endpoint	Intervention and comparator	Sample size	ECOG=0	Gleason score ≥8	High volume disease	Previous local therapy	Previous docetaxel use
GETUG-AFU 15[25] [Gravis 2013, B15] France, Belgium	Metastatic PCa with no previous chemotherapy **Primary endpoint** OS	ADT+DOC	192	99%	55%	48%	32%	**Exclusion criteria:** previous chemotherapy for metastatic disease **Allowed:** In the neo adjuvant and adjuvant settings or in the context of isolated PSA increase, previous chemotherapy or ADT, or both, were allowed, with the condition that the treatment had been discontinued at least 12 months before inclusion in the study and no metastases or PSA increase had been documented during this period. The number of patients receiving (neo)adjuvant treatment was not reported.
		ADT	193	96%	59%	47%	24%	
STAMPEDE1[18] [James 2016, B48] Subgroup with M1 UK, Switzerland	Newly diagnosed and metastatic, node-positive, or high-risk locally advanced, or recurrent PCa **Primary endpoint** OS	SOC+DOC	M1 362/592	78%	74%	Overall 60-64%	4%	**Exclusion criteria:** Prior chemotherapy for prostate cancer (excluding patients receiving docetaxel as part of the new SOC)
		SOC	M1 724/1184	78%	68%		5%	

Study name [Key reference] Country	Patient eligibility for prostate cancer (PCa) & Primary endpoint	Intervention and comparator	Sample size	ECOG=0	Gleason score ≥8	High volume disease	Previous local therapy	Previous docetaxel use
STAMPEDE1[26] [Clarke 2019] Subgroup with MI - new cut-off Clarke et al. Ann Oncol. 2019 Dec 1;30(12):1992-2003. doi: 10.1093/annonc/mdz396. Supplied at clarification (response dated 12 Dec)	Newly diagnosed and metastatic, node-positive, or high-risk locally advanced, or recurrent PCa **Primary endpoint** OS	SOC+DOC	M1 362/592	NR	70%	'High metastatic burden' 41%	NR	NR but 'Previously treated' 4%
		SOC	M1 724/1184	NR	66%	'High metastatic burden' 44%	NR	NR but 'Previously treated' 5%
STAMPEDE2[27] [James 2017, B49] Subgroup with M1 UK, Switzerland	Newly diagnosed and metastatic, node-positive, or high-risk locally advanced, or recurrent PCa **Primary endpoint** OS	ADT + ABI and prednisolone	M1 500/960	78%	74%	Overall 55.4%	7%	78%
		ADT	M1 502/957	78%	75%		5.2%	78%
STAMPEDE3[28] [Sydes 2018, B51] UK, Switzerland	Newly diagnosed and metastatic, node-positive, or high-risk locally	SOC + DOC and prednisolone	M1 115/189	79%	81%	NR	5.2%	NR

Study name [Key reference] Country	Patient eligibility for prostate cancer (PCa) & Primary endpoint	Intervention and comparator	Sample size	ECOG=0	Gleason score ≥8	High volume disease	Previous local therapy	Previous docetaxel use
	advanced, or recurrent PCa **Primary endpoint** OS	SOC + ABI and prednisolone	M1 227/377	80%	75%	NR	11.9%	NR
DAPROC[29] [Iversen 1990, B52] Denmark	Locally advanced disease or distant metastases, previously untreated **Primary endpoint** Objective assessment of disease progression	GOS (zoladex) + FLU	129	NR	NR	NR	NR	NR
		ORC	133	NR	NR	NR	NR	NR
EORTC 30853[30] [Denis 1990, B53] Europe (EORTC)	All T,N,G category with M1 category disease with no previous hormonal and/or chemotherapy **Primary endpoint** Not specified	GOS (zoladex) + FLU	164	NR	NR	NR	NR	NR
		ORC	163	NR	NR	NR	NR	NR
INTERGROUP STUDY 0036[31] [Crawford 1990, B60] USA	Previously untreated stage D2, with bone or soft tissue metastases **Primary endpoint** OS	LEU + FLU	303	93%	NR	NR	NR	NR
		LEU + PLA	300	94%	NR	NR	NR	NR

Study name [Key reference] Country	Patient eligibility for prostate cancer (PCa) & Primary endpoint	Intervention and comparator	Sample size	ECOG=0	Gleason score ≥8	High volume disease	Previous local therapy	Previous docetaxel use
SWOG-8894[32] [Eisenburger 1998, B65] USA	PCa with bone or distant soft-tissue metastases, with no previous or concomitant hormonal treatment, chemotherapy, or treatment with biologic-response modifiers **Primary endpoint** Death from any cause	ORC + FLU	700	NR	NR	NR	NR	NR
		ORC + PLA	687	NR	NR	NR	NR	NR
Janknegt 1993[33] [Janknegt 1993, B66] The Netherlands	Metastatic PCa with no previous hormonal or chemotherapy **Primary endpoint** Not specified	ORC + NIL	225	NR	41%	NR	10%	NR
		ORC + PLA	232	NR	42%	NR	12%	NR
Zalcberg 1996[34] [Zalcberg 1996, B71] Australia	Metastatic PCa, with no previous hormonal therapy of any kind, or treatment with cytotoxics or biological response modifiers **Primary endpoint** Not specified	ORC + FLU	112	52%	NR	NR	NR	NR
		ORC + PLA	110	45%	NR	NR	NR	NR

ABI: abiraterone; ADT: androgen deprivation therapy; CS: company submission; DOC: docetaxel; ECOG: Eastern Cooperative Oncology Group; ENZA: enzalutamide; EORTC: European Organization for Research and Treatment of Cancer; FLU: flutamide; GOS: goserelin; IQR: interquartile range; LEU: leuprolide; mHSPC: metastatic hormone-sensitive prostate cancer; NIL: nilutamide; NR: not reported; NSAA: nonsteroidal antiandrogen; ORC: orchidectomy; OS: overall survival; PCa: prostate cancer; PLA: placebo; rPFS: radiographic progression-free survival; SOC: standard of care

The ERG agrees with the company that the studies included in the NMA are clinically and methodologically heterogeneous. The STAMPEDE study population differs from the target population for this appraisal as both metastatic and non-metastatic HSPC patients were enrolled. The company have attempted to address this issue by including only data for metastatic patients in the NMA. The remaining studies included a mixed population of high and low risk mHSPC patients. GETUG-AFU 15 included a higher proportion of patients with ECOG 0, fewer HVD patients and fewer patients with a Gleason score ≥8, indicating that these patients might have had a better prognosis than those in the other studies included in the NMA. The company reference pooled OS for GETU-AFU 15 and CHAARTED conducted by Gravis 2018 which showed no statistical heterogeneity between HVD and LVD subgroups despite differences in the proportions of these patients between the two studies.[35] The company, therefore, included GETUG-AFU 15 in the base case but ran a sensitivity analysis removing it from the NMA. In keeping with the company's approach to the main evaluation of clinical effectiveness, only results for the ENZAMET enzalutamide plus ADT and no concomitant docetaxel patients were included in the NMA. However, the ERG notes that in ENZAMET the proportion of HVD patients was similar to that of the GETU-AFU 15 (lower compared to ARCHES, CHAARTED and STAMPEDE). Moreover, the definitions of previous local therapy and concomitant treatment differed for ENZAMET. The company did not present a sensitivity analysis excluding ENZAMET from the NMA.

The company report that seven studies comparing CAB/MAB versus ADT alone were excluded from the NMA because of the uncertainty or lack of reporting of event data, numbers at risk, HR or KM curves, or due to treatment switching, which could potentially have confounded any treatment effect. The company excluded PFS results for older studies assessing CAB/MAB in the NMA due to differences in current imaging practices and uncertainty surrounding definitions provided in the articles. The ERG agrees with this company's approach,

The studies also varied in terms of their design and outcome definition. The company excluded results for rPFS from CHAARTED and cPFS from ENZAMET from the NMA as their definitions for these outcomes could not be matched to the other studies. Similarly, STAMPEDE-1 and STAMPEDE-2 defined disease progression as failure-free survival, including biochemical failure. The company did not include these results in the NMA. STAMPEDE-3 provided results for two definitions of PFS: time from randomisation to the

first of new disease or progression of distant metastases, lymph nodes or local disease, or death due to prostate cancer; and metastatic PFS (MPFS), defined as time from randomisation to death from any cause, new metastases or progression of distant metastases. Results from both definitions were included in the NMA, with MPFS considered as the base case. The company considered the definitions of PFS were similar in the other studies. The company provide the study definitions of PFS in Table 30, Document B of the CS. The ERG considers that the characteristics of the patient population of the included studies represent an important source of heterogeneity within the NMA, which casts some doubts about the reliability of the NMA results.

It worth noting that at clarification the company provide a new cut-off data for the STAMPEDE comparison of docetaxel plus ADT vs ADT alone (STAMPEDE 1) for OS and PFS.[26]

3.4 Critique of the indirect comparison and/ or multiple treatment comparison

3.4.1 Methods used for the NMA and assessment of inconsistency

The ERG agrees with the approach and methodology used for performing the NMA. The ERG independently replicated the base case results (see text below).

3.4.2 Proportional hazards assumption

The company provide evidence (Appendix D, Document B, page 193) of the methods used to check the proportional hazard assumptions. The ERG is happy with the company's approach. On inspection, the ERG noted that the Kaplan-Meier curves for the groups being compared do not cross and do not appear to be radically different, indicating similar proportions over time. These two factors are fair indicators that the hazards are proportional as required for the Cox proportional hazards model.

3.4.3 Input parameters

The CS does not provide sufficient information regarding the datasets included in the NMAs, especially for OS. The first company clarification response (dated 10 Dec 2019) indicated that the TITAN study (not signposted in the original CS) was included in the NMA. TITAN is a phase III RCT comparing apalutamide (n=525) versus placebo (527) in mCSPC patients receiving ADT[36]. Once the studies included in the NMA were clarified, the ERG was able to

verify the company's initial results. The ERG were also concerned that in the CS had included studies that primarily assessed abiraterone in the network despite the company clearly stating in the submission that they would not include abiraterone information. The effect of removing the abiraterone arms was provided in a second company clarification response (dated 12 Dec 2019) along with updated data. In the second company's clarification response, the TITAN study was no longer included in the NMA. The company provided also two forms of updated data: i) data accommodating the removal of abiraterone and apalutamide, which were not considered relevant for this appraisal and ii) new data from the STAMPEDE-1 study. Given that apalutamide is not currently available in UK clinical practice, the ERG agrees with the removal of the TITAN study from the NMA.

3.4.4 Results of the NMA

In the original CS, NMA results are presented in Table 34, Document B, section B.2.9.5. The following results reflect the choice of data provided by the company at clarification (second response): exclusion of abiraterone and apalutamide studies and inclusion of the new data from STAMPEDE-1, now with longer follow-up (median follow-up of 78 months).

The company provided fixed effects (FE) models and, where possible, random effects (RE) models for each outcome considered in the NMA. When available, RE model results, which the ERG considers preferable, are presented below. Using the company hazard ratios (initially verified in the CS) for each treatment comparison, the ERG replicated the results successfully.

- rPFS: Using the data and results provided at clarification (which are similar to the original CS), the NMA for rPFS indicates that enzalutamide with ADT is significantly beneficial over ADT alone (FE model: HR=[redacted] based entirely on the head-to-head ARCHES trial). This is also the case to a lesser extent of enzalutamide with ADT vs docetaxel with ADT (FE model: HR=[redacted], estimated via the NMA). The CS showed that these results were not affected by the three different sensitivity analyses conducted by the company (sensitivity analyses described in Document B, section B.2.9.4.1 of the CS, page 93 - where the effect of including/excluding the GETUG-AFU 15 trial are investigated). These sensitivity analyses were not repeated using the updated data.
- OS: Three models available were based on data from the original CS and the 2 updates. The NMA results from all three show to 2dp show significant benefit of

enzalutamide with ADT over ADT alone (RE model: HR=[redacted]). While the 3 models were slightly different when comparing enzalutamide with ADT vs docetaxel with ADT, all indicate similar non-significant benefit of enzalutamide with ADT over docetaxel with ADT (RE model update2: HR=[redacted]). Looking at the data available from individual studies, the ERG was struck by the difference observed between the OS HR in ARCHES (HR=0.81; 95% CI 0.53, 1.25) and that in ENZAMET (HR=0.53 95% CI 0.37, 0.74) even after taking into account that both trials were stratified by disease volume and ENZAMET had a longer data maturity. For this reason, the ERG ran the NMA without ENZAMET. The results of this NMA showed that enzalutamide with ADT had no significant advantage over ADT alone (RE model: HR=[redacted]) as per the ARCHES study. The network without ENZAMET reassesses the difference of enzalutamide with ADT versus NSAA with ADT (HR=[redacted]) as being non-significant. It also indicates that enzalutamide with ADT has a very similar effect as docetaxel with ADT (RE model: HR=[redacted])

- TCR: These results are unaffected by the updated data and were only available using a fixed effects model. The results indicate that enzalutamide with ADT is significantly highly beneficial over ADT alone (FE model: HR=[redacted]), informed mainly by ARCHES) and slightly less so over docetaxel with ADT (FE model: HR=[redacted], informed by ARCHES and CHARTERED).
- TSSE: NMA results for this outcome are in line with those observed in the ARCHES study in the CS. Using a fixed effect, the risk of time to symptomatic skeletal events (TSSE) is significantly reduced when comparing enzalutamide with ADT vs ADT alone (RE model: HR=[redacted]). However, there was not a significant difference between enzalutamide with ADT and docetaxel with ADT with regard to TSSE (FE model: HR=[redacted]).

3.5 Additional work on clinical effectiveness undertaken by the ERG

At clarification, the company provided 'time to event' data for all relevant outcomes from the enzalutamide trials (ARCHES and ENZAMET). The company sent both the data with the original censoring rules and different censoring rules, claimed these were requested by the ERG. This may have been a misunderstanding as the ERG have no record of what these rules may have been. The company have not provided them either. Using these data the ERG

generated basic Kaplan-Meier curves, which on inspection are similar to those in the original CS. The ERG also ran Cox models to obtain unadjusted hazard ratios (Table 10).

Table 10 Hazard ratios for endpoints of enzalutamide vs comparator* HR (95% CI). Company results taken from the original submission (Document B Table 32) except for [a]

Studies	Company ARCHES	ERG ARCHES Raw HRs	ERG ARCHES Raw HRs[b]	Company ENZAMET [a]	ERG Enzamet Raw HRs	ERG Enzamet Raw HRs[b]
OS	0.81 (0.53, 1.25)	0.82 (0.53, 1.26)	0.83 (0.54, 1.28)	0.67 (0.52, 0.86)	0.67 (0.52, 0.86)	0.67 (0.52, 0.86)
rPFS ARCHES	0.39 (0.30, 0.50)	0.39 (0.31, 0.50)	0.40 (0.31, 0.51)	-	-	-
cPFS ENZAMET	-	-	-	-	0.40 (0.33, 0.49)	-
TTD ARCHES	[redacted]	[redacted]	[redacted]	-	-	-
TSSE ARCHES	0.52 (0.33, 0.80)	0.52 (0.33, 0.80)	NI	-	-	-
TINAT ARCHES	0.28 (0.20, 0.40)	0.29 (0.21, 0.41)	NI	-	-	-
TCR ARCHES	0.28 (0.22, 0.36)	0.29 (0.23, 0.36)	NI	-	-	-
TPSA ARCHES	0.19 (0.13, 0.26)	0.19 (0.14, 0.26)	NI	-	-	-

Raw: unadjusted models**; NI:** not investigated
* Comparator for ARCHES was ADT; ENZAMET used NASS + ADT
[a] extracted from Table 23
[b] Different (unspecified) censor rules

On inspection the company results are similar to the unadjusted HRs generated by the ERG. Note for OS using the ENZAMET data, the results presented here are the ITT data (regardless of concomitant docetaxel). The company also provided an HR of 0.68 (0.52, 0.87), adjusted for the stratification factors (volume of disease, use of early/planned docetaxel, use of anti-resorptive therapy, Adult Comorbidity Evaluation score and study sites). As previously mentioned, the company also presented an OS analysis that includes only patients who are not on concomitant docetaxel, a more appropriate group for this submission. It is this result (0.53, 95% CI 0.37, 0.74) that is used for the NMA. The ERG is in agreement with the use of this estimate but was unable to verify it.

The ERG where possible replicated the results of the NMAs presented in the original CS and those of the NMAs with updated data provided at clarification (Tables 11-15).

Table 11 PFS - NMA HR (95% CrI) estimates (by the ERG and the company)

Original	ERG	CS	CS Sensitivity 1	CS Sensitivity 2
DOC vs ADT	[redacted]	[redacted] $	NR	NR
ENZA+ADT vs ADT±PLA	[redacted]	[redacted]	[redacted]	[redacted]
ENZA+ADT vs DOC+ADT	[redacted]	[redacted]	[redacted]	[redacted]
ENZA+ADT vs NSAA+ADT		[redacted]	[redacted]	[redacted]

HR (95% CrI) estimates incorporated into the NMA are taken from Table 34, Document B of the CS unless specified; $ Company HR's taken from Table 4 of the company's clarification response dated 12 Dec 2019

Table 12 Updated PFS - NMA HR (95% CrI) estimates (by the ERG and the company)

Updated	ERG	CS updated results
DOC vs ADT	[redacted]	[redacted]
ENZA+ADT vs ADT±PLA	[redacted]	[redacted]
ENZA+ADT vs DOC+ADT	[redacted]	[redacted]
ENZA+ADT vs NSAA+ADT		[redacted]

Updated NMA including new STAMPEDE-1 data and excluding abiraterone and apalutamide studies. Company HR's taken from Table 4 of the company's clarification response dated 12 Dec 2019

Table 13 OS from original CS - NMA HR (95% CrI) estimates (by the ERG and the company)

Fixed Effect	ERG	CS	CS Sen 1	CS Sen 2	CS Sen 3
DOC vs ADT	[redacted]	[redacted] $	NR	NR	NR
ENZA+ADT vs ADT±PLA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ENZA+ADT vs DOC+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ENZA+ADT vs NSAA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Random Effect	**ERG**	**CS**	**CS Sen 1**	**CS Sen 2**	**CS Sen 3**
DOC vs ADT	[redacted]	[redacted] $	NR	NR	NR
ENZA+ADT vs ADT±PLA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ENZA+ADT vs DOC+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ENZA+ADT vs NSAA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

HR (95% CrI) estimates incorporated into the NMA are taken from Table 34, Document B of the CS unless specified; $ Result taken from Table 4 of the company's clarification response dated 12 Dec 2019

Once the OS NMA included the TITAN study was provided at clarification, the base case conducted by the ERG matched the CS results. The inclusion of the TITAN study was deemed clinically acceptable but was a separate spur on the network. There are some difference between the sensitivity analyses conducted by the company. The ERG did not check these, given the base cases agreed and the company had provided acceptable estimates.

Table 14 OS Updated1 - NMA HR (95% CrI) estimates (by the ERG and the company)

Fixed Effects model	ERG	CS
DOC vs ADT	[redacted]	[redacted]
ENZA+ADT vs ADT±PLA	[redacted]	[redacted]
ENZA+ADT vs DOC+ADT	[redacted]	[redacted]
ENZA+ADT vs NSAA+ADT	[redacted]	[redacted]
Random Effects model		
DOC vs ADT	[redacted]	[redacted]
ENZA+ADT vs ADT±PLA	[redacted]	[redacted]
ENZA+ADT vs DOC+ADT	[redacted]	[redacted]
ENZA+ADT vs NSAA+ADT	[redacted]	[redacted]

Updated to exclude abiraterone and apalutamide studies.
All company HR (95% CrI) estimates incorporated into the NMA are taken from Table 4 of the company's clarification response dated 12 Dec 2019

Table 15 OS Updated 2 - NMA HR (95% CrI) estimates (by the ERG and the company)

Fixed Effects model	ERG	CS
DOC vs ADT	[redacted]	[redacted]
ENZA+ADT vs ADT±PLA	[redacted]	[redacted]
ENZA+ADT vs DOC+ADT	[redacted]	[redacted]
ENZA+ADT vs NSAA+ADT	[redacted]	[redacted]
Random Effects model		
DOC vs ADT	[redacted]	[redacted]
ENZA+ADT vs ADT±PLA	[redacted]	[redacted]
ENZA+ADT vs DOC+ADT	[redacted]	[redacted]
ENZA+ADT vs NSAA+ADT	[redacted]	[redacted]

Updated to exclude abiraterone and apalutamide studies but does include new STAMPEDE-1 results
All company HR (95% CrI) estimates incorporated into the NMA are taken from Table 4 of the company's clarification response dated 12 Dec 2019

The impact of the updated data has been to improve the point estimate but to also increase the imprecision such that the benefit seen by the inclusion of enzalutamide compared with docetaxel is still non-significant. The ERG were concerned about the impact of including the EZAMET study within the OS NMA. The results with this study removed are presented in Tables 16 and 17 below.

Table 16 OS original data without ENZAMET - ERG NMA HR (95% CrI)

Random Effects model	ERG
DOC vs ADT	[redacted]
ENZA+ADT vs ADT±PLA	[redacted]
ENZA+ADT vs DOC+ADT	[redacted]
ENZA+ADT vs NSAA+ADT	[redacted]

All company HR (95% CrI) estimates incorporated into the NMA are taken from Table 4 of the company's clarification response dated 12 Dec 2019

Table 17 OS Updated 2 without ENZAMET - ERG NMA HR (95% CrI)

Random Effects model	ERG
DOC vs ADT	[redacted]
ENZA+ADT vs ADT±PLA	[redacted]
ENZA+ADT vs DOC+ADT	[redacted]
ENZA+ADT vs NSAA+ADT	[redacted]

Updated to include new STAMPEDE-1 data and exclude abiraterone and apalutamide studies.
All company HR (95% CrI) estimates incorporated into the NMA are taken from Table 4 of the company's clarification response dated 12 Dec 2019

The effect of removing ENZAMET is that enzalutamide plus ADT in ARCHES alone does not significantly improve OS compared to any of the comparator treatments for this study population.

Tables 18-20 below show the NMA results for TCR, TSSE and TPSA.

Table 18 TCR - NMA HR (95% CrI) estimates (by the ERG and the company)

Fixed Effects model	ERG	CS
ENZA+ADT vs ADT±PLA	[redacted]	[redacted]
ENZA+ADT vs DOC+ADT	[redacted]	[redacted]

All company results taken from Table 34, Document B of the CS

Table 19 TSSE - NMA HR (95% CrI) estimates (by the ERG and the company)

Fixed Effects model	ERG	CS
ENZA+ADT vs ADT±PLA	[redacted]	[redacted]
ENZA+ADT vs DOC+ADT	[redacted]	[redacted]

All company results taken from Table 34, Document B of the CS

Table 20 TPSA - NMA HR (95% CrI) estimates (by the ERG and the company)

Fixed Effects model	ERG	CS
ENZA+ADT vs ADT±PLA	[redacted]	[redacted]
ENZA+ADT vs DOC+ADT	[redacted]	[redacted]

All company results taken from Table 34, Document B of the CS

3.6 Conclusions of the clinical effectiveness section

The company decision problem is appropriate for addressing the NICE final scope for this appraisal. The ERG considers the methods used by the company to conduct the systematic review of clinical effectiveness evidence to be adequate and in line with the current methodological standards.

The key clinical effectiveness evidence for enzalutamide with ADT for treating mHSPC is based on two RCTS sponsored by the company: ARCHES and ENZAMET. ARCHES included a total of 1150 patients with mHSPC stratified by volume of disease and previous docetaxel therapy; ENZAMET included a total of 1125 patients stratified by volume of disease, planned use of docetaxel, anti-resorptive therapy, comorbidities and study sites. Only

the ENZAMET comparison between patients who received enzalutamide plus ADT and no docetaxel versus those who received ADT plus NSAA and no docetaxel (622 patients), was considered in the CS.

Results of the ARCHES trial indicate that in the overall population at a median follow up of 14.4 months enzalutamide plus ADT reduced the risk of radiographic disease progression by 61% compared with placebo plus ADT (HR 0.39, 95% CI: 0.30, 0.50; p<0.0001) but did not show a significant improvement in OS. However, the company acknowledged that OS data were immature and in the interim analysis conducted after 84 deaths (39 in the enzalutamide plus ADT group and 45 in the placebo plus ADT group) failed to show a significant benefit in favour of enzalutamide. With regard to the secondary endpoints, enzalutamide plus ADT demonstrated significant benefits compared with placebo plus ADT in TTD, TINAT ORR, time to first SSE, and time to castration resistance and a non-significant trend towards a delay in time to deterioration in urinary symptoms and time to pain progression.

The results of the ENZAMET trial indicate that, compared with NSAA plus ADT, enzalutamide plus ADT reduced the risk of death in patients receiving no concomitant docetaxel by 47.2% (HR: 0.528, 95% CI 0.370, 0.743, unstratified p=0.0002). Enzalutamide plus ADT was also associated with a 76% decreased risk of PSA PFS events (HR: 0.34, 95% CI 0.26, 0.44), 66% decrease in the risk of cPFS events (HR: 0.34, 95% CI 0.26, 0.44), [redacted] reduction in the risk of treatment discontinuation ([redacted]) and longer time to HRQOL deterioration measured by the EORTC QLQ-C30 physical functioning, cognitive functioning, fatigue and quality of life. It is unclear whether the lower proportion of participants with HVD and Gleason score ≥8 in ENZAMET compared with ARCHES may have influenced these results.

In the ERG clinical expert's opinion, the type of frequency of adverse events observed in ARCHES and ENZAMET are reflective of UK clinical practice and the ERG agrees that both trials have not raised any new safety signals in the mHSPC patient population.

With regard to the pooling of data from the ARCHES and EZAMET studies, the ERG have reservations because of the different baseline characteristics relating to volume of disease (and consequently bone metastases), despite both trials being stratified by volume if disease. This only impacts on the OS since the company concluded that pooling the two studies for

PFS was not sensible due to the fact that the clinical PFS definitions used in the two studies differ substantially. None of the other outcomes apply to the ENZAMET study. The company based their PFS NMA only on the ARCHES study and the ERG is in agreement with this approach. However, the CS does include EZAMET for the OS NMA. The CS economic models present scenario analyses using both the OS pooled estimate and the OS NMA estimate, which includes ENZAMET and the most updated data from STAMPEDE 1 but excludes the abiraterone and apalutamide studies. The ERG replicated these results and investigated also the impact of excluding the ENZAMET trial.

In general, the ERG considers the methods used by the company to conduct the network meta-analyses to be adequate and in line with the current methodological standards. The ERG has verified all the clinical effectiveness results using the raw data provided and the subsequent hazard ratios within the NMA. For OS and PFS, **the results preferred by the ERG** are those of the base cases (using the updated information provided by the company at clarification - 12 Dec 2019 and random effects models where possible) rather than those of the sensitivity analyses. Otherwise, the original CS results are acceptable. While for completeness the ERG has also presented a NMA for OS without inclusion of the ENZAMET study, they recognise that having this longer term study does provide information otherwise missing about possible benefits of enzalutamide in the long-run.

The results that the ERG has verified and consider acceptable are the following:

- Point estimates for OS for the original CS and the updates indicate an increased survival time for enzalutamide plus ADT compared to ADT alone of around [redacted] ([redacted]). Without ENZAMET the ERG generated this to be reduced to [redacted] and to be non-significant (HR=[redacted]). OS Enzalutamide plus ADT compared to docetaxel plus ADT is not significantly different compared to docetaxel with ADT (Update2 HR=[redacted] or the ERG estimate without ENZAMET HR=[redacted]).
- For PFS there is significant benefit of [redacted] when treating with enzalutamide plus ADT compared to ADT alone, and evidence also that enzalutamide plus ADT improves progression free survival by about [redacted] ([redacted]) compared to treating with docetaxel plus ADT.

- TCR is improved for enzalutamide plus ADT when compared to both ADT alone and docetaxel with ADT ([redacted]; [redacted] and [redacted], [redacted], respectively).
- However, for TSSE while there is a [redacted] benefit of enzalutamide plus ADT compared to ADT alone ([redacted]) there is no significant benefit compared to docetaxel plus ADT.

4 Cost effectiveness

4.1 ERG comment on company's review of cost-effectiveness evidence

The CS searched for previous studies in mHSPC and only selected those relating to the UK for further analysis. While it is probably more relevant to have UK studies as sources of inputs for costs, there seems no reason to restrict in this way when considering previous model structures, utility values, or using the studies as a cross validity check on extrapolations.

Of 13 cost-effectiveness studies identified, the described three which were specific to the UK.[37-39] The study by Woods et al[38] assessed the cost-effectiveness of 6 cycles of docetaxel in addition to ADT for men with non-metastatic and metastatic HSPC, providing an ICER of £5,514 for docetaxel versus ADT alone in the metastatic population. The estimated life year and QALY gains were 0.89 (undiscounted) and 0.51 (discounted), respectively. The model for NICE ID945 assessed cost-effectiveness of abiraterone plus ADT versus ADT alone and docetaxel plus ADT in men with newly diagnosed high risk mHSPC.[39]

4.2 Summary and critique of the company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 21 NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Satisfactory
Perspective on costs	NHS and PSS	Satisfactory
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Satisfactory
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Satisfactory
Synthesis of evidence on health effects	Based on systematic review	Issues with extrapolation of data results in potential over-estimate of QALYs gained
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.	Issues with values used, especially after progression. EQ-5-5L used for several states.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes, but progressed states reflect trial populations at baseline and may overestimate average utility for progressed states.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes, reflect UK preferences, with appropriate cross walk from EQ-5D-5L to EQ-5D-3L.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Satisfactory
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	Based on previous appraisals and validated by a clinical expert.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Satisfactory

PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.

4.2.2 Model structure

The CS presented an economics model with the following structure (Figure 2):

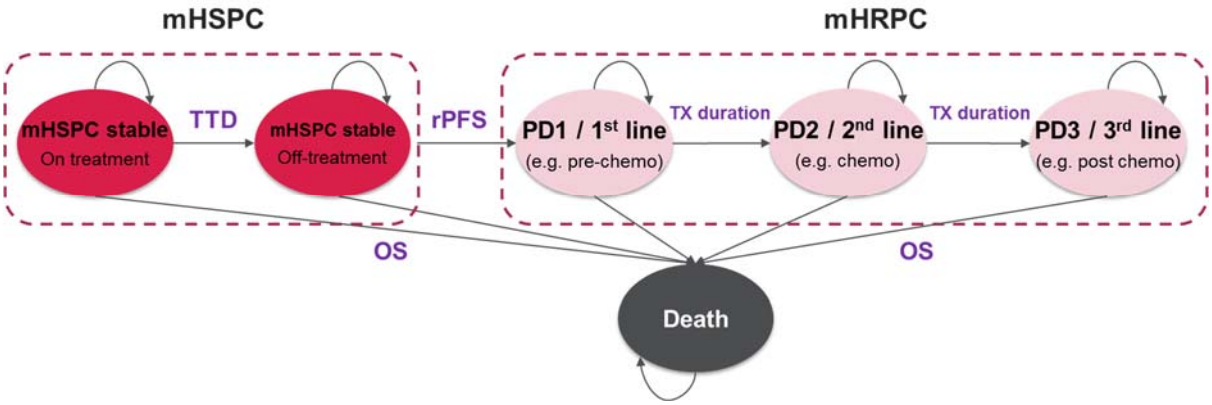


Figure 2 Company's model structure (source: Figure 19 of the company submission, document B)

The state mHSPC is divided into time on and off treatment to allow for discontinuation prior to progression.

The state mHRPC is further divided into up to three 'on treatment' states to reflect possible treatments in later line.

The company justified the selected structure as follows:

- It builds on models in NICE TAs reviewing enzalutamide in post-chemotherapy mCRPC (TA316), chemotherapy naïve mCRPC (TA377) and nmHRPC (TA580)[40-42]
- It is based on progression from mHSPC to HRPC to death

In reviewing the CS, the ERG considered the following questions:

- Given the clinical evidence presented, does the model structure offer a plausible conversion to QALYs?
- Are any important disease stages missing, specifically could QALYs have been under-estimated?
- Does the selected structure lead to a danger of over-estimating QALY gains?
- Was the model structure consistent with previous STAs?

The model could be read as the familiar oncology model of progression-free survival (PFS) – post-progression survival (PPS) – death, but with PFS divided into on and off treatment and with PPS divided into up to three lines of further treatment.

The ERG agrees that at a top-level, the categories 'PFS – PPS – death' seem a plausible way to model the clinical data that does not risk under- or over-estimation.

The PFS state is divided into on treatment and off treatment. It is plausible that utilities and costs will differ according to whether the patient is being treated or not so this also seems reasonable. Data for this state came directly from the company's ARCHES RCT at a time point where rPFS and the proportion of patients still on treatment remains high, so careful consideration of the extrapolation assumptions is required.

In the PPS state a key potential issue is the time in each subsequent treatment state which results in savings for enzalutamide versus the comparators. The main concern is that the subsequent treatment sequence should be in line with NHS practice, but also the subsequent treatments received in the clinical trials used to inform comparative efficacy of the alternative treatments. Further, the company's trials used to inform efficacy are not suited to informing the progression through subsequent treatments in PD1-PD3, and so alternative sources of data are required for informing expected times, which introduces further uncertainty in the context of the partitioned survival approach.

An alternative model structure could have been a single combined state for PPS (or mHRPC) which the company have tested in scenario analysis. However, this lacks the granularity to accurately capture the treatment pathways available in the NHS.

An additional concern is that progression is modelled as the point at which quality of life declines, but the chosen definition of progression is based on radiology results rather than symptoms. Therefore, there is the potential for the model to predict a change in quality life before it would have happened.

With these caveats the ERG agrees the structure selected is broadly appropriate.

4.2.3 Population

The CS was for the whole of the licensed indication i.e. for patients with metastatic hormone sensitive prostate cancer (mHSPC). The ERG understands mHSPC to refer to people with metastatic disease who have not yet received hormone therapy, or have received ADT but have not become resistant to it.

The CS reports clinical effectiveness results by sub-groups, but there do not appear to be any important differences. Therefore, no subgroup analyses were included in the economic model. Patient characteristics may determine which treatment patients receive currently in usual care – for example, there will be a group of patients with mHSPC who are considered unsuitable for docetaxel due to existing comorbidities or frailty (e.g. ECOG performance status >2). In the ARCHES RCT, results were reported by ECOG status but only for an ECOG of 0 and 1. The HR for PFS was very similar across the groups but there is a lack of evidence in patients with ECOG of 2 or poorer. Thus, the company's clinical effectiveness evidence is likely more suited to the population that would otherwise be considered eligible for docetaxel. The ERG acknowledges that not everyone who is considered eligible for docetaxel choose to take it.

4.2.4 Interventions and comparators

The comparators in the economics model were ADT alone and ADT-plus-docetaxel.

ERG commentary

The ERG agrees both are consistent with the Final Scope.

They are also consistent with NICE NG131 recommendations for newly diagnosed metastatic prostate cancer which indicates that (NG131; pages 30-31)[10]:

- those who do not have significant comorbidities should be offered docetaxel plus ADT.
- all patients should be offered ADT surgically or with LHRH agonist (NG131; pages 30-31)
- bilateral orchidectomy should be offered to all people with metastatic prostate cancer as an alternative to continuous luteinising hormone-releasing hormone agonist therapy

- for people with metastatic prostate cancer who are willing to accept the adverse impact on overall survival and gynaecomastia with the aim of retaining sexual function, offer anti-androgen monotherapy with bicalutamide[6] (150 mg)
- combined androgen blockade should not be offered in first line

Docetaxel does not have a specific label for mHSPC but it is commissioned by NHS England (up to 6 cycles) if patients:

- have newly diagnosed metastatic, prostate cancer;
- are either commencing, or who have commenced within 12 weeks, long-term hormone therapy (Androgen Deprivation Therapy) for metastatic disease for the first time; and
- have sufficient performance status to be treated with 6 cycles of docetaxel chemotherapy
- (dose same as label, prednisolone for first 3 weeks)

In the on-going STA of abiraterone, the ERG notes that NHS England commented:
"The current treatment pathway for newly diagnosed hormone sensitive PC consists of androgen deprivation therapy (hormone treatment) or the combination of docetaxel chemotherapy with androgen deprivation therapy. About two thirds of such patients receive ADT alone and about one third receive docetaxel plus ADT. This split of treatment choices depends on fitness for chemotherapy, visceral metastases (an adverse prognostic factor), high volume of metastatic load (another adverse prognostic factor) and patient choice. Most patients receiving chemotherapy plus ADT have adverse disease." (NICE TA10122, Committee papers, page 238, paragraph 2).[39]

It should be noted that this statement dates to June 2018, and uptake of the different comparators may have changed since the update of NG131 to include the recommendation on docetaxel + ADT in May 2019. However, it can be noted from the above statement that there are broadly two groups of patients newly diagnosed mHSPC who currently receive ADT alone in clinical practice – those who are ineligible for docetaxel, and those who are eligible but choose not to have it. The company evidence base for the effectiveness of enzalutamide plus ADT appears more suited to the latter group.

The Final Scope included monotherapy with bicalutamide as an alternative to ADT monotherapy. NICE NG131 quoted above shows this would only be used in very specific circumstances. The quote from NHS England above suggests very few patients receive this. While bicalutamide monotherapy is not included in the company submission, the ERG is satisfied that it is not an important issue.

4.2.5 Perspective, time horizon and discounting

The perspective used was NHS plus PSS for costs and health benefits for patients. The ERG notes this is in line with NICE's reference case.

A time horizon of 30 years was used, based on the median age of patients in the two RCTs being 69 and 70. The ERG note the mean is a more appropriate figure than the median. However, a 30-year time horizon does seem adequate. The ERGs clinical advisor believed that all patients would be expected to be dead by 20 years. Shorter time horizons (20 years and 10 years) were provided in the company's sensitivity analyses.

The 3.5% rate of time preference was applied to costs and to health benefits, reflecting NICE's reference case. A rate of 1.5% was used in a sensitivity analysis.

4.2.6 Treatment effectiveness and extrapolation

Within the economic model TTD and PFS are modelled using data from ARCHES that is extrapolated from approximately 2 years until the assumed lifetime horizon of 30 years. For OS, additional data from ENZAMET are also used. ENZAMET extends the period of observed data to around 4 years for OS. The same data sources are used for the enzalutamide-plus-ADT and ADT arms of the model.

Decisions regarding extrapolation of ADT data have important implications for how docetaxel enters the cost effectiveness analysis, since hazard ratios are applied to all points of the selected ADT curve to estimate PFS and OS for docetaxel-plus-ADT.

Within the cost effectiveness model, corrections are applied to ensure that PFS does not exceed OS, and that the mortality rate is not below the mortality rate amongst the general population.

PFS: enzalutamide plus ADT and ADT alone

Data on PFS from the clinical study were presented in the CS Document B, Figure 20, page 123.

Standard parametric curve fits were undertaken by the company. Clinical plausibility was assessed in comparison to long-term PFS estimates from STAMPEDE[27] CHAARTED[18] and GETUG-AFU15,[35] and through consultation with one UK clinical expert. Based on guidance in NICE DSU technical support document 14, the company applied the same parametric fit to both arms of the model.

Measures of statistical fit and PFS estimates at a range of cut-offs for each parametric fit are given in Tables 22 and 23 below. The figures were provided by the company at the clarification stage and differ slightly to the figures referred to in Document B, Section 3.3.1.1, page 122.

Table 22 Predicted PFS % at 5 years, 10 years, 20 years and 30 years for each of the six parametric fits for enzalutamide plus ADT, including measures of statistical fit

	Exponential	Weibull	Log-normal	Log-logistic	Gamma	Gompertz
Year 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 8.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 7 from the company's clarification response and company's economic model.

Table 23 Predicted PFS % at 5 years, 10 years, 20 years and 30 years for each of the six parametric fits for ADT alone, including measures of statistical fit

	Exponential	Weibull	Log-normal	Log-logistic	Gamma	Gompertz
Year 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 8.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 8 from the company's clarification response and company's economic model.

In all cases presented in Table 23, the estimates for 5-year PFS for ADT alone are less than the lowest value (19%) given in the published external studies[35] which are referenced within CS Document B. The generalised gamma or exponential curves provides 5-year PFS predictions for ADT alone which is closer to those observed in external studies. However, the decision to use the same parametric fit on both arms of the model led to generalised gamma curve not being selected since the 10-year PFS for enzalutamide plus ADT ([redacted] in Table 22 was deemed clinically implausible by the clinical expert consulted by the company. In the base case the log-normal curve was selected for both the enzalutamide-plus-ADT and ADT arms of the model. This gives a 5-year PFS prediction for ADT alone of [redacted], almost 10% lower than observed in any comparable external study referenced within CS Document B. Since the DOC arm of the model is determined by a HR being applied to the selected parametric curve from the ADT arm, it follows that the log-normal curve is also used to inform the base case for the third arm of the model. Based on measures of statistical fit only, the log-normal curve provides the second-best fit to the observed PFS data for ADT alone and the joint best fit for enzalutamide-plus-ADT.

TTD: enzalutamide plus ADT

Data on TTD from ARCHES were presented in the CS Document B, Figure 21, page 124. A further graph presenting the relationship between the base case PFS and OS extrapolations relative to three potential TTD extrapolations for ENZA was presented in the CS Document B, Figure 22, page 124.

The observed data from ARCHES were fitted to standard parametric curves by the company. The TTD curve was then selected based on measures of statistical fit (Table 24) and the relationship to the base case PFS curve for ENZA. TTD is assumed to differ from PFS for ENZA due to a lower number of PFS than TTD events being observed at the data cut-off in ARCHES.

TTD for enzalutamide is an important input for the economic model since patients do not progress immediately to a lower utility state, but move to an off-treatment pre-progression state. This low cost QALY benefit for extended progression-free time in the enzalutamide arm of the model increases with the distance between the selected PFS and TTD parametric curves.

Table 24 Measures of statistical fit of standard parametric curves for enzalutamide plus ADT time to treatment discontinuation (TTD)

	Exponential	**Weibull**	**Log-normal**	**Log-logistic**	**Gamma**	**Gompertz**
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Company's economic model.

In the CS (Document B, page 123) it is stated that "The model with the best statistical fit for ARCHES TTD was exponential, closely followed by log-logistic and Weibull". This is not fully consistent with the measures of statistical fit provided within the economic model and summarised in Table 24 above. The Gompertz curve provides a marginally better fit by the AIC, while the exponential provides the best fit according to the BIC. However, the observed AIC and BIC values across all parametric curves fall within a narrow range.

The selection of a parametric TTD curve for enzalutamide was additionally based on the relationship to the base case PFS curve. This relationship, over the full 30 years of the economic model, is presented in Figure 3 below which was provided by the company at the clarification stage. The Gompertz curve was not included on this figure. Had it been included, this curve would fall substantially below all the presented curves, with treatment discontinued for all individuals by 8 years.

Source: Figure 5 in the company's clarification response.

Figure 3 Modelled ARCHES TTD extrapolations relative to the base case rPFS OS curves

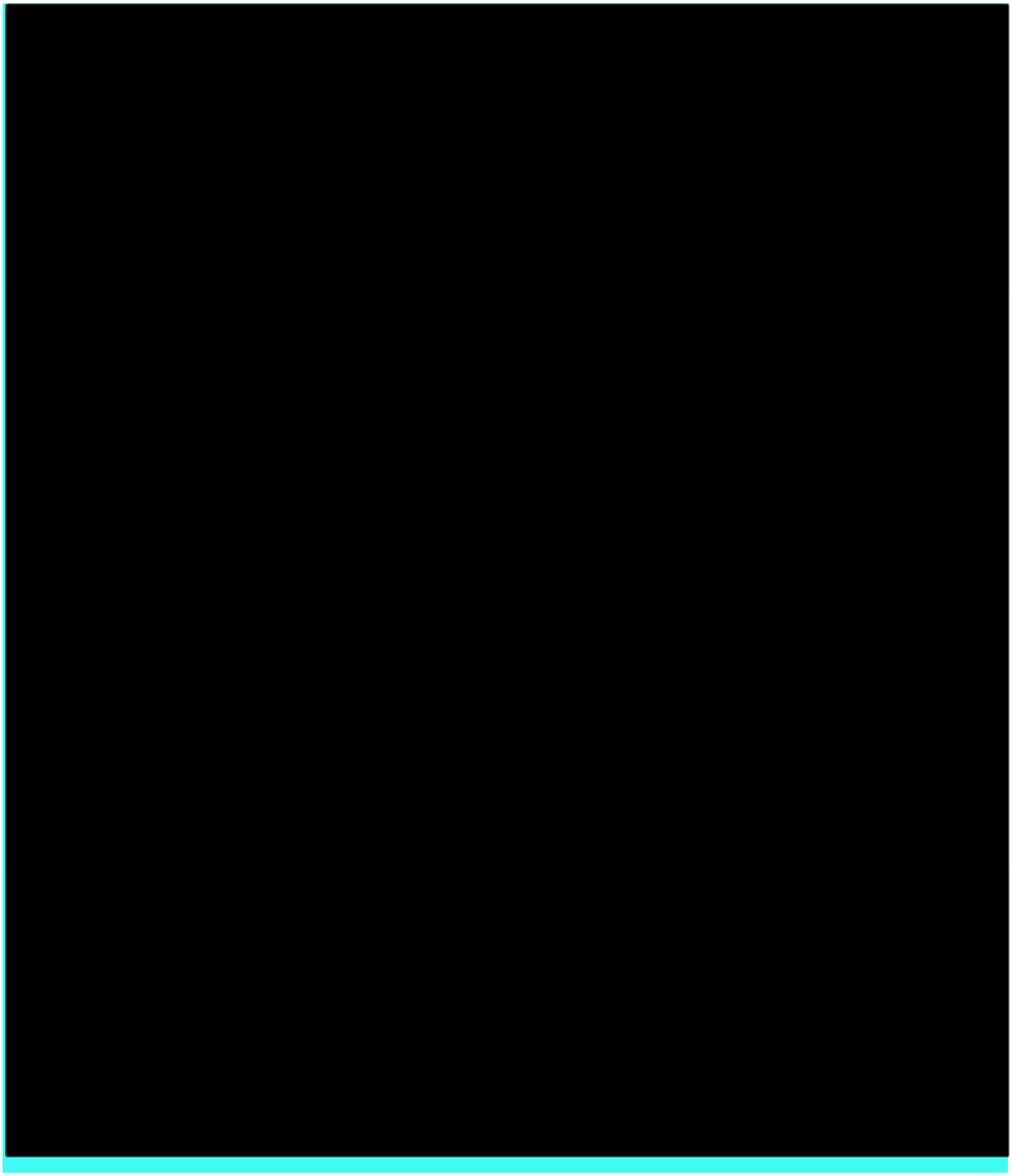
In the company's base case, the exponential curve was selected due to the close relationship with the PFS curve, but not crossing PFS at any point. The loglogistic curve also closely follows the PFS curve during the first 4 years of the analysis "when most people will be in the mHSPC health states" (CS Document B, page. 123). However, a correction would be required to ensure the loglogistic curve did not cross the PFS curve. Such a correction is available within the economic model.

OS: enzalutamide plus ADT and ADT alone

Data from patients not receiving concurrent docetaxel in ENZAMET was pooled with ARCHES data to estimate OS for enzalutamide plus ADT and ADT alone. As in the case of PFS, a HR was applied to the extrapolated ADT parametric curve to estimate OS for the docetaxel plus ADT arm.

The pooling of patient groups with differing baseline characteristics has been discussed within the clinical effectiveness chapter of this report. Since this pooling may impact on OS predictions in the economic model, the company included scenario analyses using single data sources.

At the clarification stage, the company identified an error in the presentation of parametric curves in the CS, Document B, Figure 23, page 126. Figure 4 gives the corrected figures provided by the company which have also been extended to reflect the time horizon employed in the economic analysis.



Source: Figure 6 in the company's clarification response

Figure 4 Pooled OS extrapolated by the 6 standard parametric models

In the enzaluatimade plus ADT arm of the model, shown in the upper part of Figure 4, the uppermost curves show little variation in predicted survival, while the lower three curves have substantial differences in predicted survival. Measures of statistical fit and OS predictions at key cut-offs are summarised in Table 25 below. Despite the substantial differences in long term OS predictions from the various parametric fits, the range across the measures of statistical fit neither differ greatly nor display any clear relationship with the predicted outcomes. Due to the absence of relevant long-term observed external data for the enzalutamide plus ADT arm of the model, clinical expert opinion plus observed external data on OS for ADT alone were used to select the appropriate parametric fit.

Table 25 Predicted OS % at 5 years, 10 years, 20 years and 30 years for each of the six parametric fits for enzalutamide plus ADT, including measures of statistical fit

	Exponential	Weibull	Log-normal	Log-logistic	Gamma	Gompertz
Year 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 8.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Company's clarification response and economic model.

Table 26 provides OS predictions for ADT alone. CS Document B page 125 states that external data on 7-year survival for ADT alone fall within a range of 27% to 34%. Only the log-logistic curve provides a prediction within this range. However, the decision to ensure that the same parametric fit for OS was applied to all arms of the economic model meant the log-logistic curve was rejected since the OS estimate for enzalutamide plus ADT at 16 years ([redacted]%) was deemed to be clinically implausible. Consequently, the Weibull curve was selected for the base case to ensure a level of clinical plausibility in all arms of the model, despite the 7-year OS prediction for ADT alone of [redacted] being below the range observed in external studies.

Table 26 Predicted OS % at 5 years, 10 years, 20 years and 30 years for each of the six parametric fits for ADT alone, including measures of statistical fit

	Exponential	Weibull	Log-normal	Log-logistic	Gamma	Gompertz
Year 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 8.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Company's clarification response and economic model.

Overall, the company's base case employs the log-normal curve for PFS and the Weibull curve for OS in the ADT and enzalutamide plus ADT arms of the model. This decision leads to PFS crossing OS for enzaluatimide at about [redacted] years as illustrated in Figure 3 above. A correction is applied within the economic analysis such that PFS follows OS for the final [redacted] of the model. To ensure that the mortality rate is not less than general population mortality rate, a further correction is made to OS. This correction occurs from [redacted]. Therefore, in the final [redacted] in the enzalutamide arm of the company base case, PFS is equal to OS which is equal to the mortality rate of the general population.

To obtain PFS and OS curves for the docetaxel plus ADT arm of the model, HRs from the NMA were applied to the selected ADT curves. The HR for PFS was [redacted] and for OS was [redacted]. Table 27 summarises the influence of the six parametric fits for ADT alone on the docetaxel plus ADT arm. The selection of the log-normal curve provides mid-range predictions for PFS, while the selection of the Weibull curve provides the second lowest predictions for OS.

Table 27 Predicted PFS and OS percentages for docetaxel plus ADT at 5 years and 8.5 years based on adjustment of the six parametric curves for ADT alone

	ADT Exponential	ADT Weibull	ADT Log-normal	ADT Log-logistic	ADT Gamma	ADT Gompertz
PFS - Year 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS - Year 8.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS - Year 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS - Year 8.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Company's economic model

ERG commentary

The ERG commentary on this issue considers the validity of the company model predictions, then a detailed critique of the modelling assumptions used, leading to alternative plausible scenarios.

Commentary part 1: Validity of company' model predictions

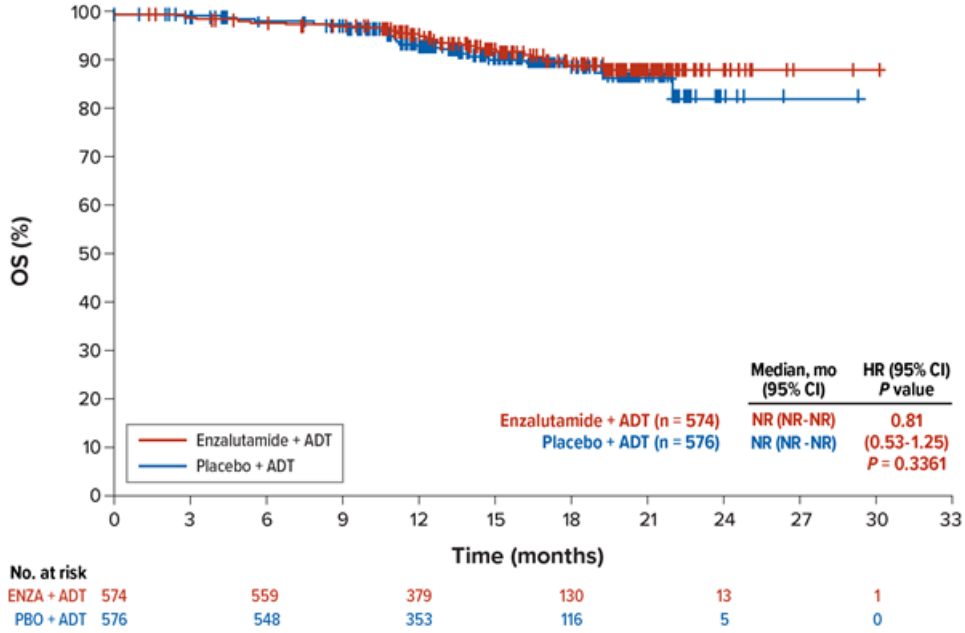
In addition to the validation checks in terms of comparing the predictions of models to the estimates provided by clinical experts, the ERG assessed face validity in several other ways:

- By comparing the model predictions back to the observed results in the RCTs for enzalutamide in mHSPC
- By comparing the predicted QALYs and QALY gains to the most relevant completed NICE HTA in prostate cancer
- By comparing to the RCT data for another medicine, abiraterone, in a similar indication in mHSPC

No single method provides a definite conclusion about the validity of the predictions of the company's model, but they offer additional information to help the Appraisal Committee judge the plausibility of the company submission.

Comparing the company's model predictions to the results of the RCTs for enzalutamide in mHSPC

There are two relevant RCTs here; ARCHES and ENZAMET. Figure 5 and figure 6 show the company's OS Kaplan-Meier plots for the ARCHES and ENZAMET trials respectively.



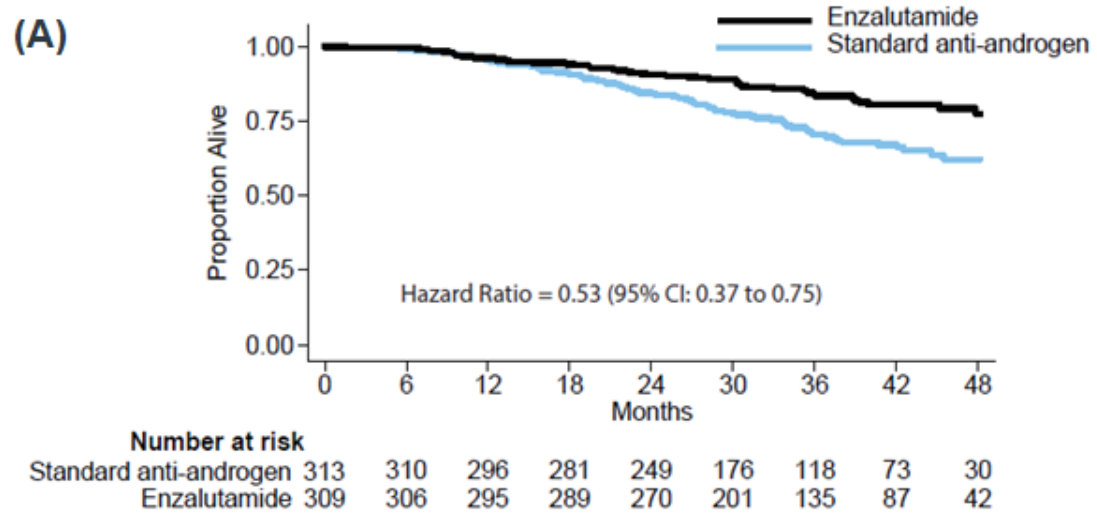
Original source: ARCHES CSR[19], Armstrong *et al*[1]

Data cut-off date: 14 Oct 2018

Time from randomisation to death from any cause. For patients still alive at the date of the analysis cut-off point, overall survival was censored on the last date the patient was known to be alive.

Abbreviations: ADT: androgen deprivation therapy; CI: confidence interval; ITT: intent-to-treat; NE: not estimable.

Figure 5 Kaplan-Meier plot of overall survival – key secondary efficacy analysis (ITT population) – Sourced by the ERG as Figure 9 of the CS, Document B, page 61



Original Source: Davis et al 2019.[16]

Data cut-off date: 28 Feb 2019

Figure 6 Kaplan-Meier plot of overall survival in (A) patients not on concomitant docetaxel and – Source by the ERG from Figure 11 of the CS, document B, page 70

The first point to make is that the OS data are immature, and so immature in the case of the ARCHES RCT that no reasonable conclusion about a difference between treatments could have been reached at this stage of follow-up. Even in the case of ENZAMET, where a statistically significant difference was shown in the group not treated with concomitant docetaxel, only 16% of patients treated with ADT plus enzalutamide and 28% of patients treated with ADT plus NSAA had died, so approximately 75% of the recruited patients are still alive. Any prediction is thus highly uncertain.

The prediction of the economics model is that the difference in life-years will be [redacted] years versus [redacted] years (discounted at 3.5%), or [redacted] versus [redacted] (undiscounted). Considering the ENZAMET results for ADT plus NSAA arm, with around 60% of patients are still alive at 4 years, the mean projected life years of [redacted] for ADT does seem quite pessimistic. Conversely, in the opinion of the ERGs clinical expert, the projected survival of [redacted] at 20 years for enzalutamide in the company base case appears very optimistic.

In ARCHES there is no significant difference in OS after 24 months, but the model predicts that even with confounding for subsequent lines of treatment, a difference in average OS of three years will emerge.

The ERG concludes:

- Any predictions about lifetime OS are highly uncertain and
- The OS gain predicted by the company's economics model, seems very optimistic, given the 'hard data' in the observed OS curves from the two RCTs

Comparing the company's model predictions to the most relevant NICE HTA

The following graph (Figure 7) is from the company submission for enzalutamide in mHRPC[41] (equivalent to PD1 in the economics model) and shows the predicted QALYs for enzalutamide, BSC and abiraterone.

Figure 7 QALY gains for enzalutamide, abiraterone and BSC in NICE TA377 - enzaluatmide in metastatic HRPC before chemotherapy; Source: Committee Papers for ACM1, Company submission page 209
https://www.nice.org.uk/guidance/ta377/documents/prostate-cancer-metastatic-hormonerelapsed-enzalutamide-id683-committee-papers-2

This gives a QALY gain for enzalutamide versus usual care of 0.62 QALYs.
In the current submission the equivalent figures for enzalutamide plus ADT are [redacted] versus [redacted] for ADT alone, to give a QALY gain of [redacted]. The absolute QALYs are higher as would be expected, but the difference is striking with the QALY gain for enzalutamide versus ADT

being double the gain in the graph above. This appears particularly optimistic when considering that those in the ADT arm of the current model might expect to have a better outlook from the time of progression compared to those who progress following enzalutamide; i.e. they can still benefit from having enzalutamide or abiraterone following progression. Adding to this, it notable that company's current base case predicts greater mean life years in the progressed states for enzalutamide plus ADT than for ADT alone; [redacted] months versus [redacted].

No firm conclusions can be drawn but the above suggests the QALYs gains from enzalutamide in the current submission have been over-estimated.

Comparing the company's model predictions to RCT data for another medicine, abiraterone, in a similar indication in mHSPC

Abiraterone is another medicine for prostate cancer, currently being reviewed by NICE for 'newly diagnosed high risk metastatic hormone-sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT)'. This is currently being reviewed by NICE through an STA.

The STAMPEDE platform multi-arm RCT included a comparison of patients directly randomised to abiraterone plus ADT or docetaxel plus ADT over a common time period. The hazard ratio for OS for all patients was 1.16 (0.82 to 1.65, p 0.404). In metastatic patients the HR for abiraterone plus ADT versus docetaxel plus ADT was 1.13 (0.77 to 1.66, p 0.528). There was no statistically significant difference in OS between abiraterone and docetaxel in direct comparison.

Of course, abiraterone and enzalutamide are not the same medicine. However, in previous NICE TAs in later stages of metastatic prostate cancer they have been shown to have benefits that are similar, although not necessarily identical. Given that abiraterone has not shown an OS benefit against docetaxel in a direct comparison RCT, there may be some caution about accepting the modelled benefits for enzalutamide plus ADT versus docetaxel plus ADT in the current analysis. These benefits are substantial in the company base case, with discounted LY and QALY gains of [redacted] and [redacted] respectively. These modelled benefits do not appear in keeping with magnitude of the estimated HR from the company's NMA, or the associated uncertainty; The HR for OS in the company's NMA comparing enzalutamide and docetaxel was [redacted], later revised to [redacted]). The company's

base case modelling approach implies a greater relative treatment benefit versus docetaxel that increases over the model time horizon. Given the uncertainties, the ERG prefers to use the NMA HRs for both enzalutamide and docetaxel and believes a scenario that equalises OS between these two arms is also justified.

Commentary part 2: critique of the company's choice of methods and assumptions

The ERG has substantial concerns that the extrapolation of relatively immature data on the enzalutamide plus ADT arm has resulted in predictions which are overly optimistic considering the best available comparative effectiveness evidence and external long-term data on these comparators. This problem is most pertinent in the modelling of OS, although the PFS and TTD predictions are also problematic. For ADT, the OS and PFS predictions both appear to be low, although more recent data from STAMPEDE[26] suggests a lower level of underprediction than comparison to the studies referenced within the CS, Document B.

The company's approach to selecting an appropriate parametric fit attempted to balance statistical fit, clinical plausibility, and consistency in curve selection across all arms of the model. However, the ERG feels that the latter point may have been too rigidly applied in this case to the detriment of the clinical plausibility of the estimates. NICE DSU Technical Support Document 14[43] allows for different parametric fits to be applied across arms in the model and states where this can be justified. In this model, the base case parametric curves for the ADT arm appear justifiable, although not without uncertainty. However, despite limited evidence of improved outcomes for enzalutamide relative to docetaxel, the company's base case predicts substantial life year and QALY gains. Additionally, the company's base case assumes [redacted] at 20 years, which the ERGs clinical expert believed was implausible. The ERG's opinion is that exploration of differing parametric fits in each arm of the model are clearly justified. Likewise, alternative approaches to modelling survival, such as applying a relevant HRs, warrant investigation.

Due to the relative immaturity of the observed data for the enzalutamide arm, the parametric curves show little variation within the observed data period. Consequently, the measures of statistical fit are broadly comparable across many parametric curves. As such, the usefulness of these measures is severely limited, especially since the extrapolations provide substantially different estimates of long-term PFS, TTD, and OS. The ERG's opinion is that the clinical

plausibility of the outcomes is the most important factor in this instance, and an assessment of this plausibility must be made using external data and expert opinion.

The ERG's clinical expert advised that STAMPEDE is the most appropriate source of comparable survival data for ADT alone and docetaxel plus ADT, with an observation period greater than ENZAMET and ARCHES. The most recent publication (Clarke et al., 2019)[26] provides observed data to a maximum of about 9 years. These data can provide an indication of OS and PFS for two arms of the model (ADT and DOC). Key cut-off points are summarised in Table 28 below. It should be noted that the 5-year failure free survival value for ADT is below the lowest value referenced in CS Document B, Section B.3.3.1.1, page 122. Therefore, this provides some support for the company's selection of the lognormal curve for ADT PFS which falls below this range. However, 5-year PFS for ADT in the company's base case is lower still than the value in Table 28.

Table 28 Overall survival (OS) and failure free survival (FFS) from STAMPEDE (Clarke et al., 2019)[26]

	OS - ADT alone	OS - Docetaxel plus ADT	FFS - ADT alone	FFS - Docetaxel plus ADT
5 years	36.5%	49.1%	12.6%	22.6%
8.5 years	21.7%	22.6%	5.7%	11.3%

Source: Clarke et al., (2019)[26]

Note: Graphs from the source have been digitised to acquire these data. As such, the values should be considered as approximate (+/- 0.5%).

Table 28 provides long-run data for two arms of the company's model only. Other sources are required to estimate the relationship between enzalutamide and the treatments in Table 27. A NMA was conducted by the company, which is summarised in the CS Document B, Table 34, page 97. This suggests a HR for PFS of [redacted] for enzalutamide plus ADT compared to ADT alone, and [redacted] for enzalutamide plus ADT compared to docetaxel plus ADT. Consequently, it would be expected for PFS on enzalutamide to be substantially greater than 22.6% at 5 years and above 11.3% at 8.5 years. For OS, the original NMA indicated a HR of [redacted] for enzalutamide plus ADT compared to ADT alone, and [redacted] (within the company's NMA scenario analysis a slightly lower value of [redacted] is inferred) for enzalutamide plus ADT compared to docetaxel plus ADT. However, there is substantial uncertainty regarding any OS advantage for enzalutamide versus docetaxel in this setting, [redacted]

[redacted]. Therefore, based on the NMA, it is plausible that OS for enzalutamide could either be equal or only marginally above both 49.1% at 5 years and 22.6% at 8.5 years. Furthermore, there is some evidence for convergence of OS between ADT alone and docetaxel plus ADT in Table 28, indicated by very similar OS by 8.5 years. The published paper by Clarke et al.[26] suggests this convergence starts from around 6.5 years, which is consistent with a diminishing proportional reduction in the hazard for mortality for docetaxel versus ADT over time. The ERG's clinical expert believed that convergence for all treatments would be expected from around this timepoint. It is worth noting here that the company's base case analysis results in an increasing proportional reduction in the monthly hazard of mortality for enzalutamide versus ADT and enzalutamide docetaxel plus ADT out to 21 years. And even beyond this time point a proportional reduction remains to the end of the modelled time horizon.

Beyond the time period covered by Table 28 it is necessary to rely on clinical expert opinion to estimate OS and PFS. In the opinion of the ERG's clinical expert, OS would be expected to be 0% at 20 years in all treatment arms, with 10-year OS for ENZA around 15%. The ERG's clinical expert provided a plausible range of PFS for ENZA, these are 20-30% at 5 years, 0-10% at 10 years, and 0% at 20 years. This range of estimates appears broadly consistent with the values provided from STAMPEDE in Table 28, especially if there was a convergence of OS across treatments between 6 and 10 years.

The ERG identified three approaches to address the low level of clinical plausibility from extrapolation in the enzalutamide plus ADT arm of the model. These are 1) apply an alternative combination of parametric curves, 2) use the hazard ratios from the NMA (as done in scenario analysis by the company), and 3) equalise hazards of progression and mortality from a fixed time point to force convergence of the PFS and OS curves. AS mentioned, the appears to be suggested by the data reported by Clarke et al.,[26] at least for docetaxel and ADT.

1. Application of an alternative combination of parametric curves

When considering alternative parametric curves, the focus was on the enzalutamide plus ADT arm of the model. The ERG recognises that extrapolations for the ADT arm based on ARCHES data consistently predict PFS below what is observed in external clinical studies.

The generalised gamma or exponential curves would reduce this discrepancy. Comparison to Table 28 above suggests the exponential curve ADT PFS provides plausible estimates.
The most important change proposed to the parametric curves is to adopt the Gompertz curve for OS on the enzalutamide arm. The Gompertz curve maintains an OS advantage for ENZA within the early years of the model before converging to the levels observed for other treatments. This provides OS predictions which are closer to those observed for STAMPEDE (Table 28 above) and are consistent with the ERG's clinical expert opinion beyond the observed data period of STAMPEDE. Of the parametric curves presented in Table 25 above, the Gompertz curve is the only alternative which would reduce the OS predictions for enzalutamide. Furthermore, selection of the Gompertz curve for enzalutamide OS would ensure that long term survival does not have to be overridden in the long term for falling below general population mortality. If parametric curves are to be used to extrapolate the observed data, the ERG believe that the Gompertz curve provides the most plausible estimates for enzalutamide OS. Since the Gompertz OS crosses below the OS curves for the other relevant treatments, a correction would be required which equalises the hazard ratio for all treatments from ten years onwards.

A second important suggested change is to adopt the log-logistic curve for TTD extrapolations. The ERG's clinical expert stated that in practice PFS and TTD would be almost identical. The log-logistic curve provides the closest fit between TTD and PFS in the company's base case, with TTD being set equal to PFS from [redacted] onwards. In the company's base case, the distance between the TTD and PFS curves increases over time, such that by [redacted] most patients remaining in the mHSPC state have discontinued treatment on enzalutamide. These patients contribute relatively high utility to the ENZA arm without incurring enzalutamide drug costs. Selection of the log-logistic curve greatly reduces such occurrences and provides predictions that are more in line with ERG's clinical expert's expectations. As such the ERG prefers selection of the log-logistic curve for enzalutamide TTD.

While the ERG feels that changes to the parametric curves for ENZA OS and TTD are essential to ensure plausible results from the economic model, changes to enzalutamide PFS are less important. The ERG suggest that the log-logistic curve may be a valid alternative which would align with the opinion of the ERG clinical expert for PFS and provide estimates closer to docetaxel PFS from STAMPEDE.[26] [redacted]

[redacted]. Therefore, the company's choice of the log-normal curve could provide plausible results in the first [redacted]. If used with the Gompertz OS curve for ENZA, the log-normal PFS would be reduced from around 10 years to ensure PFS is below OS.

2. Use the HRs from the NMA

An alternative to selecting parametric curves for the ENZA arm involves using the HRs from the NMA. The company reported such results in scenario 8 in CS Document B, Table 74, page 162.

From Figure 4 above, it can be seen that there is a large gap in enzalutamide OS between the Weibull curve (the company's base case) and the Gompertz curve (the ERG's preferred parametric fit). If more mature data was available, it is likely that extrapolations based on parametric curves would have provided options between these two curves. As such an option is unavailable from the parametric fits, the NMA provides an evidence-based alternative.

Comparing Table 29 below with Table 24 above indicates that using the NMA does provide OS estimates for enzalutamide which fall between those from extrapolations based on the Weibull and Gompertz curves. Further comparison to Table 21 demonstrates that estimates of PFS are comparable to the company's base case using the log-normal curve. As such, the NMA provides a credible alternative to extrapolation based on parametric curves.

Table 29 OS and PFS for ENZA using the NMA

	5 year	10 years	15 years	20 years
OS	[redacted]	[redacted]	[redacted]	[redacted]
PFS	[redacted]	[redacted]	[redacted]	[redacted]

Source: Company's economic model

Extrapolations using the NMA HRs provide predictions with a very small number of survivors at the 20-year time horizon used for Abiraterone in mHSPC (ID945). From 10 years onwards the controls within the model would ensure that PFS does not exceed OS.

3. Equalise HRs from a fixed time period to capture efficacy convergence

The final option to reduce potential overestimation of OS for ENZA is to introduce into the economic model equal HRs for ADT and ENZA from a particular time point. Within STAMPEDE[26] and CHAARTED[44] the OC curves for docetaxel plus ADT and ADT alone begin to converge from around 6 years and have fully converged by 7 to 9 years. This approach could be applied to the company's base case, or an alternative base case.
Each of the methods outlined provide viable alternatives to the company's base case and are investigated within the scenario analysis in chapter 6.

4.2.7 Health related quality of life

In the company submission the values attached to the health states in the model were as follows:

- Pre-progression (HSPC) [redacted] (source: ARCHES RCT, average of PFS EQ-5D values)
- Post-progression (HRPC) [redacted], [redacted], 0.69 when on 1st line, 2nd line and 3rd line treatment respectively ([redacted] from ARCHES RCT average of PPS EQ-5D values; 0.69 from AFFIRM RCT[45] baseline EQ-5D value; [redacted] average of previous two values)
- Terminal stage (defined as last three months of life) [redacted] (source: ARCHES RCT, average value of last EQ-5D before death)

The company assumed no difference in utility between patients who were on and off treatment while in PFS, although adverse event disutilities were applied to on-treatment states. The company assumed no disutility from being on docetaxel independent of adverse events.

For adverse events, disutilities were included. For enzalutamide plus ADT and for ADT alone, the rate of adverse events was taken from the ARCHES RCT. Docetaxel adverse event rates were taken from GETUG-AFU 15[3] and rates for subsequent treatments were taken from relevant RCTs. Only grade 3 or 4 events were included where an event occurred in 2% or more of patients. The disutility for each adverse event was taken from various sources and combined with expected durations to estimate average QALY losses per treatment. These inputs are summarised in Table 52 of the company submission (Document B, pages 134 to 136). Disutilities associated with skeletal related adverse events were included in a similar manner (CS, Tables 51 and 53).

ERG commentary

The ERG notes the company's search strategy for utility values in Document B, Appendix I, page 201. In Figure 33 the company states that 38 studies were identified for full text review. The number excluded, with reasons is said to be 13, leaving 13 articles for review. It is not clear what happened to the other 12 studies.

The ERG believes the progression free utility value used in the base case is uncertain and seemingly high:

- The PFS utility value used in the base case is uncertain because while ARCHES is a plausible source, EQ-5D data were also collected in ENZAMET but according to Document B, page 128, no results are available. The appropriate value could have been the pooled pre-progression value. ENZAMET was an investigator-led trial that was not sponsored by Astellas, explaining the unavailability of the EQ-5D data to the company at time of submission.
- The PFS and PPS utility values used are not consistent with the company's description of the disease (Document B, page 17): "Development of metastases is associated with potentially serious complications for patients. Health-related quality of life (HRQoL) of patients deteriorate upon the development of metastases and the symptom burden which is initially low in these patients increases. Patients with bone metastases are at high risk of skeletal-related events (SREs), including spontaneous fracture and spinal cord compression, which are a source of significant pain and decreased HRQoL." Recent SMC guidance on abiraterone in hormone sensitive prostate cancer includes a summary of the patient and clinician point-of-view as follows: "Metastatic prostate cancer is an incurable life limiting disease and symptoms associated with disease progression such as fatigue, urinary problems, pain and bone fractures can be highly debilitating. In addition to bone, prostate cancer can also metastasise to other sites including lymph nodes and internal organs (visceral metastases)."[46] Whilst the utility impact of adverse events and skeletal related events are modelled separately, the base utility values in the range [redacted] to [redacted] as in the company base case (lower in the three months before death) may under-estimate the utility loss that patients describe. The range of utility values across the progressed disease states (PD1-PD3) appear particularly narrow.

The ERG believes the post-progression utility values used in the base case may remain too high.

- AFFIRM was an RCT of enzalutamide use in mCRPC after progression with docetaxel. The baseline value used is for patients recruited to the RCT but the CONSORT diagram in the publication of the RCT shows that of 1720 patients assessed for eligibility, 521 were not randomised (30%).[45] Baseline characteristics for those randomised show average age was 69 and over 90% were ECOG status 0 or 1, suggesting a skew towards younger and fitter patients. These factors are associated with higher utility values.
- The reduction in utility values between PD1 and PD2 in the base case was [redacted] and between PD2 and PD3 was [redacted]. However, this is not consistent with the reduction on progression for enzalutamide positioned before docetaxel in TA377[41], which was 0.186 (paragraphs 3.19 and 3.20). In addition, the utility reduction on progression after PD3 was 0.085 for enzalutamide in TA316[47], paragraph 3.29, whereas in the current company submission base case there is no reduction until the end of life. The base assumptions lack face validity because it is inconsistent with the values in previous NICE HTAs.
- Given that the median age in ARCHES was 70 and that 22% of patients were already at ECOG 1, the ERG believes that by the time patients had reached 3rd line treatment post-progression they would be older and with poorer ECOG status than in the AFFIRM baseline. Therefore, the most plausible values are below the baseline figures. The relevance of the 0.69 figure relative to the plausible range is a matter of judgement, but the ERG believes it to be at the upper end of the plausible range.
- The studies identified in the company's SLR are also consistent with a figure for PPS of 0.605. While some studies quote higher values, it is not clear that these are representative of the types of patients who would be treated in the NHS. For example, the highest utility values identified are from a study only reported in abstract and giving the source as "prior literature" with no further details provided.

The ERG notes that in the ARCHES and ENZAMET studies, time to deterioration in quality of life was an endpoint, using various measures. In ARCHES, FACT-P, BPI-SF, and EQ-5D were assessed. In ENZAMET, EORTC QLQ-C30 was reported in the company submission (Figure 14). Whilst EQ-5D and PR25 were also apparently measured, these have not been

reported. The method used in the company base case to model utility decline assumes that utility decline aligns with the definition of progression used in the RCTs. In this case it is not necessary because there is a direct measure of decline in quality of life over time. The ARCHES RCT showed the following:

- Difference in time to deterioration on FACT-P was 11.3 months on ADT-plus-enzalutamide versus 11.1 on ADT alone, HR 0.96, p=0.65 (CS, Table 20)
- Difference in time to deterioration on BPI-SF was 8.3 months on ADT-plus-enzalutamide versus 8.3 on ADT alone, HR 0.92, p=0.26 (CS, Table 21)
- Difference in time to deterioration on EQ-5D using UK value set was [redacted] months on ADT-plus-enzalutamide versus [redacted] on ADT alone, HR [redacted] (CS, Table 22)

The small differences directly observed in ARCHES support the ERG's concerns detailed above that the utility assumptions may over-estimate the QALY gains with enzalutamide.

For ENZAMET the company submission provides graphs to time to deterioration on EORTC QLQ-C30 domains (CS, Figure 14), which did show benefits favouring enzalutamide versus ADT. The graphs are referenced to an abstract that contains the data but not the graphs[23], although this does flag up that another PRO was also measured, PR25, but along with EQ-5D no results are reported in the company submission.

4.2.8 Resources and costs

The company submission included costs for the following elements:

Costs of treatment of mHSPC

Treatment duration for enzalutamide was determined by extrapolation based on the parametric curve fitted to the observed TTD data from ARCHES, as described and commented on in Section 4.2.6. The ERG is concerned that company's base case extrapolation of TTD may lead to underestimation of enzalutamide treatment costs.

Concomitant medicines use is shown in Table 60, Document B, page 140. Costs of medicines were taken from the BNF or, in the case of generic medicines, from eMIT. The ERG note that the company apply G-CSF prophylaxis per docetaxel administration to 25% of patients. Based on retrospective analysis of 198 mHSPC patients receiving upfront docetaxel between April 2013 and April 2017 at three Cancer Centres in South Central England, only 16 (8.1%) reportedly received prophylactic G-CSF[48]. Thus 25% may be on the high side.

Costs of treatment when in PD1, PD2, PD3

Rates of different treatment were determined from clinical guidelines and validated using clinical expert opinion (Table 30):

Table 30 Overview of treatment sequences considered for mHSPC and mHRPC (Source: Table 61, company submission, document B, page 141)

Health states	Enzalutamide arm	ADT arm	Docetaxel arm
mHSPC	Enzalutamide	ADT	Docetaxel
PD1	20% ADT 60% Docetaxel 20% Radium-223	20% ADT 35% Enzalutamide 10% Docetaxel 35% Abiraterone	10% ADT 35% Enzalutamide 25% Docetaxel 30% Abiraterone
PD2	25% BSC 15% Docetaxel 30% Radium-223 30% Cabazitaxel	30% BSC 10% Enzalutamide 30% Docetaxel 5% Abiraterone 20% Radium-223 5% Cabazitaxel	25% BSC 5% Enzalutamide 5% Abiraterone 30% Radium-223 35% Cabazitaxel
PD3	80% BSC 10% Radium-223 10% Cabazitaxel	85% BSC 10% Radium-223 5% Cabazitaxel	80% BSC 10% Radium-223 10% Cabazitaxel

Source: UK expert[49]

Note: ADT is included in all treatment lines

Abbreviations: ADT: androgen deprivation therapy; mHSPC: metastatic hormone-sensitive prostate cancer; PD: progressed disease.

ERG commentary

The key issue here was that NHS England's policy is to only use enzalutamide once during the patient's treatment pathway; the proposed sequence takes this into account and hence seems a plausible representation. The sequences are in line with clinical guidelines and appear generally plausible, but precise market shares for subsequent treatments remain uncertain, and the company note that these have only been validated by one clinical expert.

Costs of visits to health care and testing

Frequency of NHS resource use and testing were based on previous NICE TAs (TA377[41] and TA580[42]) and on clinical expert opinion. Rates are reported in Table 55 of the CS, Document B, page 138 for mHSPC and in Table 56 through 59 for PD1 to PD3 on pages 138 to 140. Costs were taken from PSSRU sources or from NHS Reference Costs (Document B, Table 63, page 142 to 143).

ERG commentary

The ERGs clinical expert believed that the reported resource use looked plausible, but questioned the assumption that patients on abiraterone in PD1 would receive more frequent CT scans, and that patients on docetaxel plus ADT would receive more frequent CT scans and bone scans compared to those on enzalutamide plus ADT and ADT alone. With respect to the assumption that patients with mHSPC on ADT alone incur the same resources use as those on enzalutamide plus ADT, the ERGs expert noted that typically within UK ADT is GP prescribed and administered whereas Enzalutamide is initiated and continued via hospital clinics. Thus the ADT health resource use costs may be slightly overestimated from ADT alone.

Costs of managing adverse events

The cost of managing an adverse event were included in Table 64, Document B, page 144, with costs of treating skeletal-related events in Table 65 on the following page of Document B. Costs of managing SREs were taken from a previously published study.

ERG commentary

In general, the ERG is satisfied that the costing assumptions for AEs and SREs are in keeping with the accepted methods in previous appraisals of enzalutamide.

5 Cost effectiveness results

5.1 Company's cost effectiveness results

The base case results in the company submissions were presented in Table 69, Document B, pages 154 to 155. The results are reproduced below in Table 31. These figures include the PAS for enzalutamide. PAS discounts for abiraterone, radium-223, and cabazitaxel, which are included as subsequent treatments at stages PD1 and after, are not included.

Table 31 Base case cost effectiveness results (Source: Table 69 of the company submission, document B, pages 154-155).

Treatment	Total Costs (£)	Total LYs	Total QALYs	Incr. Costs (£)	Incr. LYs	Incr. QALYs	ICER (£)
Enzalutamide plus ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,911
Docetaxel plus ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,877

Abbreviations: ADT: androgen deprivation therapy; incr.: incremental; LYG: life-years gained; PD: progressed disease; QALY: quality-adjusted life years.

5.2 Company's sensitivity analyses

Appropriate univariate analyses were presented based on changing values for variables through 95% confidence intervals, plausible ranges or +/- 25% (except for medicines costs which were varied through +/- 10%).

The company presented the results, showing PFS assumptions were the most important factor, followed by OS, treatment costs, treatment durations, and health state costs. They concluded the ICER changes show results "are relatively stable when key parameters are varied across their standard error or reported upper and lower ranges" (CS, page 155).

In probabilistic analyses, the company estimates the chances of ADT-plus-enzalutamide as being cost-effective at £30k/QALY as [redacted] and [redacted] for the comparison with ADT monotherapy and with ADT-plus-docetaxel respectively.

In the scenario analysis for the comparison with ADT monotherapy, the factors that made the biggest difference to the ICER were:

- Using NMA HRs for PFS and OS for enzalutamide plus ADT versus ADT alone. This took the ICER over £30k
- Reducing the time horizon of 10 years
- Excluding the off-treatment mHSPC health state (i.e. enzalutamide treatment follows PFS)

In the comparison with ADT plus docetaxel, the factors making the biggest difference to the ICER included:

- Using the NMA HRs versus ADT alone for PFS and OS on enzalutamide
- Using only ARCHES or only ENZAMET data
- Excluding the off treatment mHSPC health state
- Reducing the time horizon of 10 years
- Using the 2nd best parametric fit for TTD and PFS

ERG commentary

The deterministic sensitivity analysis was carried out to the usual standards in a company submission. However, the ERG does not interpret the results as showing PFS is most important. In the comparison with docetaxel plus ADT, the change producing greatest variation in the ICER is the OS extrapolation intercept value. The importance of OS is confirmed in the scenario analysis that uses the NMA HRs for enzalutamide and correspondingly reduces the survival gains.

The scenario analyses were useful because they start to show the impact of changing some of the potentially more important assumptions. As noted earlier in Section 4 of the ERG report, the ERG believes the scenario using the NMA HRs for enzalutamide versus ADT offer a more plausible analysis. However, the ERG believes that there are further uncertainties related to the company economic model that have not been explored in the scenarios provided by the company in their submission. These include uncertainty regarding the long-term relative efficacy of enzalutamide plus ADT compared to the comparators, and uncertainty around the utility values applied for progressed disease. The ERG explores these issues further in chapter 6.

5.3 Model validation and face validity check

Section B.3.10 of CS Document B (page 165) summarises the model validation checks carried out by the company. These include quality control checks of the cost effectiveness model, comparison of the model outcomes to clinical trial data, and external validation of the economic model by a UK clinical expert and health economist. The CS notes the model structure was similar to previously reviewed models.

CS Document B, Appendix L, page 224 summarises the quality control checks performed by the model developers. These checks did not identify any major issues with the cost effectiveness model. In addition, the ERG checked cell calculations and conducted black box checks of the model using a range of tests suggested by Tappenden and Chilcott (2014).[50] The results of these checks are reported in Table 32. Two repeated errors in formulae across treatment arms were identified by the ERG. The first resulted in a 20-year time horizon being used for costs, but a 30-year time horizon used for QALYs. The second error resulted in the disutility from AEs and SREs being twice multiplied by the cycle length. Proposed corrections have been made by the ERG and the impact on the base case is reported in Table 33 in Section 6. Some tests could not be conducted due to the large number (>1000) of input parameters in the model.

In Table 76 of the CS, Document B, the company also demonstrate that the model predictions for OS and PFS are in line with the results of the ARCHES and ENZAMET RCTs out to 18 months (ACHES) and 24 months (ENZAMET). The CS reports comparisons of model predictions for PFS and OS with the RCTs STAMPEDE, CHAARTED and GETUG-AFU 15 (all RCTs comparing docetaxel plus ADT to placebo as an adjunct to ADT).

In addition to the comparison to clinical data outlined in CS B.3.10.2, page 165, the ERG also compared the model outcomes to recently released data from STAMPEDE. This comparison indicates that the economic model provides reliable predictions of long-term OS for docetaxel plus ADT, and adds to the comparisons on page 166 of CS, Document B. The ERG's clinical expert also provided checks and validation of the inputs and outcomes of the economic model when appropriate. The ERG has commented on the validity of the model predictions in more detail in Section 4.2.6 above.

Table 32 Results of model checks conducted by the ERG

Model component	Model test	Unequivocal criterion for verification	Issues identified in company model
Clinical trajectory	Set relative treatment effect (odds ratios, relative risks or hazard ratios) parameter(s) to 1.0 (including adverse events)	All treatments produce equal estimates of total LYGs and total QALYs	None
	Sum expected health state populations at any model timepoint (state transition models)	Total probability equals 1.0	None
QALY estimation	Set all health utility for living states parameters to 1.0	QALY gains equal LYGs	Formulae error. Disutility for AEs and SREs are twice multiplied by the cycle length before QALYs are summed in all arms of the model. Correction has a small impact on the ICER, as outlined in the ERG scenario analysis.
	Set QALY discount rate to 0	Discounted QALYs = undiscounted QALYs for all treatments	None
	Set QALY discount rate equal to very large number	QALY gain after time 0 tend towards zero	None
Cost estimation	Set intervention costs to 0	ICER is reduced*	None
	Increase intervention cost	ICER is increased*	Formulae error. Summary sheet recalculates costs rather than taking them from the PartSA worksheet. The formulae in the

Model component	Model test	Unequivocal criterion for verification	Issues identified in company model
			summary sheet are based on a 20-year time horizon for costs only. Therefore, the ICER compares QALYs over 30 years to costs over 20 years. This error will favour ENZA, with the extent varying depending on other assumptions which affect survival beyond 20 years.
	Set cost discount rate to 0	Discounted costs = undiscounted costs for all treatments	None
	Set cost discount rate equal to very large number	Costs after time 0 tend towards zero	None
Input parameters	Produce n samples of model parameter m	Range of sampled parameter values does not violate characteristics of statistical distribution used to describe parameter.	Sample tested. No issues found.
General	Set all treatment-specific parameters equal for all treatment groups	Costs and QALYs equal for all treatments	Not tested due to model complexity (>1000 input parameters).
	Amend value of each individual model parameter*	ICER is changed	Not tested due to model complexity (>1000 input parameters).
	Switch all treatment-specific parameter values*	QALYs and costs for each option should be switched	Not tested due to model complexity (>1000 input parameters).

6 Evidence review group's additional analyses

6.1 Exploratory and sensitivity analyses undertaken by the ERG

In addition to the scenario analyses conducted by the company, the ERG conducted some further scenario analyses to explore identified uncertainties in the modelling assumptions. Table 33 summarises the scenarios. Table 34, in Section 6.2, provides results from deterministic analyses from the scenario.

Table 33 Scenarios include in the ERG's cost effectiveness analysis

No	Scenario analysis	Scenario description	Justification
	Company base case corrected for time horizon	Correct formulae in the summary sheet such that costs are calculated using the full 30-year time horizon. This base case will then be used as the foundation for subsequent scenarios.	Correction of formulae error.
1	ERG proposed AE and SRE correction	Run the base case and correct formulae in the economic model such that disutility for AEs and SREs are only multiplied by the cycle length once.	Correction of formulae error.
2	Gompertz extrapolation for ENZA OS	Run the base case analysis using the Gompertz pooled OS curve to model survival on the ENZA arm and modify the analysis such that ENZA and DOC OS is determined by the period-specific hazard for ADT from 10 years onwards.	This scenario explores the impact of the distribution applied to model ENZA OS. The Weibull distribution was selected as the base case curve for ENZA OS. This may overpredict ENZA OS. The Gompertz distribution provides the only parametric curve with OS predictions below the Weibull curve. See section 4.2.6

No	Scenario analysis	Scenario description	Justification
3	Log-logistic extrapolation for ENZA TTD	Run the base case analysis using the log-logistic curve to model TTD on the ENZA arm.	This scenario investigates the impact of the distribution applied to model ENZA TTD. The exponential distribution was selected as the base case curve for ENZA TTD. The log-logistic distribution matches ENZA PFS more closely. See section 4.2.6
4	Gompertz extrapolation for ENZA OS and Log-logistic extrapolation for ENZA TTD	Run the base case analysis using the Gompertz pooled OS curve to model survival and the log-logistic curve to model TTD on the ENZA arm. Modify the analysis such that ENZA and DOC OS is determined by the period-specific hazards for ADT from 10 years onwards.	This scenario illustrates the combined impact of the distributions applied to model ENZA OS and TTD. See section 4.2.6
5	Log-logistic extrapolation for ENZA PFS	Run the base case analysis using the log-logistic PFS curve to model progression on the ENZA arm.	This scenario explores the impact of the distribution applied to model ENZA PFS. The log-normal distribution was selected as the base case curve for ENZA PFS. This may overpredict ENZA PFS. The log-logistic curve provides prediction which may be more clinically plausible. See section 4.2.6
6	Exponential extrapolation for ADT PFS	Run the base case analysis using the exponential PFS curve to model survival on the ADT arm.	This scenario investigates the impact of the distribution applied to model ADT PFS. The exponential curve provides a plausible alternative which aligns well with long-term observed data from STAMPEDE[26]. See section 4.2.6
7	Convergence of treatment efficacy (PFS and OS) from 6 years	Modify the base case analysis such that ENZA and DOC OS and PFS are	This scenario explores the impact of treatment efficacy convergence. The latest Stampede-1 data indicates convergence of OS and PFS on

No	Scenario analysis	Scenario description	Justification
		determined by the period-specific hazards for ADT from 6 years onwards.	both treatment arms. This convergence would be expected across all relevant treatment options in the opinion of the ERG's clinical expert. Convergence begins from 6 years in this scenario. See section 4.2.6
8	Convergence of treatment efficacy (PFS and OS) from 8 years	Modify the base case analysis such that ENZA and DOC OS and PFS are determined by the period-specific hazards for ADT from 8 years onwards.	This scenario explores the impact of treatment efficacy convergence. The latest Stampede-1 data indicates convergence of OS and PFS on both treatment arms. This convergence would be expected across all relevant treatment options in the opinion of the ERG's clinical expert. Convergence begins from 8 years in this scenario. See section 4.2.6
9	Convergence of treatment efficacy (OS only) from 6 years	Modify the base case analysis such that ENZA and DOC OS is determined by the period-specific hazards for ADT from 6 years onwards.	This scenario explores the impact of treatment efficacy convergence. The latest Stampede-1 data indicates convergence of OS on both treatment arms. This convergence would be expected across all relevant treatment options in the opinion of the ERG's clinical expert. Convergence begins from 6 years in this scenario. See section 4.2.6
10	Convergence of treatment efficacy (OS only) from 8 years	Modify the base case analysis such that ENZA and DOC OS is determined by the period-specific hazards for ADT from 8 years onwards.	This scenario explores the impact of treatment efficacy convergence. The latest Stampede-1 data indicates convergence of OS on both treatment arms. This convergence would be expected across all relevant treatment options in the opinion of the ERG's clinical expert. Convergence begins from 8 years in this scenario. See section 4.2.6
11	Convergence of treatment efficacy (PFS	Modify the base case analysis such that DOC OS	This scenario explores the impact of treatment efficacy convergence beginning from different

No	Scenario analysis	Scenario description	Justification
	and OS) from 6 years for DOC and 8 years for ENZA	and PFS are determined by the period-specific hazards for ADT from 6 years onwards and for ENZA from 8 years onwards.	points for each treatment. The latest Stampede-1 data indicates convergence of OS and PFS on both treatment arms. This convergence would be expected across all relevant treatment options in the opinion of the ERG's clinical expert. Convergence begins from 6 years for DOC and 8 years for ENZA in this scenario. See section 4.2.6
12	Company updated NMA	Run the company's NMA scenario with the updated HRs provided at the clarification stage.	This scenario explores the decision to model extrapolate trial data using parametric curves to model efficacy. Given the parametric curves provides few clinically plausible options, especially for ENZA OS, an alternative approach using the NMA HRs may be more suitable. The company updated the NMA HRs at the clarification stage. See section 4.2.6
13	Company updated NMA with exponential reference curve for ADT PFS	Run the company's NMA scenario with the updated HRs provided at the clarification stage and using the exponential PFS curve to model survival on the ADT arm.	This scenario explores the impact of the PFS reference curve to which the NMA PFS HRs are applied. The exponential curve provides a plausible alternative which aligns well with long-term observed data from STAMPEDE[26]. See section 4.2.6
14	Company updated NMA with OS HRs from DOC vs ADT only	Run the company updated NMA scenario with DOC vs ADT OS HRs on both the DOC and ENZA arms.	This scenario explores the uncertainty regarding an efficacy advantage for ENZA vs DOC. The HR from the NMA for ENZA vs DOC is [redacted]. See section 4.2.6
15	Company updated NMA with OS HRs from ENZA vs ADT only	Run the company updated NMA scenario with ENZA vs ADT OS HRs on both the DOC and ENZA arms.	This scenario explores the uncertainty regarding an efficacy advantage for ENZA vs DOC. The HR from the NMA for ENZA vs DOC is [redacted]. See section 4.2.6

No	Scenario analysis	Scenario description	Justification
16	Utility decrement from PD1 to PD3 equal to 0.186 (split evenly over two progressions)	Run the base case analysis with utility when on 2nd and 3rd line mHRPC treatment changed.	This scenario investigates alternative health state utilities. The health state utilities in the company's base case may not be consistent with utilities used in a prior ENZA TA377[41]. See section 4.2.7
17	Utility decrement of 0.02 when receiving docetaxel as per Woods et al. (2018)	Run the base case analysis with mHSPC utility reduced by 0.02 for the first year in the DOC arm.	This scenario investigates the possibility of a disutility in the first 12 months of treatment for DOC. No DOC disutility is included in the base case. Recent literature[38] suggests a small disutility in the first 12 months. See section 4.2.7
18	Equalising CT scan unit costs and resource use for abiraterone and ENZA in PD1-3	Run the base case analysis with CT scan cost assumptions for Abiraterone PD1 and PD2-PD3 updated to match ENZA.	This scenario investigates alternative resource use assumptions. The ERG's clinical expert stated that CT scanning frequency would be consistent for abiraterone or ENZA. See section 4.2.8
19	8% of patients requiring concomitant G-CSF treatment	Run the base case analysis with 8% of patients requiring concomitant G-CSF treatment with docetaxel, radium-223, and cabazitaxel.	This scenario investigates concomitant treatment assumptions. Published research[48] suggests 8% may be the appropriate figure in this instance. See section 4.2.8

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

Comparison of costs, QALY, LYG, and ICER of the scenarios outline in Table 33 against the company's base case are summarised in Table 34 below.

Table 34 ERG Scenario Analysis

No.	Description	Enzalutamide			ADT				Docetaxel			
		Costs	QALY	LYG	Costs	QALY	LYG	ICER vs ADT	Costs	QALY	LYG	ICER vs Doc
	Base case corrected for time horizon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,182	[redacted]	[redacted]	[redacted]	£23,252
1	ERG AE and SRE correction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,252	[redacted]	[redacted]	[redacted]	£23,273
2	Gompertz extrapolation for ENZA OS with convergence of treatment efficacy from 10 years for OS only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,570	[redacted]	[redacted]	[redacted]	£46,377
3	Log-logistic extrapolation for ENZA TTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,870	[redacted]	[redacted]	[redacted]	£29,770
4	Gompertz extrapolation for ENZA OS with convergence of treatment efficacy from 10 years for OS only and log-logistic extrapolation for ENZA TTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,932	[redacted]	[redacted]	[redacted]	£53,073
5	Log-logistic extrapolation for ENZA PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,099	[redacted]	[redacted]	[redacted]	£30,407
6	Exponential extrapolation for ADT PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,257	[redacted]	[redacted]	[redacted]	£27,221
7	Convergence of treatment efficacy (PFS and OS) from 6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£34,625	[redacted]	[redacted]	[redacted]	£51,071
8	Convergence of treatment efficacy (PFS and OS) from 8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,577	[redacted]	[redacted]	[redacted]	£38,781
9	Convergence of treatment efficacy from 6 years for OS only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,598	[redacted]	[redacted]	[redacted]	£49,053
10	Convergence of treatment efficacy from 8 years for OS only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,897	[redacted]	[redacted]	[redacted]	£38,056
11	Convergence of treatment efficacy (PFS and OS) from 6 years for DOC and 8 years for ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,577	[redacted]	[redacted]	[redacted]	£35,845
12	Company updated NMA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,534	[redacted]	[redacted]	[redacted]	£46,875
13	Company updated NMA with exponential reference curve for ADT PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,510	[redacted]	[redacted]	[redacted]	£52,411
14	Company updated NMA with OS HRs from DOC vs ADT applied to ENZA and DOC arms.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,728	[redacted]	[redacted]	[redacted]	£158,309

No.	Description	Enzalutamide			ADT				Docetaxel			
		Costs	QALY	LYG	Costs	QALY	LYG	ICER vs ADT	Costs	QALY	LYG	ICER vs Doc
15	Company updated NMA with OS HRs from ENZA vs ADT applied to ENZA and DOC arms.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,534	[redacted]	[redacted]	[redacted]	£132,853
16	Utility decrement from PD1 to PD3 equal to 0.186 (split evenly over two progressions)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,072	[redacted]	[redacted]	[redacted]	£24,452
17	Utility decrement of 0.02 when receiving docetaxel as per Woods et al. (2018)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,182	[redacted]	[redacted]	[redacted]	£22,988
18	Equalising CT scan unit costs and resource use for abiraterone and ENZA in PD1-3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,210	[redacted]	[redacted]	[redacted]	£23,279
19	8% of patients requiring concomitant G-CSF treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,992	[redacted]	[redacted]	[redacted]	£23,572

6.3 ERG's preferred assumptions

The ERG's preferred base case makes four changes to the company's base case (corrected for time horizon) model. The first change corrects formulae in the economic model such that disutility for AEs and SREs are only multiplied by the cycle length once. The second change is to use HRs (and confidence intervals) from the NMA. Both the HRs and confidence intervals were updated by company at the clarification stage. The PFS HR for DOC vs ADT is [redacted] and for ENZA vs ADT [redacted]. For OS the HR for DOC vs ADT is [redacted] and for ENZA vs ADT [redacted]. Since the HRs from the NMA are applied with reference to the ADT OS and PFS curves, a further change is made to ensure that the ADT PFS extrapolation provides results which are clinically plausible in comparison with relevant long-term observed data. As such, the exponential parametric curve is chosen for the ADT PFS extrapolation. The final change is to alter the utility decrement incurred when progressing from the PD1 to PD2 state, and PD2 to PD3 state. In each case the new state is assumed to be .093 lower than the previous state. This change is made to align the utility values more closely to those used in previous assessments of ENZA in mHRPC (TA377[41]).

The assumptions in the ERG base case give a deterministic ICER for enzalutamide of £33,719 versus ADT alone and £47,972 versus docetaxel plus ADT.

The ERG preferred base case is equivalent to running scenarios 1,13, and 16 from Table 33 simultaneously. The ERG preferred base case was used in a scenario which investigated the effect of convergence in OS across all treatment options from 8 years onwards, as suggested by recent STAMPEDE data and the ERG's clinical expert. Further scenarios investigating the effect of ENZA and DOC being equally effective in extending OS compared to ADT are included due to the wide confidence interval indicated by the NMA, which implies that we fail to reject that these treatments are equally effective. Further similar scenarios (2-2b) using the ERGs preferred parametric extrapolations are also included. For ENZA, extrapolations are based on Gompertz for OS, and log-logistic for PFS and TTD. For ADT, extrapolations are based on Weibull for OS and exponential for PFS.

Table 35 ERG's preferred scenarios

No.	Description	Enzalutamide			ADT				Docetaxel			
		Costs	QALY	LYG	Costs	QALY	LYG	ICER vs ADT	Costs	QALY	LYG	ICER vs DOC
1	ERG preferred NMA base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,719	[redacted]	[redacted]	[redacted]	£47,972
1a	ERG NMA base case with convergence of treatment efficacy from 8 years for OS only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£37,146	[redacted]	[redacted]	[redacted]	£56,354
1b	ERG NMA base case with OS HRs from ENZA vs ADT applied to ENZA and DOC arms.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,719	[redacted]	[redacted]	[redacted]	£76,042
1c	ERG NMA base case with OS HRs from DOC vs ADT applied to ENZA and DOC arms.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£42,004	[redacted]	[redacted]	[redacted]	£97,558
2	ERG preferred parametric base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,376	[redacted]	[redacted]	[redacted]	£82,029
2a	ERG parametric base case with convergence of treatment efficacy from 8 years for OS only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£44,998	[redacted]	[redacted]	[redacted]	£74,250
2b	ERG parametric base case with OS for DOC set to equal ENZA OS extrapolation.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,376	[redacted]	[redacted]	[redacted]	£345,190

6.4 Conclusions of the cost effectiveness section

Based on the discussions in the preceding sections, the ERG is of the opinion the company's economic model is appropriately structured and uses data that is relevant to the decision problem. The appropriate comparators are included, and the data used are applicable to the population included in the final scope. However, it is the ERGs opinion that the company's base case is overly optimistic in terms of modelled life year and QALY gains for enzalutamide plus ADT versus ADT alone and versus docetaxel plus ADT.

The ERG believes the following to the be the key issues and uncertainties in the cost-effectiveness evidence:

1. The PFS and OS data from ARCHES and ENZAMET are immature (i.e. median survival not reached for enzalutamide), which leads to a high degree of uncertainty around the lifetime extrapolations which inform the model (see 4.2.6).
2. Based on clinical expert opinion and uncertainties reflected in the output of the NMA, the ERG believes the company may have substantially overestimated the PFS and OS benefits for enzalutamide plus ADT. In particular, it is the ERG's opinion that the company's estimated life year and QALY gains compared to docetaxel plus ADT lack face validity when considered in the context of the estimated effect of enzalutamide versus docetaxel on OS that emerges from the NMA; i.e. the estimated HR from the NMA is modest (Company revised estimate: [redacted]) [redacted] in comparison to the relative benefits implied by the company base case (which estimated a gain of [redacted] life-years and [redacted] QALYs) (see 4.2.6).
3. Related to point 2, the company base case reliance on independently fitted curves for enzalutamide results in the hazards of mortality diverging across the treatment arms for the majority of the model time horizon; i.e. the proportional reduction in the hazard of mortality with enzalutamide versus the comparators increases out to 21 years before reducing slightly when general population mortality overrides the extrapolated mortality rate in the enzalutamide arm.
4. Based on available external sources to validate the rPFS and OS extrapolations for docetaxel plus ADT and ADT alone, the ERG believes that the company have underestimated PFS and to a lesser extent OS for the comparator arms of the model.
5. The company's base case extrapolation of TTD for enzalutamide diverges quite substantially from rPFS, resulting in a substantial proportion of patients in the

enzalutamide plus ADT arm being off-treatment (no costs of enzalutamide) and progression free.

The utility values for progressive disease appear to remain too high across the progressive disease sub-states compared to the values applied in previous TAs in the mHRPC setting.

7 End of life

Long term survival data people with mHSPC confirm that NICE end of life criteria do not apply to this appraisal.

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National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

Enzalutamide with androgen deprivation therapy for treating metastatic hormone-sensitive prostate cancer [ID1605]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm on 3 February 2020** 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.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Misplacement of a word

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On pages xi, reference to the brand name of enzalutamide is misplaced. It is included after ADT when it should be after enzalutamide	Move the brand name (in red) to after enzalutamide as shown below: *The company, Astellas, provide clinical and cost-effectiveness evidence for enzalutamide (XTANDI ®) with ADT...*	The brand name relates to enzalutamide, not to ADT	Corrected in amended report.

Issue 2 Redundant word

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 1, it is stated that "*The company's description of mHSPC in terms of prevalence, symptoms and complications appears generally accurate to the decision problem.*"	Remove he word "generally": *The company's description of mHSPC in terms of prevalence, symptoms and complications appears accurate to the decision problem.*	The ERG does not highlight any discrepancy that would support the company's description not being completely accurate	Accepted, word removed in amended report.

Issue 3 Numerical typo

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 19, the percentage of patients with fatigue in the enzalutamide arm should be 24.1% rather than 2.41%	The percentage should be amended to read as (in red): *Adverse events of special interest occurring at an event rate >2% higher in the enzalutamide plus ADT included hypertension (8.6% versus 6.3%), cognitive/memory impairment (4.5% versus 2.1%), fatigue (24.1% versus 19.5%),*	Numerical typo	The proposed revision is accepted. Report amended

	and fractures (6.5% versus 4.2%)		

Issue 4 Source for ENZAMET HRQoL data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 20, the ERG states "*The company provide a reference to an abstract (by Stockler et al 2019)[23] but this abstract reports HRQOL data for the whole trial population and does not provide separate data for the non-concomitant docetaxel group*"	The statement is correct. The abstract focuses exclusively on the overall population. The Company attaches the poster where data for patients not on concomitant docetaxel are provided	To provide the correct source of data	The ERG refer to the abstract cited by the company in their statement - not to the newly attached poster. Not a factual inaccuracy. The proposed revision is not accepted.

Issue 5 Alterative censoring rules

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG states: "*The company sent both the data with the original censoring rules and different censoring rules, claimed these were requested by the ERG. This may have been a misunderstanding as the ERG have no record of what these rules may have been. The company have not provided them either*"	Remove the statement	In the decision problem meeting held on Monday 16th of September, the Liverpool Reviews and Implementation Group (LRiG) which attended the meeting requested the time to event data to be presented as per LRiG preferred specifications for KM data	This appraisal was re-allocated from the Liverpool Reviews and Implementation Group (LRiG) to the Aberdeen HTA Group. The ERG (Aberdeen HTA Group) did not attend the decision problem meeting and therefore were not aware of the request made in that occasion by the LRiG. Not a factual inaccuracy. The proposed revision is not accepted.

Issue 6 Difference in the OS HR between ARCHES and ENZAMET

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 38, the report states "*ERG was struck by the difference observed between the OS HR in ARCHES (HR=0.81; 95% CI 0.53, 1.25) and that in ENZAMET (HR=0.53 95% CI 0.37, 0.74) even after taking into account that both trials were stratified by disease volume and ENZAMET had a longer data maturity*"	The comment should be removed.	The Company wish to emphasize that the differences in OS between studies need to be interpreted in the context of a different follow-up period between studies (14.4 months in ARCHES vs 37.3 months in ENZAMET). As highlighted by the clinical expert interviewed and mentioned in reference B83 (page 14 – related to slide 30), no prostate cancer-related deaths are expected to occur within the first 12 months. In ARCHES; deaths within the median follow-up (i.e., 14.4 months) are likely due to natural causes and thus, no differences are expected between arms. In contrast, in ENZAMET despite OS also being immature, mortality within the first 37.3 months is expected to capture prostate cancer-related deaths and the treatment benefit in this mortality. In this context, the differences between ARCHES and ENZAMET should not be surprising.	The ERG do not believe this represents a factual inaccuracy but an expression of their own opinion. With this statement they wanted to point out that despite both trials were stratified by disease volume and ENZAMET had a longer follow up, the difference between the HRs for overall survival was quite large. The proposed revision is not accepted.

Issue 7 Incorrect cross-reference

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 55, the cross-reference to Table 21 for the 10-year PFS for enzalutamide plus ADT (i.e., [redacted]) should be Table 22.	Replace Table 21 by Table 22 as per below: "*However, the decision to use the same parametric fit on both arms of the model led to generalised gamma curve not being selected since the 10-year PFS for enzalutamide plus ADT (28.4% in Table 22 was...*"	Numerical typo	Change accepted. Report amended

Issue 8 Confidentiality marking missing

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The company identified several numbers in the document where the confidentiality marking was missing. These included: - [redacted] on page 60 (should be CIC) - [redacted] on page 63 (should be CIC) - '[redacted] and '[redacted] on page 73 (should be AIC)	Apply the corresponding AIC/CIC markings	The '[redacted] and '[redacted] should be CIC to protect the confidentiality of the efficacy curves, and consequently the PAS. The '[redacted] and '[redacted] on page 73 relate to the confidentiality of the PD1 and PD2 health state utility values. Because the PD3 value is public, the differences between the PD1, PD2, and PD3 utilities need to be confidential. Otherwise, the respective PD1 and PD2 utilities can be easily back calculated.	Changes are accepted. Report amended.

Issue 9 Inaccurate wording

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 63, the ERG states "*In ARCHES there is no difference in OS after 24 months". The company believe this is not accurate, since there is a numerical, but non-significant difference observed*.	Add "significant": "*In ARCHES there is no significant difference in OS after 24 months*"	There is a numerical OS difference observed in ARCHES, so it would be inaccurate to state that no OS difference is observed	Point accepted; report amended.

Issue 10 Confidentiality marking missing

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 64, Figure 7 should be CIC	Apply the CIC marking	The Figure could be used to back calculate the PAS for enzalutamide	Figure 7 on page 64 is sourced from the published committee papers for TA377. It is in the public domain and relates to modelled QALYs in the previous TA. The ERG does see follow this could be used to back calculate the PAS in the current submission. Please ask the company to clarify.

Issue 11 Misleading conclusion

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 67, the ERG states	Add a statement elaborating that a HR below 1	The large confidence interval in the	The ERG do not believe this

"*Therefore, based on the NMA, it is plausible that OS for enzalutamide would either be equal or only marginally above both 49.1% at 5 years and 22.6% at 8.5 years."* The statement above is not accurate. Since the majority of the confidence interval falls below 1, it is misleading to only highlight the plausibility of the HR begin equal or marginally different to 1, since a HR far below 1 is equally plausible.	favouring enzalutamide is still most likely based on the full confidence interval.	initial (enzalutamide vs docetaxel HR: [redacted]) and updated NMA (HR: [redacted]) indeed suggest uncertainty. However, in both cases the HR is clearly below 1 and the 95% credible interval in both NMA estimates suggest a higher probability of the HR being <1 (i.e., favouring enzalutamide over docetaxel).	represents a factual inaccuracy since the statement does not rank the plausibility of the interpretation amongst a set of possible interpretations. Subsequent discussion on page 68 of the ERG report supports consideration of this interpretation by the ERG. We have amended the report to state that it is "*plausible that OS for enzalutamide could either be equal or only marginally above …*", to better reflect the uncertainty of this statement.

Issue 12 More nuance needed around converging OS benefit

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Several ERG arguments assume convergence of the OS benefit for enzalutamide relative to docetaxel and ADT over time. Although, the evidence supporting that is rather weak, the ERG refers to it multiple times as a realistic possibility. The company thinks more nuance around this statement is justified to highlight the questionable nature of this assumption, and all the assumptions that come from it (e.g. the predicted 10 year OS	Add more nuance where convergence of benefits is discussed, highlighting the uncertainty of this assumption. The way it is currently phrased and repeated gives too much legitimacy to the OS convergence, despite the limited evidence supporting it.	The convergence of efficacy was based solely on the STAMPEDE trial. Although STAMPEDE is a reliable source, it is only one study and it does not assess enzalutamide. The company feels that a little more nuance is warranted, considering that the evidence supporting convergence of enzalutamide's efficacy is all indirect and comes from only one study.	The ERG do not believe this represents a factual inaccuracy. The ERG discuss convergence of OS benefit as a possibility/scenario only. Consideration of this issue is warranted based on the best available long-term data and the opinion of the ERGs clinical expert. It is noted that convergence between docetaxel and ADT alone was also observed in CHAARTED,

figures for patients on enzalutamide).			as referenced on page 70-71. The proposed revision is not accepted.

Issue 13 Comparing the wrong utility values

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 72 the ERG states: "*Table 22 in Document B (page 65) shows the baseline EQ-5D using the UK value set to be* [redacted]. *However, in Table 49 on page 126 of Document B the average EQ-5D for all respondents in a PFS state at the time it was completed is shown to be* [redacted]. *The company submission has not explained these differences.*" As highlighted in Table 22, the '[redacted]' refers to the UK value set utilities. In contrast, as discussed in section 3.4 of the company submission, the mapping algorithm values were used in the model. This explains the difference between the two values.	Remove the entire bullet/comment. , as it is no longer relevant when the correct values from the mapping algorithms are compared.	The utility values that should be compared are the baseline mapping algorithm values listed in Table 22 of document B (i.e., ([redacted] and [redacted]) to the values used in the model for the PFS state ([redacted]). These values are similar and thus, the issue raised by the ERG is no longer relevant.	Point accepted; the bullet has been removed from the amended report.

Issue 14 Incorrect statement

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 47, the ERG states: "*A more detailed critique cannot be provided as the relevant appendix was missing from the company submission. This was requested but had not been provided at the time this report was being prepared.*" This appendix was provided in the company submission but was incorrectly labelled. This was flagged to the ERG on the 9th of January 2020.	Remove this statement	The appendix was not missing from the company submission but mislabelled as already flagged to the ERG in January 2020.	Point accepted. This statement escaped the final edit, and has now been removed (see amended report)

Issue 15 Outstanding ENZAMET HRQoL data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 72, the ERG states "*As the ENZAMET RCT appeared in print in June 2019 there does not seem to be a good reason why the EQ-5D analysis is not available*".	Remove the statement	As already stated in the decision problem form, ENZAMET was an investigator-led trial. It was not sponsored by Astellas but conducted by the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP) and The University of Sydney (USYD), Australia. At the time of the NICE submission,	Point accepted. Statement has been modified to acknowledge that Astellas do not own the data for ENZAMET (see amended report)

		Astellas did not have access to the full ENZAMET database. Astellas had access to patient baseline characteristics and efficacy data (i.e., overall survival and PSA and clinical progression-free survival), but not to the patient-reported outcomes (PRO) data. ERG's statement mistakenly suggests that the company is not willing to share the EQ-5D data. Astellas have now access to all PRO data and will analyse the EQ-5D data.	

Issue 16 Disutility applied to ARCHES patients who progress

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 73 the ERG states: "*In the NICE TA submission based on AFFIRM (TA316), a disutility of -0.085 was applied on progression i.e. 0.605".* However, this could be misleading. AFFIRM represents a much later disease stage than ARCHES. Patients who progressed in AFFIRM had been previously exposed to docetaxel (mean of 9 cycles and median of 8.0 cycles with first dose being given at least 12 months (mean: 17.3 months; median: 13.4 months) prior to	If the statement is retained, the differences between both populations should be included and the limitations of applying the AFFIRM disutility to the ARCHES population highlighted. Otherwise, the statement should be removed.	As mentioned in the description of the problem, AFFIRM represents a much later disease stage than ARCHES. The company considers that the health state of patients progressing in ARCHES cannot be assumed equal to the health state of patients progressing in AFFIRM.	Point accepted. The statement has been removed.

study entry and had been long diagnosed of CRPC. Progression in ARCHES may not be comparable to progression in the AFFIRM population.			

(please cut and paste further tables as necessary)

Additional issues identified by the ERG

Description of problem	Description of proposed amendment	Justification for amendment
When implementing further scenarios at the request of NICE, the ERG identified what it believes to be an error in the company's model. This relates to the aggregation of discounted costs in the "Base Case Results PartSA" worksheet of the company model. The formulas sum over a 20-year time horizon rather than the stated 30 years, which is used for QALYs. The ERG further identified what it believes to be another error in the calculation of treatment costs in the mHSPC state. This relates to the costs of ADT not being applied for those on treatment with enzaluatimde or docetaxel in the company model: Cells K34	The ERG has amended the cost calculations to sum over the full 30 years, and has made the following changes to the ERG report: • Updated text on page 80 to detail the identified errors • Updated Table 32 to record the identified errors • Updated Table 33 to describe further scenarios conducted to assess the impact of these identified issues. • Updated Table 34 with the results of additional scenarios (Note all scenarios are corrected for the aggregation of costs over 30 years rather than 20). Correction for ADT costs is included as a scenario in Table 34. • Updated text on page 91 to re-specify	AS indicated in the description of the problem.

and M34 in the "Base Case Results PartSA" worksheet.	the ERGs preferred base case, incorporating correction for the additional bugs identified. • At the request of NICE, updated text on page 91 to specify a scenario using the ERG's preferred parametric extrapolations for enzalutamide plus ADT and ADT alone. • Updated the results in page 35 for the ERGs preferred scenarios • Updated the text and summary table of the ERGs preferred cost-effectiveness analysis in the executive summary (page xix)		

Issue 17 There was no error in the model for ADT costs when ADT is given with enzalutamide or other therapies

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ADT-related costs when ADT is given with an antiandrogen or chemotherapy are included as concomitant costs in the model. No related error has been made in the model. Indeed, costs related to ADT when given with enzalutamide or docetaxel at the mHSPC health state or with any PD1-PD3 treatment are considered as part of concomitant medication costs.	• On page 80, the following text should be removed: "*Finally, the ERG identified what it believes to be another error, in that ADT costs did not appear to be counted for those on treatment with enzalutamide or docetaxel in the mHSPC state*." • In Table 33: - The 1b row should be removed - In the 1c row, the following should be removed: "*Also, add the costs of ADT to the ENZA and DOC arms of the*	Applying the ERG suggested amendment to the ADT-related costs would double count these costs as they are already considered in the "concomitant medication" costs.	Point accepted. Table 1 and discussion on page xix have been updated. Scenarios 1b and 1c have been removed from both Table 33 and Table 34. All ERG preferred scenarios in Table 35 have been recalculated and accompanying text in Section 6.3 has been amended. The requested removal of text on Page 80 has occurred.

Therefore, these costs are not included in cells K35 – K40, L36 – L40 or M35 – M40 but they are included in cells K47 - K52, L48 – L52 and M47 – M52. Details on concomitant costs are provided in tab “Treatments”, cells C45 – K45.	*model*” and “*and omission of ADT costs.*” • In Table 34: - The 1b row should be removed - The ICER in 1c row should be recalculated without double counting the ADT costs • The updated results on page 35 for the ERGs preferred scenarios and on page xix should not include the amendment of the ADT-related costs assumed error.		

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Enzalutamide with androgen deprivation therapy for treating metastatic hormone-sensitive prostate cancer

This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

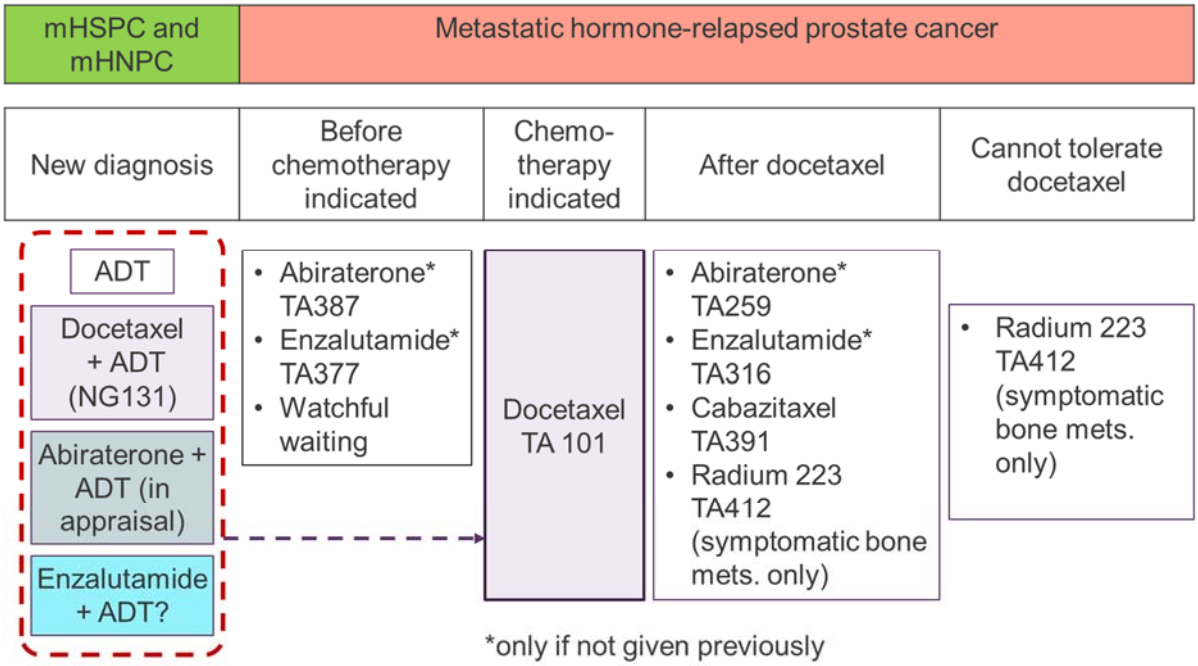
The technical report should be read with the full supporting documents for this appraisal.

1. Topic background

1.1 Disease background

- 41,201 new cases in the UK in 2017
    - Most present with localised disease (early stage); they might develop metastases later
    - About 17% have metastases at diagnosis - associated with poorer prognosis
- Population of interest for this appraisal includes both people with newly diagnosed hormone-sensitive metastatic prostate cancer and people with previously localised disease that has progressed to hormone-sensitive metastatic prostate cancer

1.2 Treatment pathway



mHNPC: metastatic hormone-naïve prostate cancer, mHSPC: metastatic hormone-sensitive prostate cancer, NG: NICE guideline, TA: technology appraisal

- In the NHS people can get either enzalutamide or abiraterone once during the treatment pathway
- People can get up to 6 cycles of docetaxel each lasting 3 weeks

1.3 The technology

Marketing authorisation	• Expected [redacted] • [redacted]
Existing marketing authorisations	• Treatment of adult men with metastatic castration-resistant prostate (mCRPC) whose disease has progressed on or after docetaxel therapy (i.e. post-chemotherapy setting) – June 2013 • Treatment of adult men with mCRPC who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated (i.e. chemotherapy naive setting) – November 2014 • Treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (nmCRPC) – November 2018
Mechanism of action	• Binds androgen receptors resulting in blocking androgen binding, inhibiting nuclear translocation and inhibiting gene transcription
Administration and dose	• Administered orally as 40mg tablets • Single daily dose of 160 mg (as 4 × 40 mg tablets)
Cost	• £2,734.67 for 112-unit pack (excluding VAT; BNF). • Enzalutamide has a simple discount patient access scheme

1.4 Decision problem

	NICE final scope	Company submission
Population	People with metastatic hormone-sensitive prostate cancer	As per final scope
Intervention	Enzalutamide plus androgen deprivation therapy (ADT)	As per final scope
Comparator(s)	• ADT (including orchidectomy, luteinising hormone-releasing hormone agonist therapy) or monotherapy with bicalutamide • Docetaxel plus ADT People with hormone-naïve high-risk disease: • Abiraterone plus ADT	• ADT (including orchidectomy, luteinising hormone-releasing hormone agonist therapy) or monotherapy with bicalutamide • Docetaxel plus ADT
Outcomes	• Time to prostate-specific antigen (PSA) progression • Progression-free survival (PFS) • Overall survival (OS) • Adverse effects of treatment • Health-related quality of life	• Time to prostate-specific antigen (PSA) progression • Progression-free survival (PFS) • Overall survival (OS) • Time to treatment discontinuation • Time to new antineoplastic therapy • Adverse effects of treatment • Health-related quality of life
Subgroups	Hormone-naïve disease High-risk disease	None

1.5 Clinical evidence

Table 1 Characteristics of clinical trials

	ARCHES	ENZAMET
Design	Double blind Open-label extension	Open-label
Population	Metastatic prostate cancer ECOG performance status 0 or 1	Metastatic prostate cancer ECOG performance status 0 to 2
Intervention	Enzalutamide + ADT	Enzalutamide + ADT
Comparator	Placebo + ADT	Conventional non-steroidal anti-androgens (NSAA) + ADT*
Subgroups[†]	Prior use of docetaxel Disease volume at baseline	Prior use of docetaxel Concomitant use of docetaxel Disease volume at baseline
1º endpoint	Radiographic progression-free survival (rPFS) by independent review	Overall survival (death from any cause)
2º endpoints	Overall survival Time to PSA progression Time to start of new therapy Time to castration resistance Time to first symptomatic skeletal event QoL[‡] (EQ-5D-5L, FACT-P, EORTC QLQ-PR25)	PSA PFS Clinical PFS (imaging, symptoms, signs) Adverse events QoL[§] (EQ-5D-5L, EORTC QLQ C-30, QLQ-PR-25)

*40% of people had concomitant docetaxel, these are excluded from the company's submission, as this is not in enzalutamide's expected marketing authorisation
[†]prespecified, of possible relevance to this appraisal
[‡]measured at baseline, week 13 and every 12 weeks thereafter
§measured at baseline, day 29, week 12 and every 12 weeks thereafter

Abbreviations: ADT: androgen deprivation therapy, ECOG: Eastern Cooperative Oncology Group, EORTC QLQ C-30: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Cancer, FACT-P: Functional Assessment of Cancer Therapy-Prostate, PSA: prostate-specific antigen, rPFS: radiographic progression-free survival, EORTC QLQ-PR-25: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Prostate

1.6 Baseline characteristics

Table 2 Baseline characteristics of trial participants in ARCHES and ENZAMET (Source: Table 6 ERG report)

	ARCHES				ENZAMET (no concomitant docetaxel)			
	ENZA+ADT (n=574)		PLA+ADT (n=576)		ENZA+ADT (n=309)		NSAA+ADT (n=313)	
	n	%	n	%	n	%	n	%
Age (years)								
Median	70		70		[redacted]		[redacted]	
Geographic region								
Europe	341	59.4	344	59.7	[redacted]		[redacted]	
North America	86	15.0	77	13.4	[redacted]		[redacted]	
South America	32	5.6	30	5.2	[redacted]		[redacted]	
Asia-Pacific	104	18.1	113	19.6	[redacted]		[redacted]	
Australia/New Z	0	0	0	0	[redacted]		[redacted]	
Other	11	1.9	12	2.1	[redacted]		[redacted]	
ECOG performance status at study entry								
0	448	78.0	443	76.9	[redacted]		[redacted]	
1	125	21.8	133	23.1	[redacted]		[redacted]	
2	0	0	0	0	[redacted]		[redacted]	
Total Gleason score at initial diagnosis								
<8	171	29.8	187	32.5	[redacted]		[redacted]	
≥8	386	67.2	373	64.8	[redacted]		[redacted]	
Unknown/missing	0	0	0	0	[redacted]		[redacted]	
Volume of disease								
Low	220	38.3	203	35.2	[redacted]		[redacted]	
High	354	61.7	373	64.8	[redacted]		[redacted]	
Prior docetaxel therapy use								
No	471	82.1	474	82.3	[redacted]		[redacted]	
Yes	103	17.9	102	17.7	[redacted]		[redacted]	
Missing	0	0	0	0	[redacted]		[redacted]	
Previous use of ADT								
No	39	6.8	61	10.6	[redacted]		[redacted]	
Yes	535	73.2	514	89.2	[redacted]		[redacted]	
Unknown	0	0	1	0.2	[redacted]		[redacted]	

ADT: androgen deprivation therapy; ENZA: enzalutamide; PLA: placebo; NSAA: non-steroid anti-androgens

1.7 Key trial results

- Overall survival data in ARCHES and ENZAMET are immature as median time to overall survival was not reached
    - Less than 10% of participants in ARCHES died at the median follow up of 14.4 months (data cut off for interim analysis); company suggests that most of these deaths are of other causes than prostate cancer
        - For final OS analysis 342 events are required
    - Less than 25% of participants in ENZAMET died at the median follow up of 37.3 months (data cut off for interim analysis, group not having concomitant docetaxel)
        - For final OS analysis 470 events are required
- In its model the company used pooled overall survival data from both trials

Table 3 Overall survival data ARCHES and ENZAMET (interim analyses)

	ARCHES		ENZAMET*	
	ENZA + ADT (n=574)	**Placebo + ADT (n=576)**	**ENZA + ADT (n=309 of 593)**	**NSAA + ADT (n=313 of 562)**
Events	n=39 (7%)	N=45 (8%)	n=50 (16%)	n=88 (28%)
HR (95% CI)	0.81 (0.53 to 1.25)		0.53 (0.37 to 0.74)	
Median OS	NYR	NYR	NE	NE
Median follow up	14.4 months		37.3 months	

*includes only people who didn't get concomitant docetaxel (in line with expected MA for enzalutamide)
ADT: androgen deprivation therapy; ENZA: enzalutamide; NSAA: non-steroidal anti-androgen; NE: not estimable, NYR: not yet reached

Table 4 Overall survival estimates from pooled analysis (ARCHES and ENZAMET*) (interim analysis)

	Enzalutamide + ADT (n=883)	ADT± NSAA (n=889)
Events	n=89 (10%)	n=133 (15%)
HR (95% CI)	[redacted]	
Median OS	NYR	NYR

*includes only people who didn't get concomitant docetaxel (in line with expected MA for enzalutamide)
ADT: androgen deprivation therapy; NSAA: non-steroidal anti-androgen; NYR: not yet reached

- ARCHES and ENZAMET defined progression-free survival (PFS) differently
    - ARCHES used radiographic progression-free survival (rPFS); ENZAMET used clinical PFS
    - Company used rPFS by independent review from ARCHES in model
    - Final analysis of rPFS was conducted when a minimum of 262 events had occurred

Table 5 Progression-free survival (PFS) in ARCHES and ENZAMET

	ARCHES		ENZAMET*	
	ENZA + ADT (n=574)	**PLA + ADT (n=576)**	**ENZA + ADT (n=309 of 593)**	**NSAA + ADT (n=313 of 562)**
Events	n=91 (16%)	n=201 (35%)	NR	NR
HR (95% CI)	0.39 (0.30 to 0.50)		0.34 (0.26 to 0.44)	
Median time to PFS, months (95% CI)	NYR	19 (17 to 22)	NYR	NYR

*includes only people who didn't get concomitant docetaxel (in line with expected MA for enzalutamide)
ADT: androgen deprivation therapy; ENZA: enzalutamide; NSAA: non-steroidal anti-androgen; NYR: not yet reached; PLA: placebo; NR: not reported

1.8 Comparative effectiveness network meta-analysis

- There are no trials directly comparing enzalutamide with docetaxel
    - ARCHES and ENZAMET compared enzalutamide with ADT
    - 3 trials compared docetaxel plus ADT with ADT
        - STAMPEDE, CHAARTED, GETUG
    - therefore the company conducted a network meta-analysis
- There was heterogeneity in the trials for example a difference in the proportion of people with high volume disease
    - ENZAMET had lower proportion of people with high volume disease ([redacted]) than ARCHES (62%) and STAMPEDE (60 to 64% overall)

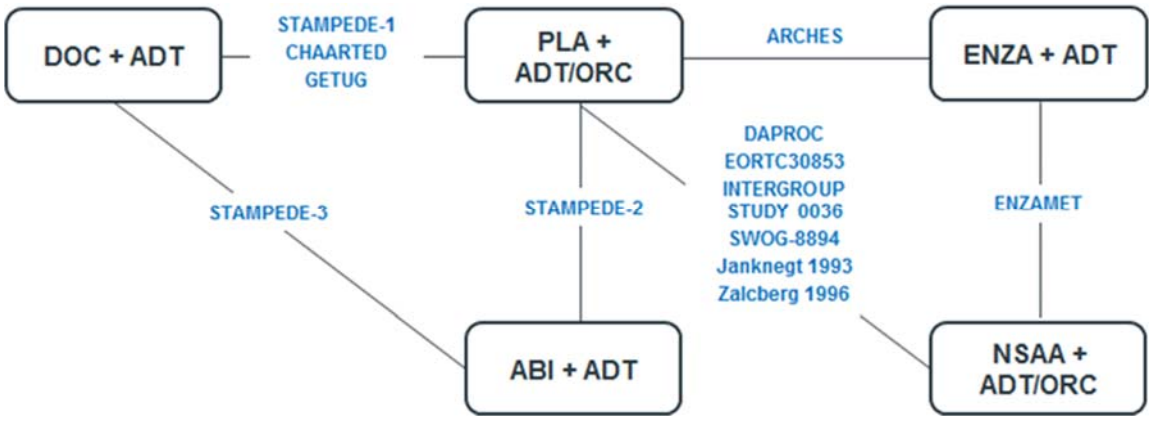


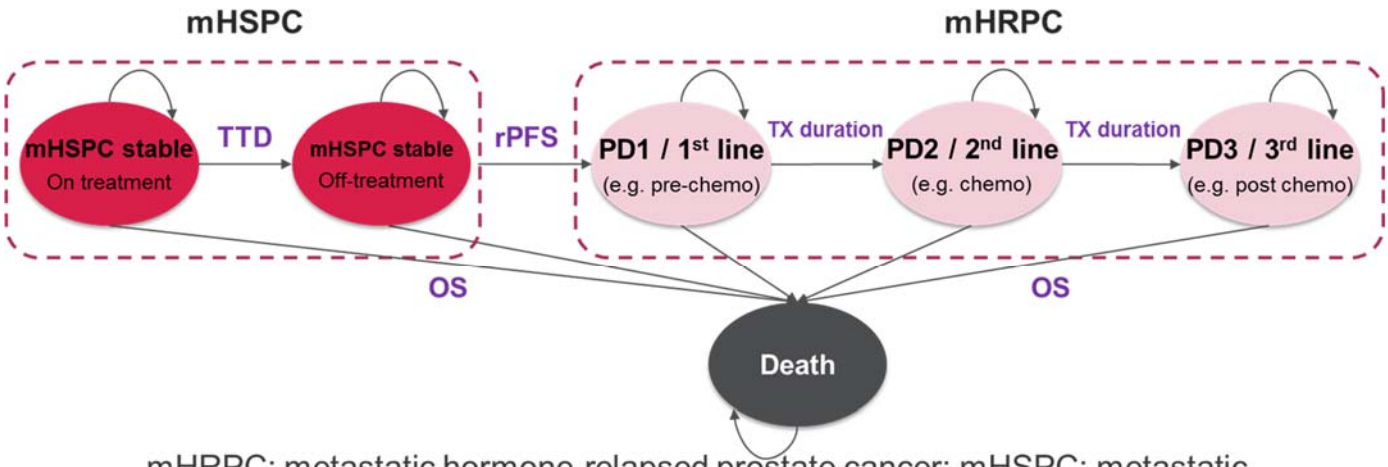
Figure 1 Evidence network for comparative effectiveness
(ABI: abiraterone; ADT: androgen deprivation therapy; DOC: docetaxel; ENZA: enzalutamide; NSAA: non-steroidal anti-androgen; ORC: orchiectomy; PLA: placebo)

Table 6 Hazard ratio for overall survival from the network meta-analysis

Fixed Effects model	Overall survival hazard ratio (95% CI)
DOC versus ADT	
ENZA + ADT versus ADT ± PLA	
ENZA + ADT versus DOC + ADT	
ENZA + ADT versus NSAA + ADT	
Random Effects model	
DOC versus ADT	
ENZA + ADT versus ADT ± PLA	
ENZA + ADT versus DOC + ADT	
ENZA + ADT versus NSAA + ADT	
ADT: androgen deprivation therapy; DOC: docetaxel; ENZA: enzalutamide; NSAA: non-steroidal anti-androgen; PLA: placebo	

1.9 Partitioned survival model

- Metastatic hormone-sensitive prostate cancer health state is divided into time on/off treatment allowing discontinuation before progression
- Metastatic hormone-relapsed prostate cancer health state is divided into 3 'on treatment' states to reflect possible subsequent treatments

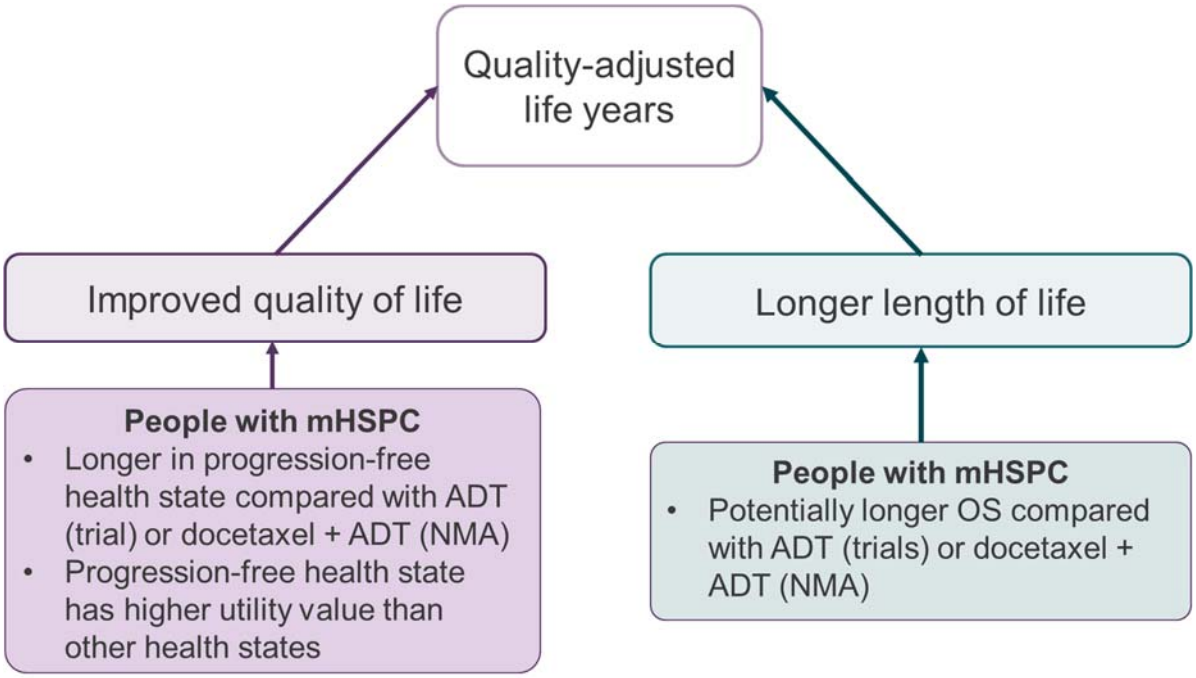


mHRPC: metastatic hormone-relapsed prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; PD: progressed disease

1.10 Key model assumptions

Assumption	Justification
30 year time horizon	There were still people alive at 20 years
ADT used indefinitely all arms	European guidelines; expert opinion
Overall survival not adjusted for subsequent treatments	Several treatments available for metastatic hormone-relapsed prostate cancer, choice depends on previous treatment; expert opinion
ARCHES and ENZAMET provide the most reliable data	Progression-free survival and OS extrapolations externally validated using STAMPEDE, CHAARTED, GETUG and expert opinion
Short gap between mHSPC and first-line mHRPC	ARCHES and ENZAMET, difference between time-to-treatment discontinuation and progression-free survival, indicating patients have short time off-treatment before progression, confirmed by clinical expert
Transition rates between mHRPC health states informed by the median TTD for each respective treatment	Uncertainty around (future) metastatic hormone-relapsed prostate cancer treatment sequences and lack of data to inform transition rates so time-to-treatment discontinuation drives transition between metastatic hormone-relapsed prostate health states. Assumption previously accepted in metastatic hormone-relapsed prostate cancer models.

1.11 Overview of how quality-adjusted life years accrue in the model



2. Summary of the draft technical report

2.1 In summary, the technical team considered the following:

Issue 1 Although there are some differences between the ENZAMET trial and UK clinical practice, it provides important information on the clinical effectiveness of enzalutamide.

Issue 2 Overall survival data is immature and the extrapolations uncertain so the company should explore several alternative scenarios, including sourcing the enzalutamide treatment effect from the network meta-analysis.

Issue 3 Progression-free survival data is immature and the extrapolations uncertain so the company should explore several alternative scenarios.

Issue 4 Most people are likely to continue enzalutamide treatment while progression-free so the time to treatment discontinuation curve should be similar to the progression free survival curve.

Issue 5 Longer-term data on other prostate cancer therapies suggests that treatment effects may be similar after several years. The company should present scenarios in which long-term treatment effects are similar.

Issue 6 People who have docetaxel plus ADT might benefit from more treatment options after disease progression. Therefore, long-term outcomes might be similar. For enzalutamide compared with docetaxel, the credible interval for the overall survival hazard ratio overlaps 1, suggesting no difference. Therefore, the company should present a scenario where overall survival is equalised.

Issue 7 The differences in quality of life between the progressed disease sub-states in the company's model are very small. The larger total utility decrement suggested by the ERG is more plausible and in line with previous appraisals.

Issue 8 Ongoing data collection in ARCHES and ENZAMET could address key uncertainties in this appraisal, so the Cancer Drugs Fund may be appropriate.

2.2 The cost-effectiveness results include a commercial arrangement (patient access scheme) for enzalutamide.

2.3 Because of the uncertainties in extrapolating the clinical data, the ERG presents 2 approaches both of which may be equally plausible. These result in a range of incremental cost-effectiveness ratios (ICERs):

- £33,719 to £45,376 per quality adjusted life year (QALY) gained for enzalutamide plus ADT versus ADT alone and,,
- £47,972 to £82,029 per QALY gained for enzalutamide plus ADT versus docetaxel plus ADT.

2.4 These estimates do not include the commercial arrangements for abiraterone, cabazitaxel and radium-223, because these are confidential and cannot be reported here. Estimates that included these commercial arrangements are higher than those reported above.

2.5 Based on the modelling assumptions, the intervention is not likely to meet the end-of-life criteria.

2.6 No equality issues were identified.

3. Key issues for consideration

Issue 1 – Generalisability of clinical trial results

Questions for engagement	1. Are trial results from ARCHES generalisable to people seen in UK clinical practice? 2. Are trial results from ENZAMET generalisable to people seen in UK clinical practice? 3. Is it acceptable to pool data from ARCHES and ENZAMET to estimate clinical efficacy of enzalutamide?
Background/description of issue	ARCHES was a multinational, double-blind, randomised, phase III trial comparing enzalutamide plus ADT with placebo plus ADT in patients with metastatic hormone-sensitive prostate cancer. This study enrolled 1,150 patients with either newly diagnosed metastatic disease or recurrent disease which had metastasised. Patients could have received up to 6 cycles of docetaxel prior to randomisation. ENZAMET was a multinational, open-label, randomised, phase III trial comparing enzalutamide plus ADT with conventional non-steroidal anti-androgens (NSAA) plus ADT. This combination regimen is not used in UK clinical practice. The study enrolled 1,125 patients with either newly diagnosed metastatic disease or recurrent disease which had metastasised. The trial protocol allowed concomitant docetaxel in both arms. This is not expected to be included in the marketing authorisation for enzalutamide, so all results that are presented are for the relevant subgroup (people with no concomitant docetaxel, n=622). Baseline charcteristics are presented in section 0 of the technical report and the trial results are presented in section 0 of the technical report. **The company** acknowledged that the 2 trials were different in their methods and people's baseline characteristics. The proportion with high-volume disease (defined as ≥4 bone metastases, at least one of which was outside the spine or pelvis, and/or visceral metastases) was around 60% in ARCHES compared with [redacted] in ENZAMET. Therefore, the company did not perform a meta-analysis but instead pooled the results to estimate enzalutamide's efficacy. **The ERG** agreed that there were important differences between the trials so a meta-analysis is not appropriate. It noted that pooling has similar limitations and so the results should be treated with caution.

Why this issue is important	Few participants in either trial were from the UK. The trials differed in important ways from UK clinical practice, including the use of NSAA in the ENZAMET comparator arm and the proportion with high volume disease in ENZAMET ([redacted]). In STAMPEDE, a British-run trial comparing several treatment options the proportion of people with high volume disease was around 60%. If these differences have an impact on the treatment effect of enzalutamide, it may perform differently in UK practice than in the clinical trials.
Technical team preliminary judgement and rationale	The baseline characteristics of patients in ARCHES may better reflect patients seen in UK clinical practice than ENZAMET, particularly in the proportion with high volume disease. However, data from STAMPEDE suggests that there is no treatment effect modification by volume for abiraterone vs ADT alone (Hoyle et al 2018). Since ARCHES only provides data for 14.4 months of follow up, it is better to also consider the ENZAMET data which has 37.3 months follow up. While the comparator in ENZAMET (NSAA + ADT) might not reflect UK clinical practice, if NSAA is effective, this would mean that the enzalutamide treatment effect is potentially underestimated. The technical team considers that any uncertainty introduced by the design and participants in ENZAMET is outweighed by the additional data.

Issue 2 - Extrapolation of overall survival

Questions for engagement	4. What proportion of people are still alive at year 10 after ADT treatment? Is 10% or 20% more plausible? 5. What proportion of people are still alive at year 10 after enzalutamide plus ADT treatment? Is 35% or 15% more plausible? 6. What proportion of people are still alive at year 20 after enzalutamide plus ADT treatment? Is 0% or 10% more plausible?
Background/description of issue	Many people were still alive at the interim analyses, so overall survival needs to be extrapolated over the model time horizon. There are 3 options for overall survival data for enzalutamide plus ADT and ADT alone: 1. Individual trial data: the 2 trials provided data for comparing enzalutamide plus ADT with placebo plus ADT (ARCHES) or NSAA plus ADT (ENZAMET) - see Table 3 2. Pooled trial data: company presented pooled overall survival data from ARCHES and ENZAMET (see Table 4) 3. Network meta-analysis (NMA): conducted by company to indirectly compare enzalutamide with docetaxel, but also provides comparative effectiveness data for enzalutamide plus ADT versus ADT (see Table 6) 4. There was 1 source for overall survival estimates for docetaxel plus ADT, the NMA. **The company** extrapolated the pooled overall survival data from ARCHES and ENZAMET in their base-case model (option 2) and applied the hazard ratios from the NMA for docetaxel to these curves. Statistical measures suggested that all parametric functions tested showed an adequate fit to the observed data. The company used data from other studies (STAMPEDE, CHAARTED and GETUG) for validation. These studies suggested 7-year survival in the ADT arm of 27% to 34%. Table 1 below indicates that the log-logistic function reflects this most closely. The company cited DSU TSD 14 as stating that best practice is to fit curves jointly to both treatment arms. As such, it highlighted that a log-logistic function for enzalutamide plus ADT gives implausibly high overall survival estimates according to company's clinical expert (see Table 8). Therefore, the company used the Weibull function for both arms. It provided scenario analyses using log-logistic fit in both arms and using the hazard ratio from the NMA for enzalutamide plus ADT applied to the ADT curve (option 3).

Table 7 Predicted overall survival for ADT alone, including measures of statistical fit (AIC/BIC) (Source: ERG report table 25 – Company's clarification response and economic model)

	Exponential	Weibull	Log-normal	Log-logistic	Gamma	Gompertz
Year 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 8.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 8 Predicted overall survival for enzalutamide + ADT, including measures of statistical fit (Source: ERG report table 26 – Company's clarification response and economic model)

	Exponential	Weibull	Log-normal	Log-logistic	Gamma	Gompertz
Year 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 8.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The ERG was concerned that year-10 and year-20 overall survival estimates for enzalutamide plus ADT were implausibly high with Weibull function. The ERG's clinical expert estimated the overall survival for enzalutamide plus ADT to be 15% at year 10 and 0% at year 20. The ERG suggested to explore:

a. using differing parametric fits in each arm of the model
    - Gompertz for enzalutamide plus ADT, because it appears to fit the observed data well and aligns with clinical experts estimates of 10-year and 15-year survival
    - Weibull for ADT as in the company base case
b. using hazard ratios from the NMA for the enzalutamide plus ADT treatment effect (ERG base case model).

The ERG considered that while the Gompertz extrapolation for enzalutamide may be too pessimistic, the immature data in ARCHES and ENZAMET means that there is relatively little difference between the other survival extrapolations, which all predict implausibly high enzalutamide survival at 10 years. The company's NMA draws on a wider range of data and the proportional hazard assumption holds true which justified using hazard ratios from the NMA in the model. When this is applied to the model the resulting estimates are less pessimistic for enzalutamide than under the Gompertz function, but more in line with expert opinion than the company's Weibull (**Table 9** and chart below).

Table 9 Overall survival for enzalutamide plus ADT using HR from NMA (Source: ERG report table 29 – Company's economic model)

	5 year	10 years	15 years	20 years
Overall survival	[redacted]	[redacted]	[redacted]	[redacted]

	[redacted]
Why this issue is important	The overall survival data from the 2 trials are immature and therefore any estimates are uncertain. Overall survival is a key driver in the model and therefore inputs can change the ICERs substantially.
Technical team preliminary judgement and rationale	The company's approach predicts implausibly high overall survival for enzalutamide at years 10 and 20. Both approaches suggested by the ERG have their strengths and caveats but are similarly plausible and should be explored to get an estimated range of plausible ICERs.

Issue 3 – Extrapolation of progression-free survival

Questions for engagement	7. What is the proportion of people whose cancer has not progressed at year 5 after ADT treatment? Is 20% to 30% or 10% more plausible? 8. What is the proportion of people whose cancer has not progressed at year 10 after ADT treatment? Is 10% or 2% more plausible?
Background/description of issue	Definitions of progression free survival (PFS) differed in the enzalutamide trials. • ARCHES: Radiographic PFS was defined as time to objective evidence of radiographic progressive disease (rPD) as assessed by independent central review or death • ENZAMET: Clinical PFS was defined as the interval from the date of randomisation to the date of first clinical evidence of disease progression or death from any cause, whichever occurs first, or the date of last known follow-up without clinical progression. Clinical progression was defined by progression on imaging (PCWG2 criteria for bone lesions and RECIST 1.1 for soft tissue lesions), development of symptoms attributable to cancer progression or initiation of other anticancer treatment for prostate cancer. **The company** did not pool PFS data because the definitions were different, and data could not be stratified. It used data from ARCHES in the model because PFS was measured as radiographic progressive disease which is in line with clinical practice. Because, these data were immature and only available for median follow up of 14 months (interim analysis), long-term PFS needed to be extrapolated over the model time horizon. The company used data from previous studies (STAMPEDE and GETUG) for validation. These suggested a 5-year PFS in ADT arm of 19%. Table 10 below suggests that the generalised gamma function best reflects this proportion at year 5 for ADT. However, this function for enzalutamide plus ADT gave implausibly high estimates according to company's clinical expert. Therefore, the company used log-normal function for both arms. The company provided scenario analysis using the generalised gamma function for both arms.

Table 10 Predicted PFS for ADT alone, including measures of statistical fit (AIC/BIC)
(Source: ERG report table 23 – Company's clarification response table 8 and economic model)

	Exponential	Weibull	Log-normal	Log-logistic	Gamma	Gompertz
Year 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 8.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 11 Predicted PFS for enzalutamide plus ADT, including measures of statistical fit
(Source: ERG report table 22 – Company's clarification response table 7 and economic model)

	Exponential	Weibull	Log-normal	Log-logistic	Gamma	Gompertz
Year 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 8.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The ERG was concerned that year-5 and year-10 PFS estimates for ADT were implausibly low with the log-normal. ERG's clinical expert estimated the PFS for enzalutamide plus ADT to be 20% to 30% at 5 years, and 0 to 10% at 10 years. These estimates are broadly like the values from STAMPEDE (13% at year 5 and 6% at year 8.5). The ERG suggested to explore:

a. using differing parametric fits in each arm
    - for example exponential for ADT is more aligned with the STAMPEDE data
    - log-logistic for enzalutamide plus ADT gives estimates that are clinically more plausible

b. using HR from the NMA for PFS of enzalutamide plus ADT (used in ERG base case model).

Table 12 PFS for enzalutamide plus ADT using HR from NMA (Source: ERG report table 29 – Company's economic model)

	5 year	10 years	15 years	20 years
PFS	[redacted]	[redacted]	[redacted]	[redacted]

	
Why this issue is important	PFS together with overall survival (0) and time to treatment discontinuation (Issue 4) is a key parameter in the model and has an impact on the model outcomes and cost effectiveness estimates.
Technical team preliminary judgement and rationale	The exponential distribution for ADT alone and the log-logistic distribution for enzalutamide plus ADT appear to provide estimates more in line with external data and clinical expert opinion.

Issue 4 – Extrapolation of time to treatment discontinuation

Questions for engagement	9. Is it plausible to assume that PFS and time to treatment discontinuation are similar? 10. What are the reasons for stopping enzalutamide before disease progression? For example, do adverse events trigger early stopping? 11. How many people would stop treatment early because of adverse events?
Background/description of issue	The model includes 3 health states; progression-free, progressed disease and death. The progression-free state is divided into on- and off-treatment allowing for treatment discontinuation before progression. This only affects enzalutamide, because ADT is taken continuously, and docetaxel is only taken for 6 cycles. **The company** used the ARCHES data extrapolated from approximately 2 years until the assumed lifetime horizon of 30 years. In the base case, the company used the exponential curve because of its close relationship with the PFS curve, without crossing PFS at any point. **The ERG** was concerned that company's base case extrapolation may underestimate the cost of enzalutamide treatment. This is because a significant proportion of patients are assumed to stop enzalutamide while progression-free. However, the ERG heard from its clinical expert that in practice most people would continue treatment until progression. The log-logistic curve provides the closest fit between time to treatment discontinuation and the PFS curve used by the company in their base case. An adjustment is needed in the model to set time to treatment discontinuation equal to PFS from 7.5 years onwards to ensure that it is not higher than PFS.
Why this issue is important	Time to treatment discontinuation is a key parameter in the model for enzalutamide because people do not progress immediately to a health state with a lower utility value. They therefore retain the quality of life benefits of being progression free without the costs of enzalutamide treatment.
Technical team preliminary judgement and rationale	People are likely to continue taking enzalutamide for as long as they are progression free. Whichever PFS curve is used in the model, the time to treatment discontinuation curve should match this as closely as possible.

Issue 5 – Similar long-term treatment effectiveness

<table>
<tr><td>Questions for engagement</td><td>12. Is it plausible that treatment effects of ADT, docetaxel and enzalutamide plus ADT are similar after 8 years?</td></tr>
<tr><td>Background/description of issue</td><td>No long-term data are available for the comparison of enzalutamide plus ADT with ADT. No head-to-head data is available for the comparison of enzalutamide plus ADT with docetaxel plus ADT. Therefore, overall survival must be estimated beyond the trials. Results from STAMPEDE (comparing docetaxel with ADT) provide long-term data for the comparison of ADT with docetaxel plus ADT. It suggests that overall survival is similar in both arms at and after 8.5 years.

Table 13 Overall survival (OS) from STAMPEDE
(Source: ERG report table 28 – Clarke et al. 2019)
<table><tr><th></th><th>OS – ADT alone</th><th>OS – Docetaxel plus ADT</th></tr><tr><td>5 years</td><td>37%</td><td>49%</td></tr><tr><td>8.5 years</td><td>22%</td><td>23%</td></tr></table>
The ERG provided a scenario analysis around its preferred base-case where long-term effectiveness was similar across all treatment options from 8 years onwards.</td></tr>
<tr><td>Why this issue is important</td><td>The overall survival data from the 2 enzalutamide trials are immature and therefore long-term estimates are uncertain. Overall survival is a key driver in the model and substantially affects the cost-effectiveness estimates.</td></tr>
<tr><td>Technical team preliminary judgement and rationale</td><td>Data suggest that overall survival is similar across all treatment options from 8 years onwards. Scenarios exploring this are therefore useful.</td></tr>
</table>

Issue 6 – Post-progression treatments

Questions for engagement	13. Do the subsequent treatments in ARCHES and ENZAMET reflect NHS clinical practice? 14. Is it plausible to assume that subsequent treatment does not influence the long-term outcome?
Background/description of issue	In UK clinical practice people with metastatic hormone-sensitive prostate cancer who progress following treatment with ADT or docetaxel can have up to 4 treatments: docetaxel, enzalutamide/abiraterone, cabazitaxel or radium-223. Treatment options for people who progress after enzalutamide are restricted to docetaxel, cabazitaxel or radium-223. Currently there are only data from ARCHES available regarding type of treatment after progression. In the enzalutamide arm some people got abiraterone or enzalutamide after progression. In addition, the subsequent treatments in ARCHES did not reflect those modelled by the company, which were based on expert opinion (columns 4 and 7 in Table 14 below).

Table 14 First subsequent antineoplastic therapies observed in the ARCHES trial and used in model (Source: company submission table 75 and company model)

	Enzalutamide + ADT (n=574)			Placebo + ADT (n=576)		
Therapy	**Observed (n)**	**% of those with subsequent treatment ***	**% used in company base case (1L)**	**Observed (n)**	**% of those with subsequent treatment ***	**% used in company base case (1L)**
Overall	46	-	-	135	-	-
Docetaxel	11	34%	60%	52	43%	10%
Abiraterone	13	41%	-	28	23%	35%
Enzalutamide	4	13%	-	28	23%	35%
ADT	4	13%	40%	12	10%	20%
Other	14	-		15	-	

*Excluding 'other'. May sum to more than 100% because of rounding

	The ERG noted that the subsequent treatment sequence should be in line with NHS practice, but also the subsequent treatments in the clinical trials used to inform comparative efficacy. Although people may have longer progression-free survival with enzalutamide, people in the ADT and docetaxel arms might have a better long-term outcome, or 'catch up' because they have more treatment options after progression. The current company base-case model predicts greater mean life years in the progressed state for enzalutamide plus ADT than for ADT alone or docetaxel. **The technical team** noted that there was no adjustment for subsequent treatment on outcomes. So, it is assumed that people with the same initial treatment but different subsequent treatments have similar outcomes.
Why this issue is important	Choice of subsequent treatment might affect the long-term outcomes and overall survival. If the subsequent treatments in the NHS do not reflect those in the trial then overall survival may differ. People may get benefit from having enzalutamide or abiraterone as a treatment subsequent to initial enzalutamide in the trial which they wouldn't get in the NHS, but the costs of this are not reflected in the model. Therefore, this could impact on the cost-effectiveness of enzalutamide.
Technical team preliminary judgement and rationale	The credible intervals for the overall survival hazard ratio for enzalutamide versus docetaxel from the NMA include 1 (see section 1.8). However, in the model the company uses the point estimate which favours enzalutamide. If the efficacy of enzalutamide might be overestimated by the trials because of the subsequent treatments, then using a hazard ratio of 1 may be more appropriate.

Issue 7 – Utility values

<table>
<tr><td>Questions for engagement</td><td>15. Compared to the general population, what is the quality of life of people with metastatic prostate cancer after 1, 2, and 3 treatments post progression?</td></tr>
<tr><td>Background/description of issue</td><td>The model includes 3 health states; progression-free, progressed disease (PD) and death. The progressed disease health state contains 3 sub-states; PD1, PD2 and PD3, denoting successive lines of treatment. Both trials collected data on health-related quality of life using EQ-5D-5L. Only data from ARCHES were available to the company at submission.

The company used utility values from ARCHES for the progression-free and the PD1 health states in their model. For PD3 they used values from AFFIRM, a trial that compared enzalutamide with placebo in men with castration-resistant metastatic cancer with or without bone metastases. The company mentioned in their factual accuracy check that HRQoL data from ENZAMET are now available and are currently being analysed.

<table>
<tr><td colspan="2">Table 15 Utility values used in the company’s base case model and sources of utility values</td></tr>
<tr><td>Health state</td><td>Utility values in company model</td></tr>
<tr><td>Progression free</td><td>[redacted] (source: ARCHES, average of PFS EQ-5D-5L values) mapped to EQ-5D-3L</td></tr>
<tr><td>Progressed disease (PD)</td><td>PD1 [redacted] (source: ARCHES average of post-progression utility values)
PD2 [redacted] (average of PD1 and PD3 values)
PD3 0.69 (source: AFFIRM baseline utility value)</td></tr>
<tr><td>Terminal</td><td>[redacted] (source: ARCHES, average value of last EQ-5D before death)</td></tr>
<tr><td colspan="2">PD: progressed disease</td></tr>
</table>

The ERG was concerned that the utility values for progressive disease are higher than values used in previous technology appraisal in the metastatic hormone-relapsed prostate cancer setting. They suggest using a utility decrement of 0.093 between the sub-states (i.e. PD2 0.63, PD3 0.53).</td></tr>
<tr><td>Why this issue is important</td><td>In the scenario analysis provided by the ERG increasing the utility decrement for the progressed disease sub-states from 0.015 to 0.093 (like in previous TAs) increases the cost-effectiveness estimates.</td></tr>
</table>

Technical team preliminary judgement and rationale	It is plausible that the utility values for the progressed-disease sub-states are too high because these sub-states are occupied by people with metastatic disease whose disease is incurable and who might experience debilitating symptoms.

Issue 8 – Cancer Drugs Fund

Questions for engagement	16. Would additional data collection reduce the uncertainty? 17. Is the technology a good candidate for use in the Cancer Drugs Fund?
Background/description of issue	The available data are based on interim analyses from 2 trials (ARCHES and ENZAMET) comparing enzalutamide plus ADT with placebo plus ADT or NASS plus ADT. Many people were still alive at the data cut point for the interim analyses and therefore the data used in the company submission is immature. **The company** acknowledged that extrapolating PFS and OS are key contributors to the decision-making uncertainty. Funding through the Cancer Drugs Fund would allow early patient access with data collection.
Why this issue is important	If enzalutamide is not recommended for routine use, but the committee thinks that there is plausible potential for enzalutamide to be cost effective, the committee could recommend it for use in the Cancer Drugs Fund while company analyses the final data cut. Additional data could also be collected in the Systemic Anti-Cancer Therapy (SACT) registry.
Technical team preliminary judgement and rationale	The main uncertainty is about the relative effectiveness of enzalutamide in terms of overall survival. The final data cut might provide more robust overall survival estimates than are currently available and therefore reduce the uncertainty.

4. Issues for information

Tables 1 and 2 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 1: Technical team preferred assumptions and impact on the cost-effectiveness estimate (calculations include patient access scheme for enzalutamide but comparator patient access schemes are not included. Estimates that included these commercial arrangements are higher than those reported below.)

Alteration	Technical team rationale	ICER vs ADT	ICER vs docetaxel
Company base case	–	£19,911	£22,877
1. ERG preferred base case using network meta-analysis for enzalutamide treatment effect	• Correction of errors (p91 ERG report) • PFS for ADT fit with exponential parametric fit, OS for ADT Weibull (same as company) • Hazard ratios vs. ADT from NMA used for enzalutamide OS and PFS • Utility decrement of 0.093 between each progressed disease sub-state	**£33,719**	**£47,972**
Scenario a): Similar OS from 8 years	0	£37,146	£56,354
Scenario b): Equal enzalutamide and docetaxel OS	Issue 6: OS HRs for enzalutamide vs ADT applied to docetaxel arm	£33,719	£76,042
2. ERG base case using extrapolated trial data for enzalutamide treatment effect	As 1. but rather than NMA for enzalutamide treatment effect, trial data extrapolated: • OS = Gompertz, PFS & TTD = log-logistic	£45,376	**£82,029**
Scenario a): Similar OS from 8 years	0	£44,998	£74,250
Scenario b): Equal enzalutamide and docetaxel OS	Issue 6 OS for docetaxel set to equal enzalutamide OS extrapolation	£45,376	£345,190

Table 2: Other issues for information

Issue	Comments
Implementation of company model	The ERG highlighted two errors in the company model • Error relating to disutilities for adverse events • Coding error in model
Equality considerations	No equalities issues were identified by the company, consultees and their nominated clinical experts and patient experts.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Enzalutamide with androgen deprivation therapy for treating metastatic hormone-sensitive prostate cancer [ID1605]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **2 April 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- 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 replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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

Your name	Philip Clarke
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Astellas Pharma Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Questions for engagement

Issue 1: Generalisability of clinical trial results

Are trial results from ARCHES generalisable to people seen in UK clinical practice?

Astellas believes the patient demographics within ARCHES are representative of the UK population and in alignment with the STAMPEDE trial.

There are no current NHSE data sources specific to the decision problem in this population and of the clinical trials conducted in the setting of mHSPC. STAMPEDE, with its large population of UK patients, is considered to best reflect UK clinical practice. However, given the duration of time since the trial commenced enrolment in 2005, consideration also needs to be given to the potential differences between this historic population and what would be seen today. Indeed, baseline median PSA, for enrolled patients, has reduced from ~100ng/ml in 2005 to ~50ng/ml in 2020, as per the February 2020 STAMPEDE accrual report[1]. Nevertheless, as STAMPEDE is still the most UK representative trial within this setting, Astellas have reviewed the patient populations. A comparison of key patient demographics and disease characteristics of ARCHES[2] and the mHSPC cohort of STAMPEDE[3] demonstrate limited differences between the two trial populations.

Table 1 shows key criteria where there are minor differences, which, as demonstrated in ARCHES, do not impact the overall outcomes. Indeed, ARCHES subgroup analysis shows benefit across all groups, an observation that is also aligned with analysis of the docetaxel arms within STAMPEDE[3] and CHAARTED[4]. In addition, as highlighted by the Technical Team, data from STAMPEDE suggests that there is no treatment effect modification by volume for abiraterone vs ADT alone[5].

Table 1. Key patient demographics and disease characteristics of mHSPC patients in ARCHES and STAMPEDE

	ARCHES[2]		**STAMPEDE[3]**	
	ENZA+ADT (n=574)	**PBO+ADT (n=576)**	**DOC+ADT (n=362)**	**ADT (N=724)**
Median age (range)	70 (46-92)	70 (42-92)	65 (60-70)	65 (60-71)
Disease volume, n (%)				
HVD	354 (61.7)	373 (64.8)	148 (41)	320 (44)
LVD	220 (38.3)	203 (35.2)	124 (34)	238 (33)
Unassessed	-	-	90 (25)	166 (23)
ECOG PS, n (%)				
0	448 (78.0)	443 (76.9)	NA	NA

	1	125 (21.8)	133 (23.1)	NA	NA
	Gleason score, n (%)				
	<8	171 (29.8)	187 (32.5)	65 (18)	158 (22)
	≥8	386 (67.2)	373 (64.8)	253 (70)	480 (66)
	Unknown	-	-	44 (12)	86 (12)

Abbreviations: ADT: androgen deprivation therapy; DOC: docetaxel; ECOG: Eastern Cooperative Oncology Group; ENZA: enzalutamide; HVD: high volume disease; LVD: low volume disease; PBO: placebo; PS: performance status.

In conclusion, Astellas considers the trial results from ARCHES to be generalisable to people seen in UK clinical practice.

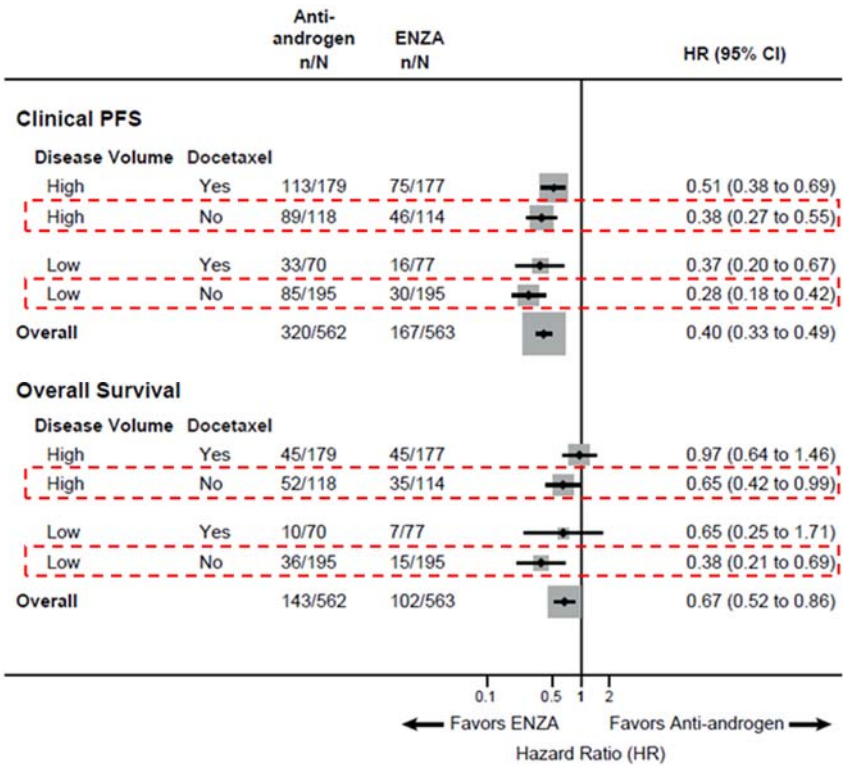
Are trial results from ENZAMET generalisable to people seen in UK clinical practice?

Astellas acknowledge that ENZAMET is not generalisable to the UK population with regards to the inclusion of non-steroidal anti-androgen (NSAA) plus ADT as the comparator arm however, it is important to include ENZAMET OS results to provide the long term data required for an effective evaluation. To ensure UK relevance, Astellas removed the patient cohort that received concomitant docetaxel. The remaining difference of the use of complete androgen blockade (CAB; i.e., ADT plus a NSAA) is not recommended as a first-line therapy in the UK[6]. However, despite of the lack of published evidence for OS benefit with this treatment, the NMA conducted by Astellas does show a trend towards a positive impact of CAB on OS ([redacted]). This could potentially underestimate the OS benefit observed with enzalutamide in ENZAMET[7].

Another potential difference between the ENZAMET study population and the UK mHSPC population resides on the proportion of patients with high volume disease (HVD). In the cohort of patients not receiving concomitant docetaxel, approximately [redacted] of patients had HVD. This proportion is lower than that

observed in STAMPEDE and ARCHES: However, enzalutamide significantly delayed disease progression and reduced mortality in both, HVD and low volume disease (LVD) patients[7](Figure 1).

Figure 1. Clinical progression and overall survival for patients with high and low volume disease in ENZAMET

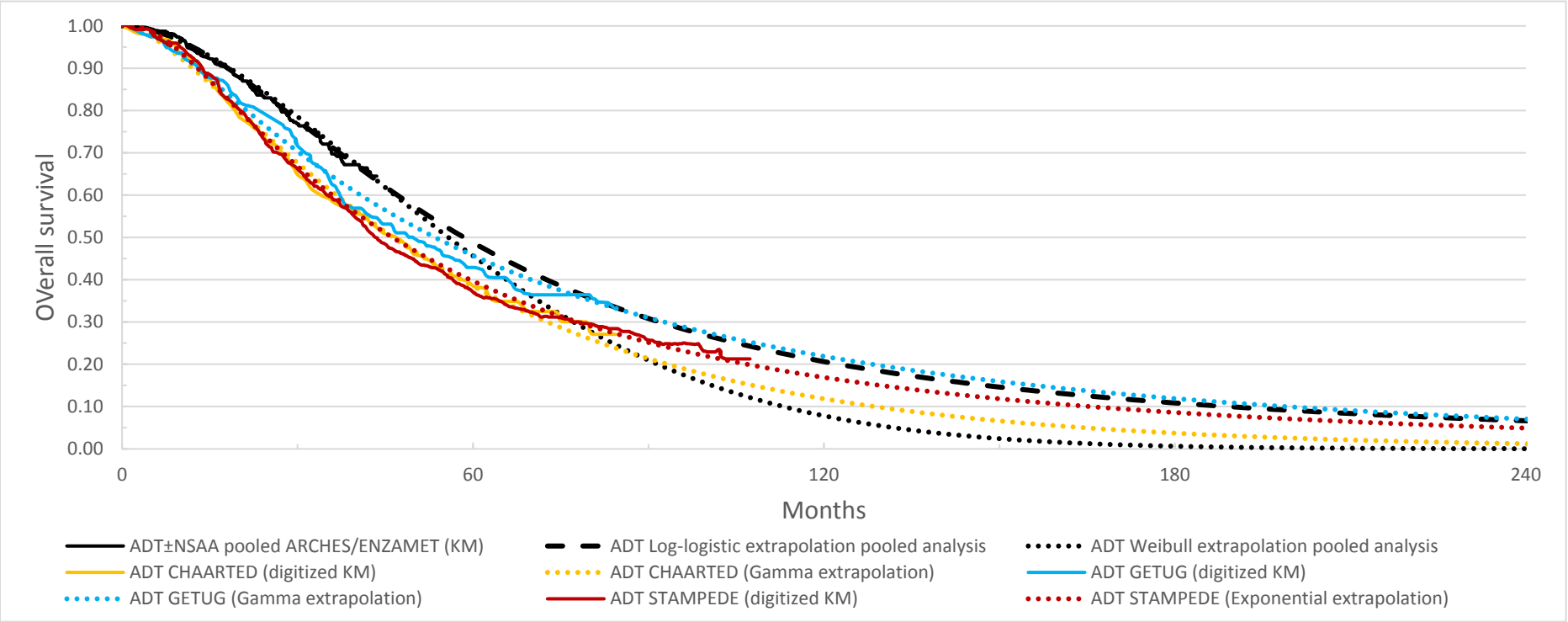


Source: Davis et al[7]. Highlighted in red, the clinical progression-free survival and overall survival for the ENZAMET cohort not receiving concomitant docetaxel.

Is it acceptable to pool data from ARCHES and ENZAMET to estimate clinical efficacy of enzalutamide?	1) Pooling of the ARCHES and ENZAMET trials was done for health economic modelling purposes. Pooling was conducted using patient-level data from ARCHES and ENZAMET; no adjustment for differences was applied. The pooling included the intent-to-treat (ITT) ARCHES population and the ITT ENZAMET population that did not receive concomitant docetaxel. 2) The pooling was attempted for three endpoints (OS, clinical PFS and time to treatment discontinuation [TTD]), but could only successfully be done for OS and TTD. Regarding clinical PFS, the ARCHES PFS definition did not match that in ENZAMET because no data were available for development of symptoms attributable to cancer progression in ARCHES. ENZAMET may not fully represent the mHSPC UK population, however, we also believe that comparative STAMPEDE data is also less likely to be a true representation of the current population. As outlined previously, ARCHES is aligned with UK clinical practice and by pooling this data with ENZAMET we can create a UK representative population that also provides the complete scope of available data to fully inform this submission. Clinical expert opinion confirms that the 2005 STAMPEDE trial population is no longer a true representation of current demography and acknowledges that pooled ARCHES/ENZAMET baseline data, especially metastatic burden, Gleason score and performance status aligns with the UK clinical practice.
Issue 2: Extrapolation of overall survival	
What proportion of people are still alive at year 10 after ADT treatment? Is 8% or 20% more plausible?	**Background:** In ARCHES, the interim OS analysis was immature with 39 (6.8%) deaths in the enzalutamide plus ADT group and 45 (7.8%) deaths in the placebo plus ADT. Similarly, in ENZAMET after a median follow-up of 37.3 months for patients not on concomitant docetaxel, OS was immature with 50 (16.2%) and 88 (28.1%) deaths in the enzalutamide plus ADT (no concomitant docetaxel) and the NSAA plus ADT (no concomitant docetaxel) arms, respectively. In this context, Astellas extrapolated OS using different models. Astellas' submission used a Weibull function to parametrically model the survival in the ADT arm. The Weibull function resulted in an estimated 10-year survival in the ADT arm of 8%. **Methods:** Median follow-up in ARCHES and ENZAMET (non-concomitant docetaxel cohort) was 14.4 and 37.3 months, respectively. In response to issue 2 further validation of extrapolation of the pooled OS trial data was conducted through digitisation and extrapolation of other studies reporting OS for ADT. Three external trials were available for validation: STAMPEDE[3] (median follow-up: 78.2 months [i.e., 6.5 years]), CHAARTED[8] (median follow-up: 53.7 months [i.e., 4.5 years]), and GETUG[4] (median follow-up: 83.9 months [i.e., 7.0 years]). The Kaplan Meier (KM) graphs from these studies have been digitised, individual patient data (IPD) was generated according to the methods proposed by Guyot et al.[9], the generated IPD data have been extrapolated to 30 years based on

	the methodology in the NICE DSU document 14, and finally the best fitting curve was selected based on visual inspection, as well as lowest AIC and BIC. The survival data and extrapolations from the ADT arm of the 3 external trials are displayed together with the ADT OS KM data and the two relevant extrapolations (Weibull and log-logistic) from the pooled ARCHES/ENZAMET analysis in Figure 8. **Results:** The extrapolations of STAMPEDE, CHAARTED, and GETUG suggest an OS rate at 10 years of between 12% to 21%. Based on these long-term data it is thus plausible that 10-year survival for the ADT arm is closer to 20% than to 8%. This was confirmed by clinical experts who suggested that survival in the ADT arm should approach 10% after 15 years[10]. The long-term data and the clinical expert opinion together suggest that the OS for ADT would be somewhere between the extrapolated Log-logistic and Weibull curves.

Figure 2. Kaplan Meier and extrapolated overall survival for ADT patients in the pooled analysis, and overall survival and extrapolation for patients randomised to ADT in STAMPEDE, CHAARTED and GETUG

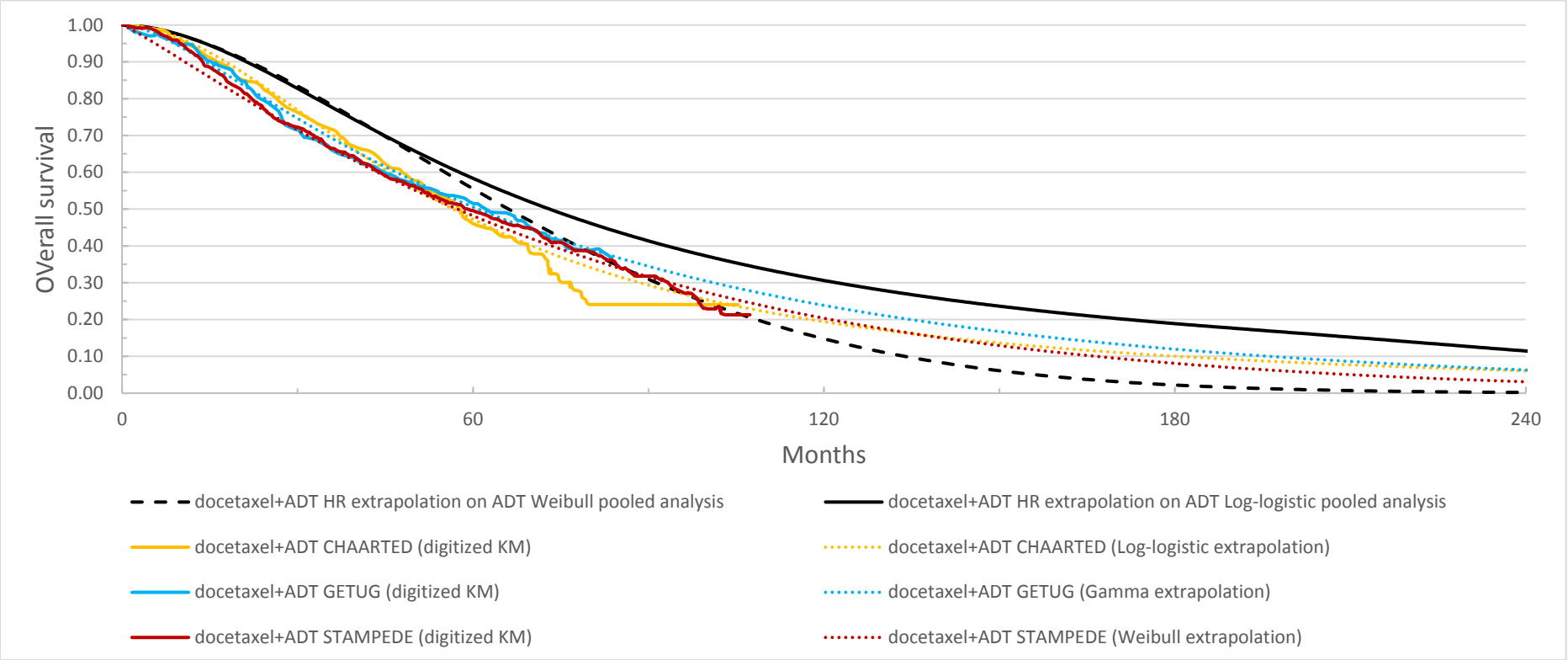


Discussion:

In Astellas' base case, the survival curves of docetaxel plus ADT are modelled using hazard ratios based on ADT. Similar to the validation of ADT survival extrapolations, Astellas must rely on other trials for external validation of long-term survival predictions for docetaxel plus ADT. However, where STAMPEDE[3], CHAARTED[4], and GETUG[8] contain reasonable long-term data on docetaxel plus ADT, no trial contains sufficiently long-term survival data of docetaxel plus ADT. These curves have been extrapolated to 30 years using the same methodology reported for the ADT curves. The survival data from the docetaxel plus ADT arms of these trials, their extrapolations, and the extrapolations for docetaxel plus ADT based on NMA hazard ratios are shown below in Figure 4.

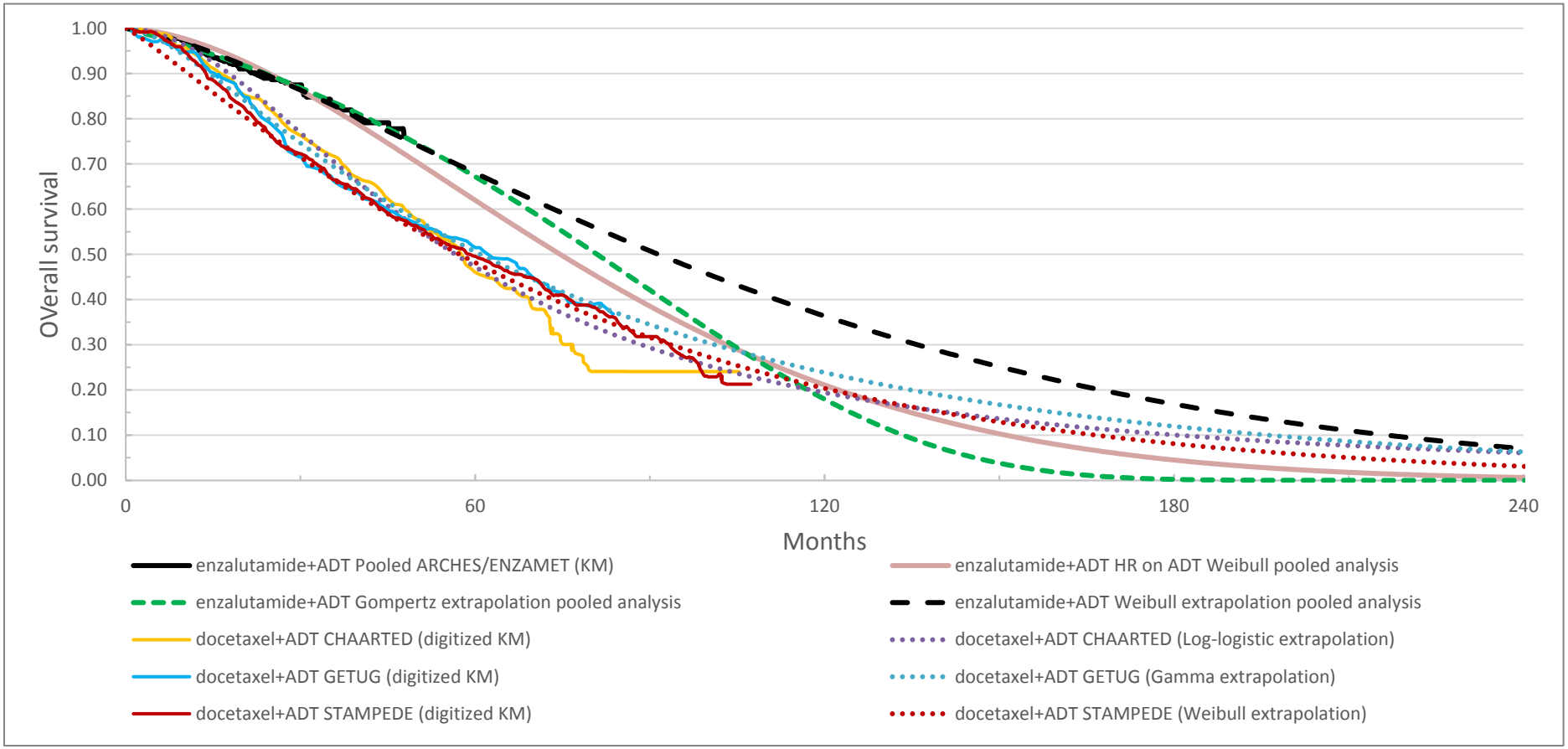
There is a large range between the three extrapolations at 10 years, with the extrapolations for the three long-term trials suggesting survival between 19% and 23%. Overall, the figure suggests that the survival for docetaxel plus ADT would be overstated with the use of hazard ratios based on the Log-logistic extrapolation for ADT, but that the application of the hazard ratio on the ADT Weibull curve would be plausible.

Figure 3. Extrapolated overall survival for docetaxel plus ADT patients based on hazard ratios and overall survival for patients randomised to docetaxel plus ADT in STAMPEDE, CHAARTED and GETUG



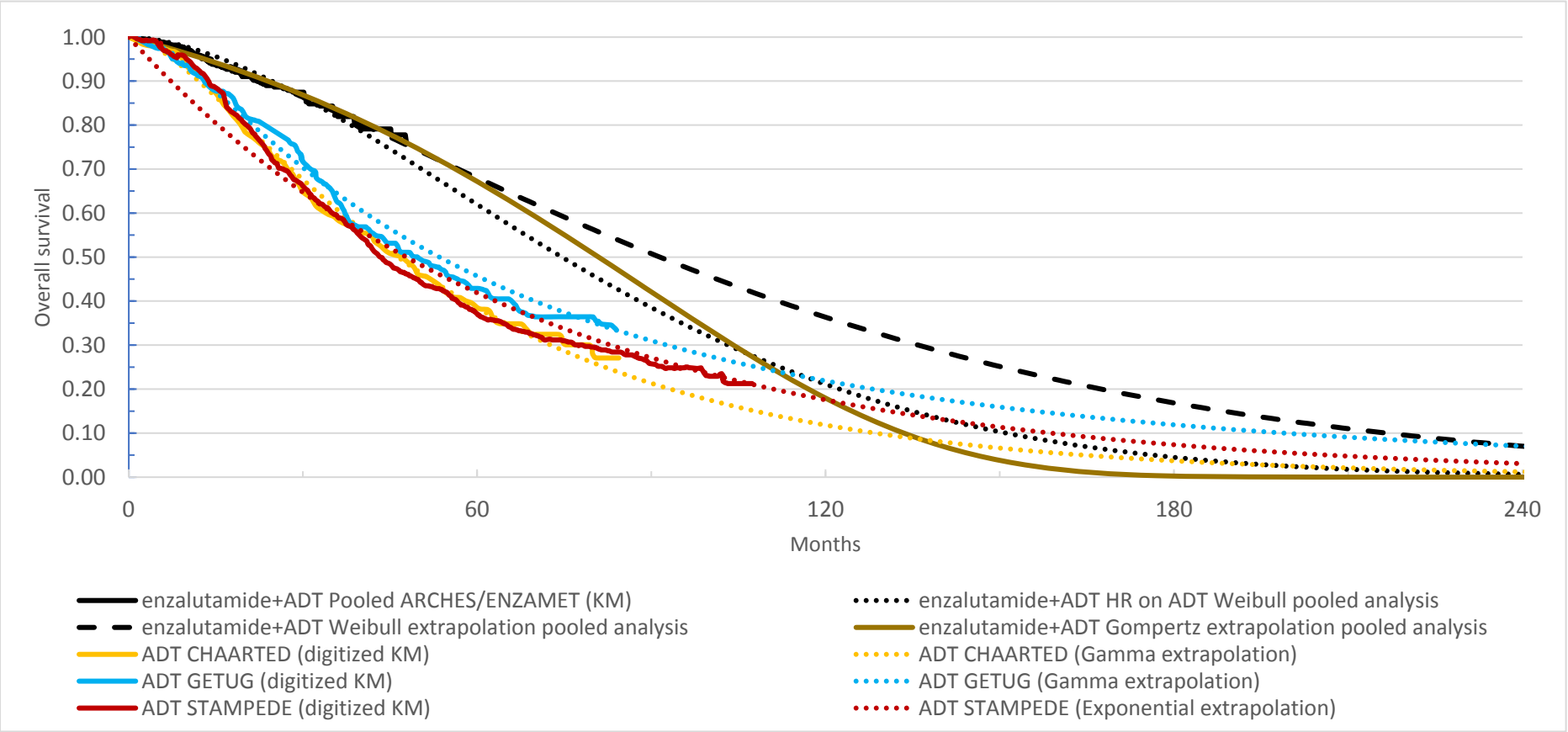
What proportion of people are still alive at year 10 after enzalutamide plus ADT treatment? Is 36% or 15% more plausible?	**Background:** Astellas' submission used a Weibull function to parametrically model the survival in the enzalutamide plus ADT arm. The Weibull function resulted in an estimated 10-year survival in the enzalutamide plus ADT arm of 36%. **Methods:** Similar to the validation of ADT survival extrapolations, Astellas must rely on other trials for external validation of long-term survival predictions for enzalutamide plus ADT. As already mentioned, no trial contains long-term survival data of enzalutamide plus ADT, but STAMPEDE[3], CHAARTED[4], and GETUG[8] contain long-term data on docetaxel plus ADT. Astellas have therefore conducted analysis versus docetaxel and versus ADT alone. **Results vs docetaxel plus ADT:** The survival data from the docetaxel plus ADT arms of the STAMPEDE, CHAARTED, and GETUG trials, their extrapolations, and the KM data of the pooled analysis for enzalutamide plus ADT are shown below in Figure 4. Survival for the most mature trial, STAMPEDE, was close to 23% at 8.5 years[3], with the extrapolation suggesting a 10-year survival of 20%. These data thus suggest that 10-year survival for the pooled analysis should be closer to 36% (the next lowest estimate suggested by an extrapolation curve) than to 15%, with 15% being an implausibly pessimistic estimate. Clinical expert opinion also stated that estimates for our pooled survival analysis would be more closely aligned with the STAMPEDE data at 8.5 years suggesting the lowest estimates for survival at 10 years are too pessimistic. **Discussion vs docetaxel plus ADT:** Astellas believes that the long-term docetaxel plus ADT data represent the lower bound for the long-term expectations for enzalutamide plus ADT given the NMA results which indicate lower mortality risk with enzalutamide plus ADT than docetaxel plus ADT (HR: [redacted]). Astellas' NMA suggest that enzalutamide plus ADT has a survival advantage compared to docetaxel plus ADT although this was not statistically significant (HR: [redacted]). In addition, the KM data for the pooled population shows a survival benefit for enzalutamide plus ADT compared to the KM data of docetaxel plus ADT from the three external trials. Given the expected treatment effect of enzalutamide plus ADT over docetaxel plus ADT and the increased benefit seen in the trial period, it would be implausible that OS of enzalutamide plus ADT after 10 years is close to 18%, as predicted by the Gompertz distribution.

Figure 4. Kaplan Meier and extrapolated overall survival for enzalutamide plus ADT patients in the pooled analysis and for patients randomised to docetaxel plus ADT in STAMPEDE, CHAARTED and GETUG



	Results vs ADT alone The survival data from the ADT alone arms of the STAMPEDE, CHAARTED, and GETUG trials, their extrapolations, and the KM data of the pooled analysis for enzalutamide plus ADT are shown in Figure 5. **Discussions vs ADT alone:** A 15% survival at 10 years would suggest the survival with enzalutamide plus ADT to be similar or below the expected survival with ADT, which is not plausible given the NMA results (HR: [redacted]) and pooled trial analysis results. Additionally, an 18% survival at 10 years is only suggested by the Gompertz extrapolation curve (see Figure 5). Astellas believe that the Gompertz curve is not a plausible extrapolation (too pessimistic) because the Gompertz curve had the worst statistical fit (BIC) to the KM data and it suggest a decline in survival between year 5 and year 10 that is not seen in the long-term external ADT or docetaxel plus ADT data (from 67.2% to 17.9%, that is 49.3%).

Figure 5. Kaplan Meier and extrapolated overall survival for enzalutamide plus ADT patients in the pooled analysis and for patients randomised to ADT in STAMPEDE, CHAARTED and GETUG



What proportion of people are still

<table>
<tr><td>alive at year 20 after enzalutamide plus ADT treatment? Is 0% or 7% more plausible?</td><td>
Long-term extrapolations from external trial data for docetaxel plus ADT (Figure 4) would suggest that 20-year survival is in the range of 3 to 6%. Given the performance of enzalutamide plus ADT vs. docetaxel in the NMA, Astellas' believes that 7% is more plausible than 0%.

In addition, the company's clinical expert expected 12% to 13% proportion of individuals to be alive at 18 years for patients on enzalutamide plus ADT.

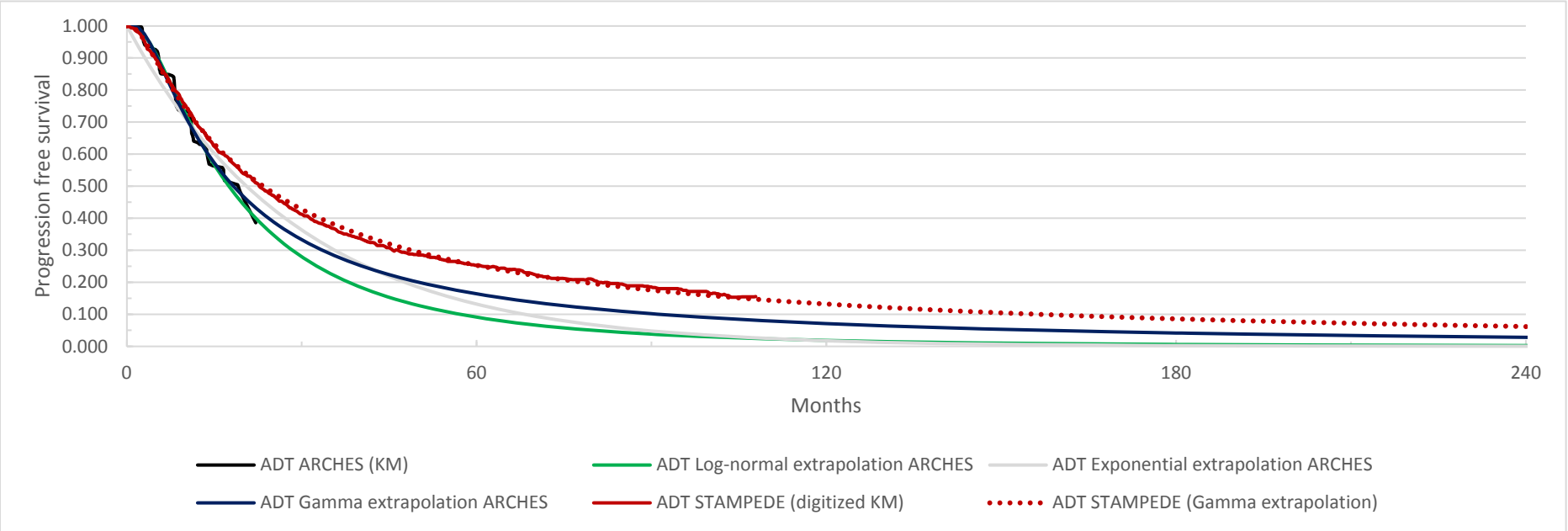
Overall, given all the available evidence stated here and in the response to the previous question, Astellas believe that the Gompertz curve, which provided the worst statistical fit to the data presents an implausible scenario for OS for enzalutamide plus ADT. Astellas believe that application of the NMA hazard ratios to the Weibull curve presents a pessimistic scenario for the OS of enzalutamide plus ADT, while the Weibull extrapolation presents a more plausible OS scenario.

Table 2, presents a summary of the combination of the OS curves for consideration by the committee, with Astellas assessment of the different approaches.. Given the limitations of predicting long-term survival, Astellas considers the use of NMA HRs to provide plausible OS scenarios.

Table 2 Four main OS scenarios considered by the Company and the ERG
<table>
<tr><th></th><th>Company original submission base case</th><th>ERG NMA HR base case</th><th>Alternative scenario based on NMA HR approach</th><th>ERG parametric case</th></tr>
<tr><td>ADT</td><td>Weibull</td><td>Weibull</td><td>Log-logistic</td><td>Weibull</td></tr>
<tr><td>Docetaxel plus ADT</td><td>NMA HR</td><td>NMA HR</td><td>NMA HR</td><td>NMA HR</td></tr>
<tr><td>Enzalutamide plus ADT</td><td>Weibull</td><td>NMA HR</td><td>NMA HR</td><td>Gompertz</td></tr>
<tr><td>Company overall assessment</td><td>Preferred scenario</td><td>Plausible scenario but pessimistic OS for enzalutamide plus ADT</td><td>An alternative scenario based on less pessimistic OS survival for all treatment arms</td><td>Implausible because it suggests better OS for docetaxel plus ADT than for enzalutamide plus ADT</td></tr>
</table>
</td></tr>
<tr><td colspan="2">Issue 3: Extrapolation of progression-free survival</td></tr>
<tr><td>What is the proportion of people whose cancer has not</td><td></td></tr>
</table>

progressed at year 5 after ADT treatment? Is 20% to 30% or 10% more plausible?	**Methods:** • The measure of progression used in ARCHES and Astellas' submission is radiographic PFS. • Data for long-term validation of the extrapolations for ARCHES PFS is available from STAMPEDE[3]. • The definition of PFS in STAMPEDE resembles most closely the ARCHES radiographic PFS. • STAMPEDE PFS has been digitised and extrapolated by Astellas up to 30 years. **Results:** • Figure 6 displays PFS for the control arm of STAMPEDE, the extrapolated curve, the KM curve for ADT in ARCHES, and three extrapolated curves for ADT in ARCHES. • Figure 6 shows that after about 18 months, PFS for ARCHES ADT KM and STAMPEDE control arm start to diverge. • The figure also shows that the slope of PFS in STAMPEDE flattens quickly after about 36 months. • The flattening was not observed in ARCHES for which no data was available at 36 months. • The 5-year PFS of patients on ADT in STAMPEDE was approximately 25%. Given the performance of ARCHES ADT KM vs. ADT in STAMPEDE (HR: 0.71 [0.63, 0.81]) it would be expected that the proportion of people whose cancer has not progressed on ADT at 5 years to be approximately 20%

Figure 6. Kaplan Meier and extrapolated PFS for ADT patients in the ARCHES trial and for patients randomised to ADT in STAMPEDE

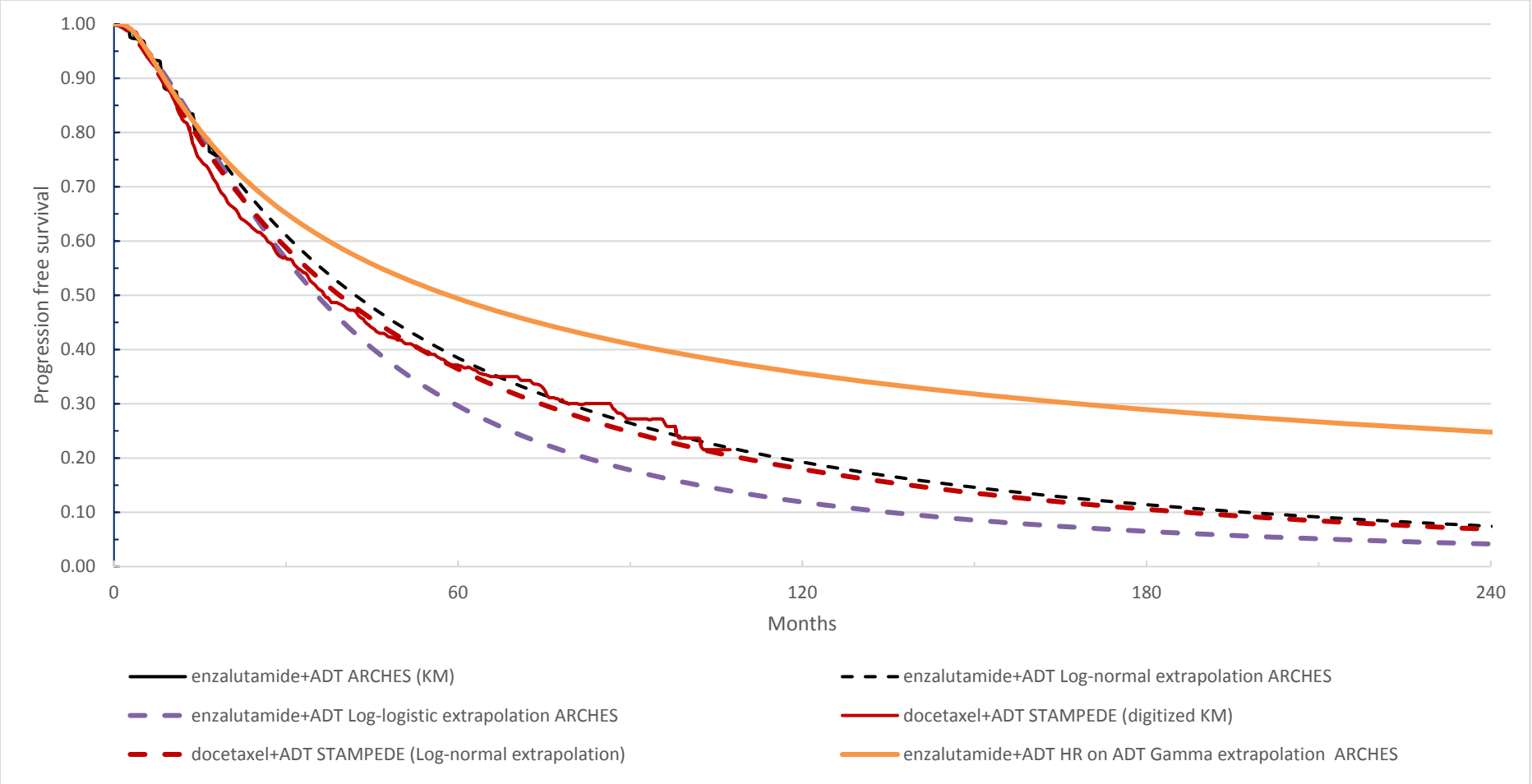


Discussion

- The ERG also assessed the most plausible curve for PFS for enzalutamide plus ADT. While this question relates to the plausibility of the ADT curve, it is important to also consider the extrapolations for the two comparator arms. The ERG's clinical expert suggested that PFS for enzalutamide plus ADT at 5 years would be 20% to 30%.
- In Figure 7, the PFS of docetaxel plus ADT in STAMPEDE and the extrapolations of the enzalutamide plus ADT arm of ARCHES are plotted. The 5-year PFS for docetaxel in STAMPEDE[3] was approximately 38%. The NMA results show that enzalutamide plus ADT is expected to perform better in terms of PFS than docetaxel plus ADT with an HR of [redacted] (95% CI [redacted]).
- Astellas believes that PFS after 5 years would be above that of docetaxel plus ADT. Astellas would estimate the 5-year PFS of enzalutamide plus ADT to be close to 40%.

- Astellas' clinical expert is in agreement with enzalutamide plus ADT 5 year PFS estimates being above the comparator and closer to 40%.

Figure 7. Kaplan Meier and extrapolated progression-free survival for enzalutamide plus ADT patients in ARCHES and for patients randomised to docetaxel in STAMPEDE



<table>
<tr>
<td>What is the proportion of people whose cancer has not progressed at year 10 after ADT treatment? Is 10% or 2% more plausible?</td>
<td>

The extrapolation of PFS to 10 years in the ADT arm of STAMPEDE[3] (Figure 6) suggest a progression-survival of 13% at 10 years. Given the lower PFS in ARCHES than in STAMPEDE for ADT, Astellas expects the proportion of people whose cancer has not progressed on ADT at 10 years likely to be lower than 10%. Overall, this would suggest that the exponential function for ADT, as suggested by the ERG, would be better in line with long-term data than the Log-normal curve. For enzalutamide plus ADT, the ERG's clinical expert suggestion that PFS at 10 years would be 0% to 10%. Astellas believe that the PFS after 10 years would be similar or above the PFS of docetaxel plus ADT in STAMPEDE (see Figure 7).The extrapolation for docetaxel PFS in STAMPEDE suggests a PFS of 18% after 10 years.
Astellas thus estimates the 10-year PFS to be close to or above 20%. Because a 10-year PFS of 0% to 10% would imply more progression than suggested by docetaxel plus ADT or ADT alone data in STAMPEDE[3]. Patients on ADT may sometimes have a long-term remission[10]. This is not observed in ARCHES because of the short follow-up. Long-term remission with enzalutamide is also plausible. This may explain the long tail observed in the ARCHES and STAMPEDE extrapolations. Overall, Astellas believes that the PFS for enzalutamide plus ADT is best approximated by the Log-normal curve or by the use of HR on the ADT exponential curve and that the Log-logistic curve is not a plausible scenario (too pessimistic). Table 3 presents a summary of the combination of PFS curves considered by Astellas and the ERG. Astellas believe that based on the above evidence other combinations would not be plausible.

Table 3 Three main PFS scenarios considered by Astellas and by the ERG
<table>
<tr><td></td><td>Company original submission base case</td><td>ERG NMA HR base case</td><td>ERG parametric case</td></tr>
<tr><td>ADT</td><td>Log-normal</td><td>Exponential</td><td>Exponential</td></tr>
<tr><td>Docetaxel plus ADT</td><td>NMA HR</td><td>NMA HR</td><td>NMA HR</td></tr>
<tr><td>Enzalutamide plus ADT</td><td>Log-normal</td><td>NMA HR</td><td>Log-logistic</td></tr>
<tr><td>Company overall estimate</td><td></td><td>Plausible scenario given long-term STAMPEDE data</td><td>Implausible because it suggests lower PFS for enzalutamide plus ADT compared to STAMPEDE observed data</td></tr>
</table>
</td>
</tr>
<tr><td colspan="2">Issue 4: Extrapolation of time to treatment discontinuation</td></tr>
<tr><td>Is it plausible to assume that PFS and time</td><td></td></tr>
</table>

to treatment discontinuation are similar?	Astellas would like to clarify that in the ARCHES trial, a proportion of patients have discontinued treatment for reasons other than progression thereby, accounting for the dissimilarity between PFS and TTD. Astellas would also like to highlight that median TTD is expected to be shorter than median PFS and, as per clinical expert opinion, particularly in clinical practice where patient choice may be more common than in the setting of a clinical trial.
What are the reasons for stopping enzalutamide before disease progression? For example, do adverse events trigger early stopping?	The main reason for treatment discontinuation was disease progression in both, ARCHES and ENZAMET trials. Other reasons include adverse events,, consent withdrawal, death, protocol deviation and lost to follow-up, the proportions of which were aligned across ENZAMET and ARCHES at 15.2% and 12.2% for enzalutamide, respectively. Further information for treatment discontinuation criteria has been outlined in the study protocols. In ARCHES[11], patients could discontinue the study treatment in the following situations: • Any adverse event that was intolerable to the patient and that could not be ameliorated by the use of adequate medical intervention and/or dose reduction or that, in the opinion of the investigator, would lead to undue risk to the patient if dosing was continued • Patient experienced a seizure or any condition that significantly predisposed the patient to seizure such as brain metastasis or clinically evident stroke • Patient experienced a confirmed event of posterior reversible encephalopathy syndrome by brain imaging, preferably by MRI • Patient initiated an investigational agent or new therapy for prostate cancer • Patient had evidence of radiological disease progression as confirmed by the independent reader and in the judgment of the investigator was no longer deriving clinical benefit • Patient had discontinued ADT and had a testosterone value in the non-castrate range (>50 ng/dL) as confirmed by the central laboratory • Patient was, in the opinion of the investigator or the medical monitor, non-compliant with the protocol requirements • Patient was lost to follow-up despite reasonable efforts by the investigator to locate the patient • Patient withdrew consent for the study. In ENZAMET[12], study treatment with enzalutamide plus ADT or NSAA plus ADT was permanently discontinued for any of the reasons below: • Clinical progressive disease, which was documented by a site investigator • Delay of hormonal treatment for greater than 30 days due to treatment-related adverse events • The investigator determined that continuation of treatment was not in the patient's best interest

- Development of adverse events during the study that would put the patient at risk if they continued study therapy, e.g., seizures or liver toxicity, whilst on enzalutamide
- The patient declined further study treatment, or withdrew their consent to participate in the study.

In addition, in ENZAMET enzalutamide should have been discontinued in the following circumstances[12]:

- Required use of a concomitant treatment that was prohibited
- Failure to comply with the protocol, e.g., repeatedly failing to attend scheduled assessments. If a patient failed to attend scheduled assessments in the study, the investigator must have determined the reasons.

After disease progression, the main reasons for study treatment discontinuation of enzalutamide in ARCHES and ENZAMET were adverse events and consent withdrawal (Table 4).

Table 4. Reasons of treatment discontinuation in ARCHES and ENZAMET

	ARCHES		**ENZAMET**	
	ENZA+ADT	**PBO+ADT**	**ENZA+ADT***	**NSAA+ADT***
Patients who discontinued	135 (23.5%)	242 (42.0%)	98 (31.7%)	196 (62.6%)
Reasons for discontinuation				
Adverse event	28 (4.9%)	21 (3.6%)	20 (6.5%)	6 (1.9%)
Death	9 (1.6%)	7 (1.2%)	4 (1.3%)	5 (1.6%)
Lost to follow-up	0	1 (0.2%)	-	-
Progressive disease	65 (11.3%)	171 (29.7%)	51 (16.5%)	127 (40.6%)
Protocol deviation	2 (0.3%)	1 (0.2%)	-	-
Consent withdrawal	25 (4.4%)	30 (5.2%)	-	-
Other reasons	6 (1.0%)	11 (1.9%)	6 (1.9%)	3 (1.0%)
Clinician preference			8 (2.6%)	39 (12.5%)
Patient preference			9 (2.9%)	16 (5.1%)

Abbreviations: ADT: androgen deprivation therapy; ENZA: enzalutamide; NSAA: non-steroidal antiandrogen; PBO: placebo. *Not on concomitant docetaxel.

How many people would

stop treatment early because of adverse events?	Please see previous response and Table 4. In ARCHES, 4.9% and 3.6% of patients randomised to enzalutamide and placebo respectively discontinued treatment due to an adverse event. In ENZAMET, these proportions were 6.5% and 1.9% in the enzalutamide and NSAA arms, respectively. In clinical practice, these percentages may be higher due to patient preference rather than clinician reported intolerance.
Issue 5: Similar long-term treatment effectiveness	
Is it plausible that treatment effects of ADT, docetaxel and enzalutamide plus ADT are similar after 8 years?	In the STAMPEDE trial the OS for docetaxel plus ADT converged at 8.5 years with OS for ADT[3]. This convergence was not seen in GETUG[8] which also includes long-term follow-up. Astellas does not believe it is plausible to assume that OS treatment effect of ADT, docetaxel plus ADT, and enzalutamide plus ADT are equalised after 8 years for three reasons: • First, there is no long-term evidence available to suggest that treatment effects would converge for enzalutamide plus ADT vs. ADT or vs. docetaxel plus ADT. • Second, the OS extrapolations shown in Figure 5 suggest that the STAMPEDE extrapolated ADT curve and the enzalutamide plus ADT curve based on NMA HR on the Weibull ADT curve converge only after approximately 15 years. The STAMPEDE extrapolated ADT curve and the enzalutamide plus ADT Weibull extrapolation curve converge only after 20 years. • Finally in STAMPEDE, the convergence shown could be due to background mortality.
Issue 6: Post-progression treatments	
Do the subsequent treatments in ARCHES and ENZAMET reflect NHS clinical practice?	Not all subsequent treatments received by patients in ARCHES and ENZAMET were aligned with the UK clinical practice (see below). However, the impact of post-progression therapies, in mHSPC, is expected to be less prominent than that of the initial therapy. This has been demonstrated in a recent trial investigating the effects of initial hormone treatment on secondary PFS (PFS2). mHSPC patients were initially treated with a hormone therapy until they progressed to mCRPC, when they most commonly received a taxane or a second hormonal treatment before progressing again (PFS2). Findings showed significant benefit in the treatment arm compared to placebo at PFS2 regardless of choice of subsequent treatment after the first progession[13]. • In ARCHES[2], (Table 5) all post-progression therapies received by patients in the placebo arm reflect NHS practice but post-progression abiraterone (n=13/574, 2.3%) or enzalutamide (n=4/574, 0.7%) in patients randomised to enzalutamide did not. Sequencing of enzalutamide and abiraterone is not recommended by NICE.

- In total only 3.0% of all patients in the enzalutamide arm received subsequent therapies not permitted for use by NHSE.

Table 5. First new antineoplastic therapy for prostate cancer after disease progression in ARCHES

	ENZA+ADT (N=574)	PBO + ADT (N=576)
Any first therapy	46/574 (8.0%)	133/576 (23.1%)
Docetaxel*	11/46 (23.9%)	52/133 (39.1%)
Abiraterone Acetate*	13/46 (28.3%)	28/133 (21.1%)
Enzalutamide*	4/46 (8.7%)	28/133 (21.1%)
Bicalutamide*	4/46 (8.7%)	12/133 (9.0%)
Other*	14/46 (30.4%)	15/133 (26.3%)

Abbreviations: ADT: androgen deprivation therapy; ENZA: enzalutamide; PBO: placebo. *Data are provided as percentage of patients among those patient receiving a post-progression therapy.

- In ENZAMET, not all post-progression therapies reflect NHS practice (Table 6). Among these, PARP inhibitors, immune checkpoint inhibitors and other novel antiandrogens, in both treatment arms, and abiraterone/enzalutamide sequencing are not in line with routine UK practice, but may be accessed in clinical trials.

Table 6. Post-progression therapies in ENZAMET

	First-line		Second-line	
	ENZA + ADT (N=50)	NSAA+ADT (N=138)	ENZA + ADT (N=50)	NSAA+ADT (N=138)
Any post-progression therapy*				
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]
Abiraterone acetate	[redacted]	[redacted]	[redacted]	[redacted]
Other novel antiandrogen	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Other chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Immune checkpoint inhibitor	[redacted]	[redacted]	[redacted]	[redacted]
PARP inhibitor	[redacted]	[redacted]	[redacted]	[redacted]
Radium-223 dichloride	[redacted]	[redacted]	[redacted]	[redacted]

Sipuleucel-T	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADT: androgen deprivation therapy; ENZA: enzalutamide; NSAA: non-steroidal anti-androgen. *Data are provided as percentage of patients among those patient receiving a post-progression therapy.

- Astellas' clinical expert cited that previous trials in mCRPC have demonstrated the benefit of early initial treatment over subsequent treatment. This is also emulated in ENZAMET (Figure 8) which shows no significant impact of second line therapies on OS.
- In ENZAMET, median OS for patients randomised to NSAA who received abiraterone as second line therapy was comparable to that of NSAA patients receiving any other second-line therapy. The same applied to patients randomised to enzalutamide receiving either abiraterone or any other antineoplastic post-progression.

Figure 8. Kaplan Meier of overall survival for patients randomised to (A) enzalutamide or (B) NSAA who received abiraterone or any other antineoplastic therapy after progression

[redacted]

The therapies in the model PD1 – PD3 health states were selected based on feedback from a single UK clinician[10]. The modelled treatments in PD1-PD3 take into account treatments currently used in NHSE, in the sequences allowed in routine clinical practice e.g. no sequential use of novel hormone therapies (**Table 7**).

Table 7. Treatment sequence modelled for PD1, PD2 and PD3

Health states	Enzalutamide arm	ADT arm	Docetaxel arm
mHSPC	Enzalutamide	ADT	Docetaxel
PD1	20% ADT 60% Docetaxel 20% Radium-223	20% ADT 35% Enzalutamide 10% Docetaxel 35% Abiraterone	10% ADT 35% Enzalutamide 25% Docetaxel 30% Abiraterone
PD2	25% BSC 15% Docetaxel 30% Radium-223 30% Cabazitaxel	30% BSC 10% Enzalutamide 30% Docetaxel 5% Abiraterone 20% Radium-223 5% Cabazitaxel	25% BSC 5% Enzalutamide 5% Abiraterone 30% Radium-223 35% Cabazitaxel
PD3	80% BSC 10% Radium-223 10% Cabazitaxel	85% BSC 10% Radium-223 5% Cabazitaxel	80% BSC 10% Radium-223 10% Cabazitaxel

Is it plausible to assume that subsequent treatment does not influence the long-term outcome?	As observed in Figure 8, the impact of post-progression therapies on OS is less marked than the impact of the first-line therapy. In addition, different post-progression therapies result in similar median OS suggesting that subsequent treatments have limited impact on long-term OS.
Issue 7: Utility values	
Compared to the general population,	

what is the quality of life of people with metastatic prostate cancer after 1, 2, and 3 treatments post progression?

Astellas are willing to accept the ERG proposed changes to the post-progression utilities as this is not a key driver of cost effectiveness and this change is unlikely to have a significant impact on the cost effectiveness of enzalutamide. For the purposes of accuracy and clarity, Astellas would like to provide some key information to support and explain their original rationale.

The ERG suggested to use a decrement of 0.093 between each PD health state. This decrement would result in utility weights lower than those used in previous NICE prostate cancer submissions. Astellas considers the proposed decrement to be unrealistically high particularly when only few patients would receive chemotherapy at these health states. A decrement of 0.093 is higher than the decrements that have been reported across treatment lines in other oncology patients[10, 14, 15].

An analysis of the health utilities based on number of post-progression therapies was not conducted in ARCHES.

The utility weights included in the model for mHSPC and PD1 originate from ARCHES. At the time of submission, the utility weights from ENZAMET were not yet available but they have now been analysed. As shown in Table 8, the ENZAMET (no concomitant docetaxel) utility weights at baseline were comparable between studies. However, the average for all utilities from baseline until progression tended to be higher in ENZAMET than in ARCHES, while utility weights after progression tended to be lower in ENZAMET than in ARCHES.

Table 8 EQ-5D-5L from ARCHES and ENZAMET after applying the Van Hout algorithm

	ARCHES	ENZAMET (no concomitant DOC)
	Both arms	Both arms
Baseline	0.816 (0.178)	0.82 (0.158)
All pre-progression assessments	0.806 (0.193)	0.82 (0.166)
First post-progression assessment	0.731 (0.242)	0.69 (0.236)
All progressed assessments	0.723 (0.240)	0.70 (0.223)
End of life	0.457	0.60 (0.302)

Table 9 provides the utility weights that have been used in previous prostate cancer NICE submissions. Based on these utility weights, the one for first-line CRPC treatment (i.e., PD1) would be higher than the average of all post-baseline and pre-progression utilities from ARCHES. Astellas considered this to be implausible and therefore, used the corresponding value from ARCHES (i.e., average of all post-progression therapies).

Table 9 EQ-5D-5L from ARCHES and ENZAMET after applying the Van Hout algorithm

	mHSPC	mCRPC pre chemo	mCRPC chemo	Post chemo mCRPC	End of life	In / decrement
ENZA mHSPC	0.806	0.723	0.706	0.688	0.457	
ERG*		0.72	0.63	0.53		
ABI mHSPC	AIC	AIC	AIC	AIC	AIC	-0.02 per year with DOC
ENZA PREVAIL	-	0.844	0.658	0.612	0.500	
ENZA AFFIRM	-	-	-	0.688		-0.085 for progression
ABI prechemo	-	0.830	0.692	0.700	0.500	ABI: +0.021
ABI post-chemo	-	-	-	AIC	0.500	

*Utility decrement suggested in the ERG report. <<<References to be added>>>

Issue 8: Cancer Drugs Fund	
Would additional data collection reduce the uncertainty?	Astellas acknowledges that OS data from ARCHES, to date, are not mature and this has created some uncertainty around the cost effectiveness outcomes. However, Astellas are expecting the final readout for OS in ARCHES as well as new readouts from ENZAMET toward the end of 2021. These data are expected to minimise uncertainty and ensure robustness of results.
Is the technology a good candidate for use in the	Astellas considers that enzalutamide would be a good candidate for use in the Cancer Drugs Fund, should it not be recommended for routine funding by NICE. Astellas strongly believes that the CDF will offer access to patients while additional data from ARCHES and ENZAMET are being collected and analysed, if not approved for baseline commissioning.

Cancer Drugs Fund?	For the above reasons, Astellas would like to collaborate with NICE and NHSE to ensure patients with mHSPC can get access to enzalutamide in a timely manner. There is evidence suggesting that outcomes for men with prostate cancer in the UK are poor compare to other countries: • The CONCORD-3 analysis published in The Lancet from the OECD countries ranks prostate cancer survival in the UK 16th out of the 27 countries[16] • The 2017 UK comparator report shows the UK performance on prostate cancer below the EU average[17] • The cancer comparator report in 2019 includes data on abiraterone and enzalutamide; the UK has the lowest uptake of either abiraterone or enzalutamide than any other wealthy EU country[18]. Astellas would like to emphasise on the importance of access to enzalutamide for patients as soon as possible will target the unmet medical need in the population of patients with mHSPC and enable the NHS to improve outcomes. Astellas would like to further highlight as well as in later stages of prostate cancer, enzalutamide now demonstrates significantly delay disease progression in both, ARCHES (radiographic) and ENZAMET (clinical) trials, and a significant OS benefit with early use of enzalutamide in ENZAMET.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Enzalutamide with androgen deprivation therapy for treating metastatic hormone-sensitive prostate cancer [ID1605]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **2 April 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- 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.
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- 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 replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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

Your name	**Sree Rodda**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**St.James Institute of Oncology**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Generalisability of clinical trial results	
1Are trial results from ARCHES generalisable to people seen in UK clinical practice?	**No , Although majority of patients (60%) recruited were European population , the number of patients recruited within UK were few. Practices could vary from UK to elsewhere and this difference could have an impact on treatment outcomes.**
Are trial results from ENZAMET generalisable to people seen in UK clinical practice?	**No, as majority of patients recruited in this trial are from Australia and New Zealand. The control arm within the trial used NSAA plus ADT which is not standard of care within UK.**
Is it acceptable to pool data from ARCHES and ENZAMET to estimate clinical efficacy of enzalutamide?	**Although both trials are aiming to estimate the efficacy of Enzalutamide in a metastatic Hormone sensitive setting. There are key differences between the trials . Control Arm in both trials are different, demographic and baseline characteristics of patients and primary end points are variable between the two trials. These differences may reduce the overall statistical power and may generate a spurious result and hence the pooled data should be interpreted with caution.**
Issue 2: Extrapolation of overall survival	
What proportion of people are still alive at year 10 after ADT treatment? Is 8% or 20% more plausible?	**8%**
What proportion of people are still alive at year 10 after enzalutamide plus ADT treatment? Is 36% or 15% more plausible?	**15%**
What proportion of people are still alive at year 20 after enzalutamide plus ADT treatment? Is 0% or 7% more plausible?	**0%**

Issue 3: Extrapolation of progression-free survival	
What is the proportion of people whose cancer has not progressed at year 5 after ADT treatment? Is 20% to 30% or 10% more plausible?	**20% to 30%**
What is the proportion of people whose cancer has not progressed at year 10 after ADT treatment? Is 10% or 2% more plausible?	**10%**
Issue 4: Extrapolation of time to treatment discontinuation	
Is it plausible to assume that PFS and time to treatment discontinuation are similar?	No
What are the reasons for stopping enzalutamide before disease progression? For example, do adverse events trigger early stopping?	Treatment could be discontinued for several reasons i.e poor tolerability of Enzalutamide due side effects or change in patients general health while they are progression free.
How many people would stop treatment early because of adverse events?	ARCHES trial : 7.2% vs 5.2% of patients in the experimental and standard arm stopped treatment due to adverse effects. ENZAMET Trial: 16.4% versus 3.9% of patients in the experimental and control arm stopped treatment due to Adverse events.
Issue 5: Similar long-term treatment effectiveness	
Is it plausible that treatment effects of ADT, docetaxel and enzalutamide plus ADT are similar after 8 years?	The overall survival data for Enzalutamide plus ADT is still immature and hence it's uncertain to estimate results at 8 Years. Based on STAMPEDE data there is no significant difference in overall survival between ADT alone (22%) versus Docetaxel plus ADT (23%)

Issue 6: Post-progression treatments	
Do the subsequent treatments in ARCHES and ENZAMET reflect NHS clinical practice?	ARCHES : Although majority of patients received Docetaxel on progression (standard practice in UK)13 patients received Abiraterone and 4 patients received Enzalutamide in the Enzalutamide plus ADT group . ENZAMET: Patients on progression in both arms received treatments not in line with UK practice such as Abiraterone, PARP inhibitors, Lutetium -177 PSMA, other chemotherapy apart from standard Docetaxel and Carbazetaxel, Immune check point inhibitors and Sipuleucel
Is it plausible to assume that subsequent treatment does not influence the long-term outcome?	No , as patients who did not receive Enzalutamide initially may get Enzalutamide /Abiraterone as part of subsequent therapies and patients who did received Enzalutamide initially will not be eligible for Enzalutamide as a subsequent therapy. Having more treatment options in patients who did not receive Enzalutamide initially might influence long-term outcome. This has to be taken into consideration when interpreting the results from both the studies.
Issue 7: Utility values	
Compared to the general population, what is the quality of life of people with metastatic prostate cancer after 1, 2, and 3 treatments post progression?	Compared to general population the quality of life score with metastaic prostate cancer generally declines with subsequent lines of therapies.
Issue 8: Cancer Drugs Fund	

Would additional data collection reduce the uncertainty?	Yes , we will have matured data from both trials with longer follow up particularly when analysing the overall survival benefit with Enzalutamide and ADT.
Is the technology a good candidate for use in the Cancer Drugs Fund?	Yes , patients can receive drug within CDF while waiting for the matured results of the study. It also allows us to collect additional data outside a clinical trial which is more representative of efficacy and toxicity of the drug in a real life setting.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Enzalutamide with androgen deprivation therapy for treating metastatic hormone-sensitive prostate cancer [ID1605]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **2 April 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- 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 replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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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)	Janssen-Cilag Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

Questions for engagement

Issue 1: Generalisability of clinical trial results	
1Are trial results from ARCHES generalisable to people seen in UK clinical practice?	Janssen believes that ARCHES is broadly generalisable to patients in the UK however 17 patients in the intervention arm received more than one novel therapy in their patient pathway which is not permitted within the NHS. Whilst eligibility for chemotherapy was not a pre-defined inclusion or exclusion criterion in ARCHES, Janssen agrees there is a significant proportion of patients with metastatic hormone-sensitive prostate cancer (mHSPC) who are not suitable for cytotoxic chemotherapy. Ineligibility for chemotherapy is multifactorial and extends beyond contraindications to docetaxel. It is ultimately a shared decision between the clinician and patient considering their co-morbidities, performance status, frailty, emotional state and social circumstances.
Are trial results from ENZAMET generalisable to people seen in UK clinical practice?	No comment
Is it acceptable to pool data from ARCHES and ENZAMET to estimate clinical efficacy of enzalutamide?	No comment
Issue 2: Extrapolation of overall survival	
What proportion of people are still alive at year 10 after ADT treatment? Is 8% or 20% more plausible?	No comment

What proportion of people are still alive at year 10 after enzalutamide plus ADT treatment? Is 36% or 15% more plausible?	No comment
What proportion of people are still alive at year 20 after enzalutamide plus ADT treatment? Is 0% or 7% more plausible?	No comment
Issue 3: Extrapolation of progression-free survival	
What is the proportion of people whose cancer has not progressed at year 5 after ADT treatment? Is 20% to 30% or 10% more plausible?	No comment
What is the proportion of people whose cancer has not progressed at year 10 after ADT treatment? Is 10% or 2% more plausible?	No comment
Issue 4: Extrapolation of time to treatment discontinuation	
Is it plausible to assume that PFS and time to treatment discontinuation are similar?	This relates to a treat-to-progression drug therapy, where most patients would continue treatment until disease progression. It is therefore plausible to assume that PFS and time to treatment discontinuation are similar.
What are the reasons for stopping enzalutamide before disease progression? For example, do adverse events trigger early stopping?	No comment
How many people would stop treatment early because of adverse events?	No comment
Issue 5: Similar long-term treatment effectiveness	

Is it plausible that treatment effects of ADT, docetaxel and enzalutamide plus ADT are similar after 8 years?	Janssen believe that it is not plausible to expect the treatment effects of these drug therapies to be similar after 8 years. On balance, novel hormonal therapies have consistently shown a maintenance of overall survival (OS) treatment effect when used to manage prostate cancer. In the phase 3 randomised controlled LATITUDE trial, durability of treatment effect was observed in the treatment of patients with newly diagnosed high risk mHSPC. After median follow-up of 51.8 months, abiraterone in combination with prednisolone or prednisone plus androgen deprivation therapy (ADT) demonstrated a statistically significant benefit over placebo plus ADT for overall survival HR, 0.66 (*P* <0.0001) (Fizazi 2019). Therefore, it is not appropriate to apply treatment effect waning to novel hormonal therapies. We acknowledge that the treatment under appraisal did not demonstrate statistically significant OS benefit in the pivotal ARCHES trial. However, it should be noted that this was due mainly to the limited follow-up duration prior to the initial trial readout. It is plausible that statistical significance would have been achieved with longer follow-up. **Reference** Fizazi, K. et. al. 2019. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. *The Lancet Oncology* 20(5) 686-700
Issue 6: Post-progression treatments	
Do the subsequent treatments in ARCHES and ENZAMET reflect NHS clinical practice?	Subsequent treatments in ARCHES do not reflect NHS clinical practice. Contrary to the NHS policy, which permits only one novel agent in the patient's treatment pathway, 17 patients in the trial's intervention arm received more than one novel agents. A determination cannot be made on the generalisability of subsequent treatments for ENZAMET due to the unavailability of relevant published data.
Is it plausible to assume that subsequent treatment does not influence the long-term outcome?	No comment

Issue 7: Utility values	
Compared to the general population, what is the quality of life of people with metastatic prostate cancer after 1, 2, and 3 treatments post progression?	No comment
Issue 8: Cancer Drugs Fund	
Would additional data collection reduce the uncertainty?	No comment
Is the technology a good candidate for use in the Cancer Drugs Fund?	No comment

Enzalutamide with ADT for treating metastatic hormone-sensitive prostate cancer [ID1605]

ERG comment on the company response to the technical engagement report

Produced by Aberdeen HTA Group

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Date completed 17 April, 2020

Contains AIC/CIC

In their response to the technical engagement report the company addressed each of the issues raised. This addendum to the ERG report provides a commentary on the company's response to each of these issues. It should be read in conjunction with the NICE Technical Engagement Report and company's technical engagement response document.

Issue 1: Generalisability of clinical trial results

Are trial results from ARCHES generalisable to people seen in UK clinical practice?

The ERG agrees that the patients enrolled in ARCHES were comparable with those with mHSPC eligible for ENZA+ADT in clinical practice in the UK.

The ERG notes that, compared with ARCHES, STAMPEDE included a lower proportion of participants with high-volume disease and a lower proportion of participants with Gleason score <8 (see Table 1 in the company's response to the technical engagement document).

The ERG appreciates that these differences might not impact on the overall outcomes; however, they are of the opinion that it is challenging to compare the treatment effects of these trials when there are differences in their baseline characteristics and establish how these characteristics may mitigate treatment effects.

Are trial results from ENZAMET generalisable to people seen in UK clinical practice?

The ERG agrees with the company that, compared with ARCHES and STAMPEDE, ENZAMET included a lower proportion of participants with high-volume disease and therefore the ENZAMET participants were likely to be less similar to those seen in clinical practice than ARCHES participants. Nevertheless, clinical advice received by the ERG was that clinical characteristics of the ENZAMET subgroup not receiving concomitant docetaxel were not clinically dissimilar to that of the broader patient population with mHSPC to which ENZA+ADT would be offered.

The ERG agrees that, in the ENZAMET participants not receiving concomitant docetaxel, clinical PFS and OS favoured ENZA+ADT compared with NSAA+ADT regardless of high or low volume of disease.

While the company acknowledge that ENZAMET is not generalisable to the UK population with regard to the inclusion of NSAA plus AST as comparator, they have decided to include it in the model because of the longer-term OS data it provides.

The ERG agrees that while, from a clinical evidence point of view, ENZAMET has some limitations, there is some justification in including it in the economic model. However, these limitations need to be emphasised.

Is it acceptable to pool data from ARCHES and ENZAMET to estimate clinical efficacy of enzalutamide?

The ERG is of the opinion that, in view of differences across ARCHES and ENZAMET in terms of comparator treatment (placebo plus ADT in ARCHES and NSAA plus ADT in ENZAMET), distribution of high and low volume disease patients and outcome definitions used for PFS (rPFS and ARCHES and cPFS in ENZAMET), pooling of data across the total

population of ARCHES and the patient subgroup with no concomitant docetaxel in ENZAMET is questionable and not recommended. However, the ERG understands the rationale for including the pooled results for overall survival in the economic model but believes some caution should be applied when interpreting this.

Issue 2 - Extrapolation of overall survival

What proportion of people are still alive at year 10 after ADT treatment? Is 8% or 20% more plausible?

The ERG agrees that the Weibull curve does provide a pessimistic prediction on 10-year OS for ADT, and that an ideal parametric curve would be somewhere between the extrapolated log-logistic and Weibull curves. However, such a parametric curve is not available, and the available parametric curves differ substantially in the predicted OS. Given these factors, the ERG agrees that the Weibull curve is the least worst of the available parametric curves. This point is particularly apparent when comparing 20-year ADT OS predictions (ERG report, Table 26). The Weibull curve predicts [redacted] 20-year OS for ADT, the equivalent figure using the log-logistic curve is [redacted] Extrapolated OS data from STAMPEDE (Woods et al., 2018) predicts 20-year OS for ADT at approximately 1%.

It should be noted that the extrapolation of STAMPEDE data in Woods et al. (2018) differs substantially to the company's extrapolation of STAMPEDE data (see Figure 1 of the company technical engagement response). For example, 20-year OS for ADT is 4.9% based on the company's extrapolation of STAMPEDE data compared to 1% in Woods et al. (2018). It is not clear how long this discrepancy persists as the company have not presented figures covering the full time horizon of the economic model. A summary of observed long-run STAMPEDE data for ADT and DOC is available in Table 28 of the ERG report.

What proportion of people are still alive at year 10 after enzalutamide plus ADT treatment? Is 36% or 15% more plausible?

The ERG agrees that the Gompertz curve does provide a pessimistic prediction of 10-year OS for ENZA. In this respect, the ERG's preferred parametric curves for OS are consistently cautious across all arms of the model, and minimise the absolute difference in comparison to observed OS data for ADT and DOC from STAMPEDE. Selecting the Weibull curve for ENZA and ADT OS carries the risk of overpredicting OS in this arm of the model while underpredicting for ADT and Docetaxel plus ADT.

As indicated in the ERG report, there are no ideal OS extrapolations for ENZA and ADT due to the observed data being immature. The available parametric extrapolations do not differ greatly during the observed data period, but differ substantially in the long-run predictions. As such, information criterion are of diminished value when selecting an appropriate parametric curve, as stated in the ERG report.

The ERG does not agree that the Gompertz curve provides implausible predictions for ENZA OS. The OS predictions are above those observed in data for DOC in STAMPEDE at 8.5 years (Clarke et al. 2019) and marginally above the extrapolated data for DOC in STAMPEDE at 10 years (Woods et al. 2018). Woods et al. (2018) predict 10-year OS for DOC at approximately 17.4%, which is comparable to the [redacted] OS for ENZA predicted by the Gompertz curve. Again it is notable that extrapolation in Woods et al. (2018) provide OS predictions below those based on the company's extrapolation of STAMPEDE data. Comparison of DOC and ENZA OS is valid since [redacted].

Based on the available evidence and the ERG's clinical expert opinion, the ERG's opinion is that 10-year ENZA OS may lie in the range of 15-20%. At the lower end of this range, ENZA OS would remain above ADT OS based on the company's preferred extrapolation of ARCHES data (7.8% 10-year OS for ADT) and the extrapolation of STAMPEDE data in Woods et al. (2018) (approximately 11.3% 10-year OS for ADT). At the high end of the ERG's stated range, the Gompertz curve may underpredict 10-year OS for ENZA by around 2%. Conversely, 10-year OS based on the Weibull curve is around 15% higher than the upper level of this range. Given the recognised underprediction of ADT OS, the ERG believe it is prudent to apply a conservative approach to ENZA OS. Such an approach is not detrimental to the internal and external validity of the model.

As stated in Table 29 of the ERG report, using the HRs from the NMA gives a prediction of [redacted] for ENZA OS at 10-years. This broadly supports the ERG opinion of the expected range for 10-year ENZA OS. The NMA also provides a valid alternative to the use of parametric curves, especially given the wide variation between predictions based on these curves.

What proportion of people are still alive at year 20 after enzalutamide plus ADT treatment? Is 0% or 7% more plausible?

Given the age and health status of this patient group, the ERG believes the 20-year OS for ENZA should be towards the lower end of this range. Extrapolations from STAMPEDE in Woods et al. (2018) indicate a figure of approximately 2.5% for DOC, which in combination with the [redacted] for ENZA in the NMA, would support using the lower end of the range.

The company raise the issue that the Gompertz curve for ENZA crosses the equivalent curve for DOC. The ERG report identified this issue and applied a correction to ENZA OS from 10 years onwards (Scenarios 2 and 4 in Table 34). In Scenario 2a in Table 35 the correction is made from 8 years onwards. However, the correction was not applied in Scenario 2 in Table 35 of the ERG report. Had this correction been made the ICERs would be £44,193 vs ADT and £73,904 vs DOC (detailed in Table below).

The ERG recognises that the preferred parametric fits may marginally underpredict 20-year ENZA OS. However, as outlined above, the ERG believe that alternative combinations of parametric curves may overestimate the absolute difference between the OS curves of the comparator arms and the OS curve of the ENZA arm.

Use of the NMA provides a valid alternative to selecting multiple parametric curves. Both the ERG and the company agree that the Weibull is the most appropriate available parametric reference curve for ADT OS. The company suggest a scenario using the log-logistic curve as the reference curve for ADT in the NMA based analysis, with the stated intention of generating more optimistic outcomes. The ERG does not believe that this provides a valid justification for the scenario. Furthermore, given the company's arguments in favour of the Weibull curve for ADT OS and arguments against the log-logistic curve, and the ERG's report supporting the use of the Weibull curve, this does not appear to be credible scenario.

Issue 3 Extrapolation of PFS

What is the proportion of people whose cancer has not progressed at year 5 after ADT treatment? Is 20% to 30% or 10% more plausible?

Clarke et al. (2019) distinguishes failure-free survival (time from randomisation to the first of any: biochemical, lymph node, distant metastatic progression or prostate cancer death) and progression-free survival (time from randomisation to the first FFS event, not including biochemical progression). By definition, FFS will be less than or equal to PFS. The ERG accepts that both measures provide relevant data.

The company note that 5-year PFS for ADT in STAMPEDE was approximately 25%. They further note on Page 15 of their response that the Kaplan-Maier PFS data from ARCHES was below the PFS data from STAMPEDE, and provide a hazard ratio of 0.71 (95% CI: 0.63-0.81) for this comparison. Based on this they expect 5-year PFS in ARCHES to be around 20%. The ERG is not clear on how exactly the HR or the 20% prediction was derived. Assuming the HR provided by the company is correct, a crude estimate of 5-year PFS for ADT based on the HR of 0.71 would be approximately 14% (=0.25^(1/0.71)) (ranging from 11% to 18% based on the confidence interval of the HR provided). This would be broadly compatible with the prediction provided by the exponential extrapolation for ADT PFS ([redacted]), as suggested in the ERG report and investigated in Scenario 6 in Table 34, although the exponential curve may be pessimistic. The exponential extrapolation remains compatible with longer term outcomes for all treatment arms.

What is the proportion of people whose cancer has not progressed at year 10 after ADT treatment? Is 10% or 2% more plausible?

The ERG agrees that the exponential curve is appropriate extrapolation of ADT PFS, despite the exponential curves predicting 10-year ADT PFS ([redacted] which is pessimistic compared to the extrapolated STAMPEDE data for ADT PFS ([redacted] Company TE response Figure 5).

Consistent with the pessimistic prediction for ADT PFS, the ERG also recognises that the log-logistic curve for ENZA PFS provides pessimistic predictions ([redacted] ERG report Table 22) compared to extrapolated STAMPEDE data for DOC PFS ([redacted] Company TE response Figure 6). The ERG maintains that the log-logistic curve provides a plausible scenario since it preserves an approximately equal level of underprediction on all arms of the model.

The log-normal curve may provide predictions which more closely aligned with the extrapolated STAMPEDE data for DOC PFS (Company TE response Figure 6). However, this curve would increase the PFS gain compared to the pessimistic ADT PFS prediction. If log-normal curve was to be used for ENZA PFS, it would be prudent to select the generalised gamma curve for ADT PFS as this is the only alternative parametric curve which is also valid at earlier time points. The ERG did not select the generalised gamma curve since this would result in OS being equal to PFS from approximately [redacted] onwards, which appears implausible. The absence of valid alternative parametric curves for ADT OS meant that this feature could not be corrected by combinations of curves.

The range of predictions provided by the parametric curves in the cost effectiveness model makes the selection of appropriate curves challenging. More mature data may shorten the range of predictions. In the absence of such data, the NMA provides a plausible alternative between parametric curves. Use of the NMA still requires OS and PFS curves for ADT to be selected, such that they can be used as a reference for HRs applied to predict other arms of the model. The ERG notes that the company agrees with the recommendation in the ERG report regarding reference curves for OS and PFS in an NMA-based cost effectiveness analysis.

Table 1 ERG preferred parametric base case with correction to stop enzalutamide OS crossing ADT and Docetaxel OS

No.	Description	Enzalutamide			ADT				Docetaxel			
		Costs	QALY	LYG	Costs	QALY	LYG	ICER vs ADT	Costs	QALY	LYG	ICER vs DOC
2	ERG preferred parametric base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£44,193	[redacted]	[redacted]	[redacted]	£73,904

Issue 4 – Extrapolation of time on treatment

The company have provided further justification for time to treatment discontinuation (TTD) being shorter than PFS. They provide information on the proportion of discontinuations that were for reasons other than progression in ENZAMET and ARCHES –being 15.2% and 12.2% respectively. They further note that adverse events and consent withdrawal were the main reasons for discontinuation after disease progression (Company response, Table 4).

The ERG acknowledge that some patients will discontinue enzalutamide prior to progression in clinical practice as a result of adverse events. However, based on the ERGs clinical advice the ERG believes that the TTD curve should track very closely to the rPFS curve in clinical practice. The ERG was therefore concerned that the company base case resulted in TTD diverging quite substantially from rPFS, resulting in an increasing proportion of progression free patients in the enzalutamide plus ADT arm being off-treatment (no costs of enzalutamide). For the above reasons, the ERG preferred the more conservative log-logistic extrapolation of TTD in scenarios that used independently fitted parametric curves for enzalutamide. The log-logistic curve falls slightly below the company's base case rPFS curve but starts to converge with it from about 4 years and is set equal to it from 7.5 years to stop it crossing. Thus, with this curve selection those who remain progression free in the long-term remain on treatment.

Issue 5 - Similar long-term effectiveness

In their report, the ERG explored scenarios that equalised the hazard of mortality from 8 years, resulting in convergence of the OS curves for enzalutamide plus ADT, and docetaxel plus ADT, with the OS curve for ADT alone.

The Company acknowledge in their response to the TE report that convergence was observed between docetaxel plus ADT and ADT alone in the STAMPEDE trial (Clarke et al. 2019), but note that it was not observed in GETUG trial which also included long-term follow-up for the this treatment comparison (Gravis et al. 2016). However, the ERG note that a similar pattern was observed in the CHAARTED trial (Kyriakopoulos et al.), with OS Kaplan-Maier curves for ADT and docetaxel plus ADT converging shortly after 72 months.

The company outline several arguments in their response for why they believe it is not plausible to assume that the OS treatment effect of ADT, docetaxel plus ADT, and enzalutamide plus ADT are equalised after 8 years. These include a lack of available evidence to support it for enzalutamide plus ADT, and the fact that extrapolated curves based on application of NMA hazard ratios for enzalutamide plus ADT, applied to ADT reference curve, do not result in the curves converging until 15 years.

The ERG acknowledges that the lack of long-term data for enzalutamide plus ADT mean that scenarios that equalise the hazrd of mortality to the ADT arm are exploratory in nature. However, the ERG do not believe that the lack of convergence in extrapolated curves based on application of a proportional hazards assumption, or independent fitting, is a valid reason for rejecting the possibility of OS convergence from an earlier time point. Thus, the ERG still

believes that their scenarios exploring convergence from 8 years are informative for assessing the impact of uncertainties in the long-term extrapolation.

Issue 6 – Post-progression treatments

The ERG recognises the issues the company faced in handling RCT data on subsequent treatments that are not typical of 'usual care' in the NHS in England. If they had not costed subsequent treatments in line with NHS practice in the model they would have been criticised, but there is no simple way to adjust the RCT efficacy data to reflect this. The Technical Team rightly pointed out the company assumed the changes they made to the subsequent treatment mix would have no important impact on efficacy.

The company response offers several pieces of evidence to support their submission, first citing analyses of the TITAN RCT of apalutamide and then presenting further data on the ARCHES and ENZAMET RCTs. We will comment on the latter first.

The company showed more data from ARCHES and ENZAMET. Relating to ARCHES the company response shows that only 3% of patients allocated to enzalutamide went on to have a subsequent treatment that is not available in the NHS in England – but this misses the point of the criticism which is that it is assumptions about the comparator arm that matters. From the data presented in Table 5 of the company's response, only 56 patients received subsequent treatment with abiraterone or enzalutamide after ADT alone (plus placebo), roughly 10% of the ITT population allocated to this treatment arm. The exact percentage of progressed patients who received these treatments was not clear, but placebo discontinuation for progressive disease was reported to be 171 in appendix D1.2 of the CS, and so approximately 33% of progressed patients may have done so. Comparing this to Table 14 of the Technical Report prior to consultation, clinicians in the NHS in England estimated the rate of use of these medicines in usual practice would be 70% of progressed patients. We know these medicines are effective (i.e. make a difference to PFS and to OS) because they have been previously reviewed and recommended for use by NICE with NHS England acting on their advice. Therefore, a two-fold higher use of effective subsequent treatments in the comparator arm of the RCT may have reduced the difference in effectiveness in ARCHES. With respect to ENZAMET, the distribution of subsequent therapies, among those in NSAA+ADT arm receiving them, looked reasonably in keeping with NHS practice. However, the exact proportion of progressed patients observed to receive subsequent therapy was not clear from the data presented. NSAA+ADT treatment discontinuation for clinical progression in ENZAMET was reported to be 244 (CS, appendix D1.2), and only 135 patients were reported to have had a subsequent therapy in Table 6 of the company's response the technical engagement report.

The company also quoted ASCO GU (2020), which is a post hoc analysis of PFS2 (that is PFS on the subsequent line of treatment) in the TITAN RCT of apalutamide plus ADT versus placebo plus ADT. They report that this favoured the apalutamide arm, irrespective of subsequent treatments. However, the statistical results presented in ASCO GU (2020) are based on the ITT population of the TITAN RCT (n=1052) whereas the more relevant

comparison for the current STA would have focused on the 227 receiving systemic therapy or the 187 who received a hormonal or taxane based subsequent treatment. This would have given a specific indication of PFS for subsequent treatment whereas the ITT based comparison still includes PFS1, and hence it is not possible to draw any conclusions about subsequent treatments.

Apart from being a post hoc analysis, patients were selected for subsequent treatments based on disease and personal characteristics and preferences, so the treatment assignment is a potential source of bias. Also, evidence from apalutamide studies may be relevant to enzalutamide, but this was not proven.

Issue 7 – Utility values

The ERG is content that the company agree to the changes proposed.

Having agreed to this, the company then provide additional evidence from ENZAMET to support their values in the submission. It is not clear how data from the studies has been analysed and how missing data were handled. For example, of a cohort of patients undergoing treatment it could be that only those who are feeling ok complete the EQ-5D thus under-representing those who are feeling poorly.

Reviewing TA377 (enzalutamide for use at a place in the treatment pathway that would be labelled PD1 in the current submission), the ERG note in paragraph 4.4:

A patient expert stated that he is currently taking enzalutamide, having previously had docetaxel. He said that he had experienced very few side effects with enzalutamide and is able to live an active life, whereas docetaxel had profoundly and negatively affected his quality of life.

The ERG interpret this as suggesting quality of life declines substantially when switching to docetaxel (which would be used at PD2 in terms of the pathway for the current submission) and hence a decrement of 0.093 is reasonable.

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Amsterdam, 25 March 2021
EMA/CHMP/169061/2021
Committee for Medicinal Products for Human use (CHMP)
EMEA/H/C/002639/II/0047/G

Opinion of the committee for medicinal products for human use on a type II variation to the terms of the marketing authorisation

Medicinal product:	**International non-proprietary name/Common name:**	**Presentations:**
Xtandi	enzalutamide	See Annex A

Basis for opinion

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Astellas Pharma Europe B.V. submitted to the European Medicines Agency on 1 July 2019 an application for a group of variations consisting of Type II variations for the above medicinal product

The procedure started on 20 July 2019.

The steps taken for the assessment of the above mentioned medicinal product are detailed in the appended assessment report.

Opinion

1. The CHMP, having considered the application as set out in the appended variation assessment report, recommends by consensus the variation(s) to the terms of the marketing authorisation, concerning the following change(s):

Variation(s) requested		**Type**	**Annex(es) affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II	I and IIIB
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II	I

C.1.6: Extension of Indication to include the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) for Xtandi in combination with androgen deprivation therapy based on the data of study 9785-CL-0335 (ARCHES).As a consequence, sections 4.1, 4.2, 5.1 and 6.6 of the SmPC are updated. Furthermore the MAH took the opportunity to make corrections to section 4.7. The Package Leaflet is updated in accordance.
The RMP version 13.0 is approved.

C.1.4: Update of section 5.1 of the SmPC based the 5-year Overall Survival (OS) results obtained from the PREVAIL study (MDV310003), a phase 3 study of enzalutamide in chemotherapy naïve patients with metastatic prostate cancer that progressed on ADT.

The Icelandic and the Norwegian CHMP members agree with the above-mentioned recommendation of the CHMP on variations to the terms of the marketing authorisation

2. The revised annexes I and IIIB are included in this opinion.

   Annexes included in this opinion for Xtandi, also include changes that have been introduced via procedures listed in the appended line-listing(s), which have not yet been included in an updated respective Commission decision.

In accordance with Article 16(4) of Commission Regulation (EC) No. 1234/2008 the marketing authorisation holder has the right to request a re-examination of this opinion within 15 days of receipt of the opinion by giving written notice to the Agency. Detailed grounds for the re-examination request must be sent to the Agency within 60 days of receipt of the opinion.

This opinion is forwarded to the European Commission, to the Member States, to Iceland and Norway and to the marketing authorisation holder, together with its full set of annexes and appendix(ces).

The European Commission shall adopt a decision within 2 months in accordance with the procedure laid down in Article 23(1a)(a) of Commission Regulation (EC) No. 1234/2008.

Annex A

MA (EU) number	(Invented) name	Strength	Pharmaceutical Form	Route of Administration	Immediate Packaging	Pack size
EU/1/13/846/001	Xtandi	40 mg	Capsule, soft	Oral use	blister (PVC/PCTFE/alu)	112 capsules
EU/1/13/846/002	Xtandi	40 mg	Film-coated tablet	Oral use	blister (PVC/PCTFE/alu)	112 tablets
EU/1/13/846/003	Xtandi	80 mg	Film-coated tablet	Oral use	blister (PVC/PCTFE/alu)	56 tablets

Enzalutamide with ADT for treating metastatic hormone-sensitive prostate cancer [ID1605]

Confidential ICERs for the company's revised PAS

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Date completed 06/04/21

Contains [redacted]

This document produces the ERGs preferred based case and the scenario which equalised OS from 8 years, using the new PAS discount ([redacted]) for enzalutamide in the mHSPC setting. The discount remains at [redacted] in the progressed states of the model. The analysis also applies the available PAS discounts on other subsequent therapies included in the modelled pathways: abiraterone, radium-223, and cabazitaxel. The discounts on subsequent therapies are as follows: Abiraterone ([redacted]); R-223 ([redacted]) per 6 x6ml vials; and cabazitaxel ([redacted]), assuming that the price per vial [redacted].

It should be noted that abiraterone has a commercial access agreement (CAA) when used before docetaxel in the metastatic hormone resistant setting. This is assumed to be at the point of first progressive disease (PD1) in the company's model. [redacted]. [redacted] in the context of the company's partitioned survival model, the ERG followed the company's alternative Markov approach to approximate the incidence of progression to PD1 in each model cycle, and then applied the total expected cost of abiraterone treatment (discounted at 3.5%) to the relevant proportion of newly progressed patients in each model cycle. To calculate the total expected cost of abiraterone treatment, the ERG used the company's assumed exponential distribution of time to treatment discontinuation (median [redacted] months), and [redacted]).

Application of the fixed cost, without the [redacted], was checked against the base case ICER, and was noted to result in a small reduction in the ICERs for enzalutamide versus ADT and docetaxel. Thus, application of the fixed cost does not appear to bias against enzalutamide [redacted]. However, there is uncertainty associated with the application of fixed, capped treatment costs in the context of a partitioned survival model, as such models to not naturally capture transitions through progressive disease states or the times individuals spend on subsequent therapies (potential to underestimate proportion receiving treatment in PD1). Therefore, the

ERG has also provided the two requested scenarios with removal of the CAA for abiraterone (applying only the PAS discounts) to illustrate the impact of the treatment cap on the ICERs. Since the company's model may not accurately capture the proportions making the transition to progressive disease, it may underestimate the proportion of time spent in the PD1 state and the associated treatment costs which are higher in the ADT and docetaxel arms (potential to bias against enzalutamide). It is further worth noting that the ICERs are potentially conservative in that application of the NMA HRs in the company model do not allow for time on treatment with enzalutamide to fall below rPFS, and some patients may discontinue prior to progression.

Table A1 ERG's preferred scenarios – including PAS discounts on subsequent therapies (end of life QALY decrement correction)

No.	Description	Enzalutamide			ADT				Docetaxel			
		Costs	QALY*	LYG	Costs	QALY*	LYG	ICER vs ADT	Costs	QALY*	LYG	ICER vs DOC
Previous enzalutamide mHSPC PAS discount ([redacted]), plus PAS discounts on subsequent therapies and CAA for abiraterone												
1	ERG preferred NMA base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1a	ERG NMA base case with convergence of treatment efficacy from 8 years for OS only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
New enzalutamide mHSPC PAS discount ([redacted]), plus PAS discounts subsequent therapies and CAA for abiraterone												
1	ERG preferred NMA base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1a	ERG NMA base case with convergence of treatment efficacy from 8 years for OS only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
New enzalutamide mHSPC PAS discount ([redacted]), plus PAS discounts on subsequent therapies and removal of CAA for abiraterone												
1	ERG preferred NMA base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1a	ERG NMA base case with convergence of treatment efficacy from 8 years for OS only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Note the very small changes in QALYs from the previous appendix. This is due to the correction of minor bug in the model calculations of the end-of-life QALY decrement: Column DB in the "PartSA ADT", PartSA Enza" and "PartSADoce" worksheets – fixed reference to the switch for aggregating PD1-3 utility in end-of-life QALY decrement calculation.

Table A2 ERG base case (probabilistic sensitivity analysis)

No.	Description	Enzalutamide		ADT			Docetaxel		
		Costs	QALY	Costs	QALY	ICER vs ADT	Costs	QALY	ICER vs DOC
New enzalutamide mHSPC PAS discount ([redacted]), plus PAS discounts subsequent therapies and CAA for abiraterone*									
1	ERG preferred NMA base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
New enzalutamide mHSPC PAS discount ([redacted]), plus PAS discounts on subsequent therapies and removal of CAA for abiraterone									
1	ERG preferred NMA base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Caveat, it has not been possible to build a distribution for the fixed cost of abiraterone with duration cap into the probabilistic analysis.

The scatter-plots and acceptability curves corresponding to the ERG base case with cPAS discounts and CAA for abiraterone applied are provided below.