CONFIDENTIAL UNTIL PUBLISHED

Evidence Review Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Apalutamide for treating prostate cancer

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
Authors	Keith Cooper, Senior Research Fellow, Health Economics. Irina Tikhonova, Senior Research Fellow in Health Technology Assessment & Modelling. Lois Woods, Senior Research Assistant, Evidence Synthesis. Lorna Hazel, Senior Research Assistant, Evidence Synthesis. Inês Souto Ribeiro, Senior Research Assistant, Health Economics. Jo Picot, Senior Research Fellow, Evidence Synthesis. David Scott, Principal Research Fellow, Statistics. Jonathan Shepherd, Principal Research Fellow, Evidence Synthesis.
Correspondence to	Dr Jonathan Shepherd Southampton Health Technology Assessments Centre (SHTAC) Wessex Institute Alpha House Enterprise Road, University of Southampton Science Park Southampton SO16 7NS www.southampton.ac.uk/shtac
Date completed	08/10/2020 (post-factual accuracy check corrected version)

Source of Funding: This report was commissioned by the National Institute for Health Research (NIHR) Systematic Reviews Programme as project number 131879.

Acknowledgements

We are grateful to the following for providing expert clinical advice for this report:

- Dr Deborah Enting, Consultant Medical Oncologist, Guy's and St Thomas' NHS Foundation Trust, London, UK.
- Professor Nick James, Professor of Prostate and Bladder Cancer Research, Institute for Cancer Research and The Royal Marsden Hospital (NHS Foundation Trust), London, UK.

We would also like to thank Professor Joanne Lord, SHTAC, for providing a quality assurance review of the draft ERG report.

Declared competing interests of the authors and advisors

- The authors report none.
- Dr Enting reports receiving speakers' fees from AstraZeneca within the last 12 months, unrelated to apalutamide.
- Professor James reports receiving consulting fees, advisory boards and lecture fees (none >£2000) in the previous 12 months from the following companies associated with this appraisal: Astellas Pharma, AstraZeneca UK, Bayer, Janssen (NB. unrelated to apalutamide), Orion Pharma UK, and Sanofi.

Rider on responsibility for report

The view expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Cooper, K; Tikhonova I; Woods, L; Hazel, L; Souto Ribeiro, I; Picot, J; Scott, D; Shepherd, J. Apalutamide for treating prostate cancer - A Single Technology Appraisal. Southampton Health Technology Assessments Centre, 2020.

Contributions of authors

Keith Cooper critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Irina Tikhonova critically appraised the health economic systematic review, critically appraised the economic evaluation and drafted the report; Lois Woods critically appraised the clinical effectiveness systematic review, conducted bibliographic searches, and drafted the report; Lorna Hazel critically appraised the clinical effectiveness systematic review, and drafted the report; Inês Souto Ribeiro critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Jo Picot critically appraised the clinical effectiveness systematic review, and drafted the report; David Scott critically appraised the clinical effectiveness systematic review and drafted the report; Jonathan Shepherd critically appraised the clinical effectiveness systematic review, drafted the report and is the project guarantor.

Table of Contents

LIST OF TABLES

LIST of FIGURES

LIST OF ABBREVIATIONS

1L	First line
2L	Second line
3L	Third line
AAP	Abiraterone
ADT	Androgen deprivation therapy
AE	Adverse event
AIC	Academic in confidence
APA	Apalutamide plus ADT
BNF	British National Formulary
BSC	Best supportive care
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CIC	Commercial in confidence
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
DOX	Docetaxel plus ADT
DSU	Decision Support Unit
EGP	Economic Guidance Panel
EMA	European Medicines Agency
EMC	Electronic Medicines Compendium
ENZA	Enzalutamide
EPAR	European Public Assessment Report
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
EQ-VAS	EuroQol Visual Analogue Scale
ERG	Evidence Review Group
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio

Incr	Incremental
IPD	Individual patient level data
ITT	Intent to treat
KM	Kaplan Meier
LY	Life-years
LYG	Life-years gain
mCSPC	Metastatic castration sensitive prostate cancer
MFS	Metastasis-free survival
mHRPC	Metastatic hormone relapsed prostate cancer
mHSPC	Metastatic hormone sensitive prostate cancer
mITT	Modified intent to treat
MP	Mitoxantrone plus prednisolone
MRU	Medical resource use
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
nmCRPC	Non metastatic castration relapsed prostate cancer
nmHRPC	Non metastatic hormone relapsed prostate cancer
NR	Not reported
OS	Overall survival
PartSA	Partitioned survival analysis
PAS	Patient Access Scheme
PSA	Prostate specific antigen
PFS	Progression free survival
PFS2	Secondary progression free survival
PP	Prednisolone plus placebo
PSS	Personal Social Services
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
rPFS	Radiographic progression free survival
RPFSTM	Rank Preserving Structural Failure Time Model
RR	Relative risk/risk ratio
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error

SLR	Systematic literature review
SmPC	Summary of product characteristics
SPARTAN	Selective Prostate AR Targeting with ARN-509
STA	Single Technology Appraisal
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TITAN	Targeted Investigational Treatment Analysis of Novel Anti-androgen
TSD	Technical Support Document
TTD	Time to treatment discontinuation
UK	United Kingdom
US	United States
VAS	Visual analogue scale

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, health technology, evidence and information on the issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the ERG's key issues

Table 1 Summary of key issues

Issue number	Summary of issue	Report sections
1	Selection of methods to adjust for treatment switching in the pivotal apalutamide clinical trials	3.2.2 (Risk of bias), 3.2.4 (Trial statistical methods), 4.2.6, 4.2.7 and 4.2.8 (Treatment effectiveness extrapolation methods).
2	Clinical and cost effectiveness of apalutamide in people with mHSPC who are ineligible or unsuitable for docetaxel chemotherapy	2.3 (Critique of the company's definition of the decision problem), 3.2.6.6 (Subgroup analyses), 4.2.3 (Economic model population)
3	Extrapolation of metastatic free survival / radiographic progression free survival	4.2.7 (Treatment effectiveness and extrapolation)
4	Utility values for second and third line metastatic hormone relapsed prostate cancer (mHRPC) health states	4.2.10 (Health related quality of life)
5	Market share of subsequent therapies used metastatic hormone relapsed prostate cancer (mHRPC)	4.2.11 (Resources and costs)
6	Duration of treatment costs for adverse events associated with docetaxel	4.2.11 (Resources and costs)

Of the key issues in Table 1, there are differences between the company's preferred and the ERG's preferred assumptions for the following parameters:

- The utility values for second and third line mHRPC health states were adjusted by first line mHRPC utility in the company's base case, but were not adjusted in the ERG's preferred base case.
- The costs of treating adverse events associated with docetaxel were applied for the whole of the mHSPC health state in the company's base case, but only for six months in the ERG's preferred base case.

The assumptions related to the remaining key issues were not changed in the ERG's preferred base case.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Table 2 and Table 3 report the base case results for apalutamide in the nmHRPC and the mHSPC indications, respectively, based on the Patient Access Scheme (PAS) discount price for apalutamide. The results show that apalutamide plus ADT dominates ADT alone for nmHRPC. For mHSPC, the ICER for apalutamide plus ADT versus ADT alone is £25,329 per QALY and versus docetaxel plus ADT is £38,983 per QALY.

Table 2 Company's base case results for nmHRPC (discounted, PAS price for apalutamide)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£/QALY)
ADT alone	[redacted]	5.03	[redacted]				
Apalutamide plus ADT	[redacted]	5.70	[redacted]	[redacted]	0.67	[redacted]	Dominates

Source: reproduced from CS Table 85.
ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gain; QALYs: quality-adjusted life years.

Table 3 Company's base case fully incremental results for mHSPC (discounted, PAS price for apalutamide)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£/QALY)	ICER (£/ QALY): APA vs. ADT
ADT alone	[redacted]	4.588	[redacted]					
Docetaxel plus ADT	[redacted]	5.501	[redacted]	[redacted]	0.913	[redacted]	9,633	
Apalutamide plus ADT	[redacted]	6.023	[redacted]	[redacted]	0.523	[redacted]	38,983	25,329

Source: reproduced from CS Table 88 and CS Table 89.
ADT: androgen deprivation therapy; APA: apalutamide plus ADT; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gain; QALYs: quality-adjusted life years.

The model results were most sensitive to the following scenario analysis parameters: selection of survival curves to extrapolate PFS; the method for the transition of patients between first and second line mHRPC health states; and the source of subsequent therapy market shares.

1.3 The decision problem: summary of the ERG's key issues

The ERG has not identified any key issues relating to the decision problem. However, please refer to Issue 2 (Clinical and cost effectiveness of apalutamide in people with mHSPC who are ineligible or unsuitable for docetaxel chemotherapy) where we discuss the implications of for the assessment of clinical effectiveness and cost effectiveness of the company's inclusion in the decision problem of a subgroup of people ineligible or unsuitable for docetaxel chemotherapy.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

Issue 1 Selection of methods to adjust for treatment switching in the pivotal apalutamide clinical trials (nmHRPC and mHSPC)

Report section(s)	3.2.2 Risk of bias; 3.2.4 Trial statistical methods; 4.2.6, 4.2.7 and 4.2.8 Treatment effectiveness extrapolation methods.
Description of issue and why the ERG has identified it as important	There is uncertainty about the company's selection of the method to adjust survival outcomes to account for the effect of patients switching between treatments in the phase III pivotal clinical trials (SPARTAN and TITAN). Adjustment was required because of: • Patient crossover in the SPARTAN trial from placebo to apalutamide, and the potential bias from this on treatment effects in the intention to treat (ITT) analysis. • Current NHS England commissioning policy which restricts use of novel agents (apalutamide, abiraterone and enzalutamide) to once per patient. This meant adjusting the configuration of subsequent treatments used by patients in the multi-national SPARTAN and TITAN trials to reflect the subsequent treatments that would be available on the NHS (i.e. only one novel therapy during a patient's cancer treatment). A range of available adjustment methods for treatment switching were considered for their appropriateness to the available trial data and a justification given for the inclusion/exclusion of each. The company selected a (currently unpublished) 'modified' version of the Rank Preserving Structure Failure Time Model (RPSFTM) which uses external clinical trial data to adjust survival estimates. This approach avoids assumptions that conflict with the SPARTAN data. However, not all of its assumptions appear to be valid and the ERG is unable to independently verify the approach used.
What alternative approach has the ERG suggested?	The company declined the ERG's request to provide cost effectiveness scenario analyses based on the alternative adjustment methods for treatment switching, explaining that they give counter-intuitive / clinically implausible results, and because of insufficient trial data to satisfy assumptions. The ERG does not have access to the necessary patient level data to replicate these analyses.
What is the expected effect on the cost-effectiveness estimates?	Uncertain at present. Some of the assumptions of the modified RPSFTM approach may underestimate the cost effectiveness of apalutamide, whilst others potentially may over-estimate its cost effectiveness.
What additional evidence or analyses might help to resolve this key issue?	Treatment effect estimates can vary widely according to the adjustment methods chosen (and the assumptions therein). Cost effectiveness scenario analyses based on the alternative adjustment methods would indicate whether the ICERs are sensitive to different assumptions about

	treatment switching and allow a fully-informed committee consideration of the available evidence.

Issue 2 Clinical and cost effectiveness of apalutamide in people with mHSPC who are ineligible or unsuitable for docetaxel chemotherapy

Report section(s)	2.3 Critique of the decision problem; 3.2.5.6 Subgroup analysis; and 4.2.3 Economic model population.
Description of issue and why the ERG has identified it as important	The decision problem specifies a sub-group of mHSPC patients 'ineligible or unsuitable for chemotherapy'. An explicit definition of this subgroup is not given. A wide variety of patient factors can inform decisions about a given patient's suitability to tolerate the adverse effects of docetaxel. Cost-effectiveness estimates are presented separately for mHSPC patients who are: • Eligible/suitable for docetaxel (apalutamide plus ADT versus docetaxel plus ADT) and • Ineligible/unsuitable for docetaxel (apalutamide plus ADT versus ADT). There are no subgroup analyses in the pivotal TITAN trial based on docetaxel eligibility/suitability. Rather, clinical effectiveness estimates for docetaxel ineligible/unsuitable (apalutamide and ADT) are based on the whole trial population of the TITAN trial. A small proportion of patients in TITAN were/had been eligible to receive docetaxel, but it is unclear which characteristics could be used to reliably identify a group of patients considered ineligible/unsuitable to receive docetaxel. It is therefore uncertain whether the implicit assumption that the results of TITAN can be applied to patients ineligible to take docetaxel is valid.
What alternative approach has the ERG suggested?	Expert clinical opinion should be sought on the feasibility of identifying a sub-group of patients in TITAN with baseline characteristics indicative of docetaxel suitability/eligibility. If feasible, their survival outcomes could inform a post hoc subgroup analysis of clinical and cost effectiveness of apalutamide plus ADT versus ADT in patients considered ineligible/unsuitable for docetaxel treatment. Given the uncertainty regarding docetaxel eligibility/suitability criteria, and the statistical limitations of a post hoc subgroup analysis, this should be an exploratory scenario analysis.
What is the expected effect on the cost-effectiveness estimates?	Uncertain at present.
What additional evidence or analyses might help to resolve this key issue?	As stated above.

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

Issue 3 Extrapolation of survival curves: metastatic free survival (MFS) for nmHRPC, and radiographic progression free survival (rPFS) for mHSPC

Report section(s)	4.2.7 Treatment effectiveness and extrapolation
Description of issue and why the ERG has identified it as important	The company's scenario analyses show that the choice of survival extrapolation for MFS/rPFS has a large impact on model results. There is some uncertainty about the most appropriate model survival curve, particularly for nmHRPC where there are no other clinical trials available with longer follow-up than the company's SPARTAN trial.
What alternative approach has the ERG suggested?	On the available evidence and advice from our clinical experts, we agree with the company's choice of the Weibull distribution for modelling MFS/rPFS.
What is the expected effect on the cost-effectiveness estimates?	In the company's analyses for nmHRPC, the ICER for apalutamide + ADT vs ADT varies from dominant (apalutamide cheaper and more effective) to £2,602 per QALY based on the log-normal distribution. For mHSPC, the ICER for apalutamide + ADT vs ADT varies from £25,329 per QALY to £40,355 per QALY, and vs docetaxel + ADT it varies from £38,983 per QALY to £68,613 per QALY (based on the exponential distribution).
What additional evidence or analyses might help to resolve this key issue?	Advice from clinical experts on the most clinically plausible extrapolation distributions for MFS/rPFS.

Issue 4 Utility values for second and third line metastatic hormone relapsed prostate cancer (mHRPC) health states

Report section(s)	4.2.10 Health related quality of life
Description of issue and why the ERG has identified it as important	Utility values were not assessed in the company's pivotal trials for patients who had progressed to the second and third-line of the mHRPC health state. The company based their values for second and third-line utility on those used in NICE TA387 (Abiraterone for mHRPC not previously treated with chemotherapy) and adjusted these values by applying a relative decline ratio to the utility for first-line mHRPC utility from TA387.
What alternative approach has the ERG suggested?	The ERG suggests that values from TA387 should be used without adjustment. We also suggest that scenario analyses should be conducted using utility values from other previous NICE appraisals, including NICE TA377 (Enzalutamide for mHRPC before chemotherapy is indicated) and NICE TA580 (Enzalutamide for nmHRPC) to estimate potential variability in cost-effectiveness based on a range of utility sources.
What is the expected effect on the cost-effectiveness estimates?	The ERG's changes to the utility values for mHRPC second line and third line have minimal effect on the comparison between apalutamide + ADT vs ADT, in both nmHRPC and mHSPC. For the comparison between apalutamide + ADT vs docetaxel + ADT, the ICER varies between £34,636 (using values from NICE TA387) and £43,475 per QALY (using values from NICE TA580).
What additional evidence or analyses might help to resolve this key issue?	We consider it is unlikely that there will be much, if any, additional published utility values for mHRPC which has not already informed previous NICE prostate cancer appraisals. Exploration of existing evidence (e.g. NICE TA580 and NICE TA377) could be informative in this current appraisal.

Issue 5 Market share of subsequent therapies used in metastatic hormone relapsed prostate cancer (mHRPC)

Report section(s)	4.2.11 Resources and costs
Description of issue and why the ERG has identified it as important	The company's scenario analyses show that the choice of market share for subsequent therapies for mHRPC have a large impact on the model results. The company sought estimates from their nmHRPC and mHSPC advisory boards, and then selected estimates from the mHSPC advisory board and applied them to both the nmHRPC and mHSPC indications. This assumes that patients in the mHRPC health state receive the same set of subsequent therapies after progressing from either nmHRPC or mHSPC. The company used estimates from the nmHRPC advisory board in scenario analyses.
What alternative approach has the ERG suggested?	Clinical advice to the ERG is that the company's estimated proportions of patients receiving the respective subsequent treatments are reasonable. However, the difference in ICERs according to which advisory board estimate is used requires further explanation. Further, the ERG notes that in the company's analysis a small proportion of patients with mHSPC treated with ADT alone received docetaxel as a subsequent treatment in the company. This is inappropriate for people ineligible/unsuitable for docetaxel in mHSPC, as by definition, they are not considered able to receive docetaxel. (However, due to the low cost of docetaxel), this is unlikely to have a large impact on the model results.
What is the expected effect on the cost-effectiveness estimates?	In the company's analysis for nmHRPC, apalutamide + ADT is dominant (cheaper and more effective) than ADT for both advisory board estimates of subsequent therapies market share. For mHSPC, the ICER for apalutamide + ADT vs ADT varies from £13,973 per QALY (scenario analysis - nmHRPC advisory board) to £25,329 (base case - mHSPC advisory board), and vs docetaxel + ADT the ICER varies from £9,633 per QALY (base case - mHSPC advisory board) to £31,311 per QALY (scenario analysis - nmHRPC advisory board).
What additional evidence or analyses might help to resolve this key issue?	Advice from clinical experts on the most clinically plausible estimates on the use of subsequent therapies for mHRPC, specific to patients progressing to mHRPC from nmHRPC and mHSPC, respectively.

Issue 6 Duration of adverse event costs for docetaxel (mHSPC)

Report section(s)	4.2.11 Resources and costs
Description of issue and why the ERG has identified it as important	The costs for treating adverse events associated with docetaxel have been applied for the whole pre-progression health state (2.7 years) in mHSPC.
What alternative approach has the ERG suggested?	We consider that the costs of adverse events for docetaxel treatment have been overestimated. Docetaxel is given for six cycles and the majority of the costs of treating side effects would be during this 18-week period. We therefore consider that adverse event costs should only be costed up to the trial follow-up duration (26 weeks).
What is the expected effect on the cost-effectiveness estimates?	The change suggested by the ERG increases the ICER for apalutamide + ADT vs docetaxel + ADT from £34,636 per QALY to £42,272 per QALY.
What additional evidence or analyses might help to resolve this key issue?	Feedback from clinical experts on managing docetaxel adverse events after 26 weeks.

The following issues identified by the ERG in the cost effectiveness evidence are not considered as key issues as they only have a small impact on model results:

- The approach to calculate mean health state durations for first, second and third line mHRPC health states;
- The duration of adverse event disutilities in the pre progression health state;
- Including unscheduled medical resource use costs.
- Cost of managing neutropenia
- Medical resource use

1.6 Other key issues: summary of the ERG's view

The ERG has not identified any other key issues.

1.7 Summary of ERG's preferred assumptions and resulting ICERs

Based on the ERG critique of the company's model (discussed in section 5.3.3), we have identified nine key aspects of the company base case with which we disagree. Our preferred model assumptions are the following:

1. **Extrapolation of OS for nmHRPC**: we use the generalised gamma model for OS because this is more consistent with the long-term survival estimates provided by our clinical experts (see section 4.2.7).
2. **Mean health state durations of first, second and third line mHRPC health states**: the ERG is unclear on the need to adjust the health state durations for the

proportion of patients not dying in the pre-progression state, as assumed by the company. Therefore, we use the unadjusted health state durations (see section 4.2.8.3).

3. **Mean health state duration of third line mHRPC**: We assume that the duration of third line mHRPC should be based on the time spent in both active treatment and best supportive care from NICE TA387, i.e. [redacted] for apalutamide plus ADT and [redacted] for ADT alone and docetaxel plus ADT (see section 4.2.11.4).
4. **Health state utilities for second and third line mHRPC health states**: We consider a more appropriate approach is not to adjust second and third line utilities by applying a relative decline ratio to the first line mHRPC utility value (that is, 0.625 for second line mHRPC and 0.5 for third line mHRPC (see section 4.2.10)).
5. **Duration of adverse event disutilities in the pre-progression health state**: We assume that the disutility from adverse events lasts for two weeks (see section 4.2.10).
6. **Duration of adverse events costs for docetaxel**: Docetaxel is given for six cycles and the majority of adverse events occur during this period. Therefore, we assume that applying the costs of docetaxel adverse events for a whole year is not adequate. The ERG applies a duration of six months as our preferred assumption (see section 4.2.11).
7. **Neutropenia cost**: We consider the company's cost an overestimation and assume that patients experiencing neutropenia would only require an additional outpatient visit and blood test, i.e. £150,16 (see section 4.2.11).
8. **Resource use**: To reflect clinical practice, we changed resource use according to the ERG's clinical advice (see section 4.2.11).
9. **Unscheduled medical resource use costs**: The company's rationale to include unscheduled medical resource use costs is unclear since AE disutility costs are already included. Therefore, we exclude these costs in our base case assumptions (see section 4.2.11).

The ICERs obtained using the ERG's preferred assumptions are shown in Table 4 and Table 5. Apalutamide plus ADT still dominates ADT alone in nmHRPC. In mHSPC, the ICER is £22,294 per QALY for the comparison between apalutamide plus ADT and ADT alone and £49,298 per QALY for the comparison between apalutamide plus ADT and docetaxel plus ADT.

Table 4 Cumulative cost-effectiveness results for ERG's preferred model assumptions for nmHRPC (discounted, PAS price for apalutamide)

Parameter	Treatment	Total costs	Total QALYs	ICER (£/QALY)
Corrected company base case	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ OS extrapolation: jointly fitted generalised gamma	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ Unadjusted duration of mHRPC health states	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ Mean health state duration for 3L based on the active treatment and BSC durations from TA387	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ Unadjusted health state utilities for 2L/3L	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ Duration of AE disutilities in the pre progression health state – 2 weeks	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ Neutropenia cost – £150.16	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ Resource use based on the ERG's clinical advice	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ Exclude unscheduled MRU costs	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
ERG preferred model	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates

Table 5 Cumulative cost-effectiveness results for ERG's preferred model assumptions for mHSPC (discounted, PAS price for apalutamide)

Scenario	Treatment	Total costs	Total QALYs	ICER (£/QALY)	
				APA vs. DOX	APA vs. ADT alone
Corrected company base case	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£34,636	£25,002
+ Unadjusted duration of mHRPC health states	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£34,665	£25,009
+ Mean health state duration for 3L based on the active treatment and BSC durations from TA387	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£38,199	£25,944
+ Unadjusted health state utilities for 2L/3L	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£40,582	£25,096
+ Duration of AE disutilies in the pre progression health state – 2 weeks	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£41,581	£24,267
+ Duration of AE costs for docetaxel – 6 months	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£49,298	£24,267
+ Neutropenia cost – £150.16	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£50,227	£24,086
	ADT alone	[redacted]	[redacted]		

+ Resource use based on the ERG's clinical advice	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£50,377	£23,763
+ Exclude unscheduled MRU costs	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£49,298	£22,294
ERG preferred model	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£49,298	£22,294

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report is a critique of the company's submission (CS) to NICE from Janssen-Cilag Ltd on the clinical effectiveness and cost effectiveness of apalutamide (Erleada®) for the treatment of metastatic hormone-sensitive prostate cancer and non-metastatic hormone-relapsed prostate cancer. It identifies the strengths and weakness of the CS. Clinical experts were consulted to advise the evidence review group (ERG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the ERG via NICE on 11th August 2020. A response from the company via NICE was received by the ERG on 3rd September 2020 and this can be seen in the NICE committee papers for this appraisal.

2.2 Background

The NICE scope for this single technology appraisal (STA) encompasses both licensed therapeutic indications for apalutamide:

- In adult men for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT).
- In adult men for the treatment of non-metastatic hormone-relapsed prostate cancer (nmHRPC) who are at high risk of developing metastatic disease.

The ERG notes that:

- The NICE scope does not explicitly restrict the nmHRPC population to high-risk but the licenced indication for apalutamide does, hence the focus of the CS is on high-risk nmHRPC.
- Although the therapeutic indication for nmHRPC does not explicitly state that apalutamide should be given in combination with ADT, section 4.2 of the Summary of Product Characteristics (SmPC) states that treatment with gonadotropin releasing hormone analogue (i.e. ADT – the current standard of care) should be continued during apalutamide treatment.
- In line with previous appraisals for prostate cancer technologies, any recommendations made by NICE for apalutamide should apply to *adults* with prostate cancer, as both cisgender men and transgender women have a prostate. The term 'men' is only used when directly quoting the therapeutic indications as stated in the SmPC for apalutamide.

2.2.1 Background information on metastatic hormone-sensitive prostate cancer (mHSPC) and non-metastatic hormone-relapsed prostate cancer (nmHRPC)

Section B.1.3 of the company submission (CS) provides background information on the course of prostate cancer, focusing on the characteristics of the high-risk nmHRPC and the mHSPC patient groups, and their clinical management. The consequences of progression from these two patient groups to metastatic hormone relapsed prostate cancer (mHRPC) is also described. Below we summarise the key points relevant to this report.

2.2.1.1 High-risk nmHRPC

Among people with nmHRPC a proportion have 'high-risk' nmHRPC (committee slides for the NICE appraisal of enzalutamide for nmHRPC (TA580) state that an estimated 60% of nmHRPC patients are defined as high risk). The pivotal phase III apalutamide randomised controlled trial (RCT) included in the CS (the SPARTAN trial) defines high risk nmHRPC as having no detectable metastases on conventional imaging (CT and bones scans), hormone-relapsed prostate cancer (three prostate specific antigen (PSA) rises at least 1 week apart, with last PSA >2 ng/ml, despite castrate levels of testosterone <50 ng/dl), and a PSA doubling time (PSADT) of 10 months or less. This is a similar, but not identical, definition of high-risk nmHRPC used in the enzalutamide NICE appraisal (TA580) (high risk defined as an absolute PSA level ≥2 ng/mL and a PSADT of ≤10 months). The clinical experts consulted by the ERG indicated that although the concept of 'high-risk nmHRPC' is somewhat artificial, they did not disagree with it as a concept from a clinical perspective.

With the increasing use of positron emission tomography (PET) imaging in clinical practice, the number of patients classified as having nmHRPC is falling. This is because PET scanning, unlike conventional imaging, can identify very small metastases and, hence, more patients are diagnosed as having mHRPC.

2.2.1.2 mHSPC

mHSPC is a prostate cancer which is responsive to hormone therapy (i.e. patients have not yet developed hormone resistance) but it has spread from the prostate to more distant body sites such as bone, non-regional lymph nodes, the lung, the liver and the brain. The mHSPC patient group is heterogenous because some patients have 'newly diagnosed mHSPC' (i.e. mHSPC is the patient's initial prostate cancer diagnosis) but some patients have 'primary progressive mHSPC' (i.e. they have been previously diagnosed and are being or have been treated for localised disease and have then relapsed with mHSPC). Patients

who are newly diagnosed with mHSPC have not previously received hormone therapy, whereas those with primary progressive mHSPC are continuing to respond to hormone therapy (Figure 1) but the level and duration of response is limited. Expert clinical opinion to the ERG is that approximately half of mHSPC cases are newly diagnosed and half are primary progressive mHSPC With newly diagnosed patients having a poorer prognosis than patients with primary progressive mHSPC.[1 2] The mHSPC patient group is also heterogenous in terms of the site(s) of metastases, burden of disease, functional status and presence of cancer-related symptoms

2.2.2 Background information on apalutamide

CS Table 2 presents information on apalutamide (Erleada®), a second-generation non-steroidal anti-androgen that targets the androgen receptor (AR) with high affinity. By competitively inhibiting androgen binding to the AR, apalutamide prevents the sequence of events that would lead to the expression of androgen-regulated genes and inhibits prostate tumour progression.

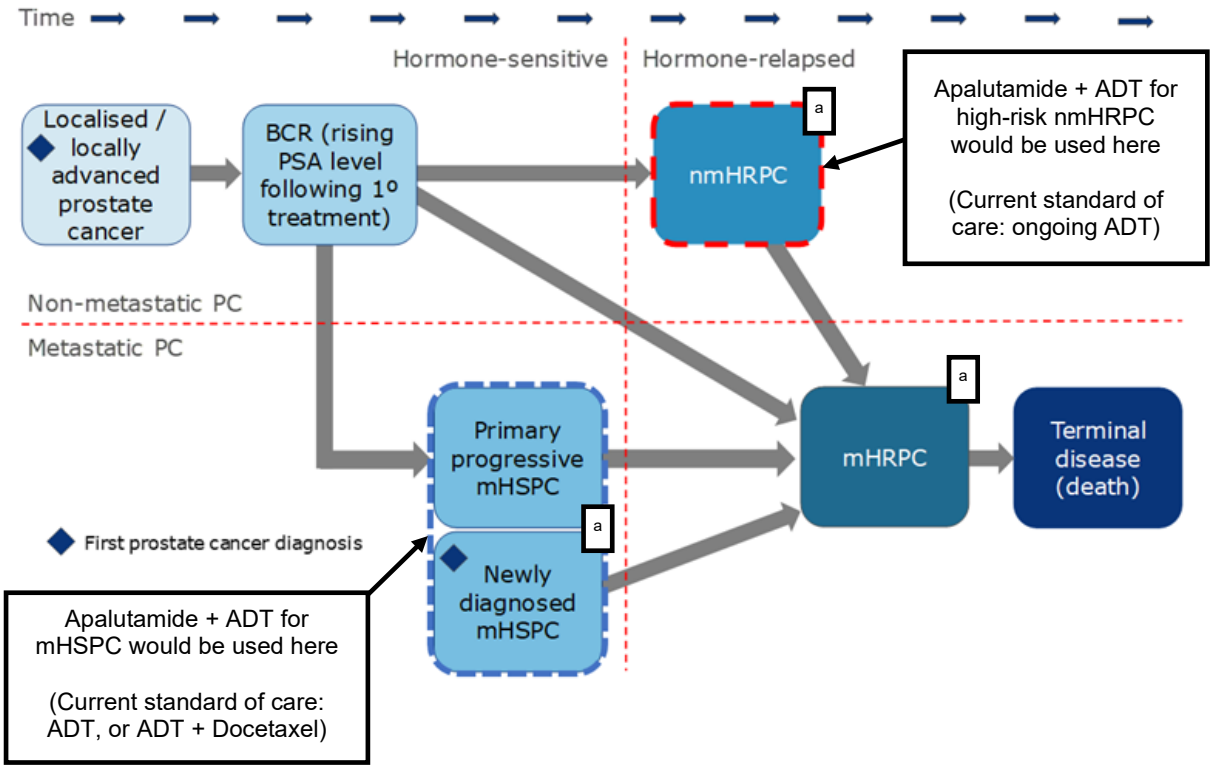
Marketing authorisation in Europe was received on 16th January 2019 for "the treatment adult men with high-risk nmHRPC" (for use in combination with ADT) and on 29th January 2020 for "the treatment of adult men with mHSPC in combination with ADT".

Apalutamide is administered orally as a single daily dose of 240mg (four 60 mg tablets) in combination with ADT. Treatment is intended to be continued until disease progression in both indications.

2.2.3 The position of apalutamide in the treatment pathway

In addition to the NICE prostate cancer guideline (NG131[3]) the European Association of Urology (EAU) and the European Society for Medical Oncology (ESMO) have also produced guidelines.[4 5]

The company outlines the clinical pathway of prostate cancer care in CS section B.1.3.3. Figure 1 shows the two places in the prostate cancer disease progression where apalutamide is licensed for use. In the non-metastatic prostate cancer setting (top half of Figure 1) apalutamide is intended to be prescribed in combination with ADT in adults with high-risk nmHRPC. In the metastatic prostate cancer setting (bottom half of Figure 1) apalutamide is intended to be prescribed in combination with ADT in adults with either primary progressive mHSPC or newly diagnosed mHSPC.



Abbreviations: BCR: biochemical recurrence; mHRPC: metastatic hormone-relapsed prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; nmHRPC: non-metastatic hormone-relapsed prostate cancer; PC: prostate cancer; PSA: prostate-specific antigen.
Notes: Blue dashed borders depict the mHSPC patient group and the red dashed borders depict the nmHRPC patient group of interest to this submission.
[a] Clinical advice to the ERG is that death from other causes should be included in this figure, particularly for the nmHRPC group.

Source: Reproduced from CS Figure 2 with additional labelling indicating where apalutamide would be used added by the ERG

Figure 1 Prostate cancer disease progression and licensed use of apalutamide

For the high-risk nmHRPC patient group the current treatment pathway in the UK and the positioning of apalutamide is presented in CS Figure 6 and the pathway for the mHSPC patient group is presented in CS Figure 7. We summarise the information in these figures and the NICE pathway for managing metastatic prostate cancer[6] in Figure 2 below.

2.2.3.1 Treatment pathway for high-risk nmHRPC

As Figure 2 shows, the only treatment option currently available to patients in England with high-risk nmHRPC is to continue ADT until distant metastases develop (mean time to occurrence between 14.7 and 18.4 months in the placebo plus ADT arms of three clinical trials,[7] including the company's pivotal phase III SPARTAN trial,[8] for nmHRPC). Once patients have evidence of distant metastases, and thus have mHRPC, alternative anti-

cancer therapies become available. Apalutamide in combination with ADT would provide a new treatment option for patients with high-risk nmHRPC, with the goal of delaying the development of mHRPC.

NICE guidance does not recommend the use of enzalutamide for nmHRPC (TA580[9]) hence why it was not considered a comparator treatment in the current appraisal. A NICE appraisal of darolutamide with ADT for treating nmHRPC (NICE ID1443[10]) is in development (first NICE Appraisal Committee meeting 9th September 2020, expected publication 25 November 2020). Darolutamide was not included as a comparator in the scope of this appraisal as at the current time a NICE recommendation has not been published.

Disease stage	High-risk nmHRPC
Current treatment option	Continue ADT
Positioning of apalutamide	Apalutamide + ADT

Disease stage	mHSPC
Current treatment options	ADT
	Docetaxel + ADT
Positioning of apalutamide	Apalutamide + ADT

Disease stage	mHRPC		
	First-line	Second-line	Third-line
Current Treatment options	Docetaxel[a]	Docetaxel	Cabazitaxel [b]
	Abiraterone [c]	Abiraterone [c]	Abiraterone [c]
	Enzalutamide [c]	Enzalutamide [c]	Enzalutamide [c]
	[d]	Radium-223 [e]	Radium-223 [f]
	Corticosteroids [g]	Corticosteroids [g]	Corticosteroids [g]

[a] For eligible patients who did not receive docetaxel in the mHSPC setting
[b] In people whose disease has progressed during or after docetaxel chemotherapy
[c] Patients can receive either abiraterone or enzalutamide but not both.
[d] Empty cells indicate the treatment that is shown in that row for other disease stages is not a treatment option
[e] Radium-223 dichloride is an option for mHRPC in people with symptomatic bone metastases and no known visceral metastases if docetaxel is contraindicated or not suitable for them
[f] Radium-223 dichloride is an option for mHRPC in people with symptomatic bone metastases and no known visceral metastases if they have already had docetaxel
[g] Corticosteroids can be considered at any stage if other treatment options are contra indicated

Figure 2 Current treatment pathway for high-risk nmHRPC, mHSPC and mHRPC in England including the positioning of apalutamide

2.2.3.2 Treatment pathway for mHSPC

For patients with mHSPC in England there are two potential treatment options: ADT or, for patients who are considered fit enough, docetaxel may be used off-label [NB. Docetaxel is licenced for the treatment of metastatic hormone-resistant prostate cancer (mHRPC). Docetaxel is not licensed for mHSPC, but NHS England commissions it for up to 6 cycles]. The ERG notes that whilst docetaxel is not suitable for all patients (due to clinical features such as performance status and comorbidities), some patients who are eligible to receive docetaxel will choose not to receive it at this point in their treatment (they may potentially choose to receive docetaxel later in the disease course).

The National Prostate Cancer Audit (NPCA), Annual Report 2019[11] states that 27% of adults with newly diagnosed metastatic disease received docetaxel in combination with standard ADT (range 0% to 39% by NHS provider in England). The NPCA report states that they expect the proportion of patients with newly diagnosed metastatic disease who receive docetaxel to increase in future years[11] but we note that this expectation was published before the COVID-19 pandemic. During the advent of the COVID-19 pandemic in early 2020 NHS England allowed the option to give enzalutamide with ADT for patients with newly diagnosed metastatic disease (administered orally at home), instead of docetaxel by intravenous infusion in hospital. The rationale is to reduce the requirement for hospital attendance, and also to reduce toxicity-related hospital admissions, both of which increase the potential for hospital-acquired coronavirus infection.[12] Patients intolerant of enzalutamide have the option to switch to abiraterone, which is also administered orally at home. Therefore, use of docetaxel will have decreased during the COVID-19 pandemic in 2020, and lower use may continue into 2021 depending on the (currently uncertain) course of the pandemic.

The CS states that ADT is not a life-prolonging treatment for patients with mHSPC, however the ERG believes it is more appropriate to state that it is not clear whether ADT improves survival in patients with mHSPC. One of the ERG's clinical advisors accepted that there is no level 1 evidence (i.e. systematic reviews of RCTs) available for to confirm the benefit of ADT on OS, but stated that it is the gold standard treatment for metastatic prostate cancer and it is considered to be life-prolonging. Apalutamide in combination with ADT would provide a new treatment option for patients with mHSPC, particularly for those who are not eligible for or who are unwilling to receive treatment with docetaxel, and in particular during the COVID-19 pandemic when docetaxel treatment is not recommended in interim guidance.[12] The goal of treatment is to delay disease progression and thus delay the development of mHRPC.

ERG conclusion

The CS provides a detailed description of the course of prostate cancer disease, and the characteristics of the high-risk nmHRPC and mHSPC patient groups and the subsequent progression to mHRPC. It adequately describes the limited treatment options that are currently available for these two patient groups and demonstrates the potential role of apalutamide in combination with ADT as an alternative treatment option.

2.3 Critique of the company's definition of the decision problem

Table 6 summarises the decision problem addressed by the company in the CS, in relation to the final scope issued by NICE and the ERG's comments on this. Aside from the issues described below, the company's decision problem either matches the NICE scope or the differences are minor and the ERG does not have any concerns about them.

The issues of uncertainty or disagreement between the NICE scope and the company's decision problem that we have identified are:

- The company have limited the nmHRPC population to people with high-risk nmHRPC. This is consistent with the marketing authorisation for apalutamide ("the treatment adult men with high-risk nmHRPC"). However, the ERG notes that there is no consistent definition in clinical practice for high-risk nmHRPC
- The CS decision problem does not include the two subgroups listed in the NICE scope, that is, people with **newly diagnosed** metastatic prostate cancer and people with **high-risk** metastatic prostate cancer).
    - For the nmHRPC population CS Figure 2 indicates people are not newly diagnosed with nmHRPC (they will have progressed to nmHRPC after primary treatment for localised/locally advanced prostate cancer) and they do not yet have metastases so neither of the subgroups appear relevant for the nmHRPC population.
    - For the mHSPC population a distinction can be made between newly diagnosed and primary progressed patients (and, as already described, the mHSPC patient group is a heterogenous population in other respects too). It is known that newly diagnosed patients have a poorer prognosis than patients with primary progressive mHSPC.[1 2] Therefore, whilst there is justification for a subgroup analysis of newly diagnosed mHSPC patients the company haven't commented on the feasibility of this. Identifying patients with high-risk mHSPC is typically based on prognostic factors such as metastatic burden,

metastasis location, time of metastatic presentation and Gleason score but there does not appear to be an agreed definition of high-risk mHSPC and key clinical trials (CHAARTED[14] and LATITUDE[15]) have used different criteria to identify high-risk patients. It is less clear whether there would have been justification for a subgroup analysis based on high-risk mHSPC but again the company have not commented on this.

- The decision problem specifies a sub-group of mHSPC 'patients ineligible or unsuitable for chemotherapy', stating that unmet need is highest in this group. The ERG considers this an appropriate justification but notes that the features that define this subgroup of patients are not defined in the decision problem or elsewhere in the CS. Base case cost-effectiveness results are presented for mHSPC patients who are eligible for docetaxel (apalutamide plus ADT versus docetaxel plus ADT) and for those who are ineligible for docetaxel (apalutamide plus ADT versus ADT). However, clinical effectiveness data are not presented separately for these subgroups and it is not explicitly stated in the decision problem or the formative sub-sections of the clinical effectiveness section (B.2) that the TITAN trial results are intended to be applicable to docetaxel ineligible patients. We discuss this issue later in this report (section 4.2.3).
- We agree that it is appropriate to have excluded abiraterone plus ADT and enzalutamide plus ADT, as comparators because the NICE appraisals for these are still currently ongoing.

Table 6 Summary of the decision problem

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	ERG comments
Population				
nmHRPC	Adults with nmHRPC	Adults with high-risk nmHRPC	The marketing authorisation for apalutamide in nmHRPC is for those at high risk of developing metastatic disease,[a] as per the SPARTAN trial.	There is no consistent definition in place for 'high-risk nmHRPC'. In the CS the definition from the phase III SPARTAN trial is used.[b]
mHSPC	Adults with mHSPC	Adults with mHSPC	N/A	Decision problem matches the NICE scope
Intervention				
nmHRPC and mHSPC	Apalutamide plus ADT	Apalutamide plus ADT	N/A	Decision problem matches the NICE scope
Comparator(s)				
nmHRPC	ADT	ADT	N/A	Decision problem matches the NICE scope
mHSPC	• ADT • Docetaxel with ADT • Abiraterone with prednisone or prednisolone and ADT (subject to ongoing NICE appraisal) • Enzalutamide with ADT (subject to ongoing NICE appraisal)	• ADT • Docetaxel with ADT	• Abiraterone received a 'not recommended' in the NICE FAD released in June 2020. As such, it cannot be considered a relevant comparator • Enzalutamide with ADT is currently being appraised by	The company have omitted two comparators from the scope: abiraterone + ADT and enzalutamide + ADT. The ERG notes that these appraisals are currently

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	ERG comments
			NICE. As such, it cannot be considered a relevant comparator	ongoing so it is appropriate to exclude them.
Outcomes				
nmHRPC	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rate • PSA response • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered include: • Overall survival • Metastases-free survival • Progression-free survival • PSA response • Adverse effects of treatment • Health-related quality of life measures • Time to symptomatic progression • Time to PSA progression • Second progression-free survival • Time to initiation of cytotoxic chemotherapy • Time to metastasis	As per scope, and additional outcome measures provide supportive efficacy data for apalutamide.	The company have not included response rate as an outcome measure which is acceptable because this was not an outcome. Captured in the company's RCT for this population.

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	ERG comments
mHSPC	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rate • PSA response • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered include: • Overall survival • Radiographic progression free survival • Progression-free survival • PSA response • Adverse effects of treatment • Health-related quality of life • Second progression free survival	As per scope and additional outcome measures provide supportive efficacy data for apalutamide.	Although the company do not list response rate as an outcome measure the outcome 'Best overall response' is reported for this population.
Subgroups of interest				
mHSPC	• people with newly diagnosed metastatic prostate cancer • people with high-risk metastatic prostate cancer	patients ineligible or unsuitable for chemotherapy	Unmet need is highest in these patients	The CS does not include the subgroups listed in the NICE scope. The CS presents separate base-case cost-effectiveness results for mHSPC patients who are docetaxel eligible/ineligible. However, effectiveness data are not

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	ERG comments
				presented separately for these subgroups.

Source: CS Table 1 with minor formatting alterations and column added for ERG comments
ADT: androgen deprivation therapy; ERG: evidence review group; MA: marketing authorization; mHSPC: metastatic hormone-sensitive prostate cancer; N/A, not applicable; NHS: National Health Service; nmHRPC: non-metastatic hormone-relapsed prostate cancer; PSA: prostate-specific antigen; PSADT: PSA doubling time
[a] A high risk for the development of metastases is defined as PSADT ≤10 months during continuous ADT
[b] The SPARTAN trial definition of high-risk nmHRPC is: detectable metastases on conventional imaging, hormone-relapsed prostate cancer (three PSA rises at least 1 week apart, with last PSA >2 ng/ml, despite castrate levels of testosterone <50 ng/dl), and a PSADT of 10 months or less].

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company carried out two systematic literature reviews (SLRs), one for the nmHRPC patient group and one for mHSPC patient group. Their literature search and review methods are reported in CS B.2.1-B.2.2 and in CS Appendix D. Below we critically appraise these reviews.

3.1.1 Clinical effectiveness review of nmHRPC treatments

The SLR for nmHRPC included the whole nmHRPC patient population, not only the high-risk nmHRPC population in the company's decision problem. The literature search included core medical databases (Medline, Medline in Process, Embase, Cochrane Database of Systematic Reviews (CDSR), Cochrane CENTRAL), all NICE recommended websites, and several relevant conferences of the past three years. Databases were searched from database inception and the several update searches reported provided coverage up until the beginning of June 2020. The trial registry ClinicalTrials.gov was searched in the penultimate search update with a limit to include only trials with published results.

Table 7 gives an overview of the company's approach to the SLR of nmHRPC studies, with references to further discussion where relevant. Overall the ERG believes the SLR to be of good quality and unlikely to be biased.

Table 7 ERG appraisal of systematic review methods for nmHRPC

Systematic review components and processes	ERG response (Yes, No, Unclear)	Comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	The framework for the eligibility criteria uses a variation of PICO as reported in CS Table D.23. The structure of the searches reflects this.
Searches: was the literature review carried out appropriately (sources, date range, in line with PICOD, correct search terms/syntax, etc.)?	Yes	Reported in CS Appendix D.1. The original search was weak regarding search terms and overall strategy. A greatly improved search was employed from the first update onwards which also searched the previous date period to compensate.
Searches: were any relevant studies missed?	No	Appears to be a gap in Embase date coverage between 29/11/2018 and 01/07/2019 – a targeted search in Embase by the ERG did not find anything missing.

Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem?	Yes	Reported in CS Table D.23. A broader nmHRPC population than the company's decision problem – the latter is restricted to *high-risk* nmHRPC patients. No specific interventions or comparators were specified. The review included RCTs measuring survival, disease progression, QoL scores and safety outcomes.
Were study selection criteria applied by two or more reviewers independently?	Yes	Database records and full texts of potentially relevant studies were assessed by two independent reviewers with a third, senior, reviewer to resolve any discrepancies. Records from other sources were assessed by a single independent reviewer.
Was data extraction performed by two or more reviewers independently?	Yes	Two independent reviewers with a third, senior, reviewer to resolve any discrepancies.
Was a risk of bias assessment or a quality assessment of the included studies undertaken? **If so, which tool was used?**	Yes	Reported in CS B.2.5 and CS Table 11. Further details are in Appendix D.5.1 (Table D.55). The company adapted the NICE single technology appraisal user guide for company evidence submission and the Centre for Reviews and Dissemination guidance for undertaking reviews in health. Discussed further in section 3.2.2 of this ERG report.
Was risk of bias assessment (or other study assessment) conducted by two or more reviewers independently?	Unknown	Not reported.
Is sufficient detail on the individual studies presented?	Yes	CS Tables D.24 and D.25 report references and key attributes of included studies. One relevant study appears to be missing as the PRISMA flow diagram reports 12 relevant RCTs whereas Table D.25 reports details of 11 studies. CS Table. D.26 reports excluded studies with reason for exclusion. Full details of the SPARTAN trial are presented in CS B.2 and section 3.2.1 of this report.
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	Not applicable	A meta-analysis was not possible as only one trial of apalutamide in nmHRPC was identified (SPARTAN). The company justifies not doing an ITC because a direct comparison with ADT was

		possible from SPARTAN. See section 3.3 of this report.

3.1.2 Clinical effectiveness review of mHSPC treatments

The SLR of the clinical effectiveness in mHSPC searched the literature for randomised and non-randomised controlled trials. All relevant sources, including grey literature, were searched as for the nmHRPC SLR above. Databases were searched from database inception and the several update searches reported provided coverage up until the beginning of June 2020.

Table 8 below gives an overview of the company's approach to the SLR of mHSPC treatment clinical effectiveness studies, with references to further discussion where relevant. Overall, the ERG considers the company's SLR to be of good quality and unlikely to be biased.

Table 8 ERG appraisal of systematic review methods for mHSPC

Systematic review components and processes	ERG response (Yes, No, Unclear)	Comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	PICOS template was predefined and used for screening. Reported in Tables D.45 and D.46. The non-RCT PICOS is more specific than the RCT PICOS: the intervention concept is searching for apalutamide studies or combination therapy studies only. The non-RCT search was conducted in case anything relevant would be missed from the RCT search. mHSPC is a narrow population and other elements of the PICO search, e.g. study type, can be made broader in order not to miss relevant studies.
Searches: was the literature review carried out appropriately (sources, date range, in line with PICOD, correct search terms/syntax, etc.)?	Yes	Reported in CS Appendix D.2. Overall, the literature searches were comprehensive. Tables of the original and first update search strategies for mHSPC are combined meaning reported search yield is unclear whether for either or both searches.
Searches: were any relevant studies missed?	No	The ERG believes that no relevant studies would have been missed. The non-RCT search did not identify any relevant prospective interventional studies.

Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem	Unclear	Reported in Tables D.45 (for RCTs) and D.46 (for non-RCTs) – the only difference being study design and that the non-RCT search only included apalutamide or combination therapy studies.
Were study selection criteria applied by two or more reviewers independently?	Yes	Review was carried out by two independent researchers.
Was data extraction performed by two or more reviewers independently?	Yes	Review was carried out by two independent researchers. For this stage, where there was a lack of consensus, a third independent researcher resolved any discrepancies.
Was a risk of bias assessment or a quality assessment of the included studies undertaken? **If so, which tool was used?**	Yes	Summary assessment in CS B.2.5 and CS Table 11. Further details in Appendix D.5.2 (Table D.56). The company adapted the NICE single technology appraisal user guide for company evidence submission and the Centre for Reviews and Dissemination guidance for undertaking reviews in health. Discussed in section 3.2.2 of this report.
Was risk of bias assessment (or other study assessment) conducted by two or more reviewers independently?	Unknown	Conduct of assessment not reported.
Is sufficient detail on the individual studies presented?	Yes	CS Tables D.47 and D.48 report references and key attributes of included records. CS Table. D49. Reports excluded studies with reason for exclusion. The included studies are discussed further in section 3.2.1 of this report.
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	Yes	A network meta-analysis was undertaken for apalutamide plus ADT versus docetaxel plus ADT. Reported in CS B.2.15.1 and discussed in section 3.3 of this report.

ERG conclusion

The CS reports two comprehensive clinical effectiveness literature searches, one each for the two patient groups in this appraisal. The ERG considers the reported methods for inclusion/exclusion reference screening to be appropriate. The CS appendices present all the search strategies, use the PRISMA flow diagram for cumulative results of all the original and update searches, and provides lists of excluded studies with reasons for exclusion. The ERG does not believe that any relevant clinical effectiveness studies have been missed by the company's literature searches.

3.2 Critique of studies of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included studies

The company's SLR identified two clinical trials of apalutamide relevant to the decision problem:

- the SPARTAN trial of apalutamide for the treatment of high risk nmHRPC[8 16-19]
- the TITAN trial of apalutamide for the treatment of mHSPC[20 21]

Both trials are company-sponsored, phase III randomised, double-blind, placebo-controlled, multinational, multi-centre trials. The ERG is satisfied that the company search has identified all studies for apalutamide that are relevant to the decision problem.

3.2.1.1 Study characteristics

The trial methodologies used in SPARTAN and TITAN are described in CS sections B.2.3.1 and B.2.3.2, respectively, and summarised in CS Table 6. We show an overview of the trial characteristics in in Table 9 below. A list of pre-planned sub-group analyses are provided in CS Table 6 and are described in more detail in section 3.2.4 of this ERG report.

Table 9 Summary of trial characteristics

Trial characteristic	SPARTAN	TITAN
Study design	Phase III randomised double-blind, placebo controlled, parallel group	Phase III randomised, double-blind, placebo controlled, parallel group
Number and location of centres	332 sites across 26 countries in North America, Europe & Asia-Pacific regions. 15 UK sites (n=99 UK patients).	260 sites across 23 countries in North and South America, Europe & Asia-Pacific regions. 10 UK sites (n=36 UK patients).
Study population	Men ≥18 years with high risk nmHRPC	Men ≥18 years with mHSPC and at least one bone lesion
Intervention (no. randomised)	Apalutamide 240mg once daily plus ADT (n=806) Continuous treatment in 28-day treatment cycles	Apalutamide 240mg once daily plus ADT (n=525) Continuous treatment in 28-day treatment cycles
Comparator (no. randomised)	Placebo plus ADT (n=401)	Placebo plus ADT (n=527)
Primary outcome(s)	Metastases free survival (MFS)	Radiographic progression free survival (rPFS) and overall survival (OS)
Randomisation ratio	2:1	1:1

Trial characteristic	SPARTAN	TITAN
Stratification factors	PSA doubling time (>6 months vs ≤6 months), use of bone-sparing agents and classification of nodal disease (local, N0 vs regional N1)	Gleason score, prior docetaxel use and region
Status	Complete, published.	Ongoing. Final results for rPFS outcome published. Final OS results unpublished.
Latest available data	1st February 2020 (final data cut)	23rd November 2018
Median duration of follow up (months)	19th May 2017 IA1 data cut: 20.3 1st Feb 2019 IA2 data cut: 41.0 1st Feb 2020 final data cut: 52.0	23rd Nov 2018 IA1 data cut: 22.7
No. (%) of discontinuations	19th May 2017 Apalutamide plus ADT: [redacted] (39%) Placebo plus ADT: [redacted] (70%) 1st Feb 2020 Apalutamide plus ADT: [redacted] Placebo plus ADT: [redacted]	23rd Nov 2018 Apalutamide plus ADT: [redacted] Placebo plus ADT: [redacted]
No. (%) of crossovers from placebo to open-label active arm at unblinding[a]	76 (19%) of whom 46 continued to receive apalutamide as of the clinical cut-off date for the final analysis (Feb 2020) in this submission.	Number not reported in CS as data was not available at the time of the first interim analysis.
No. (%) using one or more subsequent life-prolonging prostate cancer therapies	Apalutamide plus ADT:371 (46.0%) Placebo plus ADT:279 (69.6%) Denominator: ITT population	Apalutamide plus ADT:64 (37.6%) Placebo plus ADT:165 (60.9%) Denominator: number of patients alive at treatment discontinuation

ADT: androgen deprivation therapy; IA: interim analysis; MFS: metastatic-free survival; OS: overall survival; rPFS: radiographic progression-free survival;
Source: CS Tables 4-6, CS section B.2.3, CS Appendix D.4, SPARTAN CSR Tables 4 & TSIDEM02[22] Response to Clarification Question A5 Table 2.
[a] Both trials were unblinded after results of the first interim analyses showed evidence of effectiveness for apalutamide versus placebo for the trials' primary outcomes and patients randomised to placebo were subsequently allowed to crossover to the apalutamide arm.

3.2.1.2 The SPARTAN trial

The SPARTAN trial[8 16-19] compared the efficacy and safety of apalutamide 240mg orally daily plus ADT with placebo plus ADT in adult men with nmHRPC. The patient population comprised people with histologically or cytologically confirmed prostate cancer that was defined as:

- Non-metastatic: no detectable metastases on conventional imaging (CT and bone scans) assessed by blind independent central review (BICR),

- Hormone-relapsed: three prostate-specific antigen (PSA) rises at least 1 week apart, with last PSA>2ng/ml, despite castration levels of testosterone <50ng/ml), and
- High-risk: PSA doubling time of less than or equal to 10 months. Clinical experts to the ERG noted that the concept of 'high-risk' nmHRPC is largely used to provide a standardised definition in the trial setting, rather than for use in clinical practice for patient management. They did not disagree with the concept and they acknowledge that it defines the population most likely to benefit from treatment. Our clinical experts did not mention any alterative risk stratification criteria used in practice.

ADT consisted of continuous treatment with a gonadotrophin-releasing hormone (GnRH) analogue (where surgical castration had not occurred). The choice of ADT (agonist or antagonist) was at the discretion of the investigator and dosed according to the product's label. Most patients used a GnRH analogue ([redacted] in the apalutamide arm and [redacted]% in the placebo arm; based on safety population, SPARTAN CSR Table TSICM01).[22] Study treatment continued until disease progression, withdrawal of consent, or unacceptable treatment-related toxicity.

Data cuts for SPARTAN are described in CS Table 4. The first interim data cut (19th May 2017) was used as the final analysis for the primary endpoint of metastatic-free survival (MFS) while the final data cut (1st Feb 2020) was used for the analysis of longer term outcomes such as overall survival (OS) and second progression-free survival (PFS2). Trial outcomes for SPARTAN are described in more detail in section 3.2.3 of this ERG report. SPARTAN informs the economic model by providing comparative evidence of clinical effectiveness of apalutamide plus ADT versus placebo plus ADT for the outcome of MFS and longer-term outcomes of PFS2 and OS.

3.2.1.2.1 Patient crossover from placebo plus ADT to apalutamide plus ADT

Following advice from the trial's Independent Data Monitoring Committee (IDMC), the trial was unblinded at the first interim analysis due to evidence of superiority of apalutamide over placebo for the primary endpoint, MFS. Patients in the placebo arm were thus offered the option of crossing over to open-label apalutamide therapy at this point. Of the 76 (19%) patients randomised to placebo who crossed over, 46 continued and 30 discontinued open label apalutamide as of February 2020. In addition, patients who reached the primary endpoint of MFS were permitted to receive one or more subsequent therapies to treat

metastatic hormone-relapsed prostate cancer (mHRPC). These included novel therapies such as abiraterone plus prednisolone (provided as per protocol by the sponsor) or enzalutamide, chemotherapy or radium-223 therapy (CS Table 16). One or more of these subsequent treatments were used by a higher percentage of patients in the placebo plus ADT arm (69.6% of 401 patients) compared to the apalutamide plus ADT arm (46.0% of 806 patients). This refers to use of subsequent therapy considered to be life-prolonging in prostate cancer regardless of when used; i.e. an individual patient may have used more than one different type of subsequent therapy.

The crossover from placebo plus ADT to apalutamide plus ADT may potentially bias ITT results at the final analysis in favour of placebo plus ADT. The imbalance between the trial arms in the proportions of patients who use of subsequent treatments is not necessarily a source of bias, as it may reflect a difference in rates of progression to metastatic disease. However, enzalutamide and abiraterone would not be available as subsequent therapy to patients treated with apalutamide as current NHS England policy restricts use of these novel agents to once per patient. Thus, while switching from placebo to just one of the novel agents would reflect current clinical practice for patients receiving ADT alone, subsequent use of a second novel agent would not be permitted. In contrast, switching from apalutamide to any other novel agent would not be permitted in practice. In SPARTAN, use of subsequent therapy not permitted in the NHS was reported in [redacted] patients in the apalutamide plus ADT arm (who subsequently used abiraterone or enzalutamide), while [redacted] of patients in the placebo plus ADT arm subsequently used both abiraterone and enzalutamide. The higher use of NHS non-permitted (subsequent) novel therapy in the apalutamide plus ADT arm of the trial may potentially over-estimate its effect (though this effect may be reduced due to cross-resistance between the novel therapies). However, it potentially counters the bias favouring placebo plus ADT arising from crossover. The company's choice of statistical methods to address potential bias from treatment switching are further discussed later in this ERG report (section 3.2.2 (Risk of bias), section 3.2.4 (Trial statistical methods), and sections 4.2.6, 4.2.7 and 4.2.8 (Treatment effectiveness extrapolation methods).

3.2.1.3 The TITAN trial

The TITAN trial[20 21] compared the efficacy and safety of apalutamide 240mg orally daily plus ADT with placebo plus ADT in adult men with mHSPC. The patient population comprised men with prostate cancer that was metastatic defined by one or more documented bone lesions. Clinical experts to the ERG advised that approximately 60%-85% of mHSPC

patients present with bone metastases. Patients with only visceral metastases or only lymph node involvement were not included in the trial. One ERG clinical expert noted that such patients were not excluded from other pivotal RCTs in this disease population. The company suggest that around 10% of mHSPC patients have only visceral metastases, however, expert advice to the ERG suggests that this proportion is likely to be smaller and that more patients would have only lymph node disease. Expert advice confirmed that the extent/site of metastases may affect prognosis. Patients with only lymph node involvement would typically have better outcomes than those with bone metastasis. Those with visceral metastases would have the poorest outcomes but most of these patients will also have bone metastases. While the trial population may under-represent patients without bone disease, it remains unclear as to whether the treatment effect for apalutamide is likely to differ between mHSPC patients with and those without bone disease.

ADT (medical or surgical castration) must have been started at least 14 days before randomisation and continued during the trial. Prior ADT therapy was restricted to a maximum of six months duration prior to randomisation in the metastatic disease stage and no more than three years in total for prior ADT therapy started during the non-metastatic disease stage. Use of ADT during the trial comprised mainly GnRH agonists ([redacted]% for the apalutamide arm and [redacted]% in the placebo arm. (CSR Table TSICM01)[23] Prior docetaxel chemotherapy for metastatic disease was permitted if disease did not progress on or after this treatment.

The CS presents results from the first interim analysis (at 23rd Nov 2018) which provides final data for the co-primary endpoint of radiographic progression-free survival (rPFS) and interim (immature) data for the co-primary endpoint of overall survival. The study is ongoing (estimated completion date 12th July 2021).[24] Trial outcomes for TITAN are described in more detail in section 3.2.3 of this ERG report. TITAN informs the economic model by providing comparative evidence of clinical effectiveness for the outcome of rRFS, PFS2 and OS for apalutamide plus ADT versus placebo plus ADT. In addition, a network meta-analysis provides indirect evidence of comparative effectiveness between apalutamide plus ADT and docetaxel chemotherapy plus ADT.

The TITAN trial's IDMC also recommended unblinding of the study at the first interim analysis due to evidence of a survival benefit with apalutamide for the co-primary endpoint, rPFS. Patients randomised to placebo plus ADT were offered an option to crossover to open-label apalutamide plus ADT. The first interim analysis data cut presented in the CS is unaffected by this crossover. However, analysis of longer-term outcomes (OS and PFS2)

may be biased (in favour of placebo) by the crossover to apalutamide. Use of one or more subsequent life-prolonging therapies which was higher in the placebo (plus ADT) arm (60.9% of the 271 patients who were alive at treatment discontinuation) compared to the apalutamide arm (37.6% of 170 patients) (Response to Clarification Question A5; Table 2). This difference in proportions does not necessarily represent a source of bias, as it might just reflect a greater rate of progression in the placebo plus ADT arm. However, the use of more than one novel subsequent therapy ([redacted] patients in the apalutamide arm versus [redacted] patients in the placebo arm) may introduce a bias in favour of apalutamide as this would not be permitted under current NHS policy, as described earlier. These potential biases and methods to address them are further discussed in section 3.2.2 and 3.2.4 of this ERG report.

3.2.1.4 Patients' baseline characteristics

The baseline characteristics of patients in SPARTAN and TITAN are summarised in Table 10. All characteristics were well balanced between trial arms in both studies.

Expert clinical advice to the ERG suggests that the reported patient characteristics in both trials are representative of patients seen at the respective disease stages in clinical practice. An exception is that in the TITAN trial, the majority of patients with mHSPC were newly diagnosed (81% with M1 stage at diagnosis, see Table 10 below), whereas expert clinical advice to the ERG suggests that in practice around 50% of patients are newly diagnosed at the metastatic stage, while the other 50% have progressed to metastases from localised or locally advanced prostate cancer (primary progressive mHSPC).

Table 10 Baseline characteristics

Patient Characteristic	ERG comment	
	SPARTAN	TITAN
Age	The mean (SD) age of patients was 73.9 (8.02) years. This is as expected given most men with prostate cancer are diagnosed between 65 and 69 years [25] and men in this study had a median duration of [redacted] years since diagnosis	The mean age of patients was younger (68.4 years; SD 8.28) compared to the SPARTAN trial. Men with mHSPC in TITAN were more recently diagnosed (median time since initial diagnosis was 4 months) than men presenting with nmHRPC in SPARTAN.
Race	The majority of patients were White (66.3%). This is lower than the	68.3% of men were White. As in SPARTAN, this is lower than in the

Patient Characteristic	ERG comment	
	SPARTAN	TITAN
	general UK population, particularly in men aged over 60. The ERG did not find any published ethnicity distributions for the English disease population but note that the risk of prostate cancer is higher in Black men compared to White men.[26]	general UK population but may reflect the higher risk of prostate cancer in Black men.
Risk stratification/ disease severity indicators	• Most men (75.3%) had tumour grade ≥T2, • 43.6% of men had Gleason scores >7, • [redacted]% of men had no spread to regional lymph nodes (stage N0) at diagnosis, • Baseline median PSA was 7.80 ng/ml., • Mean (SD) PSA doubling time was [redacted]) months	• Most men had stage M1 metastases (81.0%), • 67.3% of men had Gleason scores >8, • 53% had bone metastases only, • 61.7% had ≤10 bone lesions, • 62.7% had high volume disease,
ECOG performance status score	Most patients (77.4%) had an ECOG score of 0 reflecting no impairment on functional status	Most patients (64.3%) had an ECOG score of 0 reflecting no impairment on functional status
Prior and concomitant ADT treatment	The majority [redacted]%) of men used GnRH agonists prior to and during the study. This is consistent with UK practice. Clinical experts to the ERG reported that goserelin and leuprorelin are the most commonly used medical castration treatments.	Over 90% of men used GnRH agonists prior to the study and approximately [redacted]% used these agents during the study. This is in keeping with UK clinical practice.
Prior surgery or radiotherapy for localised prostate cancer	Most men ([redacted]%) had had a prostatectomy or radiation therapy. This reflects current NICE guidance whereby patients with high-risk localised disease would be offered radical treatment if this is likely to have long-term benefits.	16.4% of men had received radiotherapy or a prostatectomy. This is lower than in SPARTAN reflecting the high proportion of men in TITAN who were newly diagnosed and such treatments may not be appropriate.

Patient Characteristic	ERG comment	
	SPARTAN	TITAN
Prior chemotherapy	A small proportion ([redacted]%) of men had received previous chemotherapy. Docetaxel is currently only recommended in newly diagnosed patients with high risk disease so this is less likely to have been used in patients who have progressed to hormone-resistant localised disease.	10.7% of men had received docetaxel chemotherapy. Clinical expert advice to the ERG is that chemotherapy is most often offered to younger, fitter men representing 30% of men with mHSPC.

Source: CS Tables 7 and 8; TITAN CSR Table 6 [23]

ERG conclusion

The two pivotal phase III RCTs, SPARTAN and TITAN, are appropriate study designs to inform the comparative effectiveness and safety of apalutamide plus ADT versus placebo plus ADT in this appraisal. Patients' baseline characteristics were well balanced between treatment arms in both studies and were considered to be broadly representative of patients with high-risk nmHRPC and mHSPC respectively. However, the ERG notes that the TITAN study population may be less representative of mHSPC patents who do not have bone disease and those patients who have primary disease progression.

3.2.2 Risk of bias assessment

The company reports quality assessments for the SPARTAN and TITAN trials, using the NICE recommended criteria, in Appendix D Tables D.55 and D.56 respectively, with a summary of both in CS B.2.5, including Table 11. The ERG's assessment of the trials, following the same criteria, is shown in Table 11 below. The criteria were applied by one ERG reviewer and checked by a second reviewer with differences in judgement resolved through discussion.

Table 11 Risk of bias assessment of the SPARTAN and TITAN trials

NICE criteria	SPARTAN		TITAN	
	Company	ERG	Company	ERG
Was randomisation carried out appropriately?	Yes	Agree	Yes	Agree
Was the concealment of treatment allocation adequate?	Yes	Agree	Yes	Agree
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Agree	Yes	Agree
Did groups receive same care other than intervention?	Yes	Agree	Yes	Agree
Were the care providers, participants and outcome assessors blind to treatment allocation? Could this have impacted the outcome?	Yes	Agree[a]	Yes	Agree
Was there a clear definition of the outcome? Was the measure of this outcome valid/reliable?	Yes	Agree	Yes	Agree
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Agree[b]	No	Agree
Were there any unexpected imbalances in drop-outs between groups?	No	Agree	No	Agree
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Agree	Yes	Agree
Were there any other sources of bias	No	Agree	NR	Unclear
Whether the authors of the study publication declared any conflicts of interest?	NR	NR	Yes	Agree

Source: CS Appendix Tables 55 and 56 NR: Not reported in CS

[a] Blinded until patients were allowed to crossover from placebo to the apalutamide arm at the first interim data analysis.

[b] Except for HRQoL outcomes: CS Table 4 reports that SPARTAN HRQoL data are available from the final data analysis, however CS B.2.7.4 only reports data from the first data cut.

The ERG is in agreement with the company's judgements, with the following caveats:

- Blinding was only maintained for outcome data up to the first interim data analysis in SPARTAN. Thus, with the exception of MFS (which was intentionally only reported at the first interim data analysis), all outcomes reported at later data cuts will be at potential risk of detection bias and performance bias. These include survival endpoints such as PFS2 (which informs the economic model), though survival is more objectively measured compared to other outcomes, which may offset the increased risk of bias. The outcome data for TITAN reported in the CS is from the first data analysis, and is unaffected by the unblinding which occurred in that trial.

- Time to symptomatic progression data were reported in the CS only at the first SPARTAN interim data analysis, whereas CS Table 4 indicates that it was also measured at the final analysis, indicating potential selective reporting bias. The ERG notes that the results from the first interim analysis will not be affected by bias from unblinding, but those from the final analysis will.
- HRQoL outcome data for SPARTAN are reported in the CS using data from the first interim analysis, whereas CS Table 4 indicates that there is data available from the final analysis data cut in February 2020. Thus, there is potential for selective reporting bias.

As we have mentioned earlier (section 3.2.1.2) the crossover from placebo plus ADT to apalutamide plus ADT may potentially bias the ITT results at the final analysis in favour of placebo plus ADT. The higher use of NHS non-permitted subsequent novel therapy in the apalutamide plus ADT arm of the trial may over-estimate its effect in clinical practice. It may also counter the bias favouring placebo plus ADT arising from crossover. We discuss the company's choice of statistical methods to address bias from treatment switching later in this ERG report (section 3.2.4 (Trial statistical methods), and sections 4.2.6, 4.2.7 and 4.2.8 (Treatment effectiveness extrapolation methods)).

ERG conclusion

The ERG agrees that both SPARTAN and TITAN are of good methodological quality and could be considered low risk of bias on most of the bias-related criteria. Where SPARTAN reports outcomes subsequent to the first interim data analysis, the unblinding effect of the crossover from placebo plus ADT to the apalutamide plus ADT arm could increase the risk of performance bias and detection bias. Crossover may also confound survival estimates and therefore requires a suitable method to adjust the data analysis, something we discuss later in this report.

3.2.3 Outcomes assessment

3.2.3.1 Efficacy outcome(s)

The trial outcomes for SPARTAN and TITAN are defined in CS Table 6 and are listed below in Table 12. (Further information on these outcomes is provided in Appendix 9.1 of this report). In both trials, an appropriate range of intermediate- and longer-term endpoints have been included. All outcomes listed in the NICE scope have been included with the exception of 'response rate' which is not explicitly reported in SPARTAN, however, additional relevant supporting endpoints have been included.

Table 12 List of efficacy outcomes in SPARTAN and TITAN

Endpoint	SPARTAN[1]	TITAN
Primary/Co-primary	• Metastases-free survival (MFS)	• Radiographic progression-free survival (rPFS) • Overall survival (OS)
Secondary	• Overall survival (OS) • Time to metastases (TTM) • Progression-free survival (PFS) • Time to symptomatic progression • Time to initiation of chemotherapy	• Time to cytotoxic chemotherapy • Time to pain progression • Time to chronic opioid use • Time to skeletal-related events (SRE)
Other	• Second progression free survival (PFS2) • PSA response • Time to PSA progression	• Second progression free survival (PFS2) • Time to PSA progression • Overall response • Prostate cancer-specific survival

[1] Additional endpoints are reported in the trial CSR.

The efficacy endpoints were clearly defined and appropriate methods were used to minimise measurement bias by using an objective record e.g. documented prescription or medical event, blinded independent centralised review, audit of a sample of investigator-assessed outcomes and/or the use of standardised criteria for measuring response.

In SPARTAN, the primary endpoint of MFS is a relevant outcome for men with nmHRPC since progression to metastases may represent a turning point in the disease pathway as men become symptomatic and require further healthcare intervention. Clinical experts to the ERG advised that spending longer time without metastases would be of benefit to patients. MFS has been shown to correlate well with overall survival [27] We note, however, that it is possible that metastases may be detected in trial patients who may otherwise remain asymptomatic. The secondary endpoint, time to symptomatic progression, may be more relevant from a clinical management perspective. The ERG notes that the CS defines this secondary endpoint as a composite of three endpoints: skeletal-related events, pain

progression/worsening of symptoms or symptoms related to loco-regional progression requiring intervention. Data for these three individual components are not provided but may give more specific insight into the effect of apalutamide on symptoms, their management and associated resource use.

3.2.3.2 Efficacy outcomes informing the economic model

Efficacy data from SPARTAN for MFS, PFS2 and OS contributed to the economic model for nmHRPC. We consider these data to be mature as the planned event count was reached for MFS and median survival reached for both PFS2 and OS.

In TITAN, the choice of co-primary endpoints, rPFS and OS, secondary and additional clinically meaningful endpoints are relevant and have been appropriately measured. Efficacy data from TITAN for rPFS, PFS2 and OS inform the economic model for mHSPC but data for PFS2 and OS are currently immature.

3.2.3.3 HRQoL outcomes

Changes from baseline over time were measured for a number of well-established HRQoL measures based on patient-reported outcomes. In SPARTAN, two instruments were used:

- Generic: EuroQol-5-Dimensions 3 Levels (EQ-5D-3L) questionnaire and Visual Analogue Scale (EQ-VAS) and
- Disease-specific: Functional Assessment of Cancer Therapy–Prostate Cancer (FACT-P) questionnaire. FACT-P consists of a 27-item Functional Assessment of Cancer Therapy-General (FACT-G) with four dimensions (physical, social, emotional and functional well-being) and a 12-item prostate cancer specific scale. Items are rated on a Likert scale (from 0 to 4) and combined to produce a global score and domain-based subscale scores. A higher score represents better QoL.

In TITAN, in addition to the 5-level version of the EQ-5D and FACT-P, two other HRQoL instruments were used:

- Brief Fatigue Inventory (BFI) which measures cancer-related fatigue intensity and its interference on daily functioning. Numerical rating scales are scored from 0-11 with a higher score indicating worse fatigue.
- Brief Pain Index-Short Form (BPI-SF) which measures worst pain intensity, average pain and pain interference with daily functioning. Numerical rating scales are scored from 0-10 with a higher score indicating worse pain.

HRQoL was measured at various time points as shown in Table 13. The CS describes pre- and post-progression results for HRQoL (CS B.2.7.4 and Appendix L.1) for SPARTAN but only pre-progression results for TITAN (B.2.12.4 and Appendix L.2).

Table 13 Timing of assessment for HRQoL measures

HRQoL instrument	Timing of measurement	
	SPARTAN	TITAN
EQ-5D-3L/5L & EQ-VAS	At baseline, Day 1 of each 28-day cycle in cycles 2-6, then Day 1 of every two cycles in cycles 7-13, then Day 1 of every four cycles and every four months during long-term follow up until 12 months post-progression	At baseline, Day 1 of cycles 1-7, then every other cycle until end of treatment, and every four months for up to one year after discontinuation.
FACT-P		
BFI	Not measured	From Day -6 to Day 1 of each cycle visit until the end of treatment and every 4 months for up to a year after discontinuation.
BPI-SF	Not measured	

EQ-5D-3L: EuroQol 5-Dimension 3-Level VAS: Visual Analogue Scale
Source: CS Table 6, Table 21, Section B.12.4 and Agarwal et al. 2019.[20]

The ERG considers the range of general and disease-specific HRQoL outcomes in SPARTAN and TITAN to be appropriate to the respective patient populations. The additional measures used in TITAN reflect the need to assess the impact of treatment on pain and fatigue symptoms which are more relevant in patients with metastases.

3.2.3.4 Safety outcomes

Patients were assessed at each clinical visit for adverse events (AEs) and serious AEs. Treatment-emergent AEs were graded by severity according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 and coded at preferred term and system organ class level using Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1. Numbers of and reasons for dose changes, interruptions and discontinuations were also recorded. Trial investigators assessed relatedness of Aes to study treatment.

In SPARTAN, adverse events of special interest (AESI) included skin rash, fall, fracture, hypothyroidism and seizure. In response to clarification question A2, the company report that ischaemic heart disease was not a predefined AESI in either trial but emerged as a new AESI during the course of the TITAN trial and has thus been included in the results for SPARTAN in this submission and that this will be included in subsequent data cut(s) for TITAN.

ERG conclusion

We consider the efficacy, HRQoL and safety outcomes to be appropriate to the decision problem and scope. However, data on OS and PFS2 in TITAN (mHSPC) are currently immature.

3.2.4 Statistical methods of the included studies

Table 14 provides a summary and ERG critique of the statistical methods used in the SPARTAN and TITAN trials.

Trial (patient group)	SPARTAN (nmHRPC)	TITAN (mHSPC)
Analysis populations		
	ITT population, defined as all randomised patients with study drug assignments designated according to initial randomization, regardless of whether patients receive study drug or receive a different drug (SPARTAN n=1,207; TITAN n=1,052). Safety population, defined as all randomised patients who received at least one dose of the study drug with treatment assignments designated according to actual study treatment received (SPARTAN n=1,201; TITAN n= 1,051).	
ERG comment:	Definition of ITT population accords with "true" ITT definition. Safety population as a proportion of the total number randomised was 99.5% (SPARTAN), and 99.9% (TITAN), thus minimal attrition bias.	
Sample size calculations		
	MFS (primary outcome) 372 events needed with 90% power to detect a 30% reduction in risk of metastases (HR = 0.70) for apalutamide plus ADT (two-sided α of 0.05).	rPFS (co-primary outcome) Approx ~368 rPFS events needed for at least 85% power to detect an HR of 0.67 (median rPFS of [redacted] months for ADT vs [redacted] months for apalutamide plus ADT) at a two-sided significance level of 0.005. OS (co-primary outcome) Approximately 410 events

	With an assumed median MFS of 25 months in the placebo plus ADT arm, the treatment effect would be an increase in median MFS of 11 months approx (25 to 36 months). Approximately 1,200 patients needed. (NB. The study was also powered for a decrease in risk of death, a secondary outcome)	required, with ~80% power to detect an HR of 0.75 (two tailed significance level of 0.045) with an assumed median OS of ** months for the ADT plus placebo group. Approximately 1,000 patients needed.
ERG comment:	Target sample size was reached in both trials, and therefore they can be considered sufficiently powered for their primary outcomes. The extension to median MFS in SPARTAN was greater than expected (25 months, versus 11 months, respectively). The median MFS in the placebo + ADT group was lower than expected (15.70 months versus 25 months). It is not clear why.	
Methods to account for multiplicty		
	[redacted] according to the pre-specified O'Brien-Fleming (OBF)-type alpha spending function with possible re-estimation of the required number of events necessary for the next analysis to maintain the desired conditional power. For change in EQ-5D-3L index score/VAS from baseline and least squares mean change from baseline in FACT-P and FACT-G total scores mixed models for repeated measures (MMRM)analyses were used which account for multiplicity.	Co-primary outcome rPFS was tested first at the two-sided 0.005 level of significance. If not statistically significant, the OS endpoint was to be tested at the two-sided 0.045 level of significance. Secondary endpoints were tested using a hierarchical sequence, in the order of presentation in CS section B.2.12.2 (secondary outcome results).
ERG comment:	The testing procedures specified appear to be appropriate to minimise misinterpretation due to multiple testing of outcomes.	
Analysis of outcomes		
	In both trials the analysis of outcomes was performed on the ITT population, incorporating the randomisation stratification factors (except where specified otherwise). The Kaplan-Meier method was used to summarise time-to-event outcomes. The Cox proportional-hazards model was used to estimate hazard ratios (with 95% CI)	

	Response endpoints summarised using descriptive statistics for categorical data by treatment group with the two treatment groups compared using the stratified Mantel-Haenszel test (except where expected counts in some cells are small then Fisher's exact test may be used). MFS, TTM and PFS based on BICR of radiographic tumour assessments data.	Endpoints with a binary outcome summarised by descriptive statistics for each treatment group. Treatment groups were compared using the chi-square test (except if expected counts in some cells are less than 5 when Fisher's exact test may be used). rPFS based on investigator assessed radiographic tumour assessments data.
ERG comment:	The analysis methods are considered appropriate for the outcome measures described.	
Handling of missing data		
	MFS: In the CS results are reported applying ex-US regulatory CHMP guidance. Patients without metastasis or death were censored on the date of the last tumour assessment (or date of randomisation if no tumour assessment had occurred since the baseline visit). Time of progression was determined using the first date with documented evidence of progression or death regardless of missed or unevaluable tumour assessments and regardless of any change in therapy. EQ-5D and FACT-P missing data handled as recommended in the User Manual's for these measures (and analysis by MMRM model).	[redacted]
ERG comment:	The approaches to handling missing MFS data are appropriate. The MMRM model is appropriate to account for missing HRQoL data over multiple time points.	Appropriate censoring rules were applied. There was no planned imputation for other missing or incomplete data.
Sensitivity & post-hoc analyses		
	For MFS and OS non-stratified log-rank tests were conducted as sensitivity analyses. For MFS, investigator assessed progression was conducted as a sensitivity analysis.	For rPFS and OS non-stratified log-rank tests were conducted as sensitivity analyses. For rPFS a sensitivity analysis was conducted based on central review data where the date of

	For OS, other sensitivity analyses were planned because a large number of subjects were expected to receive life-extending subsequent therapies.	progression was defined as the date of the scan showing 2 or more new bone lesions compared to the nadir of bone lesions (this was requested by the FDA). For OS other sensitivity analyses were planned to be carried out if deemed useful to interpret the result (adjusting for baseline prognostic factors, subsequent therapy use or cross-over)
ERG comment:	The sensitivity analyses described appear appropriate. No post-hoc analyses are described.	

BICR – blinded independent central review

3.2.4.1 Methods to adjust for the effects of treatment switching

The company use methods to adjust the survival estimates from both SPARTAN and TITAN RCTs to account for crossover from placebo plus ADT to apalutamide plus ADT when the trials were unblinded, and also to account for receipt of subsequent therapies not available/permitted in the NHS (to account for the one-novel-therapy-commissioning policy in England - the novel therapy analysis). The company explored the suitability of the statistical adjustments methods for treatment switching proposed in NICE DSU TSD 16:[28]

- Rank Preserving Structure Failure Time Models (RPSFTM)
- Iterative Parameter Estimation (IPE);
- Inverse Probability of Censoring Weights (IPCW);
- Two-stage method

After exploring the appropriateness of each of the above methods, the company chose to use an alternative method, which they describe as being a modification of RPSFTM using (external) patient-level data from COU-AA-302 an RCT comparing abiraterone acetate plus prednisone versus prednisone in metastatic castrate resistant prostate. The ERG's critique of the company's choice of adjustment method is provided in detail in section 4.2.6.2 of this report.

ERG conclusion

The company briefly summarise the statistical methods used in the SPARTAN and TITAN trials in the CS, with further detail given in the statistical analysis plans for these trials (sent in response to clarification question A9). The statistical methods appear appropriate for the aims and designs of the trials. The ERG did not identify any important limitations in the statistical analyses that would impact estimates of clinical effectiveness. The effects of crossover and the receipt of subsequent therapies not available in the NHS do impact clinical effectiveness and cost

effectiveness and the company has considered the available statistical adjustment methods recommended by NICE. The adjustment method they have chosen is similar to one of the NICE recommended methods with use of external data from an RCT. We provide a detailed critique of this in relation the modelling and extrapolation of survival data later in this report (Chapter 4).

3.2.5 Efficacy results for the high-risk nmHRPC population

In this section we focus on the three effectiveness outcomes that inform the economic model:

- MFS (primary outcome) in section 3.2.5.1
- OS (secondary outcome) in section 3.2.5.2
- PFS2 (other outcome) in section 3.2.5.3

We also present the OS and PFS2 results after adjustment for receipt of more than one novel therapy and patients who crossed over from the placebo plus ADT arm to the apalutamide plus ADT arm. We have not reported on effectiveness outcomes included in the CS that do not inform the economic model (time to initiation of cytotoxic chemotherapy; PSA response rate; time to PSA progression (TTPSA); and PSA kinetics in patients with advanced prostate cancer).

HRQoL outcomes (section 3.2.5.5), subgroup analyses (section 3.2.5.6) and safety outcomes (section 3.2.5.7) follow the effectiveness outcomes.

3.2.5.1 Primary outcome: Blinded independent central review (BICR) metastases-free survival (MFS)

BICR MFS was the primary outcome for the SPARTAN trial and the final analysis for this outcome took place at the first interim study analysis (clinical cut-off date 19th May 2017).

In the apalutamide plus ADT arm 209 patients (25.9%) had distant metastases or had died in comparison to 210 patients (52.4%) in the placebo plus ADT arm (Table 15). The majority of the BICR MFS events were metastases (Apalutamide plus ADT arm 204 metastases, placebo plus ADT arm 188 metastases) and Smith et al.[8] report that among the patients who had metastases, 60.5% in the apalutamide arm and 54.4% in the placebo arm had bone metastases.

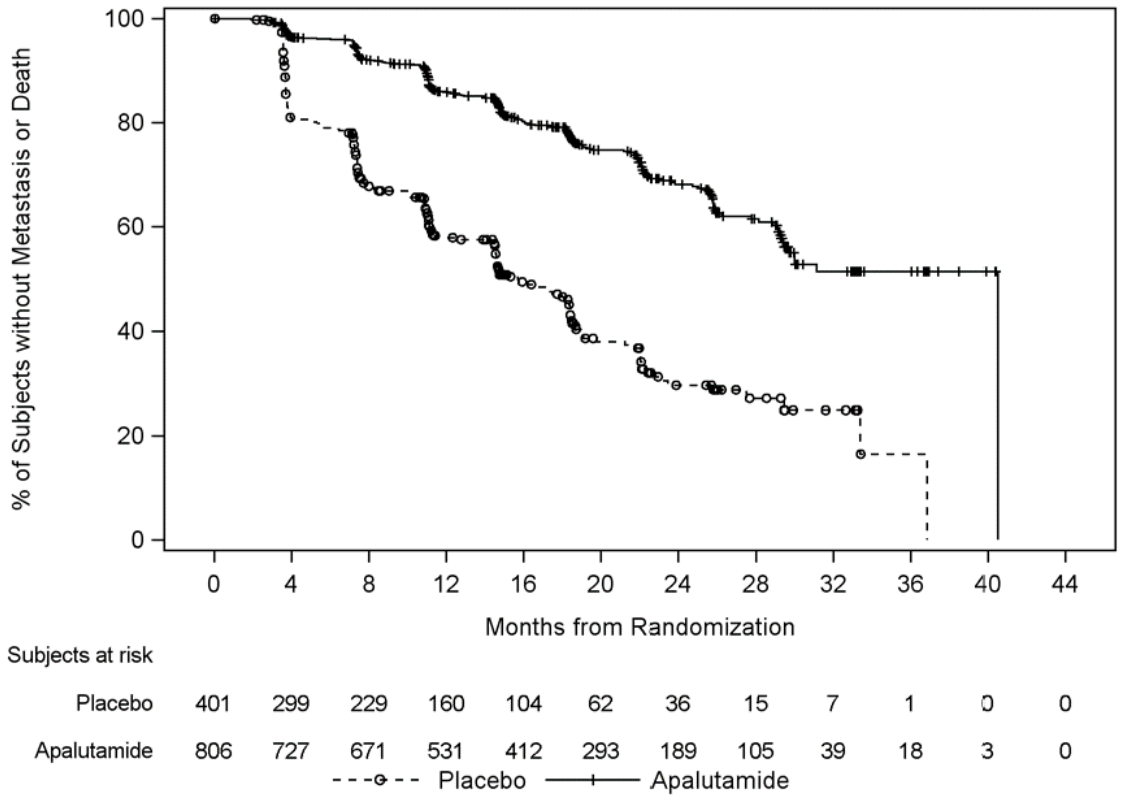
Median MFS was extended by 25 months from 15.70 months (95% CI: 14.55–18.40) for the placebo plus ADT arm to 40.51 months (95% CI: 29.70–40.51) for the apalutamide plus ADT

arm (Table 15). This is a statistically significant extension (p<0.0001) and our clinical experts agreed it is a clinically meaningful result.

Table 14 Summary of BICR MFS in SPARTAN (IA1, clinical cut-off date 19th May 2017; ITT population)

ITT population	Apalutamide plus ADT (n = 806)	Placebo plus ADT (n = 401)
Event, n (%)	209 (25.9)	210 (52.4)
Censored, n (%)	597 (74.1)	191 (47.6)
MFS (months)		
25th percentile (95% CI)	19.55 (18.23–22.14)	7.26 (5.55–7.43)
Median (95% CI)	40.51 (29.70–40.51)	15.70 (14.55–18.40)
75th percentile (95% CI)	40.51 (NE–NE)	29.47 (23.06–36.83)
Range	(0.0 [a]–40.5)	(0.0 [a]–36.8)
12-month event-free rate (95% CI)	0.861 (0.833–0.884)	0.579 (0.525–0.629)
24-month event-free rate (95% CI)	0.682 (0.638–0.722)	0.296 (0.235–0.360)
36-month event-free rate (95% CI)	0.514 (0.443–0.581)	0.165 (0.055–0.327)
p value	< 0.0001	
Hazard ratio (95% CI) [b]	0.297 (0.244–0.362)	

Source: CS Table 13
ADT: androgen deprivation therapy; BICR: blinded independent central review; MFS: metastases-free survival
[a] Censored observation.
[b] Hazard ratio is from a stratified proportional hazards model with a single factor of treatment group, stratified by PSADT (≤ 6 months vs > 6 months), bone-sparing agent use (yes vs no) and loco-regional disease (N0 vs N1). Hazard ratio < 1 favours active treatment.



Source: CS Figure 10
Notes: Analysis was performed with stratification according to PSADT (>6 months vs ≤6 months), use of bone-sparing agents (yes vs no), and classification of local or regional nodal disease (N0 vs N1) at the time of trial entry

Figure 3 Kaplan-Meier plot for BICR MFS in SPARTAN (IA1, clinical cut-off date 19th May 2017; ITT population)

3.2.5.2 Secondary outcome: Overall survival

At the final SPARTAN trial analysis (52 months median follow-up) there had been 274 deaths (34.0%) in the apalutamide plus ADT arm and 154 deaths (38.4%) in the placebo plus ADT arm (Table 16). The risk of death was decreased by 22% in the apalutamide plus ADT arm compared with placebo plus ADT (HR 0.784; 95% CI 0.643, 0.956), 2-sided p = 0.016). Median OS was extended in the apalutamide + ADT arm by 14 months (p<0.0001) to 73.9 months in the apalutamide plus ADT arm in comparison to 59.9 months in the placebo plus ADT arm (Table 16 and Figure 4).

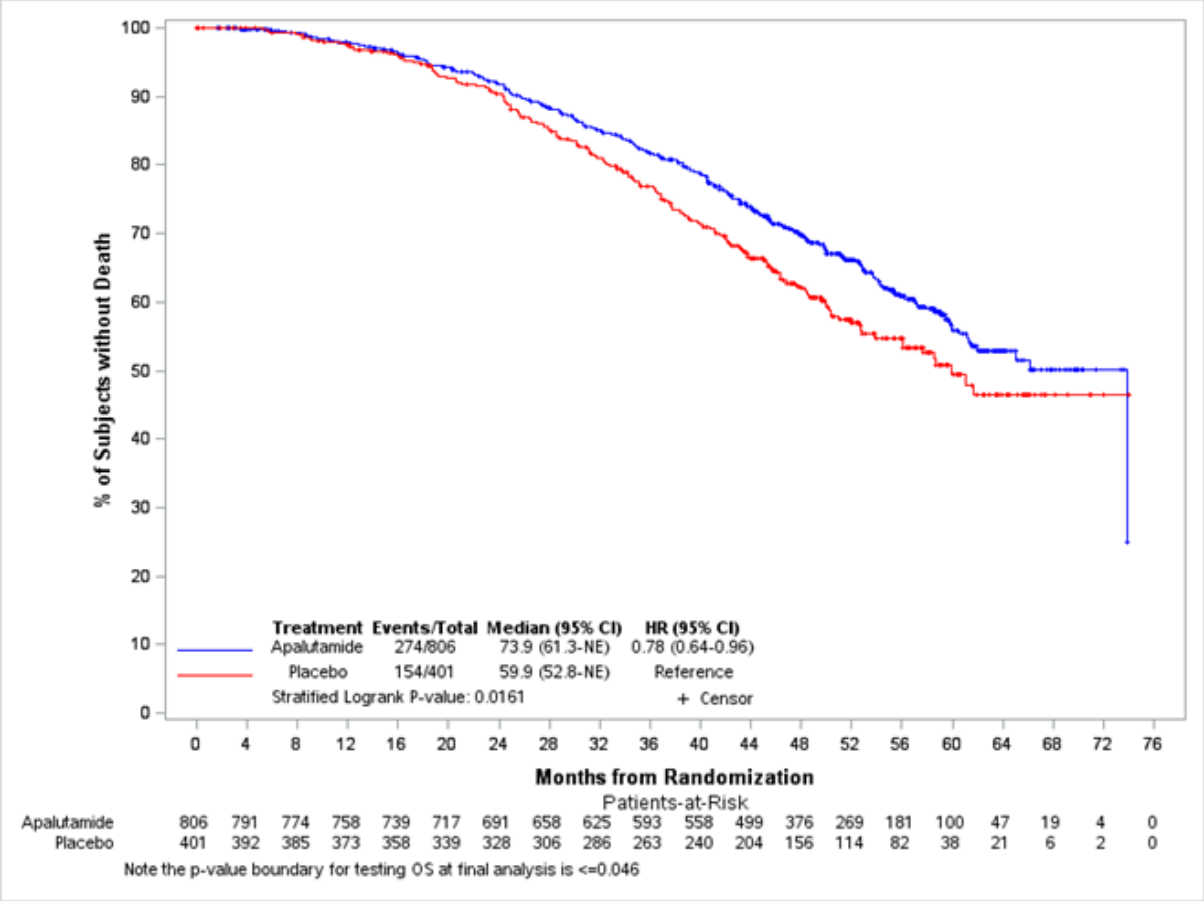
The company point out that statistically significant superiority of OS in the apalutamide plus ADT trial arm occurred despite any confounding that had occurred because of the patients who crossed over from placebo to apalutamide after the study was unblinded at the first interim analysis (n=76, which was 64% of the ongoing placebo plus ADT patients at unblinding, or 19.0% of randomised placebo plus ADT patients). Furthermore 279 (69.6%)

patients randomised to placebo plus ADT received life prolonging subsequent therapy for metastatic prostate cancer in comparison to 371 (46.0%) patients randomised to apalutamide plus ADT.

Table 15 Summary of OS in SPARTAN (Final analysis, clinical cut-off date 1st February 2020; ITT population)

ITT population	OS unadjusted for crossover	
	Apalutamide plus ADT (n = 806)	Placebo plus ADT (n = 401)
Event, n (%)	274 (34.0%)	154 (38.4%)
Censored, n (%)	[redacted]	[redacted]
OS (months)		
25th percentile (95% CI)	[redacted]	[redacted]
Median (95% CI)	73.86 (61.21–NE)	59.89 (52.80–NE)
75th percentile (95% CI)	[redacted]	[redacted]
Range	[redacted]	[redacted]
1-year survival rate (95% CI)	[redacted]	[redacted]
2-year survival rate (95% CI)	[redacted]	[redacted]
3-year survival rate (95% CI)	[redacted]	[redacted]
4-year survival rate (95% CI)	[redacted]	[redacted]
5-year survival rate (95% CI)	[redacted]	[redacted]
6-year survival rate (95% CI)	[redacted]	[redacted]
p value	0.0161	
Hazard ratio (95% CI) [b]	0.784 (0.643–0.956)	

Source: CS Table 14
ADT: androgen deprivation therapy; OS: overall survival
[a] Censored observation
[b] Hazard ratio is from a stratified proportional hazards model with a single factor of treatment group, stratified by PSADT (≤ 6 months vs > 6 months), bone-sparing agent use (yes vs no) and loco-regional disease (N0 vs N1). Hazard ratio < 1 favours active treatment.

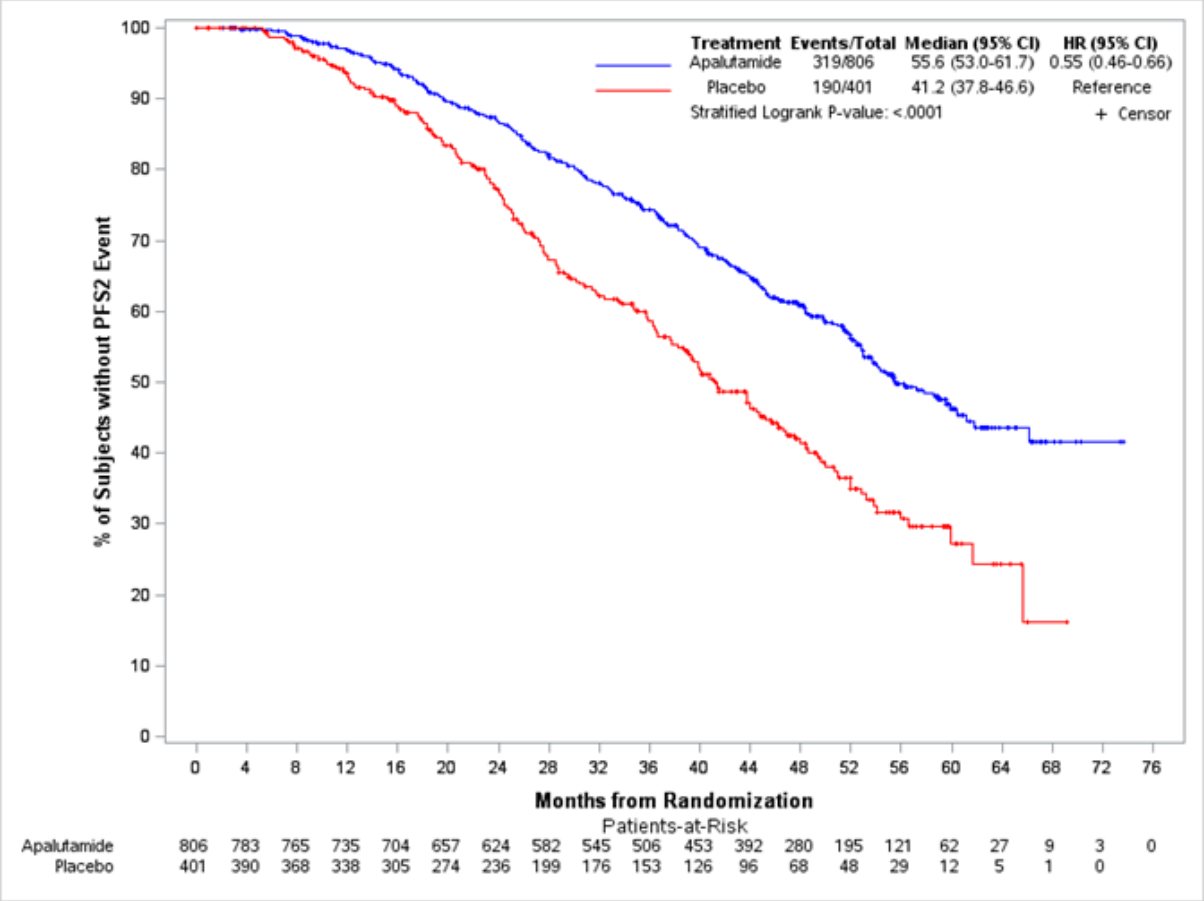


Source: CS Figure 11
NE, not estimable

Figure 4 Kaplan-Meier plot for OS in SPARTAN (Final analysis, clinical cut-off date 1st February 2020; ITT population)

3.2.5.3 Second progression-free survival (PFS2)

In the apalutamide plus ADT arm there was a statistically significant extension in PFS 2 of 14.4 months in comparison to the placebo plus ADT arm in the SPARTAN RCT (p<0.0001). In the apalutamide plus ADT arm 319 (39.6%) participants had a PFS2 event in comparison to 190 (47.4%) in the placebo plus ADT arm. The risk of a PFS2 event was decreased by 45% in the apalutamide plus ADT arm compared with placebo plus ADT (HR 0.55; 95% CI 0.46 to 0.66, p < 0.0001).



Source: CS Figure 12
NE: not estimable

Figure 5 Kaplan-Meier plot for PFS2 (SPARTAN, Final analysis, clinical cut-off date 1st February 2020; ITT population)

3.2.5.4 Adjustment of OS and PFS2

As already described earlier in this report (section 3.2) patients randomised to placebo plus ADT were permitted to crossover to receive apalutamide plus ADT after trial unblinding, and 19% of placebo plus ADT arm participants crossed over. Additionally, some patients in SPARTAN received subsequent treatment with therapies that are not available in English clinical practice, and some patients who received apalutamide also received one or more additional novel therapies (abiraterone and enzalutamide) [apalutamide plus ADT arm [redacted] received a second novel therapy in comparison to [redacted] in the placebo + ADT arm). In contrast, in England patients are only permitted to receive one novel therapy (i.e. if they had already received apalutamide they would not be permitted to receive abiraterone or enzalutamide). The CS summarises the life-prolonging subsequent therapies received in SPARTAN in CS Table 16.

The company used a modified RPSFTM approach, as described by Diels et al[29] to adjust the results for the effects of i) receiving more than one novel therapy during the course of their disease and ii) the crossover from the placebo plus ADT arm to the apalutamide plus ADT arm. Further detail on the adjustment methods can be found in section 4.2.6, 4.2.7 and 4.2.8 of this report. The adjusted results are shown alongside the unadjusted results in Table 17.

Table 16 Comparison of unadjusted OS and PFS2 with adjusted OS and PFS2 results from SPARTAN

ITT population	Unadjusted	Adjusted
OS: Hazard ratio (95% CI)	0.784 (0.643 to 0.956) p = 0.0161	0.77 (0.64 to 0.94) p-value not reported
PFS2: Hazard ratio (95% CI)	[redacted]	[redacted] p-value not reported

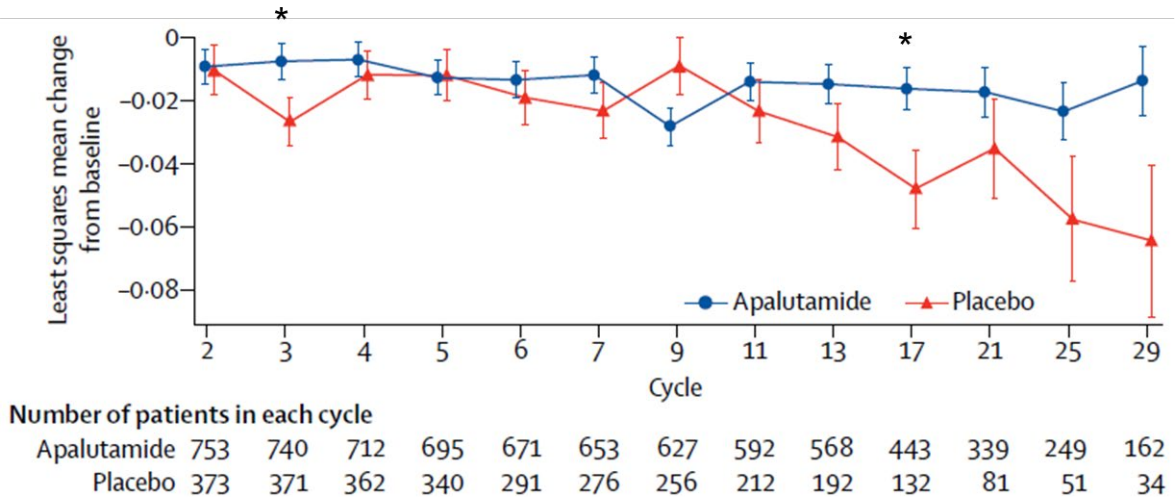
Source: CS Tables 14 and 15, supplemented with information from CS p. 78-79.

3.2.5.5 HRQoL outcomes

Two questionnaires were used to collect HRQoL data at pre-progression and post-progression disease stages; the EQ-5D-3L and the FACT-P. Further detail on how data from these outcomes were used in the economic model is provided in section 4.2.10 of this report. The company do not report on the HRQoL results in the post-progression phase in the main CS report (the data are presented in CS appendix L) and these data are not presented in this section.

3.2.5.5.1 EQ-5D-3L

Figure 6 shows the EQ-5D-3L scores were comparable across both treatment arms and HRQoL was maintained in patients who received apalutamide plus ADT. Although the mean changes in EQ-5D-3L index scores were suggestive of a decline in HRQoL in the placebo arm, particularly from cycle 11 onward, a statistically significant difference between trial arms was only observed at two time points (cycle 3 and cycle 17).

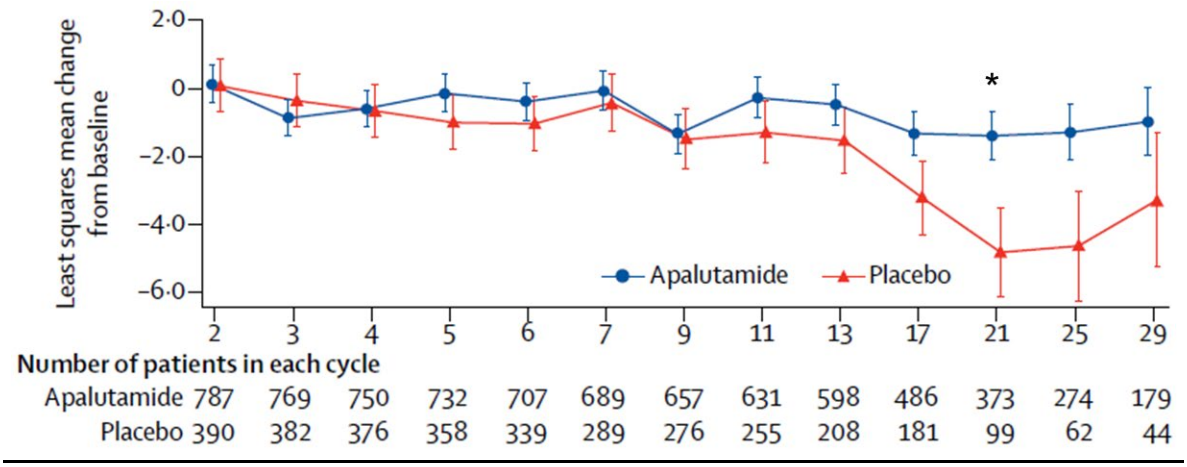


Source: CS Figure 16
Notes: * indicates $p < 0.05$. Note that the x axis intervals are not constant

Figure 6 Least squares mean change in EQ-5D-3L index score pre-progression from baseline (repeated measures analysis) in SPARTAN (IA1; clinical cut-off date 19th May 2017; ITT population)

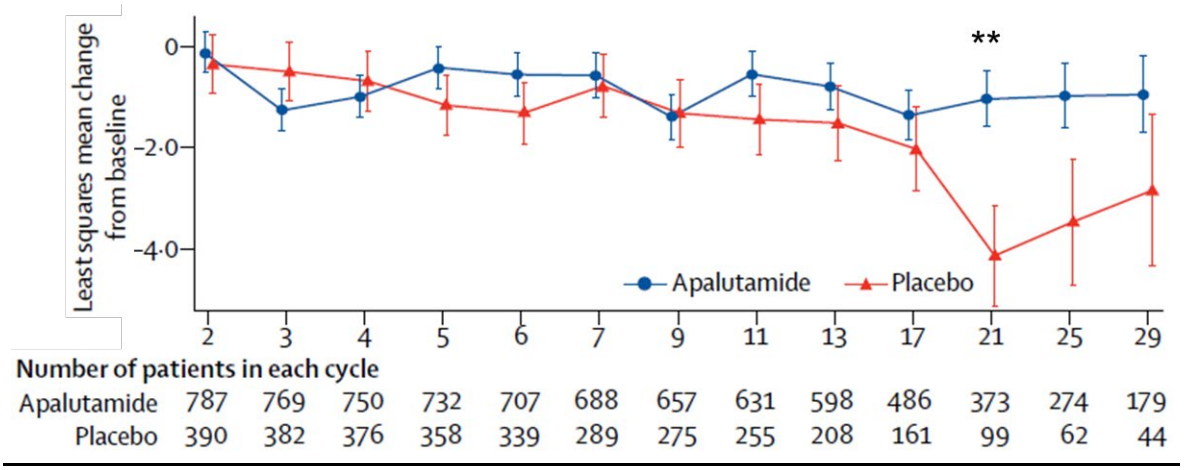
3.2.5.5.2 FACT-P

The FACT-P (which consists of the FACT-G and a 12-item prostate-specific scale) results were in line with the EQ-5D-3L results. The least squares mean changes from baseline to cycle 29 of treatment in FACT-P scores and FACT-G scores are shown in Figure 7 and Figure 8 respectively. Completion of the FACT-P questionnaire was at least 95% (range 95% to 100%) at any assessment visit and the company states the completion rates were similar between the treatment arms. At baseline the FACT-P and FACT-G scores were similar in the two treatment arms and HRQoL was maintained in patients who received apalutamide plus ADT (Figure 7 and Figure 8 respectively). In line with the EQ-5D-3L results, the FACT-P and FACT-G data were suggestive a decline in HRQoL in the placebo arm in later treatment cycles (from about cycle 11). However, statistically significant differences between trial arms were observed at cycle 21 only.



Source: CS Figure 18, ERG has deleted some abbreviations
FACT-P: Functional Assessment of Cancer Therapy – Prostate
Notes: * indicates $p < 0.05$. Note that the x axis intervals are not constant

Figure 7 Least squares mean change from baseline in FACT-P total scores (repeated measures analysis) in SPARTAN (IA1; clinical cut-off date 19th May 2017; ITT population)



Source: CS Figure 19, ERG has deleted some abbreviations
FACT-G: Functional Assessment of Cancer Therapy – General
Notes: * indicates $p < 0.05$. Note that the x axis intervals are not constant

Figure 8 Least squares mean change from baseline in FACT-G total scores (repeated measures analysis) in SPARTAN (IA1; clinical cut-off date 19th May 2017; ITT population)

3.2.5.6 Subgroup analyses

For the nmHRPC population the NICE scope did not list any particular subgroup of interest.

The company conducted analyses for the nmHRPC population on the outcomes of MFS and OS across a range of pre-defined subgroups as shown in CS Figure 20 and Figure 21 respectively.

For MFS, the results favoured apalutamide plus ADT over placebo plus ADT in all subgroups except that for black adults. However, the sample size for this subgroup was small (n=68) therefore the result is subject to uncertainty as evidenced by the wide confidence intervals for the hazard ratio (HR 0.59, 95% CI 0.23 to 1.48).

For OS, the results favoured apalutamide plus ADT over placebo plus ADT in the majority of subgroups with three exceptions. The first exception was in the subgroup of adults aged 65 to less than 75 years where the HR of 1.02 (95% CI 0.74 to 1.42) differed from the other two age subgroups (<65 years HR of 0.39, 95% CI 0.19 to 0.78) and ≥75 years HR of 0.74, 95% CI 0.57 to 10.97). The CS states there seems to be no clinical rationale why the middle of the three age subgroups should differ in response to apalutamide plus ADT in comparison to the other two age subgroups. The other two exceptions were the subgroups of Black (HR 1.11, 95% CI 0.40 to 3.09, n=68) and of Asian (HR 1.22, 95% CI 0.58 to 2.53, n=140) patients. The company suggests that the hazard ratios observed may have been due to a combination of the small sample sizes, few death events and differences between the treatment arms of these two subgroups.

3.2.5.7 Safety outcomes

The company's safety analysis includes [redacted] 803 patients in the apalutamide plus ADT arm and 398 patients in the placebo arm.

3.2.5.7.1 Treatment duration, dose interruptions and dose modifications

There was a significant difference in the median exposure to treatment between the two treatment arms (apalutamide plus ADT median of 32.9 months versus placebo plus ADT median of 11.5 months, CS Figure 22 and cumulative exposure to study treatments summarised in CS Table 22). There were still [redacted] of patients in the apalutamide plus ADT arm still on treatment at [redacted] at the final analysis whereas there were only [redacted] patients still on treatment at [redacted] in the placebo plus ADT arm. The CS therefore presents and discusses TEAE incidence in terms of events per 100 patient-years when appropriate to take account of the difference in median exposure between the two arms.

Most patients in both study arms were able to tolerate the full prescribed dose of study medication and most received no dose modifications (no dose modifications in [redacted] of the apalutamide plus ADT arm and [redacted] of the placebo plus ADT arm). The CS summarises the reasons for the dose reductions and interruptions that were necessary in CS Table 23.

3.2.5.7.2 Summary of adverse events

The company's summary table of adverse events is reproduced below in Table 18.

Table 17 Summary of adverse events SPARTAN trial (Final analysis; clinical cut-off date 1st February 2020; safety population

AE, n (%)	Apalutamide plus ADT (n = 803)		Placebo plus ADT (n = 398)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
All causality Aes	781 (97.3%)	449 (55.9%)	371 (93.2)	373 (93.7%)
Drug-related Aes [a]	[redacted]	[redacted]	[redacted]	[redacted]
Aes leading to treatment discontinuation	120 (14.9%)	[redacted]	29 (7.3%)	[redacted]
Drug-related Aes leading to treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
All-causality SAEs [b]	290 (36.1%)	[redacted]	99 (24.9%)	[redacted]
Drug-related SAEs[a]	[redacted]	[redacted]	[redacted]	[redacted]
Fatal SAEs	24 (3.0%)	[redacted]	2 (0.5%)	-
Fatal drug-related SAEs[a]	1 (0.1%)	[redacted]	[redacted]	[redacted]

Source: reproduction of CS Table 24, footnotes edited.
AE: adverse event; SAE: serious adverse event
[a] Adverse events reported as related. [b] Excludes Grade 5.
Notes: Percentages are based on the Safety population. For each category patients are counted only once even if they experienced multiple events in that category.

3.2.5.7.3 Summary of treatment emergent adverse events

The company summarised the TEAEs that occurred in more than 15% of patients in either study arm. The company's summary table is reproduced below with events ordered by the proportion in the apalutamide plus ADT arm experiencing that event (any grade).

Table 18 Summary of most frequent all-causality treatment-emergent adverse events reported in > 15% patients in SPARTAN (Final analysis; clinical cut-off date 1st February 2020; safety population)

	Apalutamide plus ADT (n = 803)		Placebo plus ADT (n = 398)	
AE (%)[a]	**Any grade**	**Grade 3-4**	**Any grade**	**Grade 3-4**
Fatigue	262 (32.6%)	7 (0.9%)	85 (21.4%)	1 (0.3%)
Hypertension	225 (28.0%)	131 (16.3%)	83 (20.9%)	49 (12.3%)
Diarrhoea	187 (23.3%)	12 (1.5%)	61 (15.3%)	2 (0.5%)
Arthralgia	160 (19.9%)	3 (0.4%)	33 (8.3%)	0
Nausea	157 (19.6%)	0	63 (15.8%)	0
Weight decreased	157 (19.6%)	12 (1.5%)	26 (6.5%)	1 (0.3 %)
Back pain	144 (17.9%)	11 (1.4%)	61 (15.3%)	6 (1.5%)
Hot flush	122 (15.2%)	0	34 (8.5%)	0

Source: CS Table 25, duplicate row for nausea deleted, rows reordered, footnotes edited.
[a] Treatment-emergent Aes were those that occurred between the date of 1st dose of study drug and date of last dose of study drug +28 days
Notes: Patients are counted only once for any given event, regardless of the number of times they experienced the event. The event experienced by the patient with the worst toxicity grade is used. If a patient had all Aes with missing toxicity grades, the patient is only counted in the "All grades" column

Grade 3 and 4 adverse events

The company summarise treatment-emergent grade 3 and grade 4 Aes (reported in 5% or more of patients) in CS Table 26. A greater proportion of patients in the apalutamide plus ADT arm experienced grade 3-4 TEAEs than in the placebo plus ADT arm (56% versus 36% respectively) with grade 3 events being more common than grade 4 events ([redacted] of patients in the apalutamide plus ADT arm and [redacted] of patients in the placebo plus ADT arm.

However, after adjustment for the longer exposure time for the apalutamide plus ADT arm the Grade 3 and Grade 4 TEAE rates were lower in the apalutamide plus ADT arm than in the placebo plus ADT arm (Grade 3: [redacted] events per 100 patient-years in the apalutamide plus ADT arm in comparison to [redacted] for the placebo arm; Grade 4: [redacted] events per 100 patient-years in the apalutamide plus ADT arm in comparison to [redacted] for the placebo arm. The results adjusted for exposure time to study treatments indicate that the addition of apalutamide to ADT was not associated with an additional incidence of grade 3 and grade 4 TEAEs.

3.2.5.7.4 Summary of serious adverse events

The most frequent treatment-emergent SAEs (reported in 1% or more of patients) are summarised in CS Table 27. A greater proportion of patients in the apalutamide plus ADT arm experienced an SAE than in the placebo plus ADT arm (36% versus 25% respectively).

After adjustment for the longer exposure time for the apalutamide plus ADT arm the number of distinct treatment-emergent SAEs was lower in the apalutamide plus ADT arm than in the placebo plus ADT arm (13.7 events per 100 patient-years in the apalutamide plus ADT arm in comparison to 22.2 for the placebo arm. The company adjusted the frequently reported SAEs (occurring in at least 1% of patients) and found that the SAE profiles were similar for both trial arms (Table 20).

Table 19 Treatment-emergent SAEs adjusted for treatment exposure

	Apalutamide plus ADT (n=803)	**Placebo plus ADT (n=398)**
Treatment-emergent SAEs per 100 patient-years	13.7	22.2
Frequently reported SAEs[a], that occurred at a higher incidence in the APA+ADT arm than the placebo arm, adjusted for exposure		
Pneumonia	[redacted]	[redacted]
Fall	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Cerebrovascular accident	[redacted]	[redacted]
Syncope	0.3	0.2
Osteoarthritis	0.3	0
Haematuria	0.6	0.7
Urinary tract infection	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]
Urinary retention	[redacted]	[redacted]
Hydronephrosis	[redacted]	[redacted]
Urinary tract obstruction	[redacted]	[redacted]
[a] Occurring in at least 1% of patients		

3.2.5.7.5 Summary of adverse events of special interest

A summary of treatment-emergent adverse events of special interest (AESI) is presented in CS Table 28. These results are not adjusted for treatment exposure. The incidence of AESI was higher for all the events (skin rash, fall, fracture, hypothyroidism, ischaemic heart disease and seizure) in the apalutamide plus ADT arm than in the placebo plus ADT arm. Overall, [redacted] of the apalutamide arm experienced an AESI compared to [redacted] of the placebo plus ADT arm. The biggest difference between arms in a single AESI was for skin rash (26.4% of the apalutamide arm compared to 6.3% of the placebo plus ADT arm). Our clinical experts highlighted the importance of adjusting for treatment exposure and suggested falls, seizures and cardiac events warranted further consideration. This information is provided in the SPARTAN CSR[17] which reports:

- The incidence of fall is still higher in apalutamide arm after adjustment for treatment exposure (12.4 events per 100-person years vs 9.6 events in the placebo arm)
- Seizures, which occurred only in the apalutamide arm, are a rare event (0.2 events per 100-patient years) and the exposure adjusted incidence suggests the risk does not diminish over time on apalutamide therapy
- [redacted]

3.2.5.7.6 Summary adverse events leading to death

The company's summary table of adverse events leading to death is reproduced below (Table 21). The data have not been adjusted for treatment exposure. A greater proportion of participants in the apalutamide plus ADT arm died within 28 days of the last dose of study medication due to an adverse event (2.2% of the apalutamide arm compared to 0.5% of the placebo plus ADT arm).

Table 20 Summary of deaths (SPARTAN, safety population)

	Apalutamide plus ADT (n = 803)	**Placebo plus ADT (n = 398)**
Number of patients with TEAEs leading to death n (%)	24 (3)	2 (0.5)
Drug related[a]	1 (0.1)	0
All deaths within 28 days of last dose	22 (2.7)	2 (0.5)
Adverse event	18 (2.2)	2 (0.5)

	Apalutamide plus ADT (n = 803)	Placebo plus ADT (n = 398)
Death due to prostate cancer	3 (0.4)	0
Other	1 (0.1)	0

Source: CS Table 29, footnotes edited.
[a] adverse events reported as related
Notes: Percentages are based on the safety population. TEAEs are those that occurred between the date of first dose of study drug and date of last dose of study drug +28 days. For each category, subjects are counted only once, even if the experienced multiple events in that category

3.2.6 Efficacy results for the mHSPC population

In this section we focus on the three effectiveness outcomes that contribute data to the economic model:

- rPFS (co-primary outcome) in section 3.2.6.1
- OS (co-primary outcome) in section 3.2.6.2
- PFS2 (other outcome) in section 3.2.6.3

We also present the OS and PFS2 results after adjustment for patients who received more than one novel therapy. We do not report on effectiveness outcomes included in the CS that do not inform the economic model. These outcomes are: time to initiation of cytotoxic chemotherapy; time to pain progression; time to opioid use; time to SREs; time to PSA progression; best overall response; prostate cancer-specific survival; and time to symptomatic local progression.

HRQoL outcomes (section 3.2.6.5), subgroup analyses (section 3.2.6.6) and safety outcomes (section 3.2.6.7) follow the effectiveness outcomes.

3.2.6.1 Co-primary outcome: radiographic progression-free survival (rPFS)

rPFS (assessed by investigator) was a co-primary outcome for the TITAN RCT with all scans collected for blinded independent review (although only about 60% we subject to independent central review). At the time of the primary analysis (clinical cut-off date 23rd November 2018) a stratified log-rank test showed rPFS was statistically significantly delayed in the apalutamide plus ADT arm in comparison to the placebo plus ADT arm (HR 0.48, 95% CI 0.39 to 0.60, p<0.0001) (Table 22). A sensitivity analysis using a non-stratified log rank test confirmed this result (HR 0.49, 95% CI 0.40 to 0.61, p<0.0001) as did supportive analyses using a multivariate Cox regression analysis (HR 0.43, 95% CI 0.34 to 0.54, p<0.0001). In response to clarification question A1 the company provided the results from the BICR analysis of rPFS. These results, from a random sample of approximately 60% of

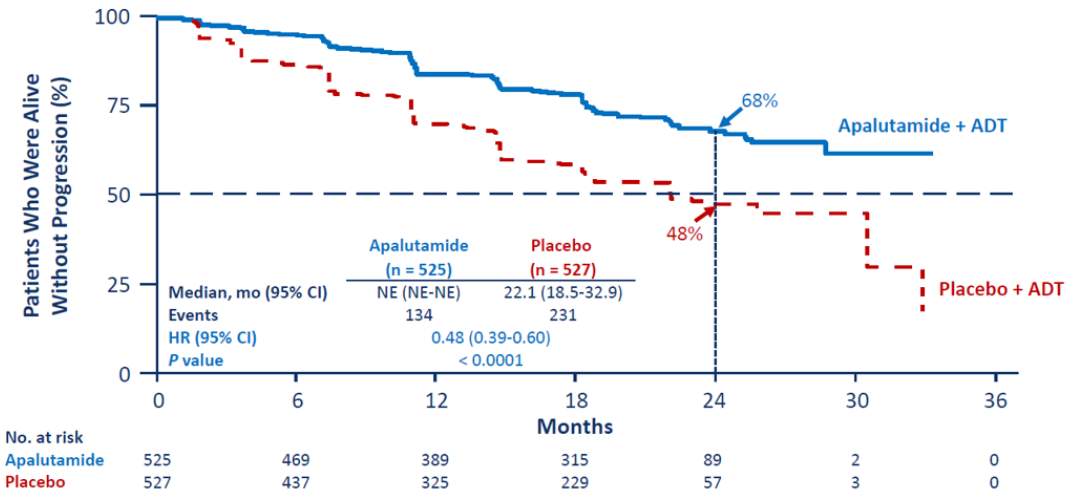
TITAN participants were in line with the investigator assessed results (HR [redacted]).

In the apalutamide plus ADT arm 134 of the ITT population (25.5%) experienced an rPFS event in comparison to 231 (43.8%) of the placebo plus ADT arm. Median rPFS was not reached in the apalutamide +ADT arm and was 22 months in the placebo plus ADT arm (Figure 9).

Table 21 Summary of rPFS in TITAN (investigator assessed, ITT population).

ITT population	Apalutamide plus ADT (n = 525)	Placebo plus ADT (n = 527)
Event, n (%)	134 (25.5)	231 (43.8)
Censored, n (%)	391 (74.5)	296 (56.2)
rPFS (months)		
25th percentile (95% CI)	18.43 (17.38, 22.11)	10.91 (8.71, 11.10)
Median (95% CI)	NE (NE, NE)	22.08 (18.46, 32.92)
75th percentile (95% CI)	NE (NE, NE)	32.92 (30.49, NE)
Range	(0.0[a], 33.3[a])	(0.0[a], 33.1[a])
62-month event-free rate (95% CI)	0.955 (0.932, 0.970)	0.870 (0.838, 0.896)
12-month event-free rate (95% CI)	0.843 (0.807, 0.873)	0.703 (0.660, 0.741)
24-month event-free rate (95% CI)	0.682 (0.629, 0.729)	0.475 (0.421, 0.528)
36-month event-free rate (95% CI)	NE (NE, NE)	NE (NE, NE)
p value [b]	< 0.0001	
Hazard ratio (95% CI) [c]	0.484 (0.391, 0.600)	

Source: CS Table 31
ADT: androgen deprivation therapy; rPFS: radiographic progression-free survival
[a] censored observation. [b] p-value is from the log-rank test stratified by Gleason score at diagnosis (≤ 7 vs >7, Region (NA/EU vs Other Countries) and Prior docetaxel use (Yes vs No). [c] Hazard ratio is from stratified proportional hazards model. Hazard ratio < 1 favours active treatment.



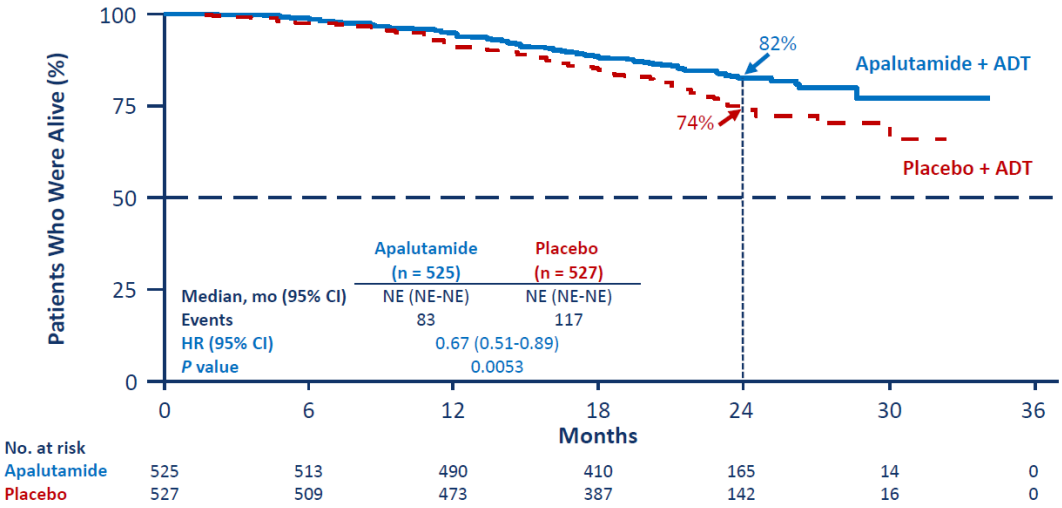
Source: CS Figure 23
NE: not estimable

Figure 9 Kaplan-Meier plot of rPFS (TITAN, ITT population)

3.2.6.2 Co-primary outcome: Overall survival

At the first interim TITAN trial analysis (clinical cut-off date 23rd November 2018, 22 months follow-up) there had been 83 deaths (15.8%) in the apalutamide plus ADT arm and 117 deaths (22.2%) in the placebo plus ADT arm. The risk of death was decreased by 33% in the apalutamide plus ADT arm compared with placebo plus ADT (HR 0.67; 95% CI 0.51 to 0.89, p = 0.0053). Median OS was not reached in either arm (Figure 10).

Results from the sensitivity analysis using a non-stratified log-rank test for OS (HR [redacted]) support those from the stratified log-rank test. Similarly, the results from a supportive analysis using a multivariate Cox regression analysis are consistent with the primary analysis (HR [redacted]).

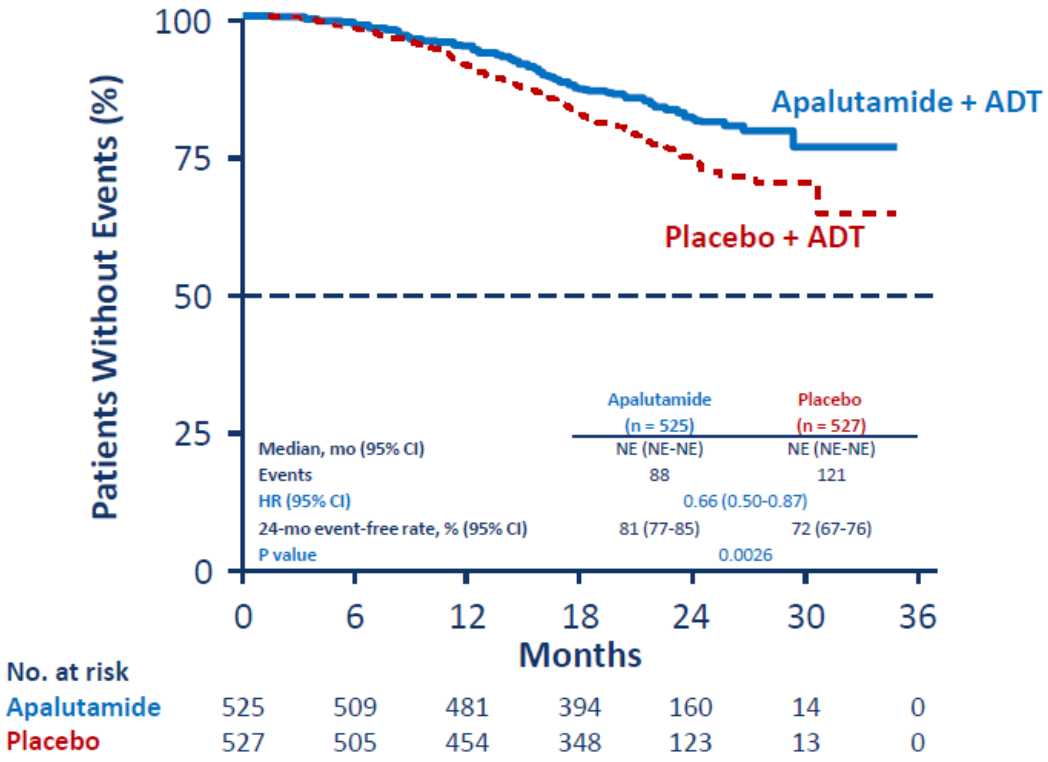


Source: CS Figure 24
NE: not estimable

Figure 10 Kaplan-Meier plot of OS (TITAN, ITT population)

3.2.6.3 PFS2

PFS 2 was statistically significantly delayed in the apalutamide plus ADT arm in comparison to the placebo plus ADT arm in the TITAN RCT. In the apalutamide plus ADT arm 88 (16.8%) participants had a PFS2 event in comparison to 121 (23.0%) in the placebo plus ADT arm. Median time to PFS 2 was not reached in either arm (Figure 11). The risk of a PFS2 event was decreased by 34% in the apalutamide plus ADT arm compared with placebo plus ADT (HR 0.66; 95% CI 0.50 to 0.87, p = 0.0026).



Source: CS Figure 25
NE: not estimable

Figure 11 Kaplan-Meier plot of time to PFS2 (TITAN, ITT population)

3.2.6.4 Adjustment of OS and PFS2

As already described earlier in this report (section 3.2), patients randomised to placebo plus ADT in the TITAN trial were permitted to crossover to receive apalutamide plus ADT after trial unblinding. Data for the trial period after unblinding and crossover is not yet available hence the OS and PFS2 data included in the CS are unaffected by confounding due to crossover. However, similarly to the SPARTAN trial, some patients in TITAN received subsequent treatment with therapies that are not available in English clinical practice, with some patients in particular receiving more than one novel therapy [apalutamide plus ADT arm [redacted] received a second novel therapy in comparison to [redacted] in the placebo + ADT arm). The CS summarises the life-prolonging subsequent therapies received in TITAN in CS Table 132.

The company used a modified version of the RPSFTM[29] and inverse probability of censored weights (IPCW) methodologies to adjust the results for the effects of patients receiving more than one novel therapy during the course of their disease. Further detail on the adjustment

methods can be found in sections 4.2.6, 4.2.7 and 4.2.8 of this report. The adjusted results are shown alongside the unadjusted results in Table 23.

For OS, both the RPSFTM and IPCW methods of adjustment had very limited impact. For PFS2 adjustment using the RPSFTM method had very limited impact. For the IPCW adjustment of PFS2 the company states that the results were counterintuitive since they did not fit with the clinical hypothesis of these analyses (i.e. the adjusted HR suggested increased benefit whereas the hypothesis was the adjustment should lower the benefit). The IPCW-adjusted PFS2 results were therefore not carried over to the cost-effectiveness modelling.

Table 22 Comparison of unadjusted OS and PFS2 with adjusted OS and PFS2 results from TITAN

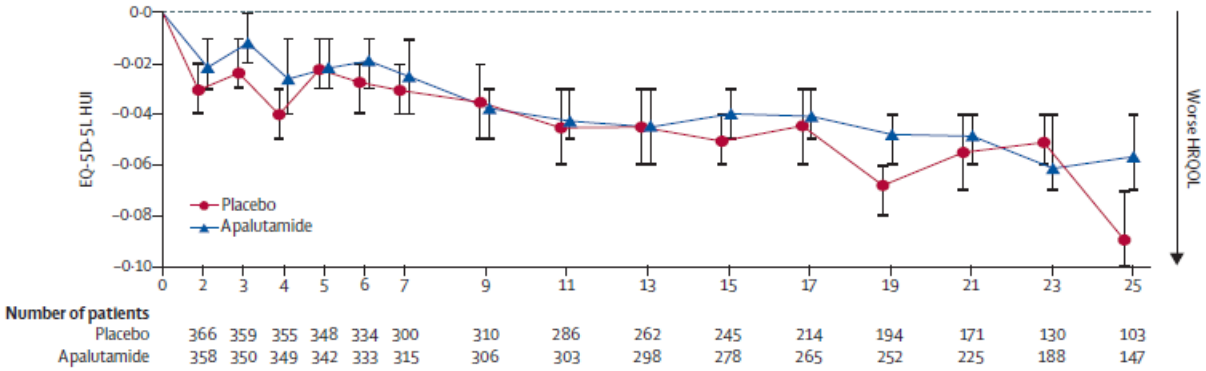
ITT population	Unadjusted	Adjusted – RPSFTM	Adjusted – IPCW
OS: HR (95% CI)	0.67 (0.51 to 0.89) p = 0.0053	0.67 (0.51 to 0.89)	0.67 (0.49 to 0.92)
PFS2: HR (95% CI)	0.66 (0.50 to 0.87) p = 0.0026	0.66 (0.51 to 0.87)	0.62 (0.46 to 0.83)

3.2.6.5 HRQoL outcomes

Four questionnaires were used to collect HRQoL over time from mHSPC participants in the TITAN RCT: the EQ-5D-5L, the FACT-P, the BFI and the BPI-SF. Further detail on how data from these outcomes were used in the economic model is provided in this report, section 4.2.10. Although HRQoL outcomes were collected in the TITAN RCT during treatment (37 cycles) and at the 4-, 8- and 12-month follow-ups, the data presented by the company in CS section B.2.12.4 are for the first 25 (EQ-5D-5L and FACT-P) or first 29 (BPI-SF and BFI) 28-day treatment cycles only.

3.2.6.5.1 EQ-5D-5L

The company present data which show there are no statistically significant differences between trial arms during treatment in the mean change from baseline in EQ-5D-5L VAS scores (CS Figure 28) or the EQ-5D-5L index scores (Figure 12 below).



Source: CS Figure 29, ERG has deleted some abbreviations
MMRM: mixed models for repeated measures

Figure 12 Mean change in EQ-5D-5L index score from baseline (MMRM; TITAN, ITT population)

3.2.6.5.2 BPI-SF

At baseline most patients either reported no pain (38%) or mild pain (38%). The MMRM analysis of mean changes in BPI-SF scores from baseline showed that mean changes were similar between the treatment arms of the trial and treatment with apalutamide plus ADT did not increase worst pain intensity (CS Figure 30) or pain interference (CS Figure 31) from baseline. The company also report that median time to worst pain intensity progression was 19.1 months in the apalutamide plus ADT arm versus 12.0 months in the placebo plus ADT arm. Median time to pain interference progression was not reached in either arm.

3.2.6.5.3 BFI fatigue scores

During 29 treatment cycles BFI fatigue scores in both trial arms remained stable for both worst fatigue intensity and for fatigue interference. The mean changes from baseline in BFI scores were similar between treatment arms (CS Figure 32 and 33).

3.2.6.5.4 FACT-P and FACT-G scores

FACT-P group mean total scores for HRQoL were maintained from baseline to the end of treatment (scores stated to be similar in both groups at baseline but data not presented). Additionally, the FACT-G group mean scores at baseline (apalutamide plus ADT 79.50; placebo plus ADT 78.81) were similar to the FACT-G population norm for adult men (80.9, SD 17.4). CS Figures 34 and 35 show that there were no statistically significant differences between the trial arms in FACT-P total scores or in FACT-G scores and patients maintained their overall HRQoL in both treatment arms.

3.2.6.6 Subgroup analyses

The company's decision problem includes a subgroup described as 'patients ineligible or unsuitable for chemotherapy' but no evidence is provided for this subgroup directly from the TITAN trial. It is not clear from the CS what proportion of TITAN patients were ineligible or unsuitable for chemotherapy but the ERG notes that 10.7% of TITAN trial participants had received prior docetaxel chemotherapy and 9.1% received docetaxel as a subsequent therapy. It is unclear what proportion of the remaining patients would be assessed as ineligible or unsuitable to receive docetaxel. The CS does not present results separately for those participants in the TITAN trial who were eligible for chemotherapy.

In CS section B.2.13 the company presents the results of analyses conducted across a range of pre-defined subgroups for the co-primary outcomes of rPFS (CS Figure 37) and OS (CS Figure 36). For both outcomes, the results for the majority of the subgroups were consistent with those of the overall TITAN trial population. Exceptions for the subgroup analyses of OS were for the subgroups by patients with prior docetaxel use (HR 1.27) and visceral disease at baseline (HR 0.99) where subgroups were small and with unbalanced sample sizes. The company formally tested interaction effects and found no statistically significant differences in the treatment effect for prior docetaxel or for visceral disease at baseline.

3.2.6.7 Safety outcomes

The company's safety analysis includes all patients randomised who received at least one dose of study treatment, 524 patients in the apalutamide plus ADT arm and 527 patients in the placebo arm.

3.2.6.7.1 Treatment duration, dose interruptions and dose modifications

At the time of clinical cut-off (23rd November 2018) treatment exposure was slightly longer in the apalutamide plus ADT arm of the TITAN trial (median of 20.5 months versus placebo plus ADT median of 18.3 months) but a greater proportion of patients in the apalutamide plus ADT arm were still receiving treatment (66% versus 46% in the placebo plus ADT arm).

The CS summarises the dose reductions and interruptions in CS Table 45. The proportion of patients requiring dose reductions was low (7.3% in the apalutamide plus ADT arm and 2.1% in the placebo plus ADT arm) whereas dose interruptions occurred in a greater proportion of patients ([redacted] in the apalutamide plus ADT arm and [redacted] in the placebo plus ADT arm).

3.2.6.7.2 Summary of adverse events

The company's summary table of adverse events is reproduced below in Table 18.

Table 23 Summary of adverse events TITAN trial (Safety population)

	Apalutamide plus ADT (n = 524)	Placebo plus ADT (n = 527)
TEAEs, total, n (%)	507 (96.8)	509 (96.6)
TEAEs, drug-related, n (%)	315 (60.1)	219 (41.6)
TEAEs, Grade 3-4, n (%)	221 (42.2)	215 (40.8)
TEAEs, Grade 3-4, drug-related, n (%)	66 (12.6)	31 (5.9)
SAEs, total, n (%)	104 (19.8)	107 (20.3)
SAEs, drug-related, n (%)	10 (1.9)	4 (0.8)
SAEs, Grade 3-4, n (%)	84 (16.0)	86 (16.3)
TEAE-related discontinuation, n (%)	42 (8.0)	28 (5.3)
TEAE-related discontinuation, drug-related, n (%)	17 (3.2)	4 (0.8)
TEAE-related deaths, n (%)	10 (1.9)	16 (3.0)
TEAE-related deaths, drug-related, n (%)	0 (0.0)	0 (0.0)
Deaths within 30 days of last dose, n (%)	18 (3.4)	23 (4.4)
Death due to prostate cancer, n (%)	8 (1.5)	7 (1.3)
Death due to AE, n (%)	10 (1.9)	16 (3.0)

Source: reproduction of CS Table 46, footnotes edited by the ERG
AE: adverse event; SAE: serious adverse event; TEAE: treatment-emergent adverse event
Notes: Aes and concomitant therapies were assessed continually from informed consent until 30 days after the last dose of study drug.

3.2.6.7.3 Summary of treatment emergent adverse events

The company state that the most commonly recorded adverse events in the TITAN trial were expected *a priori* and were consistent with the safety profile that had already been observed in the SPARTAN trial for nmHRPC patients. The company highlight skin rash which occurred in a higher proportion of TITAN trial participants in the apalutamide plus ADT arm (27.1%) in comparison to the placebo plus ADT arm (8.5%) and is considered as an AESI (see section 3.2.6.7.5 of this report).

The ERG has tabulated the most frequently reported TEAEs in the TITAN trial from the CS (Table 25) with events ordered by the proportion in the apalutamide plus ADT arm experiencing that event).

Table 24 Most frequently reported TEAEs in the TITAN trial (preferred terms reported in ≥15% of patients)

AE, n (%)	Apalutamide plus ADT N=524	Placebo plus ADT N=527
Rash (grouped term[a])	27.1%	8.5%
Hot flush	22.7%	16.3%
Hypertension	17.7%	15.6%
Back pain	17.4%	19.4%
Arthralgia	17.4%	14.8%
Weight increased	10.3%	16.9%

Source: Text in CS Section B.2.16.3
[a] A grouped term was used to combine related preferred terms to more accurately assess the incidence and characteristics of rash.

Grade 3 and 4 adverse events

The company summarise treatment-emergent grade 3 and grade 4 Aes (reported in 5% or more of patients) in CS Table 47. The results were similar for both trial arms indicating that the addition of apalutamide to ADT was not associated with an additional incidence of grade 3 and grade 4 TEAEs (42.2% in the apalutamide plus ADT arm and 40.8% in the placebo plus ADT arm) Overall only 4% of patients experienced Grade 4 events.

3.2.6.7.4 Summary of serious adverse events

The CS does not tabulate data for commonly reported SAEs (occurring in ≥ 1% of patients in either arm) but does list two events that occurred at a higher incidence in the apalutamide plus ADT arm than the placebo plus ADT arm [redacted] There were three SAEs that were only reported among patients in the apalutamide plus ADT arm [redacted].

3.2.6.7.5 Summary of adverse events of special interest

The pre-defined AESI were skin rash, fall, fracture, hypothyroidism and seizure (these were identical to the AESIs defined for the SPARTAN trial, except that ischaemic heart disease

was not included. The SPARTAN trial CSR[17] indicates that [redacted]). The incidence of AESI was higher in the apalutamide plus ADT arm for skin rash and hypothyroidism than in the placebo plus ADT arm but the rates of fall, fracture and seizure were similar in the two trial arms (CS Table 48).

The CS provides further detail on skin rash. The onset of skin rash typically occurred within the first three months of apalutamide treatment and a grade 3 skin rash was reported in [redacted] of apalutamide + ADT patients in comparison to [redacted] of placebo plus ADT patients. [redacted] When skin rash occurred, it was actively managed with steroid or antihistamines and the rate of discontinuation due to skin rash was low in both treatment arms (1.5% in the apalutamide plus ADT arm and 0.2% in the placebo plus ADT arm). Further details on the characteristics of skin rash are presented in CS Table 49.

3.2.6.7.6 Summary adverse events leading to death

Deaths that had occurred within 30 days of the last dose of study drug by the clinical cut-off (23rd November 2018) are summarised below in Table 26. The company states that no deaths in either treatment arm were related to treatment.

Table 25 Summary of adverse events leading to death in TITAN

	Apalutamide plus ADT (N=524)	**Placebo plus ADT (N=527)**
Deaths within 30 days of the last dose of study drug, %	3.4	4.4
Deaths due to an adverse event, n (%)	10 (1.9)	16 (3.0)
Deaths due to Aes occurring in follow-up, n	0	4
Source: text in CS B.2.16.2		

3.3 Critique of studies included in the indirect treatment comparison (ITC)

3.3.1 Rationale for ITC

As ADT was the only relevant comparator in the decision problem for the nmHRPC patient group the company did not consider an ITC to be necessary as apalutamide plus ADT was directly compared with ADT (plus placebo) in the SPARTAN trial. The ERG concurs with this decision. However, for the mHSPC patient group the TITAN trial did not include a comparison between apalutamide plus ADT and docetaxel plus ADT. Hence, the company conducted an ITC to assess the relative effectiveness and safety of these two treatments, for six outcome measures:

- OS
- rPFS
- PFS
- Time to PSA progression
- Overall AEs
- SAEs

In the following sub-sections describe and critique the ITC focusing on the two outcome measures that directly inform the cost-effectiveness analysis: OS and PFS.

3.3.2 Identification, selection and feasibility assessment of studies for ITC

The company's SLR identified 38 RCTs which met their predefined inclusion criteria (CS appendix D.1). These 38 RCTs were then assessed for their feasibility for inclusion in network meta-analysis (NMA). Studies were assessed on: availability of an appropriate comparator arm (i.e. ADT); reporting of comparable outcomes of interest; and sufficiently homogenous study characteristics. The feasibility assessment identified four such RCTs for inclusion in the NMA: the pivotal phase III TITAN trial, plus three RCTs linking docetaxel plus ADT to apalutamide plus ADT through the common comparator of placebo plus ADT: CHAARTED, GETUG, & STAMPEDE (Figure 13). The ERG notes that the company did not provide the reason(s) for exclusion of each of the remaining 34 trials, thus we cannot fully assess the reliability of the company's selection of included/excluded studies.

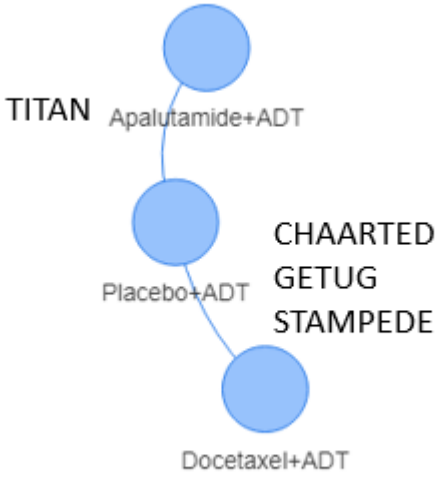


Figure 13 Network of evidence for indirect comparison of apalutamide plus ADT versus docetaxel plus ADT

NB. Diagram drawn by the ERG

The ERG asked the company to clarify whether the LATITUDE trial[15] (which compared abiraterone plus ADT plus prednisone versus placebo plus ADT) and the abiraterone plus ADT arm from the STAMPEDE trial could have been included in the NMA, as this would have provided additional indirect evidence for apalutamide plus ADT versus docetaxel plus ADT and for docetaxel plus ADT versus placebo plus ADT. We noted that these trial arms had been included in a published NMA of abiraterone acetate plus prednisone versus docetaxel in mHSPC sponsored by the company (Feyeraband et al, 2018[30]). The company clarified that LATITUDE[15] and the Feyeraband et al[30] NMA focused on narrower patient population than the decision problem: newly diagnosed patients with high-risk and/or high volume mHSPC. They also clarified that the abiraterone plus ADT arm of STAMPEDE was only included in a sensitivity analysis in the Feyeraband et al[30] NMA as data were not available for high-risk and/or high volume mHSPC patients. They also state that the abiraterone plus ADT arm does not add any additional evidence on relevant comparators when LATITUDE[15] is excluded. The ERG therefore agrees with the company's justification not to include these studies in the current NMA.

3.3.3 Clinical heterogeneity assessment

Table 37 compares study and patient characteristics, respectively, across the four included studies. The ERG observes some differences between the studies (clinical heterogeneity) in terms of the following characteristics at baseline:

- ECOG / WHO performance status score (0; ≥ 1) (GETUG higher proportion of PS 0)

- Proportion of patients with newly diagnosed mHSPC (STAMPEDE 100%)
- Proportion of patients with high volume disease (STAMPEDE lower)
- Proportion of patients with a Gleason score of 8 to 10 (indicating high-grade prostate cancer) (GETUG lower)
- Median PSA levels

In addition, the company reported an I^2 value of 67.4% from a pairwise meta-analysis of the docetaxel plus ADT vs placebo plus ADT trials, indicating moderate to substantial statistical heterogeneity. The company did not state which, if any, of the characteristics in CS Table 37 are confirmed or potential treatment effect modifiers.

The ERG requested the company to present evidence for or against treatment effect modifiers (clarification question response A12). The company examined the subgroup analyses within the four trials and reported that the following factors showed evidence as treatment effect modifiers in at least one study:

- Baseline PSA level
- Volume of disease
- Newly diagnosed patients versus patients progressed to metastatic from localised disease
- Lactic acid dehydrogenase (LDH)
- ECOG performance status score (0 versus 1)
- Number of bone lesions at baseline (<=10 vs >10)
- Presence of visceral disease

That the other three trials did not examine these factors for possible effect modification does not provide proof that they are not. The company examined the between-trial differences for each of these factors and concluded the net effect of these imbalances on the ITC was likely to be minimal. However, most of the evidence for or against treatment effect modifiers comes from TITAN subgroup analyses (Table 6, clarification question responses).
The ERG notes that the imbalances between trials in ECOG performance status, proportion of newly diagnosed disease, and Gleason Score 8-10 are likely to favour docetaxel plus ADT but the impact of PSA level is unclear.

3.3.4 Similarity of treatment effects

The NMA assumed similarity of the four ADT arms, and of the three docetaxel plus ADT arms. This was confirmed by the ERG's clinical experts. The TITAN trial has a relatively

short follow-up at time of this appraisal, thus the company's base case analysis included interim data cuts closest in follow up to TITAN's (22.7 months for TITAN, 28.9 months for CHAARTED, 43 months for STAMPEDE, and 50 months for GETUG (CS Table D.50)). A sensitivity analysis for OS included the longest data cuts available (CS Table D.51). These sensitivity analysis results were consistent with the base case (CS Table D.54). A further data cut from TITAN is expected as part of technical engagement (company decision problem form, section 1).

The definition of outcome measures appears to be comparable across the studies. For brevity we have focused our critique on OS and PFS as these directly inform the economic model.

3.3.5 Risk of bias assessment for studies included in the ITC

The company did a risk of bias / study quality assessment of the four trials (CS Appendix D3). They conclude that there was an overall low risk of bias for all studies except the CHAARTED trial, which was judged at high risk of bias due to its open-label nature, and the STAMPEDE trial which was judged to be medium risk. Only a summary of risk of bias judgements by bias domain is given, without any further detail on the rationale for the judgement, making it difficult for the ERG to verify their judgements. The ERG notes that the comparator trials have been included in previous NICE prostate cancer TAs, and there does not appear to be a sufficient rationale for excluding any of these from the ITC (e.g. in a sensitivity analysis) on the basis of risk of bias.

ERG conclusion

The ERG notes the ITC was informed by a comprehensive SLR, which is likely to have identified all relevant trials for inclusion. The four included trials are generally of good quality, and low risk of bias (with some exceptions), and they provide a sufficient evidence base for indirect comparison. There is uncertainty about which patient and study characteristics are effect modifiers for apalutamide. There is evidence of heterogeneity between the trials in terms of certain baseline patient characteristics, some of which are potential effect modifiers. The is a limitation of the NMA which should be taken into account in the interpretation of its results.

3.4 Critique of the indirect treatment comparison statistical methods

3.4.1 Data inputs to the NMA

The ERG found that the reporting of some of the data inputs to the NMA were unclear in the CS. In response to a clarification question (A15) the company provided the data used in the OS and PFS base case and sensitivity analyses (clarification question responses Table 18 & 19). Data cuts from the trials most similar to TITAN were used in the base case, as noted in section 3.3.4 above.

The company obtained individual patient data (IPD) for the STAMPEDE trial to calculate treatment effects on PFS, TTPSA, AEs, and SAEs since published data for this trial were only available for OS (clarification question response A10). The company also clarified that analysis of the IPD data was aggregated prior to inclusion in the NMA (clarification question response A10).

The ERG notes that some patients in the docetaxel comparator trials in the NMA received life-prolonging treatments later in the course of their disease, including chemotherapy and novel prostate cancer therapies. Some patients will have received more than one novel therapy during their disease, which, as discussed earlier, would not be permitted in the NHS. Survival estimates from these trials will be affected potentially confounded by the subsequent treatments, and to our knowledge these have not been adjusted for treatment switching/crossover by the trial authors. The company would not be able to adjust the survival estimates in the economic model unless they had access to IPD. Few patients in the TITAN trial had received subsequent treatments at the interim analysis, thus potential confounding is less of a problem as regards the apalutamide data.

3.4.2 Statistical methods for the NMA

The company used a Bayesian approach to NMA, using WinBUGS software. The ERG has checked the programming code (as requested from the company; clarification question response A15) and were able to replicate the company's results for OS and PFS using the data reported in Table 18 of the company's clarification question response document.

3.4.2.1 Assessment of proportional hazards

The NMA assumes that the proportional hazards assumption is applicable to the included survival data. This assumption was tested using standard available methods: the Schoenfeld test, Schoenfeld residual plots, and log cumulative hazards plots (CS section D).

The CS reports that proportional hazards assumption did not hold for the CHAARTED trial for the outcome of OS, and the GETUG trial for the outcome of PFS. The proportional hazards tests in CS Appendix D only included OS, hence the ERG requested the company report them for other time-to-event endpoints (clarification response A14). The ERG also requested the company conduct scenario analyses excluding studies where proportional hazards did not hold, or to consider using an NMA based on the assumption of time varying hazards, such use of fractional polynomials. In response, the company clarified that the proportional hazards assumption held for the NMA base case for the outcome of OS, and that it was a later data cut of CHAARTED in which proportional hazards were violated. The company conducted the requested scenario analyses on their sensitivity analysis, the results of which differed little from the NMA base case results (clarification question response tables 16 & 17).

The company also highlighted that the breach of proportional hazards in the CHAARTED trial occurred at the end of the dataset, where overlapping survival curves represents would a conservative analysis. The company therefore chose not to conduct a time-varying hazard based NMA model stating that there would be insufficient data to do this robustly and that their scenario analysis effectively demonstrated the impact on results. The ERG agrees this is reasonable. However, in the base case OS, there is also a possibility that proportional hazards may not hold for the GETUG-AFU 15 trial despite the non-significant Schoenfeld global test (p=0.143) (CS Appendix D, Figure 7). The Schoenfeld residuals plot indicates proportional hazards may be violated in the tail end of the data (around 36 months onwards). As the OS curves are diverging, this may bias analysis against docetaxel.

3.4.2.2 Choice between random effects and fixed-effect models

Only fixed effect NMA results were presented in the CS, based on the justification that fixed effect is more appropriate than random effects in the presence of a small evidence base, as is the case here (i.e. only four trials). Since there is potential clinical heterogeneity across the included trials, the ERG asked the company to present random effects results, and also to clarify whether they had considered use of an informative prior (clarification question A13). Random effects are also supported by the company's calculated I^2 statistic for the pairwise meta-analysis of the three docetaxel plus ADT trials.

In response, the company presented a range of random effects models using different priors on the random effect standard deviation (clarification response document Tables 8, 10, 12 &

14). The company also noted that the small networks mean uncertainty will be overestimated with random effects (The between studies variance was not reported, nevertheless the ERG agrees.) In response, the company used two informative priors on the random effects standard deviation: Uniform(0,1), a “somewhat” informative prior, and Uniform(0,0.4) a “more” informative prior for scenario analyses. The typical uninformative (“vague”) prior for random effects Uniform(0,5) used in the TSD documentation was not used in the company analyses as this led to implausible heterogeneity due to the low number of studies. The median HRs for the random effects models with the informative priors were very similar to the fixed effects albeit the 95% credible intervals were wider. The ERG welcomes the presentation of these analyses; given the presence of clinical heterogeneity fixed effect models are likely to underestimate uncertainty, hence the informative priors represent useful scenarios. That said, the ERG conducted a further scenario analysis for OS and PFS using an alternative informative prior; the half-normal prior referred to in NICE DSU TSD3. The results approximated the Uniform(0,1) prior used in the CS (section 3.6 below).

3.4.3 Summary of ERG critique of the NMA

- The methodology used by the company to conduct the NMA is appropriate to the clinical trial data available. The methodology has been described and applied correctly.
- Whilst the company has addressed violation of proportional hazards through sensitivity analyses, there is further evidence of a potential violation in proportional hazards in OS for the GETUG trial, which suggests a time-varying hazard based NMA could have been contemplated. The effect on the analysis is unclear but may bias against docetaxel plus ADT.
- The fixed effect models presented in the company base case will underestimate uncertainty due to heterogeneity. A random effects model is more appropriate but has limited ability to estimate between study variation due to the low number of studies in the network.
- The use of an informative prior for the random effects standard deviation offers a compromise. The company and the ERG have both conducted random effects models using different informative priors with similar results

3.5 Results of the indirect comparison

The fixed-effect NMA results for efficacy and safety are presented in Table 23 and Table 24, respectively. [redacted]

Table 26 Company base case NMA efficacy results (fixed effects)

Comparison		OS	rPFS	rPFS + PFS / FFS	TTPSA
Apalutamide plus ADT vs ADT alone	HR (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]
	Probability that HR is less than 1	[redacted]	[redacted]	[redacted]	[redacted]
Apalutamide plus ADT vs docetaxel plus ADT	HR (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]
	Probability that HR is less than 1	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; CrI, credible interval; HR, hazard ratio; NMA, network meta-analyses; OS, overall survival; rPFS, radiographic progression-free survival; SRE, skeletal related; TPSA, time to PSA progression.
Source: CS Table 40

None of the safety results were statistically significant apart from a reduction in SAEs which favoured apalutamide plus ADT versus docetaxel plus ADT.

Table 27 Company base case NMA safety outcomes (fixed effects)

Comparison		Overall AEs	SAE
Apalutamide plus ADT vs ADT alone	Median OR (95% CrI)	[redacted]	[redacted]
	Probability that OR is less than 1	[redacted]	[redacted]
Apalutamide plus ADT vs Docetaxel plus ADT	OR (95% CrI)	[redacted]	[redacted]
	Probability that OR is less than 1	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; AE, adverse events; CrI, credible intervals; NMA, network meta-analyses; SAE, serious adverse events.
Source: CS Table 42

The company's random effects model results using the informative U(0,1) prior from the response to clarification question A13 are shown in Table 29.

Table 28 Company NMA efficacy results (random effects)

Comparison		OS	rPFS	rPFS + PFS	TTPSA
Apalutamide plus ADT vs ADT alone	HR (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]
	Probability that HR is less than 1	[redacted]	[redacted]	[redacted]	[redacted]
Apalutamide plus ADT vs docetaxel plus ADT	HR (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]
	Probability that HR is less than 1	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; CrI, credible interval; HR, hazard ratio; NMA, network meta-analyses; OS, overall survival; RE, random effects; rPFS, radiographic progression-free survival; TPSA, time to PSA progression.
Source: Clarification responses Table 8

3.6 Additional work on clinical effectiveness undertaken by the ERG

The ERG conducted an additional random effects analysis for OS and PFS. Rather than use the Uniform informative priors used by the CS, the ERG adopted the half-normal informative prior Half-Normal(0,32^2) used in NICE TSD3. As stated above, these results were similar to the company results using the Uniform(0,1) "somewhat" informative prior (Table 30). The ERG believes the random effects model more accurately represents uncertainty around the mean estimates.

Table 29 ERG NMA OS and PFS results (random effects using half-normal prior)

Comparison		OS	rPFS
Apalutamide plus ADT vs ADT alone	HR (95% CrI)	[redacted]	[redacted]
Apalutamide plus ADT vs docetaxel plus ADT	HR (95% CrI)	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; CrI, credible interval; HR, hazard ratio; NMA, network meta-analyses; OS, overall survival; rPFS, radiographic progression-free survival; SRE, skeletal related; TPSA, time to PSA progression.

4 COST EFFECTIVENESS

4.1 Critique of the cost-effectiveness review

4.1.1 nmHRPC

The company conducted a SLR to identify cost-effectiveness studies for patients with nmHRPC. The original search was performed between July and August 2018 and was followed by two search updates, the first one between November and December 2018 and the second one between April and June 2020 (CS Appendix G.2).

The company performed their searches in relevant electronic databases, conference websites and HTA databases (CS Appendix Table G.1). The inclusion and exclusion criteria are presented in CS Appendix Table G.2. The ERG notes that, according to the inclusion criteria, studies for patients with nmHRPC, rather than high-risk nmHRPC, were included to retain potentially relevant data.

Seven relevant cost-effectiveness studies were identified by the SLR (CS Appendix Figure 25). Of these studies, one is the NICE technology appraisal for enzalutamide (NICE TA580), and four assess apalutamide from international healthcare perspectives. CS Appendix Tables G.32, G.33 and G.34 report the main characteristics of each included study and CS Appendix Table G.36 presents the company's quality assessment. The references of excluded studies with reasons for exclusion are reported in CS Appendix Table G.35. Table 31 presents the characteristics of the four included studies assessing apalutamide.

Table 30 Characteristics of studies assessing apalutamide identified through the systematic literature review for nmHRPC

Study name	Type of study	Population	Perspective/ Time horizon	Type of model	Intervention/ Comparator	Model health states	ICER per QALY
ICER (Draft Evidence Report, July 12, 2018)	Cost–utility	Patients with nmHRPC who were at high risk for the development of metastases, which was defined as a PSA doubling time of 10 months or less during continuous ADT	US health care and societal/ Lifetime	Combination of partitioned survival approach and Markov approach	APA plus ADT, ENZA plus ADT, ADT alone	MFS, asymptomatic progression, symptomatic progression, death	APA plus ADT vs. ADT alone: US$68,000
CADTH 2018 (Manufacturer's submission)	Cost–utility		Canadian health system/ 15 years (Manufacturer's submission), 10 years (EGP reanalysis)	Partitioned survival approach	APA plus ADT, ADT alone	MFS, mHRPC, death	CAN$151,811 (Manufacturer's submission), CAN$198,826 (EGP reanalysis)
Zhou 2018	Cost effectiveness analysis	Patients with nmHRPC	US societal/ Lifetime	Markov model	APA versus placebo as first-line therapy in nmHRPC, AAP plus prednisone, ENZA, DOX and Sipuleucel-T as second-line therapy	Stable disease, progressed disease, death	US$680,089
Tsiatas 2019	Cost-utility	Patients with nmCRPC	Greek health care/ NR	Partitioned survival model	APA plus ADT, ENZA plus ADT	nmHRPC, mHRPC, death	€6,998-€34,814

Source: reproduced from CS Appendix Tables G.32, G.33 and G.34.
AAP: abiraterone, ADT: androgen deprivation therapy, APA: apalutamide, DOX: docetaxel, EGP: Economic Guidance Panel, ENZA: enzalutamide, MFS: metastasis-free survival, mHRPC: metastatic hormone resistant prostate cancer, nmHRPC: non-metastatic hormone resistant prostate cancer, nmCRPC: non-metastatic castration resistant prostate cancer, NR: not reported, PSA: prostate specific antigen, US: United States of America.

4.1.2 mHSPC

The company conducted a SLR to identify cost-effectiveness studies for patients with mHSPC published since 2005. The original search was conducted in September 2015 and was followed by five search updates: July 2017, May 2019, June 2019, November 2019 and May 2020 (CS Appendix G.6.1).

The company performed their searches in relevant electronic databases and conference websites (CS Appendix Table G.37, CS Appendix G.6.2). No HTA databases were searched. The inclusion and exclusion criteria are presented in CS Appendix Table G.56.

Forty-four relevant studies from 49 publications were identified through the SLR: 30 are cost-effectiveness studies and 14 are studies focused on costs and healthcare resource use (CS Appendix Figure 26). Of the cost-effectiveness studies, four are conducted from a UK perspective but do not include apalutamide. One cost-effectiveness study evaluates apalutamide from a Canadian perspective. CS Appendix Tables G.57, G.58, G.59, G.60 and G.61 report the main characteristics of each cost-effectiveness study and CS Appendix Table G.63 presents an assessment of their quality. CS Appendix section I.2 Table I.1 summarises the cost and healthcare resource use studies. Excluded studies with reasons for exclusion are reported in CS Appendix Table G.62. Table 32 presents the characteristics of the included study assessing apalutamide.

Table 31 Characteristics of the study assessing apalutamide identified through the systematic literature review for mHSPC

Study name	Type of study	Population	Perspective/ Time horizon	Type of model	Intervention/ Comparator	Model health states	ICER per QALY
Parmar et al.	Cost-utility analysis	Patients with mCSPC	Canadian healthcare/ Lifetime	State-transition model with probabilistic analysis	APA plus ADT, ADT alone	NR	CAN$ 160,483

Source: reproduced from CS Appendix Tables G.57, G.58, G.59, G.60 and G.61.
ADT: androgen deprivation therapy, APA: apalutamide, mCSPC: metastatic castration sensitive prostate cancer, NR: not reported.

ERG conclusion

The ERG considers the company's review of cost-effectiveness evidence comprehensive and appropriate. The sources searched (including all recommended databases) is adequate, the search structure and syntax are accurate, the search

strategies reflect the disease population, the volume of searches is large but consistent, the searches are reasonably up to date and the reporting is clear.

4.2 Critique of the submitted economic evaluation

4.2.1 NICE reference case checklist

Table 33 shows the requirements of the NICE reference case and the ERG's judgment on whether that the company's economic analysis adequately meets the reference case.

Table 32 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	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes, lifetime horizon (32 years)
Synthesis of evidence on health effects	Based on systematic review	Yes
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes, EQ-5D used in economic model.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes

Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

4.2.2 Model structure

4.2.2.1 Overview of the model structure

The model structure was based on three factors: the disease pathway, the availability of data to inform the analysis and feedback from the NICE appraisal committee on previous NICE submissions for prostate cancer.

The prostate cancer disease pathway is described earlier in this report (see section 2.2.3). Patients with high-risk nmHRPC and mHSPC progress over time and develop mHRPC, at which time they may receive a number of subsequent therapies until death. The company assumes that progression to mHRPC is driven by MFS for patients with nmHRPC and by rPFS for patients with mHSPC. The definition of each of these measures is described in in CS Table 51.

Efficacy data to inform the comparison between apalutamide plus ADT and ADT alone for nmHRPC are from the SPARTAN trial which has MFS as its primary endpoint. The TITAN trial informs the same comparison for mHSPC, with rPFS and OS as co-primary endpoints. The comparison of apalutamide plus ADT versus docetaxel plus ADT for the mHSPC indication is based on the NMA as described in section 3.3.

CS Tables 52 and 53 summarise the model structures and main features of the economic analysis for prostate cancer previously submitted to NICE and feedback from the NICE appraisal committees and/or ERGs on those submissions. In general, partitioned survival models have been accepted and considered appropriate, although models including multiple health states for post-progression survival have raised some concerns mainly around the ability of this approach to truly represent UK clinical practice.

In addition to the three factors described above, the selection of the model structure for the current appraisal was also based on the guidance reported in NICE TSD 19,[31] which recommends using a partitioned survival analysis alongside state transition modelling. The company also argues that with a partitioned survival analysis it is possible to apply more than one key outcome, more than one trial data cut and also HR to the independent curves.

Therefore, considering all these factors, the company constructed a partitioned survival analysis model with multiple health states to model post-progression transitions. This approach was validated by experts advising the company. The model has weekly cycles and a lifetime horizon (32 years). The structure is described in CS B.3.2.2 and illustrated in CS Figure 40, reproduced in Figure 14 below.

The model consists of three main health states: progression-free survival (PFS), progressive disease and death. Patients with nmHRPC or mHSPC start in the PFS health state, in which they receive treatment with either apalutamide plus ADT or the comparator intervention(s) (ADT alone for nmHRPC; ADT alone or docetaxel plus ADT for mHSPC). In each cycle, patients can remain progression-free or they can progress to mHRPC according to the MFS/rPFS rates, respectively. In the PFS health state, patients receiving apalutamide can be on-treatment or off-treatment, according to the time to treatment discontinuation (TTD) data. Once patients progress, they will receive up to three lines of subsequent therapy. PFS2 curves inform the transition between the first and second and third line mHRPC health states. Survival curves are used to model PFS, PFS2 and OS.

The proportion of patients in each health state is informed by the area under the curve approach, where the area between MFS/rPFS and PFS2 is calculated to estimate the time spent in the first line mHRPC health state and the area between PFS2 and OS to estimate the time spent in the second and third line mHRPC health states. Due to the absence of data from the SPARTAN and TITAN trials, mean health state durations are based on those used in NICE TA387 for abiraterone for treating mHRPC before chemotherapy is indicated.

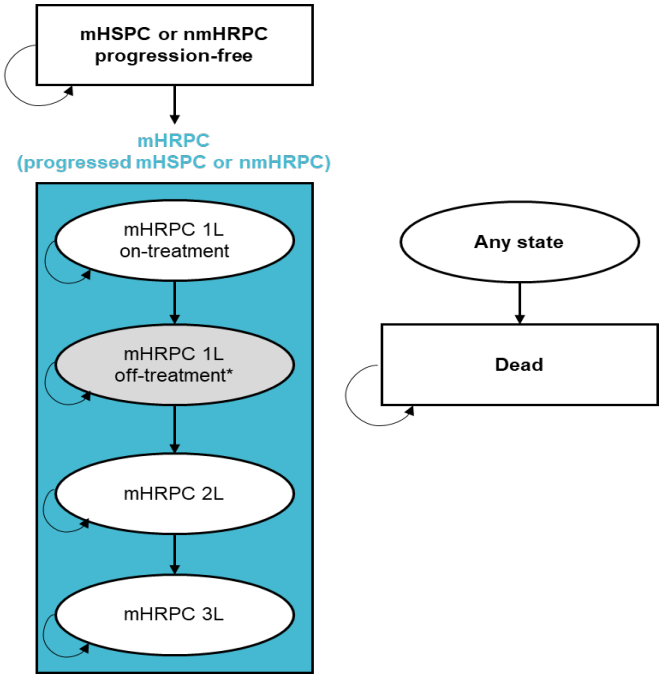


Figure 14 Economic model diagram

Source: reproduced from CS Figure 40.
1L: first-line; 2L: second-line; 3L: third-line; mHRPC: metastatic hormone-relapsed prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; nmHRPC: non-metastatic hormone-relapsed prostate cancer.
*mHRPC 1L off-treatment is only included in the scenario analysis of the model.

The progression rates (PFS and PFS2) and death rates (OS) are discussed in more detail later in this report (section 4.2.6).

4.2.2.2 ERG critique of model assumptions

The CS includes a table of modelling assumptions (CS Table 84). The ERG's views of these assumptions are presented in Table 34.

Table 33 Company model assumptions

Assumption	Justification	ERG comments
Generalisability		
Patient characteristics, efficacy and safety were derived from the TITAN and SPARTAN trials and were assumed to be representative of the mHSPC and nmHRPC populations in the UK.	• Clinical feedback confirmed that the patients in the TITAN and SPARTAN trials were reasonably reflective of patients in UK clinical practice. The potential impact of the one novel therapy restriction in UK clinical practice has also been accounted for in the survival analysis.	• We agree
Model structure		

The partitioned survival model is a suitable model structure.	• This is based on the guidance set out in NICE DSU TSD 19, the data available for this submission and committee feedback from previous submissions.	• We agree
Radiographic progression-free survival and metastases-free survival are suitable proxies for disease progression in mHSPC and nmHRPC, respectively.	• This was firstly based on the findings from the clinical advisory boards and precedent from previous prostate cancer submissions (as summarised in CS Table 53).	• We agree
Docetaxel is given for a maximum of six cycles.	• This is applied according to NHS England commissioning policy. This is also in line with the dosing schedules used in the CHAARTED and STAMPEDE studies and reflects UK clinical practice. In GETUG-AFU 15, patients received up to 10 cycles of therapy. Therefore, the model overestimates docetaxel effectiveness relative to the cost, and thus assuming six cycles of therapy is a conservative assumption.	• We agree
Survival projections		
It was assumed that: • TTD cannot be longer than PFS • PFS cannot be longer than PFS2 • PFS2 cannot be longer than OS • OS cannot be longer than survival in the general population	• TTD: In clinical practice, apalutamide is a therapy where patients are treated until progression • PFS: Patients need to progress on treatment before starting a first-line treatment for mHRPC. Therefore, MFS/rPFS is always shorter than PFS2 • PFS2: Patients cannot be treated after death • OS: It is unlikely that patients with mHSPC or nmHRPC live longer than the general population with the same age	• We agree
Utilities		
Baseline utility in nmHRPC and mHSPC was assumed to be similar for patients receiving apalutamide plus ADT and ADT alone.	• Baseline utility before start of treatment was similar in the apalutamide plus ADT arm compared with the placebo plus ADT arm in the SPARTAN and TITAN trials.	• We agree
Patients receiving docetaxel in mHSPC are assumed to experience a utility decrement of -0.02 while they are receiving treatment (18 weeks).	• This value was taken from a time trade-off study utility study and is consistent with the utility decrement of -0.02 estimated from the STAMPEDE trial was applied for one year in a cost-	• We agree

	effectiveness model presented in the Woods et al. (2018) publication.[32]	
Subsequent treatments		
Post-progression survival data are reflective of outcomes in UK clinical practice.	• The novel therapy analysis that adjusted survival outcomes for the one novel therapy restriction in UK clinical practice demonstrated that this restriction has only a small impact on the survival data.	• There is uncertainty because the adjustments for treatment switching conducted by the company could not be verified by the ERG because the IPD from the pivotal trials were not provided
Most patients will receive three or fewer lines of active treatment for mHRPC.	• This assumption was validated during the clinical advisory board, with clinicians stating that patients would typically receive up to two active therapies, followed by BSC, but some could receive a third.	• We agree
ADT is received until death.	• This is reflective of UK practice, as advised by UK clinicians. It is also supported by TA404 (degarelix for treating advanced hormone-dependent prostate cancer).[33] This is a conservative assumption as patients in the apalutamide arm have longer OS compared with those treated with ADT alone or docetaxel. Therefore, this assumption increases treatment costs for patients treated with apalutamide relative to patients on docetaxel or ADT alone.	• We agree
Source: reproduced from CS Table 84. 1L: first line; 2L+: second and later lines; ADT: androgen deprivation therapy; AE: adverse event; BSC: best supportive care; HRQL: health-related quality of life; mHRPC: metastatic hormone-relapsed prostate cancer; MFS: metastases-free survival; mHSPC: metastatic hormone-sensitive prostate cancer; nmHRPC: non-metastatic hormone-relapsed prostate cancer; OS: overall survival; PartSA: partitioned survival analysis; PFS: progression-free survival; PFS2: secondary progression-free survival; TTD: time to treatment discontinuation.		

Treatment waning assumption

The company states that the OS data from both SPARTAN and TITAN demonstrate a statistically significant treatment effect with no evidence that the OS curves converge over time. Therefore, no additional treatment waning was applied to the OS curves in the company's base case. Given the absence of data to allow for the assessment of the long-

term treatment effect of apalutamide, the company conducted a scenario to assess the impact of treatment waning on OS over time (see section 5.2 below). In this scenario, the waning effect reduces the treatment effect from 100% to 0% over a 5-year period starting from year 10.

According to NICE guidance, the duration of treatment effect is an important model assumption, therefore an analysis of the intervention's hazards from clinical trials coupled with clinical expert opinion and biological plausibility should be considered in order to assess the validity of extrapolated data. In addition, some scenarios changing these assumptions are also recommended.

The ERG plotted the hazard curves for each intervention from the KM data of the relevant clinical trials (SPARTAN for nmHRPC and TITAN for mHSPC), however it was inconclusive whether there is a tendency for declining treatment benefit or not. The clinical experts advising the ERG do not expect to see a treatment waning effect with apalutamide since no waning effect was observed with abiraterone in a longer follow-up setting, in particular, in the STAMPEDE trial [34]

As reported by Antonarakis[35], in the first-line castration-resistant prostate cancer (CRPC) setting, resistance to abiraterone or enzalutamide typically develops after 9 to 15 months of treatment with either agent. Given that there is some similarity in the mechanisms of action between apalutamide and enzalutamide, [36] [37] it would not be unreasonable to assume that waning effect and its time frame are likely to be similar (or at least not very different) for these treatments. Our expert considers this assumption reasonable. However, this study was conducted in a more advanced phase of the disease, therefore it is unclear how generalizable these results are for the earlier states of the disease, namely nmHRPC and mHSPC. In addition, resistance to abiraterone or enzalutamide does not necessarily imply that there would be a treatment waning effect.

Based on the above, we do not have sufficient evidence to conclude on the best approach regarding the duration of treatment benefits. Therefore, we agree with the company's assumption of not including treatment waning in the base case but inclue it as a scenario analysis (as recommended by NICE guidance). The ERG also added a scenario analysis changing the treatment waning period from 5 to 10 years since this has not been explored in the CS (see section 6.1).

ERG conclusions

A partitioned survival analysis model is a common approach in economic evaluation for oncology and has been applied in previous NICE appraisals for prostate cancer. The company used multiple health states to model post-progression survival. The ERG considers that the chosen approach is appropriate, is consistent with NICE guidance and reflects UK clinical practice. The ERG explores different treatment waning periods as scenario analyses.

4.2.3 Population

The patient population included in the economic evaluation is people with high risk nmHRPC and people with mHSPC. As stated earlier in this report (section 2.3), the population for nmHRPC differs from that in the NICE scope, which included all adults with nmHRPC. However, the marketing authorisation for apalutamide is for those at high risk of developing metastatic disease, as per the SPARTAN registration trial. The populations used in the model are based on the characteristics of patients in the SPARTAN and TITAN trials (shown in CS Table 7 and Table 8). Clinical advice to the ERG is that the populations in the clinical trials were broadly similar to those seen in UK clinical practice.

As noted earlier, the CS does not define the factors that determine whether a person would be fit enough to receive docetaxel. Prior docetaxel use was a stratification factor in the trial's analysis, with 11% of randomised patients previously receiving docetaxel. Around a nine per cent of patients received docetaxel as a subsequent therapy. Thus, it appears that at a small proportion of patients were fit enough to take docetaxel. However, the ERG notes that is not clear what proportion of patients, if any, in the TITAN trial could be considered ineligible to receive docetaxel.

This is important because survival estimates from the ITT population of TITAN (which appears to include some patients fit enough to take docetaxel, and, presumably, some who were not fit enough for docetaxel) inform the cost effectiveness results for the docetaxel eligible population *and* the docetaxel ineligible population groups. An implicit assumption, therefore, is that the results of TITAN are also applicable to patients ineligible to take docetaxel (i.e. the direct comparison of apalutamide plus ADT versus ADT only).

It is not clear whether the clinical effectiveness of apalutamide differs according to docetaxel eligibility/ineligibility as no such subgroup analysis was presented in TITAN. The ERG notes that a similar issue was discussed recently in the NICE appraisal of abiraterone for the treatment of mHSPC (ID945). The final appraisal determination (FAD) states that "The committee was not presented with evidence of abiraterone's effectiveness in people who

cannot take docetaxel. Without this evidence, it could not say whether abiraterone would be safe or effective in this group" (page 5).

The abiraterone FAD also cites the NHS England commissioning policy which states the following factors indicative of a patient being unfit for docetaxel: poor overall performance status (World Health Organization [WHO] performance status 3 to 4); pre-existing peripheral neuropathy; poor bone marrow function or a life-limiting illness. In addition, it states that docetaxel should be used with caution in people with a WHO performance status of 2, and that there are few absolute contraindications for docetaxel therapy. Of these factors the ERG is only able to discern the (ECOG) performance status scores of TITAN patients, which were almost exclusively in the range of 0 to 1 (as per the eligibility criteria), thus not meeting the NHS England performance status criterion to be considered as unfit for docetaxel treatment. The ERG acknowledges that criteria to determine fitness for docetaxel may vary between treatment centres and that the decision to offer docetaxel is also informed by the circumstances of the individual patient (e.g. age, co-morbidities, extent of disease) and their preferences. Thus, any attempt to dichotomise TITAN patients into docetaxel eligible and ineligible groups may be imprecise. For this reason the applicability of the results from TITAN to a patient population ineligible for docetaxel is uncertain.

One other factor to note is that the majority of patients in TITAN were newly diagnosed metastatic patients, as opposed to progressing to metastases from local disease. Evidence suggests that these patients have a poorer prognosis than primary progressors. This needs to be taken into account in assessing the applicability of the results of the cost effectiveness analysis to other populations.

ERG conclusion

The patient populations in the economic model appropriately reflect the licensed indications for apalutamide and the clinical trial populations. However, survival estimates from the TITAN trial inform the cost effectiveness results for both the docetaxel eligible population and the docetaxel ineligible population groups. There is evidence that a proportion of patients in TITAN were/had previously been eligible to receive docetaxel, but there is no evidence to suggest whether any patients were ineligible to receive docetaxel. It is therefore uncertain whether the implicit assumption that the results of TITAN are also applicable to patients ineligible to take docetaxel is valid.

4.2.4 Interventions and comparators

The intervention of interest is apalutamide, administered orally as a single daily dose of 240 mg (4x60 mg tablets), in combination with ADT.

The comparators included in the company's base case are:

- For nmHRPC: ADT only;
- For mHSPC: ADT only, and docetaxel and ADT (in patients who can tolerate docetaxel).

For mHSPC, other possible comparators are listed in the NICE scope: abiraterone with prednisone or prednisolone and ADT; and enzalutamide with ADT. These treatments are currently subject to ongoing NICE appraisal and therefore are not considered eligible comparators.

ERG conclusion

The ERG agrees with the comparators selected by the company for the current appraisal.

4.2.5 Perspective, time horizon and discounting

The company includes all direct health effects of treatments. Costs are estimated from the NHS and Personal Social Services (PSS) perspective. Costs and outcomes are discounted at 3.5% in the base case and at 0% and 6% in deterministic sensitivity analysis.

In the base case, the model outcomes are estimated over a lifetime horizon (32 years). Alternative time horizons of 10, 20 and 30 years are considered in scenario analyses (CS Tables 95, 96 and 97). Changing the time horizon to 10 years leads to a significant increase in the ICER. The ERG notes that previous NICE appraisals for prostate cancer (TA259

TA391, TA316 and TA377) applied a 10-year time horizon, however they were focused on the mHRPC setting, in which the disease is more advanced, and it is expected that patients experience lower survival.

ERG conclusion

The company adopted an appropriate perspective, used recommended discounting rates and an appropriate time horizon, which are in line with the NICE reference case.

4.2.6 Treatment effectiveness and extrapolation

4.2.6.1 Clinical efficacy inputs: overview

The company presents their approach to survival analysis and selection of clinical inputs for the economic model in CS section B.3.3.2. As mentioned earlier, the company considered adjusting survival estimates from both SPARTAN and TITAN trials for 'indirect switching', to reflect the one-novel-therapy-commissioning policy in England, as well as for crossover from placebo plus ADT to apalutamide plus ADT, or 'direct' switching, in SPARTAN.

The suitability of the following adjustment methods proposed in the NICE DSU TSD 16[28] was explored:

- Rank Preserving Structure Failure Time Models (RPSFTM)
- Iterative Parameter Estimation (IPE)
- Two-stage method
- Inverse Probability of Censoring Weights (IPCW)

The MFS and rPFS, PFS2 and OS estimates were fitted with parametric models (the proportional hazards-based exponential, Weibull and Gompertz, and the accelerated failure time-based log-normal, log-logistic and generalised gamma) and extrapolated for the model time horizon. Two approaches were considered:

- Fitting independent models to each treatment arm
- Fitting a dependent model in which placebo curve is used as a reference

The most appropriate approach was chosen by investigating whether the assumption of proportional hazards (PH) was reasonable. This was done by inspecting the log-cumulative hazard plots and was supported by assessment of Schoenfeld plots and the Schoenfeld test.

The parametric models were assessed based on their clinical plausibility, consistency with the other survival curves selected for the analysis, and goodness-of-fit statistics (AIC and BIC scores).

Table 35 below provides an overview of survival estimates utilised in the company's base-case and scenario analyses. As shown in the table, the estimates from TITAN were not adjusted: adjustment for novel therapy was explored but not included in the cost-effectiveness analysis because, as the company stated, the adjusted analysis failed to demonstrate any significant impact on survival outcomes and gave counter-intuitive results in some scenarios (see section 4.2.8.2 below); as for crossover to apalutamide, the TITAN data used to inform this submission does not cover the trial period post-unblinding and, as such, is not affected by confounding due to crossover (see section 3.2.6.4 above).

We describe and critique the company's approach in sections 4.2.7 and 4.2.8.

Table 34 Survival estimates used in the company's base-case and sensitivity analyses

Outcome measure	Base case	Scenario(s)
Apalutamide plus ADT versus ADT alone: nmHRPC (SPARTAN trial)		
MFS	Independently modelled using Weibull distributions (both arms)	Independently modelled: log-logistic or log-normal (both arms)
PFS2	Jointly modelled with Weibull distributions fitted to data adjusted for novel therapy restriction and crossover[a]	- Log-logistic, log-normal or generalized gamma - Unadjusted for treatment switching - Independently modelled
OS	Jointly modelled with Weibull distributions fitted to data adjusted for novel therapy restriction and crossover[a]	- Generalized gamma - Unadjusted for treatment switching - Independently modelled
Apalutamide plus ADT versus ADT alone: mHSPC (TITAN trial)		
rPFS	Independently modelled with Weibull distributions fitted to data unadjusted for novel therapy restriction	- Exponential, log-logistic or log-normal - Jointly modelled

Outcome measure	Base case	Scenario(s)
PFS2	Jointly modelled with Weibull distributions fitted to data unadjusted for novel therapy restriction	NA
OS	Independently modelled with Weibull distributions based on 'informed fits' approach,[38] unadjusted for novel therapy restriction	- Log-normal, log-logistic, generalised gamma or Gompertz - Jointly modelled not using 'informed fits'
Apalutamide plus ADT versus docetaxel plus ADT: mHSPC (Bayesian NMA)		
rPFS	Weibull distribution and HRs from Bayesian NMA	Exponential, log-logistic or log-normal
PFS2	Weibull distribution and HRs from Bayesian NMA	NA
OS	Weibull distribution and HRs from Bayesian NMA; informed fits	- Log-normal, log-logistic, generalised gamma or Gompertz - Unstratified fits

NA not applicable
a Survival estimates adjusted for treatment switching using a 'modified' RPFSTM following Diels et al.[29]
Note: When survival estimates are modelled jointly, the proportional hazards assumption is made, and survival in the treatment arm is estimated by applying HR to the parametric curve selected for the comparator arm used as reference. When survival estimates are modelled independently, parametric models are fitted separately to both treatment and comparator arms.

4.2.6.2 Methods of adjustment for treatment switching

The company followed Diels et al.[29] when considering adjustment of the survival estimates for treatment switching. The source appears to be a conference abstract. The company confirmed in clarification response B10 that the approach proposed in Diels et al.[29] has not yet undergone the peer-review process.

The objective of the approach described in Diels et al.[29] was to estimate the OS benefit of apalutamide in SPARTAN by adjusting for subsequent exposure to abiraterone and enzalutamide. The authors stated that their approach was similar to **RPSFTM** but was using (external) patient-level data from COU-AA-302, a randomized-trial comparing abiraterone acetate plus prednisone versus prednisone in mCRPC, to adjust for the survival benefit of the subsequent novel therapies. The COU-AA-302-patient population was matched to the subgroup of metastatic patients with subsequent therapy from SPARTAN using Inverse Probability Weighting (IPW) approach, and the adjusted HR was estimated based on the

counterfactual re-censored survival times. The ‘modified’ RPFSTM approach is further described in section 4.2.7.2 below.

Diels et al.[29] and the company argue that the ‘modified’ RPSFTM approach does not require the standard assumptions of RPSFTM, IPCW and two-stage method,[28] and that these assumptions were not valid for SPARTAN. Here, we outline the company’s argument. For further details refer to CS Appendix R.1 pages 844-846.

The company states that RPSFTM is typically applied when only the relative treatment effect of one active therapy versus control needs to be estimated based on the trial data; the main assumption of this method is that the benefit of the treatment is equal in patients exposed to it later in time and patients initiated on this therapy earlier (the common treatment effect assumption). The argument goes that the same approach can be applied in a setting with switching to more than one active therapy, with separate acceleration factors for those therapies, but estimation of these multiple parameters reliably from data collected in one trial would not be possible due to data limitations. The company states that the same limitations would also hold for the **IPE** approach which is conceptually identical to RPFSTM.

Another approach, **IPCW**, was not deemed to be valid for the nmHRPC indication (SPARTAN) because, as the company states, it produced counter-intuitive and clinically implausible results, with the survival estimates in the apalutamide arm shifting upwards (see a detailed argument in CS Appendix R page 846). This method, however, was considered suitable for mHSPC but was not used in the company’s base-case and sensitivity analyses because of a low proportion of patients who had more than one novel therapy in the TITAN trial (see section 4.2.8.2).

The two-stage method was judged not to be applicable either because of insufficient data to estimate multiple parameters or to sufficiently account for time varying confounding. The method also requires a secondary baseline at the time of switching, which may not be true for SPARTAN and TITAN, because the time between progression and/or discontinuation of randomized treatment and treatment switching was long in a subset of patients in the placebo arm (as illustrated in CS Appendix R Figures 84 and 85 (SPARTAN), and 92 and 93 (TITAN). The additional company’s argument is that conducting a reliable analysis for SPARTAN would be challenging as data would be taken from IA1 for MFS whereas OS and PFS2 data would be based on the final analysis set to provide the longest available follow-up.

The appropriateness of adjusting different survival estimates for treatment switching is discussed in sections 4.2.7 and 4.2.8 below.

ERG conclusion

- The novel therapies (abiraterone or enzalutamide) received by patients in the pivotal trials who were randomized to apalutamide would not be available in clinical practice to patients who have already received apalutamide. Our clinical advisors clarified that this is due to potential cross-resistance between treatments and, therefore, these patients, if eligible for subsequent active therapy, will require a different treatment modality (such as radium or chemotherapy). Also, the restriction of not using abiraterone or enzalutamide as subsequent treatment would apply not only if patients had received apalutamide for mHSPC but also if patients had previously received apalutamide for nmHRPC.
- The '**modified' RPSFTM** approach used by Diels[29] requires a number of assumptions: (1) that there would be a similar OS benefit post-metastasis between ADT and prednisone, and (2) a similar OS benefit post-metastasis between abiraterone and enzalutamide in both arms in SPARTAN and TITAN. Our experts consider these assumptions reasonable. This is also confirmed by literature. In a meta-analysis reported by Sathianathen et al.,[39] abiraterone plus ADT and enzalutamide plus ADT in mHSPC were found to be statistically comparable to each other, with HR=1.3 (95% CrI 0.91, 1.9) when using enzalutamide as a reference.
- Another implicit assumption in the company's analysis is that the efficacy of novel therapy is not impacted (decreased) by prior exposure to any other novel therapy. According to clinical advice to the ERG, it is unclear how effective enzalutamide and abiraterone would be following earlier use of apalutamide, but cross-resistance is likely to apply. This is also supported by literature. Antonarakis,[35] reports that patients who receive enzalutamide or abiraterone as first-line therapy and subsequently become resistant have only a 15% to 30% rate of response to the alternative agent as second-line CRPC treatment. Therefore, using evidence from COU-AA-302 (where enzalutamide and abiraterone were used first-line) to adjust for novel therapies not available in the NHS is likely to underestimate the effectiveness of apalutamide.
- We note that evidence from the COU-AA-302 trial was used in NICE TA387 of abiraterone for treating mHRPC not previously treated with chemotherapy.[40] Although COU-AA-302 included only 9% of patients from the UK, it was considered to be generalisable to clinical practice in England, and the trial population

representative of patients who would be offered abiraterone; the life expectancy of people in the comparator arm of COU-AA-302 reflected that of patients in the NHS because the subsequent active treatments in this arm were similar to those patients receive in clinical practice.

- We note that COU-AA-301 trial was also included in NICE TA387, but patients in the COU-AA-302 trial appear to be a better match to SPARTAN trial participants (see Appendix 9.2). We, therefore, consider that using external data from the COU-AA-302 trial for novel therapy adjustment would be appropriate because after progression (post-metastasis in SPARTAN, and post-radiographic in TITAN) patients from both pivotal trials were quite similar to those in COU-AA-302, and the treatment effect modifiers were adjusted for (for a further discussion see sections 4.2.7.2 and 4.2.8.2).
- It is unclear, however, whether the survival estimates from COU-AA-302 had been adjusted for crossover in that trial when estimating the shrinkage factors for novel therapy in SPARTAN and TITAN. We note that in the company's submission for the NICE TA387, survival estimates were not adjusted for crossover, but this was done in an additional analysis on request from the NICE appraisal committee. Therefore, if the COU-AA-302 estimates used in the 'modified' RPFSTM had not been adjusted for crossover, the clinical effectiveness of apalutamide is likely to be overestimated.
- The implementation of the 'modified' RPFSTM approach could not be independently verified because the IPD from the pivotal trials were not available to the ERG (see clarification question response B6).
- The company's argument against using the **two-stage** method because of lack of MFS data at the final analysis stage is not supported by the evidence because MFS had already been mature at IA1 cut-off date (see Figure 3). We agree, however, that using the two-stage approach would have a caveat because of the switching mechanism in SPARTAN which was based on the trial data.[28]
- The **IPCW** analysis, which was not included in CS, was requested by the ERG but not provided (see clarification response B8). Therefore, the suitability of this method to adjust for treatment switching in SPARTAN could not be established.

4.2.7 Survival curves: nmHRPC

Clinical effectiveness evidence for nmHRPC was sourced from the SPARTAN trial.[22] SPARTAN provided MFS, PFS2, and OS data (see section 3.2.5).

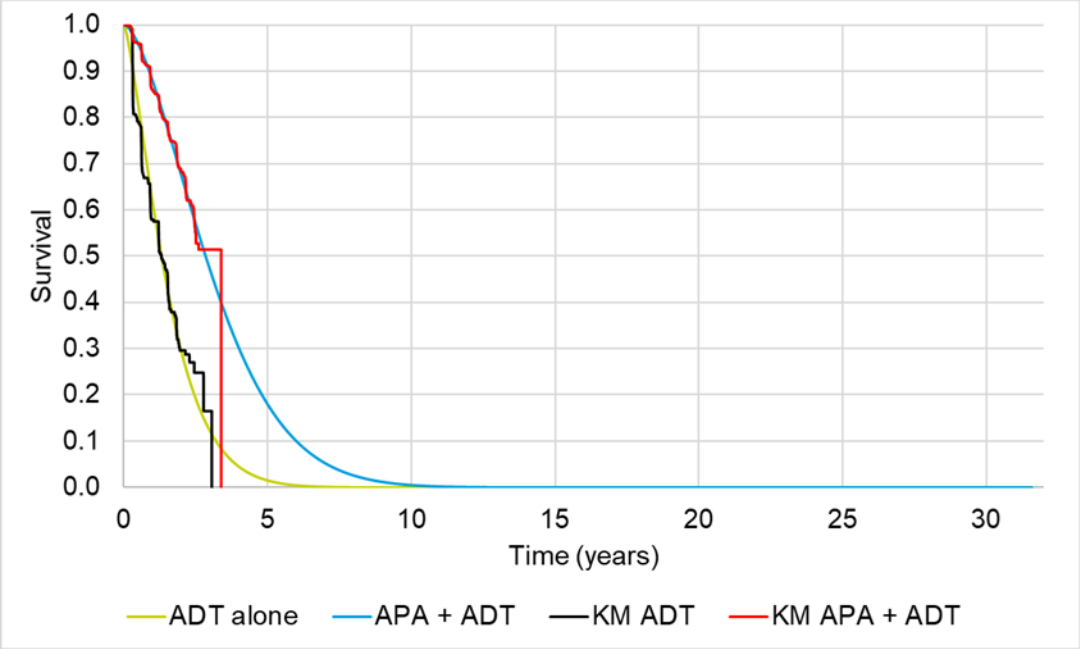


Figure 15 Metastases-free survival: nmHRPC

Source: prepared by the ERG using the company's model

4.2.7.1 Metastases-free survival (MFS): nmHRPC

Pre-progression in the nmHRPC population is modelled using MFS estimates as a proxy for clinical progression (CS Table 53). Based on the log-cumulative hazard plot for MFS (CS Figure 41) and the Schoenfeld test used to assess the proportionality of hazards (PH), the company concluded that the PH assumption did not hold: the curves were not parallel over the entire follow-up period, and the Schoenfeld test produced a significant p-value (p=0.0118). Therefore, standard parametric models were fitted independently to the MFS data for each treatment arm. CS Figure 42 shows the extrapolated curves for the treatment and comparator arms along with the Kaplan–Meier estimates from the SPARTAN trial. Summaries of the goodness-of-fit statistics and MFS estimates over time are shown in CS Table 56.

The company concluded, based on clinical advice and AIC and BIC criteria (CS Table 56), that on balance, the Weibull models (shown in Figure 15) were the most clinically plausible for the extrapolation of MFS in both treatment arms (a detailed argument is presented in CS page 180). Therefore, these curves were applied in the company's base case, with log-logistic and log-normal tested in scenarios (see Table 35).

ERG conclusion

- In the company's analysis, MFS was not adjusted for crossover to apalutamide. We note that the Kaplan-Meier curve for the ADT arm in SPARTAN was mature

at the IA1 cut-off date when the study was unblinded (see Figure 3 above) and, therefore, adjustment for crossover was not needed.

- Expert advice to the ERG suggests that none of the parametric forms used in the company's analysis adequately capture MFS: the selected models underestimate MFS in the ADT arm at 5 and 10 years, except generalised gamma which has a clinically implausible long tail, but may be overestimating it in the apalutamide arm. Therefore, using more flexible models, such as piecewise parametric models, would be more appropriate.[41]
- We assume the Weibull fits in the ERG base case, and test the structural uncertainty around the parametric distributions by applying log-logistic and log-normal models independently fitted to the observed data (see section 6.3 below). We also note that Kaplan-Meier data in SPARTAN were mature and, therefore, we conduct an additional scenario applying these estimates (as explained in section 6.3).

4.2.7.2 Second progression-free survival (PFS2): nmHRPC

4.2.7.2.1 PFS2 adjustment for treatment switching: nmHRPC

The 'modified' RPFSTM approach used by the company to adjust PFS2 from SPARTAN for treatment switching is outlined below. For a detailed explanation refer to CS Appendix R page 847.

STEP 1: Run g-estimation to estimate the shrinkage factor for abiraterone/enzalutamide, exp(ψ^{ST}), from COU-AA-302 using ATT weights to match the COU-AA-302 population to SPARTAN switching population.

STEP 2: Estimate shrinkage factor for apalutamide:

2.1: Estimate counterfactual survival time (in both treatment arms) adjusted for subsequent therapy with abiraterone/enzalutamide by applying the shrinkage factor derived in step 1.

2.2: Apply RPSFTM to estimate the shrinkage factor for apalutamide, exp(ψ^{a}), using counterfactual survival time from step 2.1.

STEP 3: Estimate counterfactual survival time (with or without re-censoring) following the UK one-novel-therapy rule using the estimated shrinkage factor for abiraterone/enzalutamide derived in step 1 and for apalutamide in step 2.

Here it is assumed that once patients switched to a non-permitted subsequent therapy, they remain on that therapy from the time of switch until they experience a PFS2 event.

The effect of re-censoring of the counterfactual surviving times on the shrinkage factors was estimated (as described in Appendix 9.3): in a Cox PH regression model, applied to the counterfactual survival times, HRs for RPSFTM analyses with and without re-censoring were [redacted] and [redacted], respectively (CS Appendix R Table R.9). We note that the HR in the ITT analysis was 0.553.

ERG conclusion

- In a simulation study conducted by Latimer et al.,[42] RPSFTM with re-censoring consistently overestimated effectiveness of the active treatment and produced a higher bias when compared with RPSFTM without re-censoring. We note, however, that Latimer et al.[42] considered performance of the RPFSTM adjusting for switching from control to active arm only, and therefore, the results of this simulation study might not be directly applicable to the 'modified' RPFSTM approach with two different types of adjustment for treatment switching. Hence, it is not clear which of the approaches to re-censoring, undertaken in the 'modified' RPFSTM, is likely to be less biased.
- The estimates applied in the company's economic analysis were obtained without re-censoring. Conducting an additional analysis with re-censoring is also recommended (see Latimer et al.[42]) because, as explained above, it is not clear whether the analysis without re-censoring would result in a smaller bias.

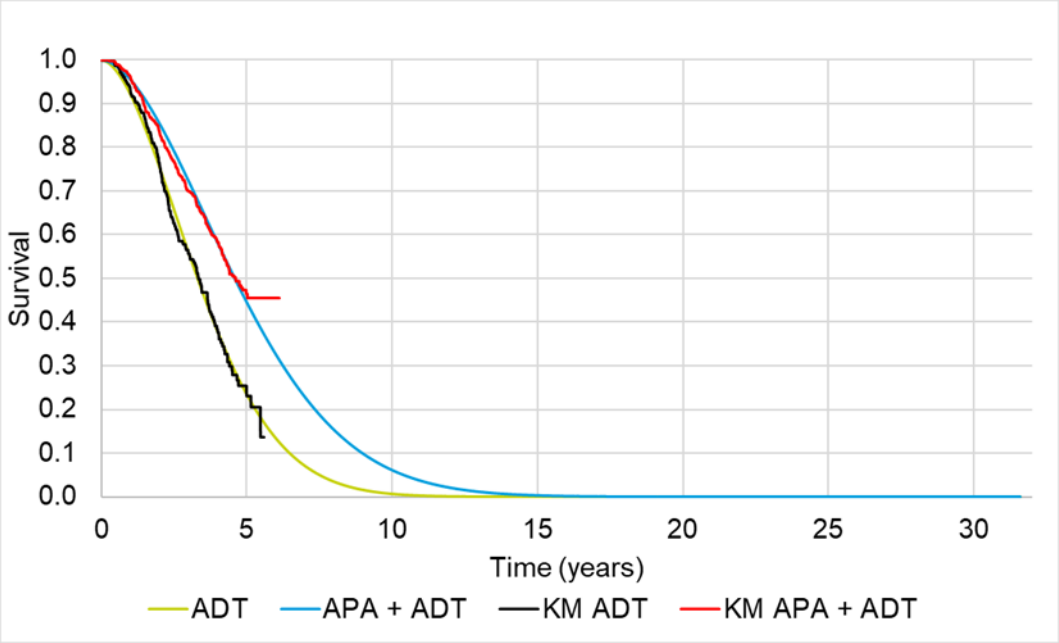


Figure 16 PFS2: nmHRPC

Source: prepared by the ERG using the company's model

4.2.7.2.2 PFS2 extrapolations: nmHRPC

The log-cumulative hazard plots for PFS2 (CS Figure 46) show that the curves remain relatively parallel over time for data adjusted for the one-novel-therapy restriction and crossover. Therefore, the company concluded that the PH assumption held, and that it would be appropriate to apply jointly fitted models in the base case. We note that the log-cumulative hazard plot for unadjusted data (CS Figure 46) also suggests proportionality.

The company fitted six parametric distributions to the adjusted PFS2 Kaplan–Meier data for the placebo arm and applied a hazard ratio for the apalutamide arm (CS Figure 47). Based on the statistical fits (AIC/BIC scores), the log-logistic, lognormal and generalized gamma distributions had the best fits to the adjusted PFS2 data (CS Table 58).

The Weibull models (shown in Figure 16), selected by the company for extrapolation of the PFS2 data, were considered to be most clinically plausible. We note, however, that they have average AIC and BIC when compared to the scores for the other models (see CS Table 58). The use of the log-logistic, lognormal and generalized gamma distributions was explored in scenarios along with the impact of using unadjusted data (see Table 35 and section 5.2). The full argument is presented in CS section B.3.3.5.2 page 190.

ERG conclusion

- The ERG adopts the company's approach to modelling PFS2 in the base case and scenario analyses (see section 6 below).

- The PFS2 estimates for the apalutamide arm in SPARTAN were relatively immature (see Figure 16), which is likely to contribute to the uncertainty in the economic outcomes.

4.2.7.3 Overall survival (OS): nmHRPC

4.2.7.3.1 Historical OS data: nmHRPC

The company considered using external data for modelling OS from the SPARTAN trial following the 'informed fits' approach proposed by Pennington et al.[38]

The underlying assumption of this method is that the shape parameter of any parametric distribution is a study independent parameter and could be used from external data to inform the shape parameter for the new clinical trial. The temporal bias between the trials can be adjusted for by applying a relative treatment effect. This means that the hazards between the historical and the SPARTAN trial ADT arms need to be proportional.

The company conducted an exploratory analysis using external data from three trials identified in a systematic review.[43] Kaplan–Meier curves for the placebo arms of the three studies were digitized, and individual patient data (IPD) datasets were created using methodology described by Guyot et al.[44] The reconstructed IPD from the studies were used to create a pooled Kaplan–Meier placebo curve. It is shown in CS Appendix S.2 Figure 104 along with the adjusted placebo arm from SPARTAN. A survival comparison between the historical trials and the SPARTAN trial (adjusted OS) is presented in CS Appendix S.2 Table S.4.

The PH assumption was visually assessed with a log-cumulative hazards plot (see CS Appendix S.2 Figure 105) and statistically tested with the Schoenfeld test. Based on visual assessment, the curves are parallel, and the proportional hazards assumption was considered to hold. This was further confirmed by the Schoenfeld test which was not significant (p=0.267).

As the PH assumption between the SPARTAN trial and the historical ADT arm held, the historical ADT arm data was included as a third arm in addition to apalutamide and placebo arms from the SPARTAN trial. In the model fitting, apalutamide and placebo were used as covariates to define the treatment effect compared to the historical clinical trial ADT arm.

The company concluded that given the limited number of historical ADT OS data available from literature and the fact that SPARTAN had longer follow-up than the studies identified in

the systematic review, the 'informed fits' approach[38] was not carried through into the modelling.

ERG conclusion

- The company did not utilise the historical ADT arm in the base case because, as the company stated, the 'informed fits' approach[38] was thought to provide only minimal additional benefit, and no exploratory analysis based on the 'informed fits' approach has been provided.
- The ERG critique of the searches conducted by the company for the 'informed fits' approach is provided in Appendix 9.4. Due to limited reporting of the searches, it was not possible to assess whether any relevant studies might have been missed.

4.2.7.3.2 OS proportional hazards (PH) assessment: nmHRPC

CS Figure 51 presents the log-cumulative hazard plot for OS in the apalutamide and placebo arms of the SPARTAN trial. The plot shows that the curves are relatively parallel over time. Based on the Schoenfeld test, the proportional hazards assumption seems to hold, as the resulting p-value was not significant (p=0.7321). Therefore, the company considered it appropriate to apply jointly fitted models in the base case. The company states that the adoption of this approach was supported at an advisory board.[45]

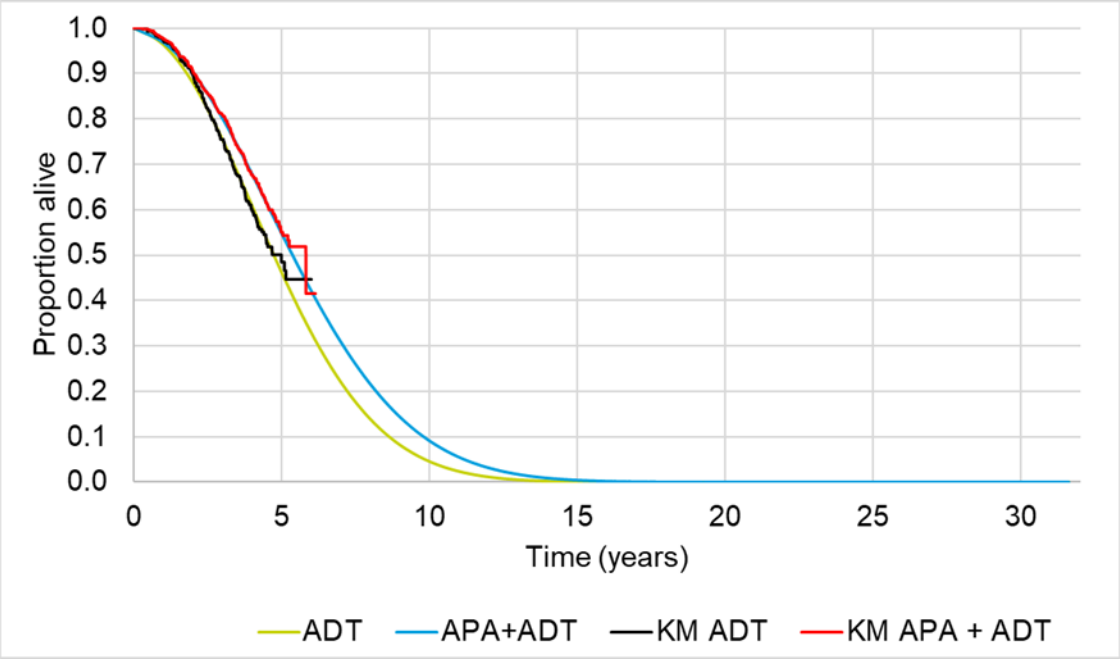


Figure 17 Overall survival: nmHRPC

Source: prepared by the ERG using the company's model

4.2.7.3.3 OS extrapolations: nmHRPC

OS estimates from the SPARTAN trial were adjusted for novel therapy and crossover to apalutamide using the same approach as for PFS2 (see section 4.2.7.2.1).

Six parametric functions were fitted jointly to the adjusted OS data (see CS Figure 52). The goodness-of-fit statistics and survival outcomes over time are presented in CS Table 60. The company chose the Weibull distribution for the extrapolation of OS because of its clinical plausibility. The use of the generalized gamma distribution, the second statistically best-fitting model, to extrapolate OS was explored in a scenario analysis (Table 35).

ERG conclusion

- The assumption that PH would hold in the extrapolated part of the survival curves could not be verified due to lack of evidence. We note that the survival estimates from SPARTAN, on which the PH assumption was tested, were immature (see Figure 4). Therefore, using models fitted to the treatment arms separately would be more appropriate, because this approach does not require the PH assumption which may be clinically implausible.[46] We note, however, that this assumption seems to have only a moderate impact on the results based on the drug list prices, and does not change the outcome of the cost-effectiveness analysis (see section 6.3).
- We have been advised that both Weibull curves used in the company's base case are likely to underestimate the overall survival at 10 years, and possibly 15 years (see CS Figure 52). Based on this advice, we select the fitted jointly generalised gamma models (shown in Figure 17) for our base case. These models have a good visual fit to the Kaplan-Meier estimates from SPARTAN, and lower AIC and BIC scores when compared to the Weibull models (see CS Table 60). In scenarios, we test the independently fitted generalised gamma and jointly fitted Weibull curves (section 6.3).

4.2.8 Survival curves: mHSPC

For mHSPC, the comparison of apalutamide plus ADT to placebo plus ADT was made using head-to-head data from the TITAN trial (see section 3.2.6). The extrapolation of rPFS, PFS2 and OS data, and the novel therapy adjustment of PFS2 and OS estimates, considered by the company, are outlined in sections 4.2.8.1 – 4.2.8.3. Note that crossover from placebo to apalutamide was not present in the TITAN data used in this appraisal and, therefore, this type of adjustment was not implemented.

The comparison of apalutamide plus ADT to docetaxel, informed by the NMA (critiqued in sections 3.3 and 3.4) is described in section 4.2.8.4 below.

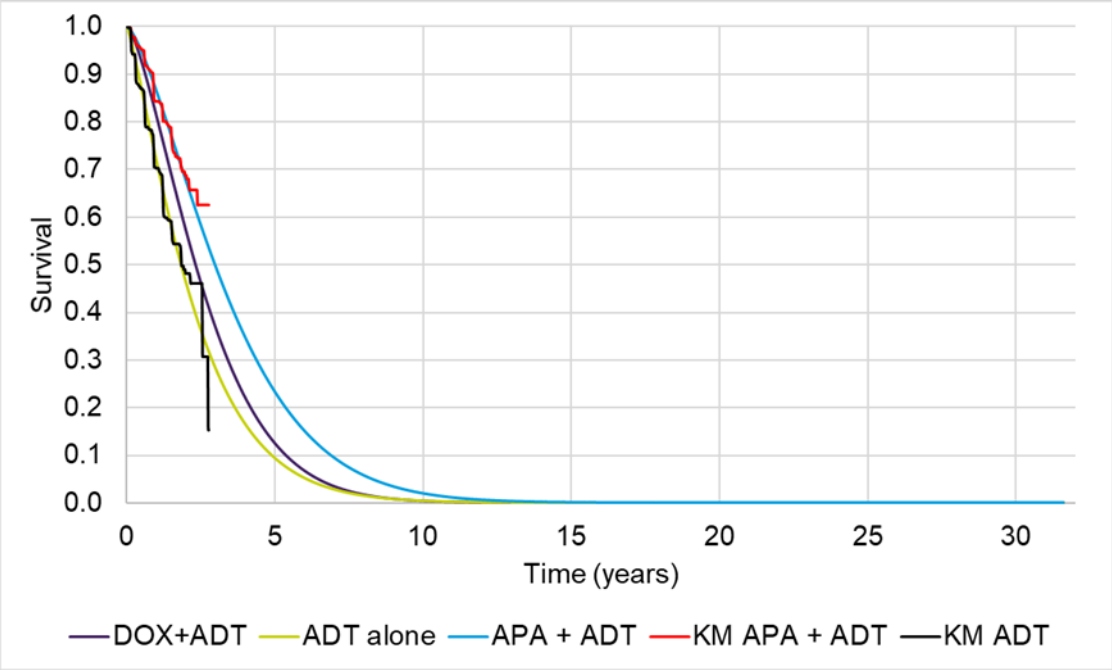


Figure 18 Radiographic progression-free survival: mHSPC

Source: prepared by the ERG using the company's model

4.2.8.1 Radiographic progression-free survival (rPFS): mHSPC

In the company's model, rPFS was considered as a proxy for clinical progression in mHSPC. PFS2 data from the 23rd November 2018 data cut of the TITAN trial were used in the company's analysis (Figure 9).

The log-cumulative hazard plot for rPFS (CS Figure 43) and Schoenfeld test (p=0.0586) indicate that the PH assumption may be violated. Given this assessment, the company concluded that parametric curves should be fitted for apalutamide and placebo independently.

Six parametric functions were fitted to the rPFS data from TITAN (see CS Figure 44 and CS Appendix J.1). Summaries of the goodness-of-fit statistics and the predicted survival over time are presented in CS Table 57. Based on clinical advice, Weibull curves (Figure 18) were selected for the company's base case, and exponential, log-logistic and generalized gamma were tested in scenarios (see sections 5.1 and 5.2).

ERG conclusion

- The Kaplan-Meier curves for the apalutamide arm in TITAN were highly immature (see Figure 18) which is likely to contribute considerably to the uncertainty in the cost-effectiveness of apalutamide for this indication, because the model predictions are sensitive to variations in rPFS.
- On balance, we apply the same models, Weibull, for our base case. We note, however, that the Weibull models have higher AIC and BIC scores compared to the log-logistic models. Besides, based on clinical advice, the Weibull fits are likely to underestimate the proportion of ADT patients radiographic-progression-free at 5, 10 and possibly 15 years.
- We note, however, that the historical ADT arm with a follow-up of about 9 years (discussed in section 4.2.8.3.2 below) appears to have a rather complex hazard function increasing during the first three years which correspond to the follow-up in TITAN (see Figure 21). If the shapes of the hazard functions for rPFS and OS are likely to be similar, more flexible models for rPFS which could accommodate complex hazard functions, such as piecewise models, would be required because none of the parametric models considered in the CS would be suitable. We note that only Weibull and Gompertz have increasing hazards (see CS Appendix Figure 49). However, the assumption that rPFS and OS are likely to have similarly shaped hazard functions might be too strong, and it can be proved, or disproved, only by more extended follow-up data.
- We test the other parametric distributions in scenarios reported in section 6.3.

4.2.8.2 Second progression-free survival (PFS2): mHSPC

In TITAN, 5% of patients randomised to apalutamide received novel therapies as first subsequent treatments (see CS Table R.11). Therefore, the company considered adjusting PFS2 and OS survival estimates for the impact of having more than one novel therapy, as outlined in sections 4.2.8.2.1 and 4.2.8.3.1 below. For further details refer to CS Appendix R.3.

4.2.8.3 PFS2 adjustment for novel therapy: mHSPC

PFS2 data from the 23rd November 2018 data cut of the TITAN trial was utilised in the company's analysis. Two methods, **IPCW** and the 'modified' **RPSFTM**,[29] were considered to adjust for biases introduced by the use of novel therapies not available in the NHS.

The implementation of the 'modified' RPSFTM method[29] was similar to that in SPARTAN, with the only exception that the propensity score-based approach used to match the COU-AA-302 population to the SPARTAN switching population was not implemented for TITAN because, as stated in the submission, "impact for SPARTAN was limited, and there was no indication that this would be different for TITAN". The shrinkage factor for abiraterone/enzalutamide estimated for SPARTAN population in step 1 (see section 4.2.7.2.1) was applied in the following steps when estimating counterfactual survival times for TITAN.

Regarding IPCW (described in CS Appendix R.3.2 page 872), the company stated that "the IPCW method assumes no unmeasured confounders related to both baseline and time-dependent patient characteristics; although this assumption cannot be tested, most clinically relevant prognostic factors available in the trial were included in the statistical modelling". Baseline and time-varying covariates used in the analysis are shown in CS Appendix R.3.2 Table R.13.

The adjusted PFS2 Kaplan-Meier curves for apalutamide obtained using IPCW and RPSFTM (without re-censoring) are shown in CS Appendix R.3.3 Figure 97 along with apalutamide and placebo Kaplan-Meier curves from the ITT analysis.

The resulting HR estimates based on RPSFTM with and without re-censoring were [redacted] and [redacted], respectively (CS Appendix R.3.3 Table R.15). In the RPFSTM propensity-score-based analysis (requested by the ERG), the respective estimates were [redacted] and [redacted] (see clarification response B12).

The HR derived using IPCW was [redacted] (CS Appendix R.3.3 Table R.15).

We note that HR in the ITT analysis was 0.657 (CS Appendix R.3.3).

We discuss the appropriateness of the novel therapy adjustment for PFS2 in section 4.2.8.3.1 below.

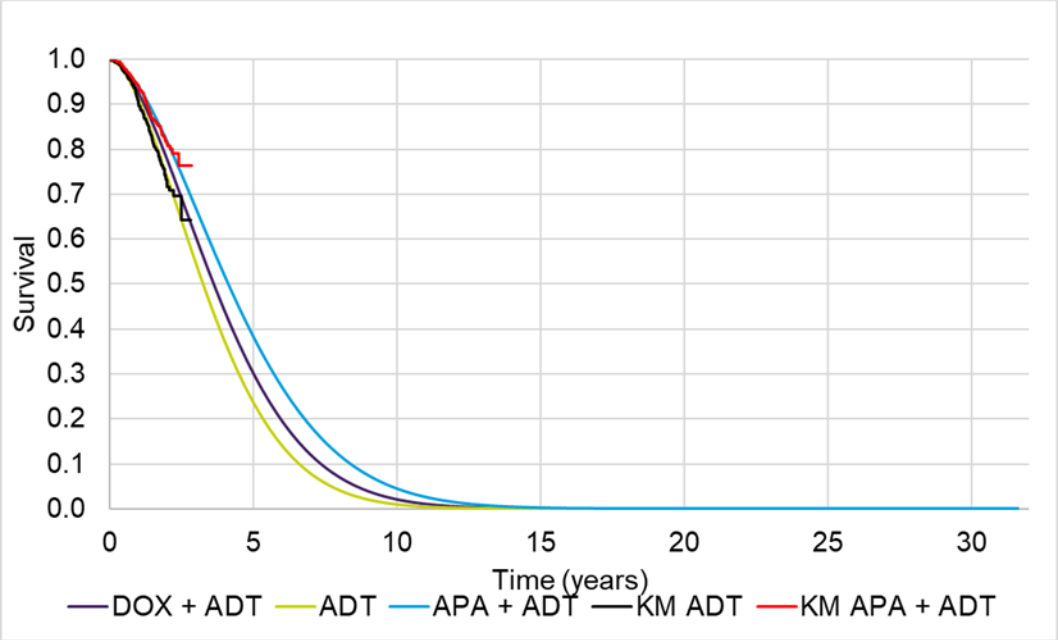


Figure 19 Second progression-free survival: mHSPC

Source: prepared by the ERG using the company's model

4.2.8.4 PFS2 extrapolations: mHSPC

PFS2 data unadjusted for the one novel agent restriction were used for PH assessment. The log-cumulative hazard plot (CS Figure 48) shows that the curves remained relatively parallel over time. Therefore, the company concluded that the PH assumption held, and that it was appropriate to apply jointly fitted models in the base case, with the placebo arm as the reference curve.

Fitted parametric distributions are shown in CS Figure 49 and CS Appendix J.1. We note that the Weibull and Gompertz models have the lowest AIC and BIC scores (see CS Table 59). The Weibull fits applied in the company's base case (see Figure 19) were selected on the basis of clinical plausibility and consistency with the curves for rPFS and OS (as explained in CS page 194). No sensitivity analyses were conducted to test the uncertainty in these estimates.

ERG conclusion

- We apply the Weibull fits in the ERG base case because of their consistency with rPFS and OS curves. The other plausible models, Gompertz, are tested in a scenario (see section 6).

- We note that the PFS2 estimates in TITAN (Figure 19) were immature and, therefore, the long-term PFS2 extrapolations assuming proportional hazards are likely to be highly uncertain.

4.2.8.5 Overall survival (OS): mHSPC

4.2.8.5.1 OS adjustment for novel therapy: apalutamide plus ADT versus placebo plus ADT in mHSPC

OS estimates from TITAN were adjusted for novel therapy using the same approach as that used for PFS2 (see section 4.2.8.2.1). CS Appendix R.3.3 Figure 96 shows the adjusted OS Kaplan-Meier curves for both arms obtained using IPCW and RPSFTM (without re-censoring) and those from ITT analyses. CS Appendix R.3.3 Table R.14 provides the respective hazard ratios.

As with PFS2, the COU-AA-302 population was not matched to the TITAN population in the company's RPFSTM analysis. This has been done in an additional scenario (see clarification response B12).

When the COU-AA-302 and TITAN populations were not matched, the HR estimates derived in the analyses with and without re-censoring were [redacted] and [redacted]. The respective HR estimates derived from the propensity-score-based RPSFTM were [redacted] and [redacted]. We note that HR derived from the ITT analysis was 0.671 (Table 23).

The company concluded that the novel therapy analysis failed to demonstrate any significant impact on survival outcomes (see CS Appendix R Figures 96 and 97) and gave counter-intuitive results in some scenarios. Therefore, the unadjusted TITAN data were used in the base-case analysis (Table 35).

As has been mentioned in section 4.2.8.2.1 with regard to IPCW, the most clinically relevant prognostic factors available in TITAN were included in the statistical modelling (see CS Appendix R.3.2 Table R.13).

ERG conclusion

- The IPCW and RPFSTM exploratory analyses could not be verified because the IPD from TITAN was not available to the ERG.
- We agree that, based on the estimates provided by the company, there seems to be an inconsistency between the HRs derived from the RPFSTM and IPCW analyses adjusting for treatment switching and that for ITT. Therefore, excluding the

adjustment for novel therapy from the base case is reasonable. It is certain, however, that the company's base case ICER was underestimated, because a higher number of patients in the apalutamide arm had non-permitted life-prolonging treatments when compared to the control arm ([redacted]% and [redacted]%, respectively, see CS Table R.11).

4.2.8.5.2 Historical OS data: apalutamide plus ADT versus placebo plus ADT in mHSPC

OS Kaplan-Meier estimates from TITAN were immature (see Figure 10). To reduce uncertainty in the long-term extrapolation of the OS estimates, an 'informed fits' analysis,[38] where historical survival data are used to inform survival extrapolations, was conducted, and the results of this analysis were adopted in the company's base case. The analysis is reported in CS Appendix S.

Seven published studies selected in a systematic literature review (see CS Appendix S.1.1 Figure 98) had longer follow-up relative to that in TITAN. We note that all the selected studies were published after 2013. Kaplan–Meier curves for the placebo arms of these studies were digitized, pseudo-IPD datasets were created[44] and pooled together (see Figure 20).[redacted] This is discussed in the next section.

On request from the ERG, the pseudo-IPD datasets were provided (see clarification response B11), and we were able to recreate the pooled historical ADT arm (Figure 20). The hazard function for this arm is shown in Figure 21 below.

Figure 20 OS Kaplan-Meier curve for ADT arm in TITAN versus pooled historical ADT arm

Source: CS Appendix S.1.2 Figure 99

ERG conclusion

- The ERG critique of the searches conducted by the company for the 'informed fits' analysis is presented in Appendix 9.4.
- The implementation and the outcomes of the 'informed fits' approach could not be verified because the IPD were not made available to the ERG.
- We note, however, that based on feedback from the advisory board,[45] current patients in clinical practice would perform better than patients from the historical ADT arm. Therefore, using the historical ADT arm in the economic analysis is likely to increase uncertainty in the economic outcomes.

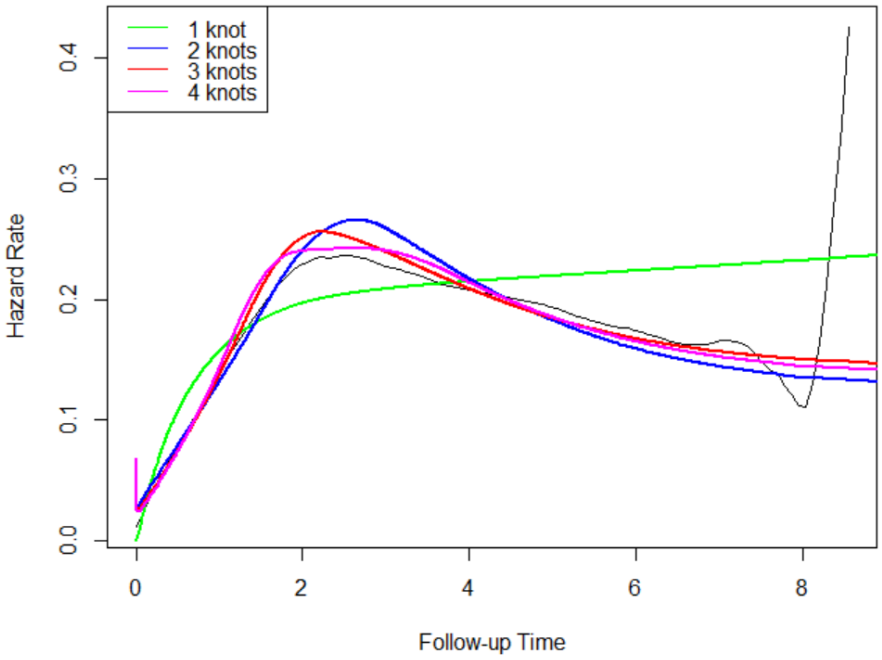


Figure 21 Hazard function for the historical ADT arm

Source: the plot was generated by the ERG using R function flexsurvspline[47] which implements a spline model of Royston and Parmar[48] with 1-4 knots (R version 4.0.2)

4.2.8.5.3 OS proportional hazards (PH) assessment: apalutamide plus ADT versus placebo plus ADT in mHSPC

The log-cumulative hazard plots for apalutamide versus placebo from TITAN, and placebo from TITAN versus the pooled historical ADT data are presented in CS Figure 53. The plots show that the curves remain parallel throughout the trial follow-up. The resulting p-value from the Schoenfeld tests were statistically non-significant (p=0.9803 for apalutamide versus placebo, and p=0.9754 for placebo versus the pooled historical data). Therefore, the company concluded that the assumption of common shape between the curves (required for the 'informed fits' analysis[38]) seemed to hold.

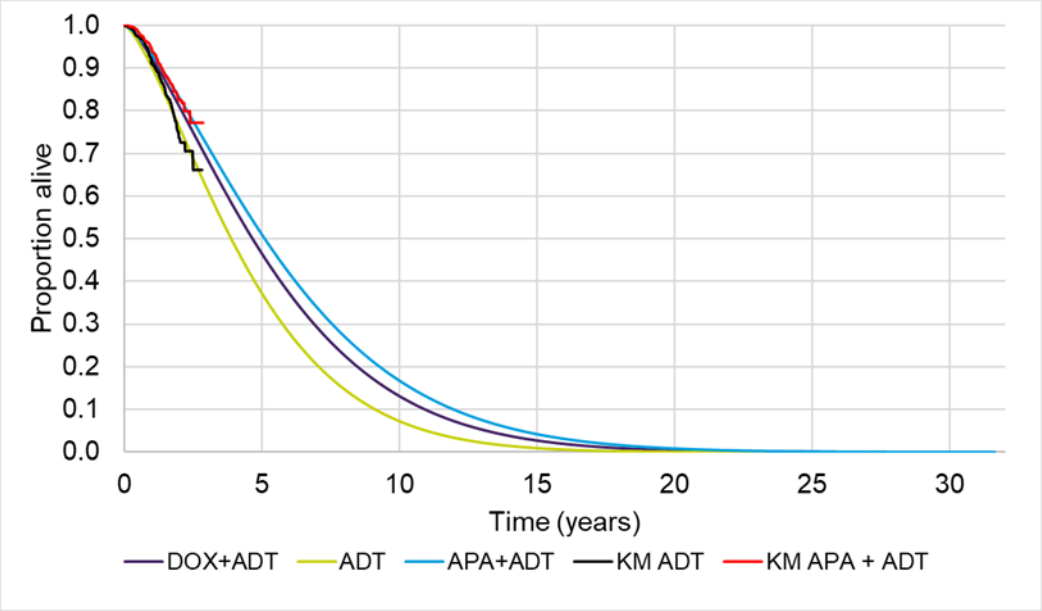


Figure 22 Overall survival: mHSPC

Source: prepared by the ERG using the company's model

4.2.8.5.4 OS extrapolation: apalutamide plus ADT versus placebo plus ADT in mHSPC

Parametric functions fitted to the historical OS 'informed fits' for each treatment arm from the TITAN trial are shown in CS Figure 54 and Appendix J.1. Summaries of the goodness-of-fit statistics and survival estimates over time are presented in CS Table 61. The fitted distributions were validated against overall survival estimates from the external sources identified in the company's literature review (see CS Figure 66 and section 4.2.8.3.2 above). The company states that, based on expert opinion, the Weibull curves (see Figure 22) provided the most clinically plausible extrapolations. They were applied in the company's base case, with the lognormal, log-logistic, generalized gamma and Gompertz tested in scenarios.

ERG conclusion

- The clinical expert from the advisory board[45] noted, when discussing the pooled historical ADT arm, that it would be unusual for patients to die from prostate cancer within a year of diagnosis. We note, however, that all OS parametric curves considered by the company for apalutamide and placebo drop sharply from the very beginning of the observation period (see Figure 22).
- In our expert's opinion, the Weibull models, adopted in the base case, are likely to slightly underestimate patient survival at 5, 10 and possibly 15 years in both treatment arms. The generalised gamma curves, which have lower AIC and BIC

scores than Weibull, appear to be the next most clinically plausible fits, but they have tangibly longer tails. Therefore, on balance, we select the Weibull models (which are more conservative) for the base case and test the other curves in scenario analyses (see section 6.1).

- We note, however, that the OS estimates in TITAN (Figure 19) were immature and, therefore, the long-term extrapolations assuming proportional hazards are likely to be highly uncertain. Moreover, the historical ADT arm (see Figure 20) used in the 'informed fits' approach seems to have a complex hazard function and, therefore, more flexible models are likely to be more appropriate.[41]

4.2.8.6 Comparison of apalutamide plus ADT versus docetaxel plus ADT

The cost-effectiveness analysis for apalutamide plus ADT versus docetaxel plus ADT was based on the HR estimates derived from the Bayesian NMA (see sections 3.3 and 3.4).

The mean HR estimates derived in the NMA were [redacted] for rPFS and [redacted] for OS (Table 27).

To estimate rPFS for docetaxel plus ADT, the respective HR estimate from the NMA was applied to the selected rPFS curve for apalutamide plus ADT. The resulting rPFS is shown in Figure 18 along with the estimates for apalutamide plus ADT and ADT alone.

The OS curve for docetaxel plus ADT (see Figure 22) was derived in the same manner as for rPFS, i.e. using HR from the NMA (Table 27).

PFS2 for docetaxel plus ADT (Figure 19) was estimated using the HR for rPFS, [redacted] as a proxy because PFS2 data were not available for docetaxel plus ADT (see sections 3.3 and 3.4 above).

Some of the trials used in the Bayesian NMA had subsequent novel therapies which would not be available in the NHS. This is discussed in sections 3.3 and 3.4.

According to CS Table 97, OS curve fitting approach in the company's main analysis was based on 'informed fits', and unstratified approach was tested in a sensitivity analysis. The company, however, does not provide any further details on the implementation of the 'informed fits' approach in the comparison of apalutamide with docetaxel.

ERG conclusion

- The company's economic analysis for apalutamide versus docetaxel was based on the clinical efficacy results from the NMA, where adjustment for novel therapy was

not considered. This is likely to increase uncertainty in the ICER for apalutamide versus docetaxel.

- Using the HR estimate for rPFS as a proxy to model PFS2 (as described above) also contributes to the uncertainty in the cost-effectiveness of apalutamide.

4.2.9 Adverse events

The model includes all serious adverse events of grade 3-4 that occurred for any treatment. CS Table 82 reports the incidence of these adverse events. The ERG found some inconsistencies between the values used in the model, the values reported in CS Table 82 and the values presented in the cited sources. Following the ERG clarification question B18, the company acknowledged these discrepancies and provided an updated model with the correct inputs.

The occurrence of adverse events in the pre-progression phase is based on the SPARTAN trial for nmHRPC, on the TITAN trial for mHSPC and on a study by Gravis et al.[49] for the comparison against docetaxel plus ADT. The most frequent grade 3-4 adverse event is neutropenia (32% in docetaxel arm), with the remaining adverse events occurring in less than 17% of patients. For the apalutamide plus ADT arm, the most frequent grade 3-4 adverse event is hypertension (16.3% for nmHRPC and 8.4% for mHSPC).

The occurrence of adverse events in the post-progression phase was informed by relevant clinical trials, which are detailed in CS Table 82. Neutropenia is also the most frequent grade 3-4 adverse event occurring in patients with mHRPC (82% of patients receiving cabazitaxel and 32% receiving docetaxel).

Adverse events were incorporated by using a aggregated per cycle probability of adverse events. In the base case, the impact of adverse events was accounted for by weighted disutilities and costs per patient, as detailed in sections 4.2.10 and 4.2.11.

4.2.10 Health related quality of life

4.2.10.1 Systematic literature review of utility data

The company conducted a SLR to identify HRQoL data for patients with nmHRPC and mHSPC (CS Appendix H). For nmHRPC, the searches were performed in July and August 2018 and the final update search was performed in May and June 2020. For mHSPC the original searches were performed in September 2015 and the final update was in May 2020.

For nmHRPC, seven publications were identified, and these are summarised in CS Appendix H. Of these, two publications fully adhered to the NICE reference case, while four others used the EQ-5D but did not apply a UK tariff. The two publications that met the NICE reference case were the NICE appraisal of enzalutamide for nmHRPC (TA580) and the Scottish Medicines Consortium appraisal of enzalutamide for nmHRPC. The utility values from these publications are shown in Table 36.

For mHSPC, 29 studies were identified (CS Appendix H). None of these studies fully adhered to the NICE reference case – they either did not report utility values or the reported utility values were not estimated using the EQ-5D.

The company did not provide a review of HRQoL in patients with mHRPC and so the ERG requested this (clarification question B15). The company responded that they were unable to obtain all utility values from previous NICE technology appraisals as some data were redacted. This information is provided below in Table 36. The values used in the company's model for second and third-line mHRPC are much lower than in TA377 and TA580. We report scenario analyses using utility values from the NICE appraisals of enzalutamide for nmHRPC (TA377 and TA580) in section 6.

Table 35 Health state utility values for mHRPC from previous NICE appraisals

Appraisal	Utility values
ID945: Abiraterone	High risk mHSPC: 0.792 1L mHRPC: 0.704 2L mHRPC: 0.525 3L mHRPC: 0.420 Note the mHRPC utility values were calculated using the exact same method that is outlined in the response to clarification question B15
TA580: Enzalutamide	1L mHRPC: 0.81[a] 2L mHRPC: 0.8 [a] 3L mHRPC: 0.688 End-of-life utility: 0.590 (applied for 3 months period prior to death)
TA391: Cabazitaxel	mHRPC (stable disease): 0.704-0.819 mHRPC (progressive disease): 0.6266 (until last 3 months of life which are set to 0)
TA387: Abiraterone	1L mHRPC: 0.83 2L mHRPC: 0.625 3L mHRPC: 0.5
TA377: Enzalutamide	mHRPC (stable disease): 0.844 Post progression 1: 0.658 Post progression 2: 0.612 Palliative care: 0.5
TA316: Enzalutamide	mHRPC (Disutility progression): -0.085
TA259: Abiraterone	Pre-progression: 0.780 mHRPC (Post-progression): 0.5
Key: 1L, first line, 2L, second-line, 3L, third-line, mHRPC, metastatic hormone relapsed prostate cancer. [a] Values reported in the Scottish Medicines Consortium appraisal of enzalutamide for nmHRPC	

4.2.10.2 Study-based health related quality of life

HRQoL was measured in the SPARTAN and TITAN trials (section 3.2.3.3 and 0) using the EQ-5D preference-based method, as recommended by NICE. [50] SPARTAN used the EQ-5D 3L as recommended in the NICE reference case, while TITAN used the EQ-5D 5L scale and then mapped values to the 3L scale using the crosswalk algorithm[51] as recommended by NICE.

For the SPARTAN trial, HRQoL measurements were taken for the pre-progression and post progression periods (until 12 months post-progression) as described in CS Table 63. The number of patients who had EQ-5D measured is shown in CS Figure 16. The CS states that rates of completion for the EQ-5D were more than 92% up to cycle 29 and more than 63% for the end of treatment visit and post-progression.

For the TITAN trial, HRQoL measurements were taken for the pre-progression and post progression periods (until 12 months post-progression) as described in CS Table 63. The number of patients who had EQ-5D measured is shown in CS Figure 29. The CS states that rates of completion for the EQ-5D ranged from 78% to 85% up to cycle 13 and 80% thereafter.

The company used regression models to estimate utilities for the nmHRPC and mHSPC health states from their clinical trial utility data. More details of the methods are described in CS Appendix R.

The utility values used for pre-progression and post-progression (1L mHRPC) are taken from the company trials. The company derived the utility values for 2L and 3L mHRPC by applying a relative decline ratio, estimated by dividing the 2L mHRPC utility by the 1L mHRPC utility from TA387. This ratio was then multiplied by the utility from the post-progression health state (1L mHRPC) from the company's trials. This process was repeated to estimate the 3L mHRPC utility. The utility values used in the company model are shown in Table 37 (CS Table 65).

Table 36 Summary of utility values for company base-case cost-effectiveness analysis

State	Indication	Mean
Pre-progression	nmHRPC	[redacted]
	mHSPC	[redacted]
Pre-progression (with AE/SRE)	nmHRPC	[redacted]
	mHSPC	[redacted]
1L mHRPC	nmHRPC	[redacted]
	mHSPC	[redacted]
2L mHRPC	nmHRPC	[redacted]
	mHSPC	[redacted]
3L mHRPC	nmHRPC	[redacted]
	mHSPC	[redacted]

Abbreviations: 1L: first line; 2L: second-line; 3L: third-line; ADT: androgen deprivation therapy; AE: adverse event; mHRPC: metastatic hormone-relapsed prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; SRE: skeletal-related event.

The problem with the company's approach is that it assumes that there will be a similar relative decline in utility for patients between health states in TA387 and the current appraisal. We find this unlikely as the trial had different starting populations and the effect of this appears to be underestimate utility values for 2L and 3L mHRPC. The ERG prefers to use the utility values from TA387 without any adjustment. The unadjusted utility values for

second-line and third-line mHRPC are shown in Table 38. We use these utility values in the ERG base case (section 6)

Table 37 ERG's preferred utility values for second-line and third-line treatment in mHRPC

Health state	Indication	Mean
2L mHRPC	nmHRPC	[redacted]
	mHSPC	[redacted]
3L mHRPC	nmHRPC	[redacted]
	mHSPC	[redacted]

4.2.10.3 Adverse event disutilities

In the company base case analysis, the adverse event disutilities were taken from EQ-5D values collected in the TITAN and SPARTAN trials as estimated using the regression analysis described in CS Appendix R. For each cycle, the utility decrement is calculated by multiplying the adverse event disutility with the incidence of adverse events and the proportions of patients in that health state. Scenario analyses are also conducted using literature values for the AE disutility values (CS Table 95 and 96).

In addition, a further utility decrement of 0.02 was applied for the first year for all patients receiving docetaxel (mHSPC only). This value was taken from the STAMPEDE trial and applied for one year, based on the assumption used in Woods et al.[32] For mHRPC health states, disutilities were estimated from the literature, based on relevant clinical trials for each subsequent treatment.

We consider that the adverse event disutility is overestimated for the mHSPC/nmHRPC health states as in the model when patients suffer an AE, a disutility for these patients is then applied for the remainder of that health state. However, Aes mostly only last for up to two weeks (CS Table 64). We have made this change for the adverse events in the ERG base case (section 6).

4.2.10.4 Age-related disutility

The company does not include age-related disutility in the model. The ERG notes that including age-adjusted utility is recommended by NICE DSU Technical Support Document 12. [52] Further we note that utility values for patients with nmHRPC have a lower utility value than the general population norm for the UK. Age-related disutility is unlikely to have a large impact on the model results as utility values are estimated for each treatment line and these

would have incorporated the age of patients. The ERG base case analysis therefore does not include an age-related disutility. We have included a scenario analysis that includes age-related disutility for the pre-progressed health state with utility values set to no more than the UK population norm (section 6).

ERG conclusion

The company's approach to estimating utility values is reasonable and consistent with the NICE reference case. The utility values for the mHSPC / nmHRPC / mHRPC 1st-line are taken from the company's TITAN and SPRTAN trials. The ERG has concerns on the estimation of the mHRPC second, and third line health state utility values and AE utilities and suggest alternative values.

4.2.11 Resources and costs

The economic model includes drug acquisition costs for the nmHRPC and mHSPC groups and subsequent treatments used on progression to mHRPC (first, second and third line), health state management costs, costs for managing adverse events and terminal care costs incurred at the end of life.

The company conducted a systematic literature review (SLR) to identify any relevant cost and healthcare resource use data associated with the treatment of patients with nmHRPC and mHSPC. The original searches were performed between 19th July 2018 and 13th August 2018. The final update was performed between 01 May 2020 and 04th June 2020.

Details of the search strategy and eligibility criteria are shown in CS Appendix I. The searches identified 16 relevant studies for nmHRPC. Of these, the most relevant is NICE TA580 for enzalutamide.[9] For mHSPC, the search identified 14 studies, with no studies from the UK.

The resource use in the company's model was largely based upon those used in the company submission for TA387 (Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated).[40]

4.2.11.1 Drug acquisition

The acquisition costs for each drug is taken from the Monthly Index of Medical Specialties (MIMS),[53] the UK drugs and pharmaceutical electronic market information tool (eMIT)[54] and from the British National Formulary (BNF).[55] Intended dosages were adjusted by the dose intensity observed in the trials for apalutamide and docetaxel.

Apalutamide is an oral treatment and is licensed at 4 x 60mg QD. The list price of apalutamide is £2,735 for 112 tablets (course of 28 days). Apalutamide is supplied to the NHS with a confidential patient access scheme (PAS) price discount.

The dosing, frequency and unit costs of the drugs are shown in Table 39 (CS Table 67). Docetaxel, cabazitaxel and radium-223 are given for a fixed duration whilst other treatments are given until disease progression (or intolerable side effects).

The company has reported all analyses using the list price of all subsequent treatments and the PAS price for apalutamide. The ERG replicated the company's analyses using the subsequent treatment PAS prices in a separate confidential appendix to this report.

Table 38 Dosing, frequency and unit costs per administration

Treatment		Drug acquisition costs			Dose / Frequency
		Cost per pack	Pack size	Unit	
Intervention and comparators	Apalutamide	£2,735.00 (list price)	112	Tablets	4 tabs / day
	Docetaxel	£20.96	1	Vial	Every 3 weeks
ADT individual therapies	Leuprorelin	£225.72	1	Syringe	Every 3 months
	Triptorelin	£207.00	1	Syringe	Every 3 months
	Goserelin	£70.00	1	Syringe	Every 28 days
	Bicalutamide	£1.74	28	Tablets	One per day
Subsequent therapies (if not included as a comparator)	Abiraterone	£2,735.00	56	Tablets	2 tabs / day
	Enzalutamide	£2,734.67	112	Tablets	4 tabs / day
	Cabazitaxel	£3,696.00	1	Vial	Every 3 weeks
	Radium-223	£4,040.00	1		Every 3 weeks
	BSC (prednisolone)	£0.28	28	Tablets	One per day

Abbreviations: ADT: androgen deprivation therapy; BSC: best supportive care.

Oral treatments are assumed to have no administration cost. ADT treatments are administered by syringe and require a nurse appointment and those administered by IV require a day case appointment (CS Table 68).

4.2.11.2 Subsequent treatment

The CS assumes that patients with mHRPC receive the same set of subsequent therapies after progressing from either nmHRPC or mHSPC. The proportion of patients receiving subsequent treatments is estimated from the company's mHSPC advisory board and is shown in CS Table 72. Scenario analyses were conducted by the company using alternative

market shares taken from the nmHRPC advisory board and the SPARTAN and TITAN trials (CS Table 95 and 96). However, it should be noted that many patients in the SPARTAN and TITAN trials had more than one novel therapy. The company provides an adjustment to the PFS2 and OS survival curves to remove the effect of patients having more than one novel therapy, as we have discussed earlier in section 4.2.6.2. The market shares for the nmHRPC advisory board and the SPARTAN and TITAN trials are shown in CS Appendix P.

Clinical advice to the ERG agrees that the estimated proportions of patients taking subsequent treatments in the company's model are reasonable. However, the ERG notes that patients with mHSPC treated with ADT alone also received docetaxel as a subsequent treatment. This is inappropriate for the company's analyses for people ineligible/unsuitable for docetaxel in mHSPC, as by definition, they are not able to receive docetaxel. Due to the low cost of docetaxel, this is unlikely to have a large impact on the model results.

The subsequent therapies consist of those administered continuously (abiraterone, enzalutamide and BSC) and those with a fixed duration (docetaxel, cabazitaxel and radium-223). The drug costs of continuous therapies are estimated by multiplying the per-cycle cost of each treatment by their market share and the number of patients in the relevant mHRPC health states. The costs of fixed therapies are estimated by multiplying the number of incident patients in first-line, second-line and third-line mHRPC by the market share and the total cost of the therapy. The number of vials administered for the fixed duration treatments are shown in CS Table 74.

The ERG notes an error in the calculation of third-line costs for fixed duration treatments for docetaxel + ADT (cells Q139 and,Q140) in the subs therapy costs worksheet. We correct this error in section 6.

The ERG notes an error in the estimation of incident patients for third-line mHRPC whereby the total number of incident patients for third-line mHRPC is greater than for second-line. This is clearly implausible and we correct it in section 6.

4.2.11.3 Time on treatment

Patients receive apalutamide plus ADT until disease progression or emergence of Aes. The time on treatment KM curves are shown in CS Figure 56 and 57 for the SPARTAN and TITAN trials respectively. The company fitted parametric curves to the time-on-treatment

data for apalutamide plus ADT. The CS notes that there is some crossover of the curves of predicted TTD and PFS. [redacted] The ERG agrees with the approach taken by the company and the curve chosen for TTD for apalutamide plus ADT.

For the ADT and the docetaxel plus ADT arms, the company assumes that all surviving patients will receive all treatments, i.e. TTD = PFS. A similar approach is taken for subsequent treatment lines of treatment. For subsequent treatments for mHRPC, the time on treatment is assumed to be equal to the time spent in the health states for first line, second-line and third-line.

4.2.11.4 Estimation of mean health state durations

The time spent in mHRPC on second-line and third-line treatments is estimated according to the mean health state durations from NICE TA387, shown in Table 40. The total time patients spend in the 2L and 3L mHRPC health states is determined by the area between the PFS2 and OS curves. Therefore, the mean health state durations are simply used to split patients between the 2L and 3L health states.

Constant probabilities were estimated to model the transition between health states by applying an exponential distribution to the mean time in health states. The durations from the abiraterone arm for TA387 are applied to the ADT alone and docetaxel plus ADT arms as the majority of patients in clinical practice are likely to receive an active first-line treatment for mHRPC. In a similar way, the durations from the ADT arm from TA387 are applied in the apalutamide plus ADT arm as these patients are not expected to receive a novel agent as a subsequent therapy.

Table 39 Mean health state durations in TA387

Health state	AAP	BSC
1L mHRPC	[redacted]	[redacted]
2L mHRPC	[redacted]	[redacted]
3L mHRPC	[redacted]	[redacted]
3L mHRPC (ERG estimate)	[redacted]	[redacted]
mHRPC LYs	[redacted]	[redacted]

The mean health state durations in TA387 are adjusted by multiplying by the mean post progression survival in the model and dividing by the mean life years in TA387 (see CS section B3.3.7.2). They are further adjusted by dividing by the proportion of patients who did not die in the pre-progression health state in the TITAN and SPARTAN. The ERG is unclear on the rationale for dividing by this value. We do not include this adjustment in the ERG base case in section 6.

The company provide more details on the mean health state durations in the response to clarification question B3 and the unredacted values of the mean health state durations in TA387 are shown in Table 20 of the clarification response. The ERG notes that there is some uncertainty over the mean health state durations for 2L and 3L mHRPC as the treatments differ for patients in TA387 to those in the current appraisal, particularly for estimates of the mean health state durations for the apalutamide plus ADT arm. Further we note that health state duration for 3L mHRPC is only for those on active treatment, whereas the majority of patients in 3L mHRPC are on best supportive care (CS Table 72). Therefore, we consider it is more appropriate to estimate the mean health state duration for 3L mHRPC by including those on BSC in TA387. The ERG's estimates for 3L mHRPC mean health state duration are shown in Table 40 and these are used in the ERG's base case, reported in section 6.

We note that there appears to be an error in cell 'PF_DOX!AJ9', see section 5.3.2 for more details. We correct this error in section 6.

4.2.11.5 Health state unit costs

Health state costs consisted of scheduled and unscheduled medical resource costs. Scheduled medical resource use and their frequency is shown in CS 77-79 for mHSPC, nmHRPC and mHRPC. The CS states that these were elicited from clinical experts at two advisory boards.

Clinical advice to the ERG suggests minor differences to the frequency of investigations as follows: for mHSPC, patients treated with apalutamide would receive PSA and other blood tests every 4 weeks for the first 3 months (rather than every 12 weeks) and then every 12 weeks thereafter. For nmHRPC patients treated with ADT would receive MRI scan every 26 weeks (rather than every 52 weeks).

Unplanned medical resource use (MRU) costs for all treatment for mHSPC, nmHRPC and mHRPC were assumed to be £21.57 per weekly cycle. The unplanned MRU costs were based upon NICE TA387.[56] The ERG asked for more clarification on the unplanned MRU costs (clarification question B13). The company stated that "It is unclear whether this cost captures all unscheduled resource use including or excluding the treatment of adverse events and therefore whether there is any risk of double counting" (Clarification question B13, p45)". The company provided a scenario where unscheduled resource use costs were omitted and they stated that omitting these costs had a minimal effect on model results. As unscheduled MRU costs should be counted for by the adverse event management costs, we have omitted unscheduled resource costs in the ERG base case analysis (section 6).

Health state unit costs are not reported in the CS but are shown in the economic model (Resource use costs worksheet). These were taken from 2018/2019 NHS reference costs[57] and 2019 PSSRU costs.[58] The health state costs for each of the treatments are shown in CS Table 80.

4.2.11.6 Cost of terminal care

The company's model includes a cost of end-of-life care of £15,786 taken from Round et al[59]). The reported cost in that study was inflated to 2018/19 prices using the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care.[58]

4.2.11.7 Adverse event costs

The model includes the costs of managing grade 3+ adverse events, shown in CS Table 81. These AE costs were taken from TA387[56] and inflated to 2018/19 costs using the PSSRU inflation indices. The ERG notes that the values used in the model differ from those presented in CS Table 81 and appear to have been inflated twice. In addition, the inflation indices used by the company are for prices only whereas the ERG prefers to use the prices and pay inflation indices. In response to clarification question B14, the company acknowledged that inflation had been applied twice in error. They provided a scenario with corrected values and stated that these changes had a minor impact on the model results.

The cost of managing neutropenia in CS Table 81 is £862.79. We consider this an overestimate as patients with neutropenia would not be hospitalised and would only require an additional outpatient visit and blood test (£150.16). The ERG has changed the costs of managing this adverse event in section 6.

The cost of all AEs for each comparator in the model is calculated by estimating a weighted average of the probability of experiencing each event from the relevant trial data, multiplied

by the cost of each event. The cost per cycle is calculated by dividing the total incidence from each study by the median follow-up. Adverse events are applied each model cycle for all patients remaining on treatment.

We consider that the costs of adverse events for docetaxel treatment have been overestimated for mHSPC. Docetaxel is given for six cycles and the majority of the costs of managing side effects would be during this 18-week period. We therefore consider that AE costs should only be costed up to the trial follow-up duration (26 weeks). The ERG changes the costs of adverse events for docetaxel in section 6. The CS states that real world data on the usage of docetaxel suggest higher rates of grade ≥3 neutropenia and febrile neutropenia of 36.3% and 18.2%.[60] The ERG includes these estimates of Aes in a scenario analysis in section 6.

ERG conclusion

The approach taken by the company for estimating costs and resource use are reasonable and appropriate and consistent with previous technology appraisals for prostate cancer. The ERG has identified errors in the calculation of adverse events costs and subsequent therapy costs and suggest minor changes to the cost outpatient visits, the cost of managing neutropenia and health state resource use.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

5.1.1 nmHRPC

CS Section B.3.7.1 reports the base case results for apalutamide plus ADT versus ADT alone for the nmHRPC indication. The results show that apalutamide plus ADT offers [redacted] of [redacted] and a mean QALY gain of [redacted] compared with ADT alone (Table 41). Apalutamide plus ADT therefore dominates ADT alone, i.e. it is cheaper and more effective. Disaggregated results by health state are shown in CS Table 87.

Table 40 Company's base case results for nmHRPC (discounted, PAS price for apalutamide)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£/QALY)
ADT alone	[redacted]	5.03	[redacted]				
Apalutamide plus ADT	[redacted]	5.70	[redacted]	[redacted]	0.67	[redacted]	Dominates
Source: reproduced from CS Table 85.							

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£/QALY)
ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gain; QALYs: quality-adjusted life years.							

5.1.2 mHSPC

CS Section B.3.7.2 reports the base case results for apalutamide plus ADT versus ADT alone and docetaxel plus ADT for the mHSPC indication. The results show that apalutamide plus ADT offers a mean QALY gain of [redacted] for an additional mean cost of [redacted], giving an ICER of £38,983 per QALY compared with docetaxel plus ADT (Table 42). In the subgroup of patients ineligible to receive docetaxel, apalutamide plus ADT provides an ICER of £25,329 compared with ADT alone (Table 42). Disaggregated results by health state are shown in CS Table 87.

Table 41 Company's base case fully incremental results for mHSPC (discounted, PAS price for apalutamide)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£/QALY)	ICER (£/QALY): APA vs. ADT
ADT alone	[redacted]	4.588	[redacted]					
Docetaxel plus ADT	[redacted]	5.501	[redacted]	[redacted]	0.913	[redacted]	9,633	
Apalutamide plus ADT	[redacted]	6.023	[redacted]	[redacted]	0.523	[redacted]	38,983	25,329
Source: reproduced from CS Table 88 and CS Table 89. ADT: androgen deprivation therapy; APA: apalutamide plus ADT; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gain; QALYs: quality-adjusted life years.								

The cost-effectiveness results presented include a confidential PAS discount price for apalutamide but do not include existing PAS discounts for the subsequent therapies. Therefore, the ICERs do not reflect actual prices that would be paid by the NHS. The results including all agreed PAS discounts for subsequent therapies as well as the company's proposed price discount for apalutamide are presented in a separate confidential addendum to this ERG report.

5.2 Company's sensitivity analyses

5.2.1 Deterministic sensitivity analyses

The company lists the parameters included in the deterministic sensitivity analyses in CS Appendix P. The upper and lower bounds of the parameters were varied as (i) ± 1.96 *

standard error (SE) of the base case value (or mean), (ii) within ± 10% of the base case value when SE is unknown, (iii) and for discount rate, the variation advised by NICE (0% and 6%).

Results of the deterministic sensitivity analyses are presented as net monetary benefit at a willingness to pay of £30,000 per QALY since the ICER is negative for some of them. CS Figures 63, 64 and 65 present tornado diagrams for nmHRPC (apalutamide plus ADT versus ADT alone), mHSPC (apalutamide plus ADT versus ADT alone) and mHSPC (apalutamide plus ADT versus docetaxel plus ADT), respectively. The diagrams show that the urologist/oncologist unit cost, second line health state utility value and unplanned resource use annual costs are the key drivers of the model results for the nmHRPC indication. For the mHSPC indication, unplanned resource use annual costs, subsequent treatment durations and mean health state durations are the key drivers of the model results when comparing apalutamide plus ADT versus ADT alone. For the comparison against docetaxel plus ADT, the PFS2 and OS HR have the most significant impact on the results.

The ERG notes that clinical effectiveness parameters (namely, the parameters related with PFS, PFS2 and OS parametric curves) were not varied in these analyses. Additionally, we note that the deterministic sensitivity analysis does not include the variation of the discount rate because there is an error in the model. The active cells for discount rate in the ‘Parameters’ sheet that are being used for the deterministic sensitivity analysis are not the same active cells that are being used to calculate discounted results in the model. This error and the suggested correction are listed in 5.3.2. Figure 23 shows the corrected net monetary benefit results of the deterministic sensitivity analyses for nmHRPC.

The ERG considers that, where possible, results should be presented as ICERs because it enables a more intuitive interpretation. In the case of the mHSPC, the ICER is negative for only one scenario, therefore the results of the deterministic sensitivity analyses for this indication, with the discount rate error amended, are presented as ICERs in Figure 24 and Figure 25. For both nmHRPC and mHSPC indications, the discount rate is the parameter which has most impact on the model results, with the exception of the HR for the comparison against docetaxel plus ADT.

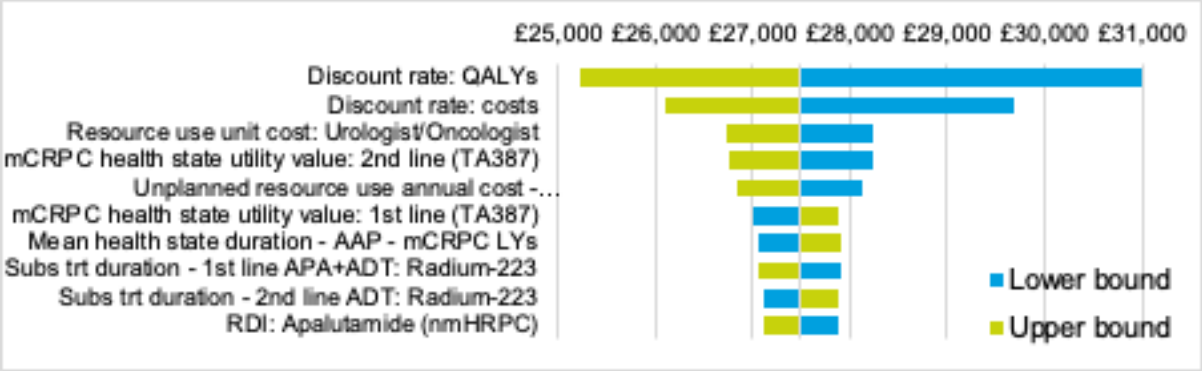


Figure 23 Net Monetary Benefit results of deterministic sensitivity analyses for nmHRPC: apalutamide plus ADT versus ADT alone (ERG analysis with discount rate correction)

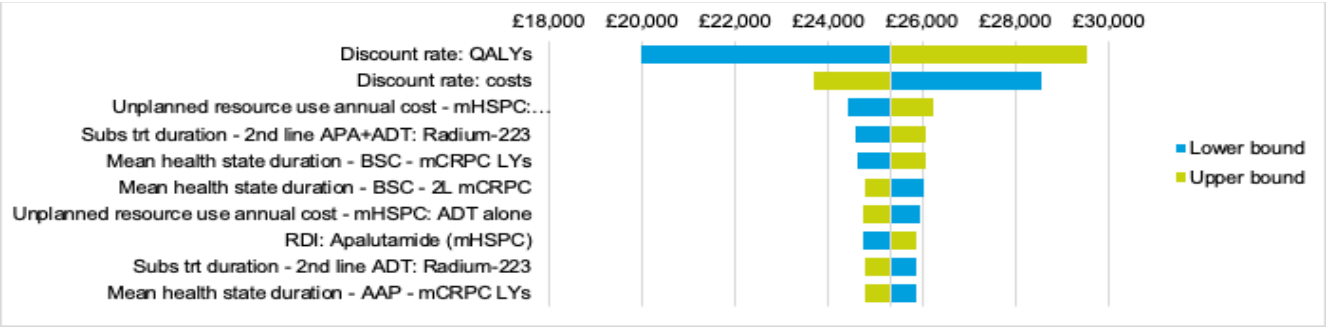


Figure 24 ICER results of deterministic sensitivity analyses for mHSPC: apalutamide plus ADT versus ADT alone (ERG analysis with discount rate correction)

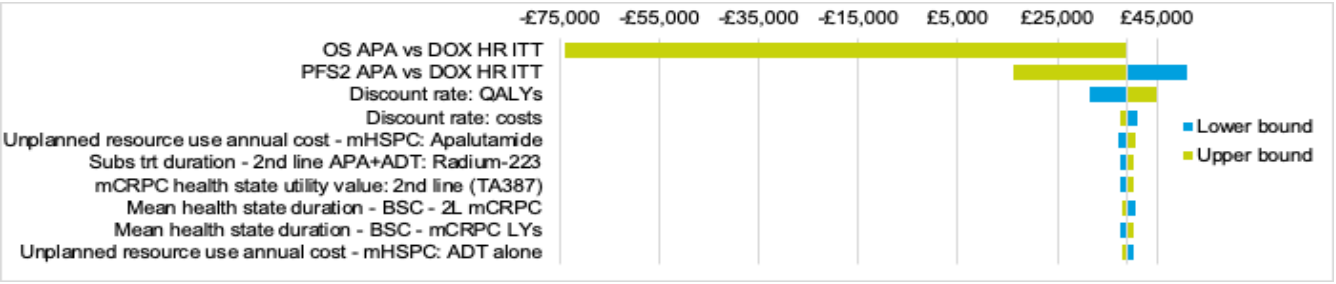


Figure 25 ICER results of deterministic sensitivity analyses for mHSPC: apalutamide plus ADT versus docetaxel plus ADT (ERG analysis with discount rate correction)

CS Table 95 reports the results of the scenario analyses for nmHRPC and CS Tables 96 and 97 report the results for mHSPC.

Most of the scenario analyses do not have a significant impact on the model results, with the exception of survival curve selections for PFS, the method for the transition of patients between first and second line mHRPC health states and the subsequent therapy market shares. The company states that using alternative extrapolation curves for PFS results in the PFS and PFS2 curves crossing, which is implausible. They also state that the use of PFS2

instead of mean health state durations is more appropriate to split patients between first and second line mHRPC since PFS2 is an endpoint from the trials that inform most of the clinical parameters of this appraisal (SPARTAN and TITAN) and mean health state durations come from an external study with a slightly different population and characteristics. Regarding the alternative subsequent therapy market shares, the company argues that the market shares from SPARTAN and TITAN trials are not relevant “as they do not align with the NHS England one novel therapy commissioning policy” (CS page 248).

We extend the range of scenario analyses to include alternative survival extrapolation approaches, alternative utility values, alternative treatment waning start and end points and inclusion of age-related disutility (see section 6)

5.2.2 Probabilistic sensitivity analysis

The company conducted a probabilistic sensitivity analysis to assess parameter uncertainty. They assigned a normal distribution for mean health state durations, subsequent treatment durations, adverse event durations, median trial follow-ups, drug dosages and costs; and the beta distribution for relative dose intensity, docetaxel completion rates, ADT market shares, adverse event incidences, mHRPC utilities and adverse event disutilities. The ERG notes that the gamma distribution is the most standard distribution for costs but was not used in this model. A multinormal distribution was assigned to the nmHRPC and mHSPC pre-progression utilities but it remains unclear whether and how these utilities were included in the probabilistic sensitivity analysis. CS Tables 93 and 94 summarise the probabilistic results for nmHRPC and mHSPC, respectively; CS Figures 58, 59 and 60 present the cost-effectiveness planes; and CS Figures 61 and 62 present the cost-effectiveness acceptability curves (CEAC). The probabilistic results are consistent with the deterministic results, as stated in the CS. At a willingness-to-pay threshold of £30,000 per QALY, apalutamide plus ADT has a 100% probability of being cost-effective compared to ADT alone for nmHRPC; and 31.1% probability compared to ADT alone and docetaxel plus ADT for mHSPC.

5.3 Model validation and face validity check

The company describes their approach to model validation in CS section B.3.9. Expert opinion, from four clinical experts and three health economists for nmHRPC and five clinical experts and three health economists for mHSPC, validated the model inputs and assumptions listed in CS section B.3.9.2.

The model was validated by an independent modeller who (1) checked all formulae and labelling in the model and (2) changed each model parameter to a sensible upper and lower bound and checked the resulting outcomes against the expected ones. More details can be found in CS section B.3.9.3.

Post-progression survival was compared against estimates from previous NICE appraisals for mHRPC (TA387 TA377 TA259]). The mean post-progression survival from the model was calculated by dividing the mean life years spent in mHRPC health states by the proportion of patients who progress. The proportion of patients who progress was estimated by dividing the number of MFS/rPFS events that were deaths reported in the SPARTAN and TITAN trials by the total number of deaths in these studies. CS Table 98 reports the predicted post-progression survival for the current model and for the previous appraisals. The post-progression survivals estimated from the model are not widely different from the TA387 and TA377 estimates. However, they are significantly different from the TA259 estimates, which are much lower than the others. The company argues that this is expected "since this submission focussed on later stages of mHRPC, following prior cytotoxic therapy, where patients would have poorer survival rates" (CS page 254).

The ERG considers that comparing the life-years spent in the mHRPC health states of the model directly against the previous NICE appraisals' post-progression survival results would be more reasonable than adjusting the model life-years for the proportion of patients who progress. Therefore, we update CS Table 98, without the adjustment, as part of the ERG's model validation (see Table 46).

Overall survival estimates of ADT alone for both indications were also compared against long-term survival data from the literature (the same studies used to inform the 'informed fits' analysis). CS Figure 66 shows the OS KM curves from the literature and CS Table 99 summarizes the percentage of patients alive at given timepoints (1, 2, 3, 5, 7 and 9 years) based upon the OS estimated from the model and from the literature. OS historical data are consistent with modelled OS for mHSPC. The company claims that these cross-validity checks are not as relevant for nmHRPC as the SPARTAN trial has a longer follow-up than the studies in the literature.

ERG conclusions

The company conducted face validity checks, a comprehensive model functionality validation as well as cross validity checks and external validation, comparing the model results with previous NICE appraisals and long-term data from literature.

However, they did not report that they had conducted any internal validity checks, i.e., comparing the model results with the trial data. Moreover, we believe that they did not use the best approach to compare post progression survival estimates and we adopted a different one in the ERG's model validation below.

5.3.1.1 ERG model validation

The ERG checked the economic model for transparency and validity. We conducted a range of tests to verify model inputs, calculations and outputs:

- Cross-checking all parameter inputs against values reported in the CS and cited sources;
- Checking the individual equations within the model;
- A range of extreme value and logic tests to check the plausibility of changes in results when parameters are changed;
- Checking all model outputs against results cited in the CS, including the base case, probabilistic sensitivity analyses, deterministic sensitivity analyses and manually-run scenarios.

The model is generally well-implemented, with some minor errors in parameter inputs and coding. The company provided an updated model with their clarification response, in which some original issues were corrected – KM data for ADT in nmHRPC, rates of adverse events and adverse event unit costs. Nevertheless, the ERG found other errors, listed in Appendix 9.5.

5.3.1.2 Cross-validity checks

As explained above, we compared the modelled life-years spent in mHRPC health states with the previous NICE appraisals post-progression survival for mHRPC TA387, TA377, and TA259 (Table 43). The modelled outcomes reported below come from the company's updated model provided with their clarification response. The mean life years spent in the post progression health states of the current model are generally consistent with the post progression survival from the previous NICE appraisals. The post progression survival of ADT alone for mHSPC are lower than all the previous NICE appraisals' estimates and the post progression survival of docetaxel plus ADT for mHSPC are lower than the TA387 and TA377 estimates. We note that changes in the post progression health state durations were explored by the company in their deterministic and probabilistic sensitivity analysis and were among the main key drivers of the model results for both indications (Figure 23, Figure 24 and Figure 25).

Table 42 Comparison of modelled post progression survival against previous NICE appraisals for mHRPC

Source (time horizon)	Indication	Treatment	Post progression survival (years)	
			1L+2L+3L [a]	2L+3L [b]
Current appraisal (32 years)	nmHRPC	Apalutamide plus ADT	2.51	0.71
		ADT alone	3.46	1.42
	mHSPC	Apalutamide plus ADT	2.55	1.51
		ADT alone	2.29	1.05
		Docetaxel plus ADT	2.79	1.83
TA387 (until 100 years of age)	mHRPC	Abiraterone acetate	3.34	-
		BSC	2.72	-
TA377 (10 years)	mHRPC	Enzalutamide	3.06	-
		Abiraterone acetate	2.86	-
		BSC	2.61	-
TA259 (10 years)	mHRPC (2L)	Abiraterone acetate	-	1.75
		PP	-	1.385
		MP	-	1.385

[a] The life-years spent in first, second and third line health states.
[b] The life-years spent in second and third line health states.
1L: first line; 2L: second line; 3L: third line; ADT: androgen deprivation therapy, BSC: best supportive care; LYs: life years; mHRPC: metastatic hormone resistant prostate cancer; mHSPC: metastatic hormone sensitive prostate cancer, MP: mitoxantrone plus prednisolone; nmHRPC: non-metastatic hormone resistant prostate cancer; PP: prednisolone plus placebo.

We also compared the modelled OS estimates for docetaxel from the current appraisal with a previous study performed in the UK for patients with mHSPC in the STAMPEDE trial.[61] We note that the OS estimates from the current appraisal are consistent with the STAMPEDE estimates (Table 44).

Table 43 Comparison of the modelled OS estimates with STAMPEDE OS estimates for docetaxel in mHSPC

Treatment	Data	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 9
OS								
Docetaxel plus ADT	Modelled data	0.924	0.810	0.688	0.573	0.466	0.372	0.173
	STAMPEDE data	0.930	0.780	0.680	0.580	0.500	0.420	0.210

ADT: androgen deprivation therapy, mHSPC: metastatic hormone sensitive prostate cancer, OS: overall survival.

5.3.1.3 Internal validity checks

We compared the company's modelled estimates with the observed clinical data. We summarise these results for nmHRPC in Table 45 and for mHSPC in Table 46. The

modelled and observed data reported below come from the company's updated model provided with their clarification response. The estimates for PFS, PFS2 and OS from the observed data and the model are generally comparable for both treatment arms and both indications.

Table 44 Comparison of the modelled estimates with the observed clinical data for nmHRPC

Treatment	Data	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
PFS							
Apalutamide plus ADT	Observed data	0.859	0.682	0.514	-	-	-
	Modelled data	0.879	0.675	0.468	-	-	-
ADT alone	Observed data	0.579	0.296	0.165	-	-	-
	Modelled data	0.617	0.295	0.120	-	-	-
PFS2							
Apalutamide plus ADT	Observed data [a]	0.962	0.839	0.699	0.583	0.464	0.454
	Modelled data	0.953	0.853	0.720	0.579	0.445	0.326
ADT alone	Observed data [a]	0.931	0.766	0.557	0.377	0.231	-
	Modelled data	0.921	0.756	0.558	0.378	0.235	-
OS							
Apalutamide plus ADT	Observed data [a]	0.978	0.907	0.810	0.677	0.550	0.415
	Modelled data	0.969	0.903	0.802	0.679	0.549	0.423
ADT alone	Observed data [a]	0.974	0.898	0.755	0.597	0.485	0.447
	Modelled data	0.964	0.881	0.755	0.610	0.463	0.331

[a] Novel agent adjusted
ADT: androgen deprivation therapy, nmHRPC: non-metastatic hormone refractory prostate cancer, OS: overall survival, PFS: progression-free survival, PFS2: secondary progression-free survival

Table 45 Comparison of the modelled estimates with the observed clinical data for mHSPC

Treatment	Data	Year 0.5	Year 1	Year 1.5	Year 2	Year 2.5
PFS						
Apalutamide plus ADT	Observed data	0.953	0.844	0.789	0.689	0.626
	Modelled data	0.948	0.865	0.772	0.676	0.584
ADT alone	Observed data	0.871	0.703	0.592	0.483	0.461
	Modelled data	0.868	0.719	0.582	0.463	0.364
PFS2						
Apalutamide plus ADT	Observed data	0.981	0.942	0.870	0.813	0.765
	Modelled data	0.974	0.932	0.876	0.810	0.738

Treatment	Data	Year 0.5	Year 1	Year 1.5	Year 2	Year 2.5
ADT alone	Observed data	0.971	0.901	0.816	0.728	0.697
	Modelled data	0.963	0.901	0.821	0.730	0.634
OS						
Apalutamide plus ADT	Observed data	0.985	0.946	0.883	0.825	0.771
	Modelled data	0.974	0.933	0.885	0.832	0.777
ADT alone	Observed data	0.973	0.923	0.848	0.737	0.706
	Modelled data	0.963	0.903	0.835	0.764	0.691
ADT: androgen deprivation therapy, nmHRPC: non-metastatic hormone refractory prostate cancer, OS: overall survival, PFS: progression-free survival, PFS2: secondary progression-free survival						

5.3.2 ERG corrections to the company's model

As previously stated, the company's model was generally well-implemented, with no substantive errors. However, there are some minor errors that we identified. In addition, the ERG notes that the incidence of patients in the third line mHRPC health state is incorrectly modelled, because the incidence of patients in the third line is higher than the incidence of patients in second line, which is not clinically plausible. Therefore, a correction has been made in the ERG base case. Appendix 9.5 – Table A lists the errors that the ERG considers should be amended as they have some impact on the model results. The remaining issues, which do not affect the model results, are presented in Appendix 9.5 – Table B.

The ERG re-ran the analyses with the corrected formulas. These changes, added to the company's corrections, maintain the dominance of apalutamide plus ADT versus ADT alone for nmHRPC (Table 47) and lead to a decrease in the base case ICER from £38,983 (company's base case) to £34,636 per QALY for the comparison against docetaxel, and from £25,329 to £25,002 per QALY against ADT alone, for mHSPC (Table 48).

Table 46 Cost-effectiveness results from ERG corrections for nmHRPC (discounted, PAS price for apalutamide)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£/QALY)
ADT alone	[redacted]	5.03	[redacted]				
Apalutamide plus ADT	[redacted]	5.70	[redacted]	[redacted]	0.67	[redacted]	Dominates
ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gain; QALYs: quality-adjusted life years.							

Table 47 Cost-effectiveness results from ERG corrections for mHSPC (discounted, PAS price for apalutamide)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£/QALY)	ICER (£/ QALY): APA vs. ADT
ADT alone	[redacted]	4.59	[redacted]					
Docetaxel plus ADT	[redacted]	5.50	[redacted]	[redacted]	0.91	[redacted]	14,102	
Apalutamide plus ADT	[redacted]	6.02	[redacted]	[redacted]	0.52	[redacted]	34,636	25,002
ADT: androgen deprivation therapy; APA: apalutamide plus ADT; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gain; QALYs: quality-adjusted life years.								

We re-ran the company's scenario analysis (summarised in CS Tables 95, 96 and 97) with the ERG corrected model. The results are presented in Table 49 for nmHRPC and in Table 50 for mHSPC. These results show that, in general, the ICERs decrease slightly (no more than £6,000 per QALY) in comparison to the results from the company's scenarios.

Table 48 Results of the company's scenario analysis using the ERG corrected model for nmHRPC (discounted, PAS price for apalutamide)

Scenario	ICER (£/QALY)
Base case (ERG corrected)	Dominates
Time horizon: 30 years	Dominates
Time horizon: 20 years	Dominates
Time horizon: 10 years	Dominates
Unadjusted SPARTAN data for one novel therapy rule	Dominates
MFS extrapolation: Log-logistic	£3,007
MFS extrapolation: Log-normal	£3,151
PFS2 extrapolation: Log-logistic	Dominates
PFS2 extrapolation: Log-normal	Dominates
PFS2 extrapolation: Generalized gamma	Dominates
OS extrapolation: Generalized gamma	Dominates
Mean health state durations from TA387 for 1L mHRPC	Dominates
Treatment waning between 10-15 years	Dominates
Subsequent therapy market shares: SPARTAN trial	£31,543
Subsequent therapy market shares: nmHRPC advisory board	Dominates
AE disutilities: literature values	Dominates
mHRPC utilities: assumed constant through mHRPC	Dominates
1L: first line; ADT: androgen deprivation therapy; AE: adverse event; APA: apalutamide plus ADT; ERG: Evidence Review Group; ICER: incremental cost-effectiveness ratio; MFS: metastatic-free survival; mHSPC: metastatic hormone sensitive prostate cancer; mHRPC: metastatic hormone resistant prostate cancer; nmHRPC: non metastatic hormone resistant prostate cancer; OS: overall survival; PFS2: secondary progression-free survival; QALYs: quality-adjusted life years.	

Table 49 Results of the company's scenario analysis using the ERG corrected model for mHSPC, versus ADT alone (discounted, PAS price for apalutamide)

Scenario	ICER (£/QALY) vs. ADT alone	ICER (£/QALY) vs. DOX
Base case (ERG corrected)	£25,002	£34,636
Time horizon: 30 years	£25,002	£34,636
Time horizon: 20 years	£25,042	£34,792
Time horizon: 10 years	£27,185	£40,441
rPFS extrapolation: Exponential	£38,317	£63,111
rPFS extrapolation: Log-logistic	£37,370	£55,837
rPFS extrapolation: Log-normal	£39,609	£61,906
OS extrapolation: Log-logistic	£23,712	£27,651
OS extrapolation: Log-normal	£21,688	£22,110
OS extrapolation: Generalized gamma	£23,267	£29,350
OS extrapolation: Gompertz	£27,834	£36,673
OS curve fitting approach: Unstratified curves	£29,178	£45,199
Mean health state durations from TA387 for 1L mHRPC	£27,573	£3,104
Treatment waning between 10-15 years	£25,630	£35,822
Subsequent therapy market shares: TITAN trial	£58,111	£82,864
Subsequent therapy market shares: nmHRPC advisory board	£16,987	£27,401
Utility source: STAMPEDE	£25,094	£33,563
AE disutilities: literature values	£24,168	£35,131
mHRPC utilities: assumed constant throughout mHRPC	£22,868	£38,634

1L: first line; ADT: androgen deprivation therapy; AE: adverse event; APA: apalutamide plus ADT; DOX: docetaxel plus ADT; ERG: Evidence Review Group; ICER: incremental cost-effectiveness ratio; mHSPC: metastatic hormone sensitive prostate cancer; mHRPC: metastatic hormone resistant prostate cancer; nmHRPC: non metastatic hormone resistant prostate cancer; OS: overall survival; QALYs: quality-adjusted life years, rPFS: radiographic progression-free survival.

5.3.3 ERG summary of key issues and additional analyses

A full summary of ERG observations on key aspects of the company's economic model is presented in Table 51.

Table 50 ERG observations of the key aspects of the company's economic model

Parameter	Company base case	ERG comment	ERG base case
Survival curves – nmHRPC			
MFS	Independently modelled using Weibull distributions (for both arms) fitted to data unadjusted for crossover.	We agree with the company's assumption.	Independently modelled using Weibull distributions (for both arms) fitted to data unadjusted for crossover.
PFS2	Jointly modelled with Weibull distributions fitted to data adjusted for the novel therapy restriction and crossover without re-censoring, satisfying criteria listed in Table 28.	We agree with the company's assumption. Nevertheless, both analyses with and without re-censoring are recommended for treatment switching. RPFSTM with re-censoring has been shown to be more biased. It is not clear, however, whether this is relevant to the 'modified' RPFSTM.	Jointly modelled with Weibull distributions fitted to data adjusted for the novel therapy restriction and crossover without re-censoring.
OS	Jointly modelled with Weibull distributions fitted to data adjusted for novel therapy restriction and crossover without re-censoring.	Based on expert's advice, the Weibull model for ADT underestimates survival at 10 and 15 years, while the generalised gamma model better predicts long-term survival. The generalised gamma curves for both arms have a good visual fit to the Kaplan-Meier estimates from SPARTAN, and have lower AIC and BIC scores compared to those for the Weibull models.	Jointly modelled using generalised gamma distributions (for both arms) fitted to data adjusted for novel therapy restriction and crossover without re-censoring.
Survival curves – nmHRPC			
rPFS	Independently modelled with Weibull distributions fitted to data unadjusted for novel therapy restriction.	We agree with the company's assumption.	Independently modelled with Weibull distributions fitted to data unadjusted for novel therapy restriction.
PFS2	Jointly modelled with Weibull distributions fitted to data unadjusted for novel therapy restriction.	We agree with the company's assumption.	Jointly modelled with Weibull distributions fitted to data unadjusted for novel therapy restriction.

OS	Independently modelled with Weibull distributions based on 'informed fits' approach, not adjusted for novel therapy restriction.	We agree with the company's assumption.	Independently modelled with Weibull distributions based on 'informed fits' approach, not adjusted for novel therapy restriction.
Treatment waning	Not included in the base case	Literature suggests that resistance to novel therapies, such as enzalutamide and abiraterone, is likely to develop with time, but relevant long-term clinical evidence is not available. This has been confirmed by our clinical expert. Therefore, we explore potential impact of treatment waning in scenario(s) only.	Not included in the base case
Duration of health states (2L and 3L mHRPC)	The duration for health states used in the model use the durations from TA387, applied to the total duration in post progression in the model. This is adjusted by dividing by the proportion of patients who did not die in the pre-progression health state in the TITAN and SPARTAN.	The ERG is unclear on the rationale of dividing by this value, which appears counterintuitive.	We do not include this adjustment in the ERG base case in section 6.
3L mHRPC	Mean health state duration for 3L mHRPC only includes active treatment.	3L mHRPC health state duration includes time spent with active treatment and BSC.	Should also include time spent in BSC. 3L mHRPC: AAP [redacted]; ADT [redacted].
Utility	Company base case model estimates: nmHRPC: Pre-progression: 0.8233 1L mHRPC: 0.7713 2L mHRPC: 0.5808 3L mHRPC: 0.4626 mHSPC: Pre-progression: 0.8047 1L mHRPC: 0.6981 2L mHRPC: 0.5257 3L mHRPC: 0.4206	The ERG considers a better approach is to use unadjusted utility values from TA387 for the second-line and third-line mHRPC utilities.	ERG base case model estimates: nmHRPC Pre-progression: 0.8233 1L mHRPC: 0.7713 2L mHRPC: **0.625** 3L mHRPC: **0.50** mHSPC: Pre-progression: 0.8047 1L mHRPC: 0.6981 2L mHRPC: **0.625** 3L mHRPC: **0.50**

AE disutility	When patients suffer an AE, a disutility for these patients is then applied for the remainder of that health state.	Disutility should be only applied for a short period for patients with Aes.	Disutility applied for 2 weeks for patients with Aes.
Health state costs	Unscheduled health state costs are included.	As unscheduled MRU costs should be counted for by the adverse event management costs, the ERG have omitted unscheduled resource costs	Unscheduled health state costs are omitted.
AE costs	AE costs for docetaxel are applied for the whole duration of pre-progression.	Docetaxel is given for six cycles and the majority of side effects would be during this 18-week period.	AE costs for docetaxel are applied for first ½ years of pre-progression.
	The cost of managing neutropenia in CS Table 81 is £862.79.	We consider this an overestimate as patients with neutropenia would not be hospitalised and would only require an additional outpatient visit and blood test	The cost of managing neutropenia is £150.16.
Resource use	Resource use shown in Table CS Table 77, 78 and 79.	Some changes to resource use suggested by our clinical experts.	Resource use shown in Appendix 9.6.
1L: first line; 2L: second line; 3L: third line; ADT: androgen deprivation therapy; AE: adverse event; BSC: best supportive care; ERG: evidence review group; MFS: metastasis-free survival; mHRPC: metastatic hormone relapsed prostate cancer; mHSPC: metastatic hormone sensitive prostate cancer; MRU: medical resource use; nmHRPC: non metastatic hormone relapsed prostate cancer; PFS": secondary progression free survival; OS: overall survival; rPFS: radiographic progression free survival; RPFSTM: Rank Preserving Structural Failure Time Model.			

6 ERG'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

Based on the ERG critique of the company's model assumptions (as described in Table 51), we performed a range of additional scenario analyses (presented in Table 52 and Table 53) on the following model assumptions:

- Use KM data for MFS until week 120 and extrapolated tail thereafter (in nmHRPC) (see section 4.2.7.1);
- Use independently fitted curves with log-logistic, log-normal and generalised gamma to extrapolate PFS2 for nmHRPC;
- Use jointly and independently fitted curves with generalised gamma to extrapolate OS for nmHRPC;

- The mean health state durations of first, second and third line mHRPC health states were not adjusted for the proportion of patients not dying in the pre-progression state;
- The mean health state duration of third line mHRPC health state includes both the time spent in active treatment and BSC from TA387;
- Varying the treatment waning start and end points;
- The health state utilities for second and third line mHRPC health states were not adjusted for the first line mHRPC utility value;
- The duration of AE disutilities in the pre progression health state is two weeks;
- Include age-related disutility for pre-progression health state
- The duration of AE costs for docetaxel is 6 months;
- The neutropenia cost does not include hospitalization (=£150.16);
- The resource use for nmHRPC and mHSPC is based on the ERG's clinical advice; and
- The unscheduled MRU costs were excluded.

The scenario analyses were performed on the ERG's corrected company model. We note:
For nmHRPC:

- Apalutamide plus ADT dominates ADT alone in all the scenarios tested for nmHRPC, i.e. it is cheaper and more effective.

For mHSPC:

- The ICERs range from £22,709 per QALY (scenario: second and third line mHRPC health states utility values from TA580) to £28,516 per QALY (scenario: PFS2 extrapolated as jointly fitted curves with Gompertz) for apalutamide plus ADT compared to ADT alone.
- For the comparison against docetaxel plus ADT, the ICERs range from £33,569 per QALY (scenario: unscheduled MRU costs excluded) to £43,475 per QALY (scenario: second and third line mHRPC health states utility values from TA580).
- Assuming jointly fitted curves with Gompertz to extrapolate PFS2 and a treatment waning between 5 and 10 years had the greatest impact on the cost-effectiveness results versus ADT alone; the ICER increased to £28,516 per QALY and £27,947 per QALY, respectively.
- Assuming TA580 as the source for second and third line mHRPC health states utility values and a duration of adverse event costs for docetaxel of 6 months had the greatest impact on the cost-effectiveness results versus docetaxel plus ADT; the ICER increased to £43,475 per QALY and £42,272 per QALY, respectively.
- The remaining scenarios did not change the ICER more than £5,000 per QALY.

Table 51 Additional analyses conducted by the ERG on the company's base case for nmHRPC (ERG corrected, discounted, PAS price for apalutamide)

Scenario	Treatment	Total costs	Total QALYs	ICER (£/QALY)
Corrected company base case	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
MFS extrapolation: use KM data and extrapolated tail	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
PFS2 extrapolation: independently fitted log-logistic	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
PFS2 extrapolation: independently fitted log-normal	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
PFS2 extrapolation: independently fitted generalised gamma	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
OS extrapolation: jointly fitted generalised gamma	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
OS extrapolation: independently fitted generalised gamma	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
Unadjusted duration of mHRPC health states	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
Mean health state duration for 3L based on the active treatment and BSC durations from TA387	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
Treatment waning: 5-10 years	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
Unadjusted health state utilities for 2L/3L mHRPC	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
2L/3L mHRPC utility values from TA580	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
2L/3L mHRPC utility values from TA377	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
Duration of AE disutilies in the pre progression health state – 2 weeks	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
Include age-related disutility	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
Neutropenia cost – £150.16	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
Resource use based on the ERG's clinical advice	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
Exclude unscheduled MRU costs	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates

2L: second line, 3L: third line; ADT: androgen deprivation therapy; AE: adverse event; APA: apalutamide; BSC: best supportive care; ERG: evidence review group; ICER: incremental cost-effectiveness ratio; KM: Kaplan-Meier; MFS: metastasis-free survival; mHRPC: metastatic hormone relapsed prostate cancer; MRU: medical resource use; OS: overall survival; PFS2: secondary progression free survival; QALY: quality-adjusted life-years.

Table 52 Additional analyses conducted by the ERG on the company's base case for mHSPC (ERG corrected, discounted, PAS price for apalutamide)

Scenario	Treatment	Total costs	Total QALYs	ICER (£/QALY)	
				APA vs. DOX	APA vs. ADT alone

Corrected company base case	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£34,636	£25,002
PFS2 extrapolation: jointly fitted Gompertz	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£38,993	£28,516
Unadjusted duration of mHRPC health states	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£34,665	£25,009
Mean health state duration for 3L based on the active treatment and BSC durations from TA387	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£38,172	£25,936
Treatment waning: 5-10 years	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£39,531	£27,947
Unadjusted health state utilities for 2L/3L	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£37,544	£24,231
2L/3L mHRPC utility values from TA580	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£43,475	£22,709
2L/3L mHRPC utility values from TA377	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£37,819	£23,460
Duration of AE disutilities in the pre progression health state – 2 weeks	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	35,500	£24,139
Include age-related disutility	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£36,246	£25,842
Duration of AE costs for docetaxel – 6 months	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£42,272	£25,002
Neutropenia cost – £150.16	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£38,508	£24,777
Resource use based on the ERG's clinical advice	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£34,742	£24,630
Exclude unscheduled MRU costs	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£33,569	£23,411

2L: second line, 3L: third line; ADT: androgen deprivation therapy; AE: adverse event; APA: apalutamide; BSC: best supportive care; DOX: docetaxel; ERG: evidence review group; ICER: incremental cost-effectiveness ratio; mHRPC: metastatic hormone relapsed prostate cancer; MRU: medical resource use; PFS2: secondary progression free survival; QALY: quality-adjusted life-years.

6.2 ERG's preferred assumptions

Based on the ERG critique of the company's model discussed in Table 51, we have identified nine key aspects of the company base case with which we disagree. Our preferred model assumptions are the following:

1. **Extrapolation of OS for nmHRPC**: We use the generalised gamma models for OS because they are more consistent with the long-term survival estimates provided by our clinical experts.
2 **Mean health state durations of first, second and third line mHRPC health states**: It is unclear the company's rationale to adjust the health state durations for the proportion of patients not dying in the pre-progression state. Therefore, we assume in our base case to use the unadjusted health state durations (for further discussion, see section 4.2.8.3).
3. **Mean health state duration of third line mHRPC**: We assume that the duration of 3L mHRPC should be based in the time spent in both active treatment and BSC from TA387, i.e. [redacted] for apalutamide plus ADT and [redacted] for ADT alone and docetaxel plus ADT (for further discussion, see section 4.2.8.3).
4. **Health state utilities for second and third line mHRPC health states**: We assume a better approach to not adjust these utilities for the 1L mHRPC utility value, i.e.0.625 for 2L mHRPC and 0.5 for 3L mHRPC (for further discussion, see section 4.2.7.2).
5. **Duration of adverse events' disutilities in the pre-progression health state**: We assume that the disutility from adverse events lasts for two weeks (for further discussion, see section 4.2.7.3).
6. **Duration of adverse events costs for docetaxel**: Docetaxel is given for six cycles and the majority of adverse events occur during this period. Therefore, we assume that applying the costs of docetaxel adverse events for a whole year is not adequate. The ERG applies a duration of six months as our preferred assumption (for further discussion, see section 4.2.8.4).
7. **Neutropenia cost**: We consider the company's input an overestimation and assume that patients experiencing neutropenia would only require an additional outpatient visit and blood test, i.e. £150,16 (for further discussion, see section 4.2.8.4).
8. **Resource use**: To reflect clinical practice, we changed resource use according to the ERG's clinical advice (for further discussion, see section 4.2.8.3 and Appendix 9.6).
9. **Unscheduled MRU costs**: It is unclear the company's rationale to include unscheduled MRU costs since AE disutility costs are already being included. Therefore, we assume to exclude these costs in our base case assumptions (for further discussion, see section 4.2.8.3).

6.2.1 Results from the ERG preferred model assumptions

Table 54 and Table 55 show the cumulative cost-effectiveness results of applying the ERG preferred model assumptions to the corrected company's base case for nmHRPC and mHSPC, respectively. Incorporating the ERG assumptions do not have a significant impact on the overall results for nmHRPC, in which apalutamide plus ADT still dominates ADT alone. For mHSPC, the ICER decreases from £25,002 per QALY to £22,294 per QALY versus ADT alone, but considerably increases from £34,636 per QALY to £49,298 per QALY versus docetaxel plus ADT.

- The change that has the biggest impact on the cost-effectiveness results is the assumption that adverse events costs for docetaxel only lasts 6 months. Using the mean health state duration of third line mHRPC based both on the active treatment and BSC durations from TA387 and using unadjusted health state utilities for second and third line mHRPC also significantly increases the ICER for apalutamide plus ADT versus docetaxel plus ADT.
- Incorporating the remaining ERG assumptions influence the ICER to a lesser extent.

Table 53 Cumulative cost-effectiveness results for ERG's preferred model assumptions for nmHRPC (discounted, PAS price for apalutamide)

Parameter	Treatment	Total costs	Total QALYs	ICER (£/QALY)
Corrected company base case	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ OS extrapolation: jointly fitted generalised gamma	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ Unadjusted duration of mHRPC health states	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ Mean health state duration for 3L based on the active treatment and BSC durations from TA387	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ Unadjusted health state utilities for 2L/3L	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ Duration of AE disutilies in the pre progression health state – 2 weeks	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ Neutropenia cost – £150.16	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ Resource use based on the ERG's clinical advice	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ Exclude unscheduled MRU costs	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
ERG preferred model	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates

2L: second line, 3L: third line; ADT: androgen deprivation therapy; AE: adverse event; APA: apalutamide; BSC: best supportive care; ERG: evidence review group; ICER: incremental cost-effectiveness ratio; mHRPC: metastatic hormone relapsed prostate cancer; MRU: medical resource use; OS: overall survival; QALY: quality-adjusted life-years.

Table 54 Cumulative cost-effectiveness results for ERG's preferred model assumptions for mHSPC (discounted, PAS price for apalutamide)

Scenario	Treatment	Total costs	Total QALYs	ICER (£/QALY)	
				APA vs. DOX	APA vs. ADT alone
Corrected company base case	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£34,636	£25,002
+ Unadjusted duration of mHRPC health states	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£34,665	£25,009
+ Mean health state duration for 3L based on the active treatment and BSC durations from TA387	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£38,199	£25,944
+ Unadjusted health state utilities for 2L/3L	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£40,582	£25,096
+ Duration of AE disutilities in the pre progression health state – 2 weeks	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£41,581	£24,267
+ Duration of AE costs for docetaxel – 6 months	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£49,298	£24,267
+ Neutropenia cost – £150.16	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£50,227	£24,086
+ Resource use based on the ERG's clinical advice	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£50,377	£23,763
+ Exclude unscheduled MRU costs	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£49,298	£22,294
ERG preferred model	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£49,298	£22,294

2L: second line, 3L: third line; ADT: androgen deprivation therapy; AE: adverse event; APA: apalutamide; BSC: best supportive care; DOX: docetaxel; ERG: evidence review group; ICER: incremental cost-effectiveness ratio; mHRPC: metastatic hormone relapsed prostate cancer; MRU: medical resource use; QALY: quality-adjusted life-years.

Table 56 and Table 57 show the results from the ERG's preferred base case disaggregated by health state.

Table 55 ERG's preferred base case results disaggregated by health state for nmHRPC (discounted, PAS price for apalutamide)

Outcome	Health state				
	Pre-progression	1L mHRPC	2L mHRPC	3L mHRPC	Newly dead
Apalutamide plus ADT					
Life years	3.19	1.80	0.62	0.65	-
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADT alone					
Life years	1.57	2.04	0.86	1.04	-
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1L: first line; 2L: second line; 3L: third line; ADT: androgen deprivation therapy; ERG: Evidence Review Group; mHRPC: metastatic hormone resistant prostate cancer; nmHRPC: non metastatic hormone resistant prostate cancer; QALYs: quality-adjusted life years.					

Table 56 ERG's preferred base case results disaggregated by health state for mHSPC (discounted, PAS price for apalutamide)

Outcome	Health state				
	Pre-progression	1L mHRPC	2L mHRPC	3L mHRPC	Newly dead
Apalutamide plus ADT					
Life years	3.48	1.04	0.73	0.77	-
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADT alone					
Life years	2.30	1.24	0.47	0.57	-
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel plus ADT					
Life years	2.71	0.96	0.83	1.00	-
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1L: first line; 2L: second line; 3L: third line; ADT: androgen deprivation therapy; ERG: Evidence Review Group; mHSPC: metastatic hormone sensitive prostate cancer; mHRPC: metastatic hormone resistant prostate cancer; QALYs: quality-adjusted life years.					

6.3 Scenario analyses conducted on the ERG's preferred assumptions

We performed a range of scenario analyses with the ERG base case in order to analyse the impact of changing some of the model assumptions in the final cost effectiveness results. Most of the scenarios replicates the company's scenario analysis (as previously described in section 5.2.2). The remaining scenarios were conducted to assess the impact of changing the following model assumptions:

- Use KM data for MFS until week 120 and an extrapolated tail thereafter;
- Use independently fitted curves with log-logistic, log-normal and generalised gamma to extrapolate PFS2 for nmHRPC;
- Use jointly fitted curves with the Gompertz distribution to extrapolate PFS2 for mHSPC;
- Use independently and jointly fitted curves with generalised gamma to extrapolate OS for nmHRPC;
- Using alternative treatment waning start and end points (between 5 and 10 years)
- Using alternative sources to estimate utility values for second and third line mHRPC health states (TA377 and TA580);

- Include age-related disutility for pre-progression health state.

Table 58 presents the results for nmHRPC and Table 59 for mHSPC. The ERG notes:
For nmHRPC

- Apalutamide plus ADT dominates ADT alone in all the scenarios except when the subsequent therapy market shares are based on the SPARTAN trial (ICER increases to £24,176 per QALY) and when using log-logistic and log-normal independently fitted curves to extrapolate MFS (ICER increases to £146 and £203 per QALY, respectively).

For mHSPC

- The ICERs range from £13,732 per QALY (scenario: subsequent therapy market shares from nmHRPC advisory board) to £51,958 per QALY (scenario: subsequent therapy market shares from TITAN trial) for apalutamide plus ADT compared to ADT alone.
- For the comparison against docetaxel plus ADT, the ICERs range from £30,143 per QALY (scenario: mean health state durations for first line mHRPC health state from TA387) to £91,658 (scenario: subsequent therapy market shares from TITAN trial).
- The scenario that lead to a higher increase in the ICER is using the subsequent therapy market shares from the TITAN trial (£51,958 per QALY for apalutamide plus ADT versus ADT alone and £91,658 per QALY versus docetaxel plus ADT).
- Using different survival curves to extrapolate rPFS have also a significant effect on the cost-effectiveness results comparing apalutamide plus ADT versus ADT alone (£34,439 per QALY for exponential, £33,656 per QALY for log-logistic and £35,685 per QALY for log-normal) and apalutamide plus ADT versus docetaxel plus ADT (£79,379 per QALY for exponential, £71,407 per QALY for log-logistic and £78,018 per QALY for log-normal).

Additionally, when comparing apalutamide plus ADT versus ADT alone:

- Using the mean health state durations for first line mHRPC health state from TA387 increases the ICER to £30,217 per QALY.
- The remaining scenarios do not change the ICER more than £5,000 per QALY.

When comparing apalutamide plus ADT versus docetaxel plus ADT:

- Using the unstratified curves as the OS curve fitting approach increases the ICER to £62,174 per QALY.
- Using the log normal survival curve to extrapolate OS decreases the ICER to £36,370 per QALY.

- The remaining scenarios do not change the ICER more than £10,000 per QALY.

Table 57 Scenario analyses using the ERG's preferred model assumptions for nmHRPC (discounted, PAS price for apalutamide)

Scenario	ICER (£/QALY)
ERG preferred model	Dominates
Time horizon: 30 years	Dominates
Time horizon: 20 years	Dominates
Time horizon: 10 years	Dominates
Unadjusted SPARTAN data for one novel therapy rule	Dominates
MFS extrapolation: independently fitted log-logistic	£146
MFS extrapolation: independently fitted log-normal	£203
MFS extrapolation: use KM data and extrapolated tail	Dominates
PFS2 extrapolation: jointly fitted log-logistic	Dominates
PFS2 extrapolation: jointly fitted log-normal	Dominates
PFS2 extrapolation: jointly fitted generalised gamma	Dominates
PFS2 extrapolation: independently fitted log-logistic	Dominates
PFS2 extrapolation: independently fitted log-normal	Dominates
PFS2 extrapolation: independently fitted generalised gamma	Dominates
OS extrapolation: independently fitted generalised gamma	Dominates
OS extrapolation: jointly fitted weibull	Dominates
Mean health state durations from TA387 for 1L mHRPC	Dominates
Treatment waning between 10-15 years	Dominates
Treatment waning between 5-10 years	Dominates
Subsequent therapy market shares: SPARTAN trial	£24,176
Subsequent therapy market shares: nmHRPC advisory board	Dominates
AE disutilities: literature values	Dominates
mHRPC utilities: assumed constant through mHRPC	Dominates
2L/3L mHRPC utility values from TA580	Dominates
2L/3L mHRPC utility values from TA377	Dominates
Include age-related disutility	Dominates
1L: first line; 2L: second line; 3L: third line; ADT: androgen deprivation therapy; AE: adverse event; APA: apalutamide plus ADT; ERG: Evidence Review Group; ICER: incremental cost-effectiveness ratio; MFS: metastatic-free survival; mHSPC: metastatic hormone sensitive prostate cancer; mHRPC: metastatic hormone resistant prostate cancer; nmHRPC: non metastatic hormone resistant prostate cancer; OS: overall survival; PFS2: secondary progression-free survival; QALYs: quality-adjusted life years.	

Table 58 Scenario analyses using the ERG's preferred model assumptions for mHSPC (discounted, PAS price for apalutamide)

Scenario	ICER (£/QALY) vs. ADT alone	ICER (£/QALY) vs. DOX
ERG preferred model	£22,294	£49,298

Time horizon: 30 years	£22,293	£49,300
Time horizon: 20 years	£22,350	£49,610
Time horizon: 10 years	£24,685	£58,362
rPFS extrapolation: independently fitted exponential	£34,439	£79,379
rPFS extrapolation: independently fitted log-logistic	£33,656	£71,407
rPFS extrapolation: independently fitted log-normal	£35,685	£78,018
PFS2 extrapolation: jointly fitted Gompertz	£24,777	£53,891
OS extrapolation: log-logistic (informed fits)	£22,197	£40,659
OS extrapolation: log-normal (informed fits)	£20,806	£36,370
OS extrapolation: generalised gamma (informed fits)	£21,161	£42,850
OS extrapolation: Gompertz (informed fits)	£25,380	£53,036
OS curve fitting approach: jointly fitted Weibull (unstratified)	£26,224	£62,174
Mean health state durations from TA387 for 1L mHRPC	£30,217	£30,143
Treatment waning between 10-15 years	£22,992	£51,341
Treatment waning between 5-10 years	£25,627	£57,774
Subsequent therapy market shares: TITAN trial	£51,958	£91,658
Subsequent therapy market shares: nmHRPC advisory board	£13,732	£42,504
Utility source: STAMPEDE	£21,969	£49,621
AE disutilities: literature values	£22,319	£48,792
mHRPC utilities: assumed constant throughout mHRPC	£21,378	£55,805
2L/3L mHRPC utility values from TA580	£20,984	£57,096
2L/3L mHRPC utility values from TA377	£22,354	£49,141
Include age-related disutility	£22,984	£51,615
1L: first line; 2L: second line; 3L: third line; ADT: androgen deprivation therapy; AE: adverse event; APA: apalutamide plus ADT; DOX: docetaxel plus ADT; ERG: Evidence Review Group; ICER: incremental cost-effectiveness ratio; mHSPC: metastatic hormone sensitive prostate cancer; mHRPC: metastatic hormone resistant prostate cancer; nmHRPC: non metastatic hormone resistant prostate cancer; OS: overall survival; QALYs: quality-adjusted life years, rPFS: radiographic progression-free survival.		

6.4 Conclusions on the cost effectiveness evidence

The key issues identified by the ERG in the cost effectiveness evidence are the following:

- Extrapolation of MFS/rPFS survival curves;
- Selection of methods to adjust for treatment switching in the pivotal apalutamide clinical trials;
- Utility values for second and third line mHRPC health states;
- Market share of subsequent therapies for mHRPC;
- Duration of adverse event costs for docetaxel.

As minor issues, the ERG also disagrees with the company about other assumptions (all of them are described in Table 51).

The ERG's preferred model assumptions do not change the dominance of apalutamide plus ADT versus ADT alone for nmHRPC, i.e., apalutamide plus ADT is still cheaper and more effective than ADT alone. However, for mHSPC, our assumptions decrease the ICER for apalutamide plus ADT versus ADT alone to £22,294 per QALY and increases the ICER for apalutamide plus ADT versus docetaxel plus ADT to £49,298 QALY. The overall results are most sensitive to changes in the subsequent therapy market shares, mean health state durations for mHRPC health states and the survival curves to extrapolate PFS and OS.

7 END OF LIFE

The CS does not discuss whether NICE end of life considerations are satisfied. The ERG is of the opinion that apalutamide plus ADT does not meet the first end of life criterion as the life expectancy of patients treated with ADT would normally be greater than 24 months. For nmHRPC, the median OS for patients treated with ADT was 59.89 months in the SPARTAN trial. In the TITAN trial, median OS has not yet been reached. The mean OS for ADT in the company's base case was 4.6 years.

However, there is sufficient evidence to indicate that treatment with apalutamide plus ADT offers an extension of life of more than three months. The median improvement in life expectancy for apalutamide plus ADT for nmHRPC was 14 months. The mean gain in life expectancy for mHSPC was six months for apalutamide plus ADT vs docetaxel plus ADT and 17 months vs ADT alone.

8 References

1. Francini E, Gray KP, Xie W, et al. Time of metastatic disease presentation and volume of disease are prognostic for metastatic hormone sensitive prostate cancer (mHSPC). *Prostate* 2018;78(12):889-95. doi: 10.1002/pros.23645 [published Online First: 2018/05/01]
2. Frees S, Akamatsu S, Lynch K, et al. 845 Timing of the development of metastasis and initiation of treatment are important prognostic factors in prostate cancer. *European Urology Supplements* 2016;15(3):e845. doi: https://doi.org/10.1016/S1569-9056(16)60847-3

3. National Institute for Health and Care Excellence (NICE). Prostate cancer: diagnosis and management NICE guideline [NG131] 2019 [Available from: https://www.nice.org.uk/guidance/ng131 accessed 11 March 2020 2020.
4. European Association of Urology (EAU). EAU Guidelines on Prostate Cancer (2020). 2020
5. Parker C, Gillessen S, Heidenreich A, et al. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology : official journal of the European Society for Medical Oncology* 2015;26 Suppl 5:v69-77. doi: 10.1093/annonc/mdv222 [published Online First: 2015/07/25]
6. National Institute for Health and Care Excellence. Prostate Cancer overview [Available from: https://pathways.nice.org.uk/pathways/prostate-cancer#path=view%3A/pathways/prostate-cancer/prostate-cancer-overview.xml&content=view-index accessed 14/09/2020.
7. Oudard S, Juárez Soto A. A multi-disciplinary review of the evidence supporting metastasis-free survival (MFS) and the benefit of delaying metastasis in high-risk non-metastatic castration-resistant prostate cancer (NMCRPC). *European Medical Journal: Urology* 2019;6(Suppl 2):2-11.
8. Smith MR, Saad F, Chowdhury S, et al. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. *The New England journal of medicine* 2018;378(15):1408-18. doi: 10.1056/NEJMoa1715546 [published Online First: 2018/02/09]
9. National Institute for Health and Care Excellence (NICE). TA580: Enzalutamide for hormone-relapsed non-metastatic prostate cancer 2019 [Available from: https://www.nice.org.uk/guidance/ta580 accessed 05 August 2019.
10. National Institute for Health and Care Excellence. Darolutamide with androgen deprivation therapy for treating non-metastatic hormone-relapsed prostate cancer [ID1443] 2020 [Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10476/documents accessed 14/09/2020.
11. (NPCA) NPCA. Annual Report 2019: Results of the NPCA Prospective Audit in England and Wales for men diagnosed from 1 April 2017 to 31 March 2018 (publshed January 2020), 2020.
12. NHS England. NHS England interim treatment options during the COVID-19 pandemic 2020 [Available from: https://www.nice.org.uk/guidance/ng161/resources/nhs-england-interim-treatment-changes-during-the-covid19-pandemic-pdf-8715724381 accessed 14/09/2020.
13. Aly A, Mullins CD, Hussain A. Understanding heterogeneity of treatment effect in prostate cancer. *Current opinion in oncology* 2015;27(3):209-16. doi: 10.1097/cco.0000000000000172 [published Online First: 2015/02/18]
14. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. *The New England journal of medicine* 2015;373(8):737-46. doi: 10.1056/NEJMoa1503747 [published Online First: 2015/08/06]
15. Fizazi K, Tran N, Fein L, et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. *The New England journal of medicine* 2017;377(4):352-60. doi: 10.1056/NEJMoa1704174 [published Online First: 2017/06/06]
16. Janssen. SPARTAN Clinical Study Report. 2018
17. Janssen Research & Development L. Update to the Original Clinical Study Report dated 25 September 2017 Final Analysis of Overall Survival, Efficacy, and Safety A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase III Study of ARN-509 in Men with Non-Metastatic (M0) Castration-Resistant Prostate Cancer, 2020.
18. Saad F, Cella D, Basch E, et al. Effect of apalutamide on health-related quality of life in patients with non-metastatic castration-resistant prostate cancer: an analysis of the SPARTAN randomised, placebo-controlled, phase 3 trial. *The Lancet Oncology* 2018:DOI: 10.1016/S470-2045(18)30456-X.

19. Small EJ, Saad F, Chowdhury S, et al. Apalutamide and overall survival in non-metastatic castration-resistant prostate cancer. *Annals of Oncology* 2019 doi: 10.1093/annonc/mdz397
20. Agarwal N, McQuarrie K, Bjartell A, et al. Health-related quality of life after apalutamide treatment in patients with metastatic castration-sensitive prostate cancer (TITAN): a randomised, placebo-controlled, phase 3 study. *Lancet Oncol* 2019;20(11):1518-30. doi: 10.1016/s1470-2045(19)30620-5 [published Online First: 2019/10/04]
21. Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. *The New England journal of medicine* 2019;381(1):13-24. doi: 10.1056/NEJMoa1903307 [published Online First: 2019/06/01]
22. Janssen. SPARTAN Clinical Study Report (CSR), 2019.
23. Janssen. A Phase 3 Randomized, Placebo-controlled, Double-blind Study of Apalutamide Plus Androgen Deprivation Therapy (ADT) Versus ADT in Subjects with Metastatic Hormone-sensitive Prostate Cancer (mHSPC), 2019.
24. US National Library of Medicine. A Study of Apalutamide (JNJ-56021927, ARN-509) Plus Androgen Deprivation Therapy (ADT) Versus ADT in Participants With mHSPC (TITAN): U.S. National Library of Mediciine; 2015 [updated 26/06/2020. Available from: https://clinicaltrials.gov/ct2/show/NCT02489318 accessed 15/09/2020.
25. Cancer Research UK. Prostate cancer statistics. 2017
26. Lloyd T, Hounsome L, Mehay A, et al. Lifetime risk of being diagnosed with, or dying from, prostate cancer by major ethnic group in England 2008-2010. *BMC Med* 2015;13:171. doi: 10.1186/s12916-015-0405-5 [published Online First: 2015/08/01]
27. Xie W, Regan MM, Buyse M, et al. Metastasis-Free Survival Is a Strong Surrogate of Overall Survival in Localized Prostate Cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2017;35(27):3097-104. doi: 10.1200/jco.2017.73.9987 [published Online First: 2017/08/11]
28. Latimer N, Abrams K. NICE DSU TSD 16: Adjusting Survival Time Estimates in the Presence of Treatment Switching Decision Support Unit, ScHARR, University of Sheffield2014 [Available from: http://nicedsu.org.uk/wp-content/uploads/2016/03/TSD16_Treatment_Switching.pdf.
29. Diels J, Perualila N, Sermon J, et al. PCN248 ESTIMATING THE UNBIASED OS-BENEFIT FOR APALUTAMIDE (APA) VERSUS ANDROGEN DEPRIVATION THERAPY (ADT) IN PATIENTS WITH NON-METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (NMCRPC) FROM SPARTAN, ADJUSTING FOR SUBSEQUENT THERAPY USING RANDOMIZED DATA EXTERNAL TO THE TRIAL. *Value in Health* 2019;22 doi: https://doi.org/10.1016/j.jval.2019.04.369
30. Feyerabend S, Saad F, Li T, et al. Survival benefit, disease progression and quality-of-life outcomes of abiraterone acetate plus prednisone versus docetaxel in metastatic hormone-sensitive prostate cancer: A network meta-analysis. *European journal of cancer (Oxford, England : 1990)* 2018;103:78-87. doi: 10.1016/j.ejca.2018.08.010 [published Online First: 2018/09/16]
31. Woods B, Sideris E, Palmer S, et al. DSU TSD 19: Partitioned Survival Analysis For Decision Modelling In Health Care: A Critical Review Decision Support Unit, ScHARR, University of Sheffield2017 [Available from: http://nicedsu.org.uk/wp-content/uploads/2017/06/Partitioned-Survival-Analysis-final-report.pdf accessed 15 May 2020.
32. Woods BS, Sideris E, Sydes MR, et al. Addition of Docetaxel to First-line Long-term Hormone Therapy in Prostate Cancer (STAMPEDE): Modelling to Estimate Long-term Survival, Quality-adjusted Survival, and Cost-effectiveness. *European urology oncology* 2018;1(6):449-58. doi: 10.1016/j.euo.2018.06.004 [published Online First: 2019/06/04]
33. National Institute for Health and Care Excellence (NICE). TA404: Degarelix for treating advanced hormone-dependent prostate cancer 2016 [Available from: https://www.nice.org.uk/guidance/ta404 accessed 5 May 2020.

34. Clarke CS, Brawley CD, Ingleby FC, et al. Addition of abiraterone to first-line long-term hormone therapy in prostate cancer (STAMPEDE): Model to estimate long-term survival, quality-adjusted survival, and cost-effectiveness. *Journal of Clinical Oncology* 2020;38(6_suppl):204-04. doi: 10.1200/JCO.2020.38.6_suppl.204
35. Antonarakis ES. Current understanding of resistance to abiraterone and enzalutamide in advanced prostate cancer. *Clin Adv Hematol Oncol* 2016;14(5):316-9. [published Online First: 2016/07/06]
36. Chong JT, Oh WK, Liaw BC. Profile of apalutamide in the treatment of metastatic castration-resistant prostate cancer: evidence to date. *Onco Targets Ther* 2018;11:2141-47. doi: 10.2147/OTT.S147168
37. Teply BA, Antonarakis ES. Novel mechanism-based therapeutics for androgen axis blockade in castration-resistant prostate cancer. *Current opinion in endocrinology, diabetes, and obesity* 2016;23(3):279-90. doi: 10.1097/MED.0000000000000254
38. Pennington M, Grieve R, der Meulen JV, et al. Value of External Data in the Extrapolation of Survival Data: A Study Using the NJR Data Set. *Value Health* 2018;21(7):822-29. doi: 10.1016/j.jval.2017.12.023 [published Online First: 2018/07/15]
39. Sathianathen NJ, Koschel S, Thangasamy IA, et al. Indirect Comparisons of Efficacy between Combination Approaches in Metastatic Hormone-sensitive Prostate Cancer: A Systematic Review and Network Meta-analysis. *European urology* 2020;77(3):365-72. doi: 10.1016/j.eururo.2019.09.004 [published Online First: 2019/11/05]
40. National Institute for Health and Care Excellence (NICE). TA387: Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated, 2016.
41. Latimer N. NICE DSU Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data School of Health and Related Research, University of Sheffield: Decision Support Unit, ScHARR, University of Sheffield; 2011 [updated March 2013. 2013 update:[Available from: https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0089910/pdf/PubMedHealth_PMH0089910.pdf accessed 14 December 2017.
42. Latimer NR, White IR, Abrams KR, et al. Causal inference for long-term survival in randomised trials with treatment switching: Should re-censoring be applied when estimating counterfactual survival times? *Stat Methods Med Res* 2019;28(8):2475-93. doi: 10.1177/0962280218780856 [published Online First: 2018/06/27]
43. Aly M, Hashim M, Heeg B, et al. Time-to-event Outcomes in Men with Nonmetastatic Castrate-resistant Prostate Cancer-A Systematic Literature Review and Pooling of Individual Participant Data. *Eur Urol Focus* 2019;5(5):788-98. doi: 10.1016/j.euf.2018.03.010 [published Online First: 2018/04/09]
44. Guyot P, Ades AE, Ouwens MJ, et al. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol* 2012;12:9. doi: 10.1186/1471-2288-12-9 [published Online First: 2012/02/03]
45. Janssen. Apalutamide in nmCRPC and mHSPC Clinical validation meeting - 17 April 20. *Data on File* 2020
46. Latimer NR. Survival analysis for economic evaluations alongside clinical trials--extrapolation with patient-level data: inconsistencies, limitations, and a practical guide. *Med Decis Making* 2013;33(6):743-54. doi: 10.1177/0272989X12472398 [published Online First: 2013/01/24]
47. Jackson CH. flexsurv: A Platform for Parametric Survival Modeling in R. *J Stat Softw* 2016;70 doi: 10.18637/jss.v070.i08 [published Online First: 2016/05/12]
48. Royston P, Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. *Stat Med* 2002;21(15):2175-97. doi: 10.1002/sim.1203 [published Online First: 2002/09/05]

49. Gravis G, Fizazi K, Joly F, et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2013;14(2):149-58. doi: 10.1016/s1470-2045(12)70560-0 [published Online First: 2013/01/12]
50. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal. 2013.
51. van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health* 2012;15(5):708-15. doi: 10.1016/j.jval.2012.02.008 [published Online First: 2012/08/08]
52. Ara RW, A.;. NICE DSU Technical Support Document 12: The use of health state utility values in decision models. 2011.
53. Monthly Index of Medical Specialities. Database of prescription and generic drugs, clinical guidelines | MIMS online 2020 [Available from: https://www.mims.co.uk/ accessed 5 May 2020.
54. Department of Health and Social Care. Drugs and pharmaceutical electronic market information tool (eMIT) 2020 [Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit accessed 5 May 2020.
55. Joint Formulary Committee. British National Formulary. https://www.bnf.org/: BMJ group, 2020.
56. National Institute for Health and Care Excellence (NICE). TA387: Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated 2016 [Available from: https://www.nice.org.uk/guidance/ta387 accessed 08 December 2017.
57. National Health Service. 2018/19 National Cost Collection data 2019 [Available from: https://improvement.nhs.uk/resources/national-cost-collection/ accessed 5 May 2020.
58. Burns A, Curtis L. Unit Costs of Health and Social Care 2019 2019 [Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/ accessed 5 May.
59. Round J JL, Morris S. Estimating the cost of caring for people with cancer at the end of life: A modelling study. *Palliative Medicine* 2015;29(10):899-907. doi: 10.1177/0269216315595203
60. Patrikidou A, Uccello M, Tree A, et al. Upfront Docetaxel in the Post-STAMPEDE World: Lessons from an Early Evaluation of Non-trial Usage in Hormone-Sensitive Prostate Cancer. *Clinical oncology (Royal College of Radiologists (Great Britain))* 2017;29(10):e174-e75. doi: 10.1016/j.clon.2017.06.006 [published Online First: 2017/06/28]
61. 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. *Annals of oncology : official journal of the European Society for Medical Oncology* 2019;30(12):1992-2003. doi: 10.1093/annonc/mdz396 [published Online First: 2019/09/29]
62. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *The New England journal of medicine* 2013;368(2):138-48. doi: 10.1056/NEJMoa1209096 [published Online First: 2012/12/12]
63. Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol* 2012;13(10):983-92. doi: 10.1016/s1470-2045(12)70379-0 [published Online First: 2012/09/22]

9 Appendices

9.1 Efficacy outcome definitions in the SPARTAN and TITAN trials

SPARTAN – Efficacy outcome definitions

Endpoints	Outcome definition	Data cut	Used in Economic Model	ERG comments
Primary				
Metastasis-free survival (MFS)	Time from randomisation to the time of the scan that showed first evidence of BICR-confirmed radiographically detectable bone or soft tissue distant metastasis or death due to any cause (whichever occurred earlier)	19th May 2017	Yes	• Appropriate to use an intermediate primary endpoint as prostate cancer has a relatively long disease course. • Case definition is appropriate. BICR used to minimise bias through objective outcome assessment. • Deaths were included as events based on the assumption that they occur at random. This is a reasonable assumption in this setting as deaths prior to metastases are likely to be from unrelated causes.
Secondary				
Overall survival (OS)	Time from randomisation to the date of death due to any cause.	1st Feb 2020	Yes	Appropriate. Considered gold standard. Data are considered mature.
Time to initiation of chemotherapy	Time from randomisation to documentation of a new cytotoxic chemotherapy being administered to the patient (e.g. survival follow-up CRF)	1st Feb 2020	No	• Important clinical outcome from patient perspective as progression to mHRPC and need for chemotherapy may have significant burden on quality of life.. • Measurement based on objective record of drug administration
Time to metastasis (TTM)	Time from randomisation to the time of the scan that showed first evidence of BICR-confirmed radiographically detectable bone or soft tissue distant metastasis (death not included as an event).	19th May 2017	No	This outcome is closely related to MFS but patients who die are censored rather than being included as having events. Censoring at death is likely to be non-informative as deaths prior to

Endpoints	Outcome definition	Data cut	Used in Economic Model	ERG comments
				metastases are likely due to other, unrelated causes.
Progression-free survival	Time from randomisation to first documentation of BICR-confirmed radiographic progressive disease (based on RECIST v1.1) or death due to any cause (whichever occurs first)	19th May 2017	No	• This outcome includes metastases as well as loco-regional progression. • Objective assessment using BICR with standardised criteria (RECIST).
Time to symptomatic progression	Time from randomisation to documentation in the case report form (CRF) of any of the following (whichever occurred earlier): o Development of a skeletal-related event (SRE): pathologic fracture, spinal cord compression, or need for surgical intervention or radiation therapy to the bone o Pain progression or worsening of disease-related symptoms requiring initiation of a new systemic anti-cancer therapy o Development of clinically significant symptoms due to loco-regional tumour progression requiring surgical intervention or radiation therapy	1st Feb 2020	No	• Composite endpoint. ERG notes that these may be relevant as separate outcomes of interest. • These sub-outcomes are largely objectively measured. It is not clear if pain progression alone was considered here or if this also required initiation of a new systemic anti-cancer therapy, or which therapies were considered.
Other				

Endpoints	Outcome definition	Data cut	Used in Economic Model	ERG comments
Second progression-free survival (PFS2)	Time from randomisation to investigator-assessed disease progression (PSA, radiographic, symptomatic, or any combination) during first subsequent anti-cancer therapy or death (any cause) prior to the start of the second subsequent anti-cancer therapy, whichever occurs first	1st Feb 2020	Yes	This is an appropriate endpoint in this setting as it provides further information in the post-progression phase to assess whether earlier survival benefits (i.e. MFS) are sustained following progression and subsequent therapy.
PSA response	Proportion of patients who achieved at least a 50% decline in PSA value from baseline assessed by a central laboratory according to Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria. The PSA response was confirmed by a central laboratory measurement obtained 4 or more weeks later	19th May 2017	No	Centralised measurement to ensure objective assessment using standardised criteria.
Time to PSA progression	Assessed at the time of the primary analysis of MFS according to the PCWG2 criteria	19th May 2017	No	Centralised measurement to ensure objective assessment.

BICR: blinded independent central review; CRF: case report form; mHRPC metastatic hormone-relapsed prostate cancer; PCWG2: Prostate Cancer Working Group 2; PSA: prostate-specific antigen; SRE skeletal-related event
RECIST: Response Evaluation Criteria in Solid Tumors
Source: CS Table 5 and 6, section 2.7.1-2.7.3

TITAN – Efficacy outcome definitions

Endpoints	Outcome definition	Data cut	Used in Economic Model	ERG comments
Primary				
Radiographic progression - free survival (rPFS)	Time from randomisation to the time of first evidence of radiographic progression identified by bone scan, or for soft tissue lesions by CT or MRI, as defined by modified RESIST 1.1 criteria and assessed by the investigator. A more precise definition is detailed in CS Table 6.	23rd Nov 2018	Yes	Standardised criteria (RECIST) have been used to determine progression and a BICR audit based on 60% of patients selected at random had 85% concordance rate with investigator assessment.
Overall survival (OS)	Time from randomisation to the date of death due to any cause.	23rd Nov 2018	Yes	Appropriate; gold standard. Data immature in current submission.
Secondary				
Time to pain progression	Time from randomisation to an increase by 2 points from baseline in the BPI-SF worst pain intensity (item 3) observed at two consecutive evaluations ≥3 weeks apart; with an average worst pain score of >4 in patients who had no decrease in opioids or initiation of chronic opioids, whichever occurs first	23rd Nov 2018	No	Appropriate choice of outcome. Potential for measurement error due to subjective nature of measuring pain but not anticipated to be differential between treatment arms.
Time to initiation of chemotherapy	Time from randomisation to date of initiation of cytotoxic chemotherapy	23rd Nov 2018	No	Important clinical outcome from patient perspective as progression to mHRPC and need for chemotherapy may have greater impact on quality of life. Objective measurement.

Endpoints	Outcome definition	Data cut	Used in Economic Model	ERG comments
Time to skeletal-related event	Time from randomisation to occurrence of symptomatic pathological fracture, spinal cord compression, radiation to bone, or surgery to bone.	23rd Nov 2018	No	Objective measurement.
Time to chronic opioid use	Time from randomisation to first date of confirmed chronic opioid use.	23rd Nov 2018	No	Based on objective record of prescription.
Other				
Second progression-free survival (PFS2)	Time from randomisation to date of first occurrence of disease progression on first subsequent prostate cancer therapy or death (any cause), whichever occurs first	23rd Nov 2018	Yes	This is an appropriate endpoint in this setting as it provides further information in the post-progression phase to assess whether earlier survival benefits (i.e. rPFS) are sustained following progression and subsequent therapy. Data immature in current submission.
Overall response	Defined by RECIST 1.1	23rd Nov 2018	No	Based on complete response according to standardised criteria.
Time to PSA progression	Time from randomisation to to PSA progression was based on PCWG2 criteria	23rd Nov 2018	No	Centralised measurement to ensure objective assessment.
Prostate cancer specific survival	Time from randomisation to prostate cancer related death	23rd Nov 2018	No	Data are immature.

BICR: blinded independent central review; CRF: case report form; CT computerised topography; mHRPC metastatic hormone-relapsed prostate cancer; MRI magnetic resonance imaging; PCWG2: Prostate Cancer Working Group 2; PSA: prostate-specific antigen; RECIST: Response Evaluation Criteria in Solid Tumors
Source: CS Table 5 and 6

9.2 Comparative analysis of patient populations in COU-AA-302 and COU-AA-301 versus the SPARTAN population

The characteristics of patients from the COU-AA-302 and COU-AA-301 trials were compared with the characteristics reported for the SPARTAN trial. As shown in Table 60 patients from the COU-AA-302 trial[62] had mHRPC and had not received prior chemotherapy. Patients in the COU-AA-302 trial therefore appear to be a better match to SPARTAN trial participants than those from the COU-AA-301 trial[63] where all patients had received prior docetaxel.

Table A Comparison of SPARTAN, COU-AA-302 and COU-AA-301 trials patient characteristics

	SPARTAN				**COU-AA-302**				**COU-AA-301**			
Patient population at study entry	High-risk nmHRPC, no prior chemotherapy[a]				mHRPC, no prior chemotherapy				mHRPC progressing after docetaxel			
	Apalutamide plus ADT		Placebo plus ADT		Abiraterone plus prednisone		Prednisone		Abiraterone plus prednisone		Prednisone	
Age, median years (range)	74.0 (48-94)		74.0 (52-97)		71 (65-77)		70 (63-76)		69 (42-95)		69 (39-90)	
Age categorization												
≥ 75 and < 79	23.0%		20.0%		34%		30%		28%		28%	
≥ 80 and < 84	17.9%		17.7%									
> 85	7.9%		9.5%									
Gleason score at initial diagnosis	< 7	19.4%	< 7	18.6%	≤7	46%	≤7	50%				
	=7	37.1%	=7	37.7%					≤8	49%	≤8	46%
	> 7	43.5%	> 7	43.7%	≥8	54%	≥8	50%	≥8	51%	≥8	54%
ECOG performance status score	0	77.3%	0	77.8%					0 or 1	90%	0 or 1	89%
	1	22.7%	1	22.3%								

[a] except in adjuvant/neoadjuvant setting

9.3 Estimation of counterfactual survival time

Table B Estimation of counterfactual survival time for the comparison of apalutamide versus placebo

Patient sub-population	Estimation of the counterfactual survival time, CF_{UK}	Survival estimates adjusted	Trials	Arm(s)
Patients who switched to second novel treatment	CF_{UK}=time to switch + time after switch * exp(ψ^{ST})[a]	OS, PFS2	SPARTAN	APA+ADT placebo+ADT
Patients who switched (crossed over) from placebo to apalutamide	CF_{UK}=time to crossover + time after crossover * exp(ψ^{a})[b]	OS, PFS2	SPARTAN	placebo+ADT
	CF_{UK}^{RC}=minimum (CF_{UK}, exp(ψ^{ST})*C)[c]	OS, PFS2	SPARTAN	APA+ADT placebo+ADT
Non-switcher patients	CF_{UK}=observed time to event data	OS, PFS2	SPARTAN, TITAN	APA+ADT placebo+ADT

Source: CS Appendix R.1 page 854

APA apalutamide

a exp(ψ^{ST}) is the shrinkage factor associated with subsequent enzalutamide/abiraterone use estimated following Diels et al.[29]

b exp(ψ^{a}) is the shrinkage factor attributed to apalutamide, estimated using RPSFTM.

c CF_{UK}^{RC} is counterfactual re-censored survival time, where C denotes the time between randomization to analysis cut-off date/censor date (CS Appendix R.1 page 856).

9.4 ERG review of the searches conducted by the company for the informed fits analyses

The SLR to identify appropriate studies for the company's informed fits analysis is briefly reported in CS Appendix S. For both prostate cancer indications, the CS states they are looking for historical data from ADT arms of other clinical trials (CS Appendix S). It does not define historical data, and we assume that this means studies which have completed and published results, rather than studies in progress. We also assume that they are looking for comparative studies (i.e. not single-arm or cohort studies) but we do not know if they did not include single-arm studies. ERG comments on the SLR specific to each indication are below.

nmHRPC

- The company use a recent (2018 accepted, 2019 fully published) systematic review on time to event outcomes in nmCRPC.[43]The ERG believes the population and outcomes are relevant to the informed fits analysis and that using a recent systematic review to identify relevant studies is appropriate.
- As for the mHSPC SLR above, there is limited documentation reported in the CS: there is no PICO, no inclusion or exclusion criteria, no record of which databases or registries were searched, no search strings, no PRISMA flow diagram, no excluded studies listed, and no reviewer methods described. We do not know how the Aly 2018 systematic review was identified, and, as above for the mHSPC search, without this documentation we cannot verify, assess or replicate the search, nor screen results for any search we might perform ourselves.
- Three clinical trials with a similar patient population to SPARTAN were identified from Aly et al.[43](CS Table S.2). The ERG assumes that *high-risk* nmHRPC might be one of the inclusion criteria because the reason for not searching patient registries and real-world data was because the company believe it would not be possible to separate high-risk from low-risk patients in those types of study.

Table S.3. shows the baseline characteristics alongside those of the three historical trials identified from Aly et al. Baseline characteristics were not reported for the three historical trials for many of the reported SPARTAN trial population characteristics, this makes comparison difficult. However, from CS Table S.3 we can see that:

- The three historical trials had a higher proportion of white participants than the SPARTAN trial (over 80% vs 66%).

- ECOG performance status at baseline was similar in the SPARTAN trial and the single historical trial (Smith 2012) that reported this characteristic.
- Gleason score at initial diagnosis appears similar between the SPARTAN trial and the Nelson 2008 trial but the other two historical trials (Smith 2005 and Smith 2012) appear to have a lower proportion of participants with a Gleason score >7 (approximately 30% compared with 43% in SPARTAN).

The ERG carried out a citation search on the company identified systematic review, Aly 2018, and found three citations. Two are on alkaline phosphatase values and on radiotherapy, however, one is a systematic review and meta-analysis of systemic management for nmCRPC. It is published too recently to have been included in the company's search.

mHSPC

- We know that 19 studies were identified, of which seven were included. All 19 studies, and reasons for exclusion, are reported in CS Table S.1.
- The search is inadequately documented: there is no PICO template, no inclusion and exclusion criteria, no record of which databases or registries were searched, no search strings, no PRISMA flow diagram, and no reviewer methods described. Without these we cannot verify, assess or replicate the search, nor screen results for any search we might perform ourselves.
- The CS describes the population as patients with "mHSPC-like" diseases. This is unclear, the ERG does not know if that means any prostate cancer, any metastatic prostate cancer, or includes any other disease.
- The CS describes pooling IPD from the seven included studies, therefore the ERG could assume that reporting Kaplan-Meier survival estimates is one of the inclusion criteria. The reasons for exclusion in Table S.1 could inform ERG of some exclusion criteria, but not enough to assess or replicate the searches or screening.
- Several studies were excluded because they were an "older study" (range 1986-2009), from which we could assume a date limit within the inclusion criteria but not the searches.

The ERG carried out a brief targeted search of the Scopus database (because it includes records from both Medline and Embase) only for an mHSPC population (not “mHSPC-like”), a few relevant outcomes and ADT, as described in the search string below.

- Scopus search string: TITLE-ABS-KEY (hspc OR "metastatic hormone-sensitive prostate cancer" OR "metastatic hormone-naive prostate cancer" OR "metastatic castrate-sensitive prostate cancer" OR "metastatic castration-sensitive prostate cancer") AND TITLE-ABS-KEY (("time" PRE/1 (event OR "bone metastasis" OR metastasis OR progression)) OR "clinical outcome" OR "survival time" OR "overall survival") AND TITLE-ABS-KEY (adt PRE/0 (arm OR only OR alone))

This search identified 34 publications, one of which is a systematic review of combination therapies compared to ADT alone. This systematic review is published too recently for the company to have missed it in their search, but it is potentially useful to the ERG in identifying relevant studies.

ERG conclusion

Lack of documentation of these SLRs forces the ERG to make assumptions about, for example, the population and the inclusion/exclusion criteria; and there remain things, such as which sources were searched, that is unclear. Therefore, we are unable to assess whether any relevant studies might have been missed. Some brief targeted searching by the ERG identified two systematic reviews that could be a potential source of relevant evidence.

9.5 Model functionality issues

Table A Model functionality issues (amended by the ERG)

Issue	Cell formula	Original formula [a]	Corrected formula [a]	ERG comments
1	Subs therapy costs!O138: Q140	=$E129*O88***Parameters!S327:** $E131*Q90***Parameters!Y335**	=$E129*O88***Parameters!S336:** $E131*Q90***Parameters!S344**	These corrections have a minor impact on the final results.
2	PF_DOX!AJ9:AM9	=AJ8*((**$AE$9**/(1-p_con_preprog_events_DOX))/$AN$8): AM8*((**$AE$9**/(1-p_con_preprog_events_DOX))/$AN$8)	=AJ8*((**SUM($AE$9:$AF$9)**/(1-p_con_preprog_events_DOX))/$AN$8): AM8*((**SUM($AE$9:$AF$9)**/(1-p_con_preprog_events_DOX))/$AN$8)	The formulas used for docetaxel are different from the formulas used for apalutamide and ADT. These corrections have some impact on the final results.
3	PF_APA!AS14: AS1662	=**AL13*($AL$10-Y14):AL1661*($AL$10-Y1662)**	=**MAX(AM14-AM13,0): MAX(AM1662-AM1661,0)**	Incident patients on third line mHRPC are greater than incident patients on second line, which is implausible (see section 4.2.6.1). Therefore, the ERG suggests the use of a new formula. These corrections have some impact on the final results.
4	PF_ADT!AS14: AS1662	=**AL13*($AL$10-Y14):AL1661*($AL$10-Y1662)**		
5	PF_DOX!AS14: AS16	**=0**		
6	PF_DOX!AS17: AS1662	=**AL16*$AL$10:AL1661*$AL$10**		
7	PF_APA!AW14: AW1662,	=1/((1+**con_DR_LYs**)^$N14): 1/((1+**con_DR_LYs**)^$N1662)	=1/((1+**p_con_DR_LYs**)^$N14): 1/((1+**p_con_DR_LYs**)^$N1662)	These corrections impact the deterministic sensitivity analysis results only.
8	PF_APA!AX14: AX1662,	=1/((1+**con_DR_QALYs**)^$N14): 1/((1+**con_DR_QALYs**)^$N1662)	=1/((1+**p_con_DR_QALYs**)^$N14): 1/((1+**p_con_DR_QALYs**)^$N1662)	
9	PF_APA!AY14: AY1662,	=1/((1+**con_DR_costs**)^$N14): 1/((1+**con_DR_costs**)^$N1662)	=1/((1+**p_con_DR_costs**)^$N14): 1/((1+**p_con_DR_costs**)^$N1662)	

Issue	Cell formula	Original formula [a]	Corrected formula [a]	ERG comments
10	PF_DOX!BG14: BG1662	=BA14*(final.util_preprog+(IF(con_AE_disutils_source="Utility regression parameters",final.util_AE_dox***AU16**,final.util_AE_dox))+(IF(N14>1,0,p_util_TTO_dox_dec))): BA1662*(final.util_preprog+(IF(con_AE_disutils_source="Utility regression parameters",final.util_AE_dox***AU1664**,final.util_AE_dox))+(IF(N1662>1,0,p_util_TTO_dox_dec)))	=BA14*(final.util_preprog+(IF(con_AE_disutils_source="Utility regression parameters",final.util_AE_dox***AU14**,final.util_AE_dox))+(IF(N14>1,0,p_util_TTO_dox_dec))): BA1662*(final.util_preprog+(IF(con_AE_disutils_source="Utility regression parameters",final.util_AE_dox***AU1662**,final.util_AE_dox))+(IF(N1662>1,0,p_util_TTO_dox_dec)))	These corrections have a minor impact on the final results.
ADT: androgen deprivation therapy, APA: apalutamide plus ADT, DOX: docetaxel plus ADT, ERG: evidence review group, ICER: incremental cost-effectiveness ratio, mHRPC: metastatic hormone refractory prostate cancer. [a] The differences between the original formula and the corrected one are presented in bold.				

Table B Model functionality issues (not amended by the ERG)

Issue	Cell formula	Original formula	Corrected formula	ERG comments
1	Drug costs!H22	=**p_dc_pack_aap_1L***(1-con_PAS_aap_2L)	=**p_dc_pack_aap_2L***(1-con_PAS_aap_2L)	This correction could have an impact on the final results if the price of first line abiraterone is different from the price of second-line abiraterone.
2	Subs therapy costs!C121	=$E103***C88**	=$E103***C91**	These cells don't seem to be used in the model – These corrections have no impact on the final results.
3	Subs therapy costs!D121	=$E103***D88**	=$E103***D91**	

Issue	Cell formula	Original formula	Corrected formula	ERG comments
4	Subs therapy costs!E121	=$E103***E88***	=$E103***E91***	
5	Subs therapy costs!I120	=***$E105****I87	=***$E102****I87	
6	Subs therapy costs!I121	=***$E106*I88***	=***$E103*I91***	
7	Subs therapy costs!J120	=***$E105****J87	=***$E102****J87	
8	Subs therapy costs!J121	=***$E106*J88***	=***$E103*J91***	
9	Subs therapy costs!K120	=***$E105****K87	=***$E102****K87	
10	Subs therapy costs!K121	=***$E106*K88***	=***$E103*K91***	
11	Subs therapy costs!O121	=***$E103*O88***	=***$E106*O91***	
12	Subs therapy costs!P121	=***$E103*P88***	=***$E106*P91***	
13	Subs therapy costs!Q121	=***$E103*Q88***	=***$E106*Q91***	
14	Subs therapy costs!O146	=$C129*O88****Parameters!S327***	=$C129*O88****Parameters!S336***	These cells don't seem to be used in the model – These corrections have no impact on the final results.
15	Subs therapy costs!O147	=$C130*O89****Parameters!S328***	=$C130*O89****Parameters!S337***	

Issue	Cell formula	Original formula	Corrected formula	ERG comments
16	Subs therapy costs!O148	=$C131*O90***Parameters!S329**	=$C131*O90***Parameters!S338**	
17	Subs therapy costs!P146	=$C129*P88***Parameters!S330**	=$C129*P88***Parameters!S339**	
18	Subs therapy costs!P147	=$C130*P89***Parameters!S331**	=$C130*P89***Parameters!S340**	
19	Subs therapy costs!P148	=$C131*P90***Parameters!S332**	=$C131*P90***Parameters!S341**	
20	Subs therapy costs!Q146	=$C129*Q88***Parameters!S333**	=$C129*Q88***Parameters!S342**	
21	Subs therapy costs!Q147	=$C130*Q89***Parameters!S334**	=$C130*Q89***Parameters!S343**	
22	Subs therapy costs!Q148	=$C131*Q90***Parameters!S335**	=$C131*Q90***Parameters!S344**	
23	Results!K13	=IF(J13="Dominated","Strictly Dominated",IF(J13>J14,"**Extendedly dominated**",""))	=IF(J13="Dominated","Strictly Dominated",IF(J13>J14,"**Extendedly dominates**",""))	The ERG notes that docetaxel should not be considered extendedly dominated as ICER DOX vs. ADT < ICER APA vs. ADT. The ERG notes that this incorrection does not exist in the CS.
24	Results!L13	=IF(OR(K13="**Extendedly dominated**",K13="Strictly dominated"),K13,(C13-C12)/(E13-E12))	=IF(OR(K13="**Extendedly dominates**",K13="Strictly dominated"),K13,(C13-C12)/(E13-E12))	
25	Results!L14	=IF(OR(K14="**Extendedly dominated**",K14="Strictly dominated"),K14,IF(OR(K13="**Extendedly**	=IF(OR(K14="**Extendedly dominates**",K14="Strictly dominated"),K14,IF(OR(K13="**Extendedly**	

Issue	Cell formula	Original formula	Corrected formula	ERG comments
		dominated",K13="Strictly dominated"),(C14-C12)/(E14-E12),(C14-C13)/(E14-E13)))	**dominates**",K13="Strictly dominated"),(C14-C12)/(E14-E12),(C14-C13)/(E14-E13)))	
26	Results!C90	=TRANSPOSE(**E64:E66**)	=TRANSPOSE(**E58:E60**)	These corrections have no impact on the final results but could lead to misinterpretations.
27	Results!D90	=TRANSPOSE(**E64:E66**)	=TRANSPOSE(**E58:E60**)	
28	Results!E90	=TRANSPOSE(**E64:E66**)	=TRANSPOSE(**E58:E60**)	
29	OWSA!P84	=IF(B84="","",((**J84-L84**)*con_WTP)-(**I84-K84**))	=IF(B84="","",((**D84-F84**)*con_WTP)-(**C84-E84**))	These cells don't seem to be used in the model – These corrections have no impact on the final results.
30	OWSA!T84	=IF(B84="","",**L84***con_WTP-**K84**)	=IF(B84="","",((**J84-L84**)*con_WTP)-(**I84-K84**))	
31	OWSA!V84	=IF(B84="","",**N84***con_WTP-**M84**)	=IF(B84="","",((**J84-N84**)*con_WTP)-(I**84-M84**))	
ADT: androgen deprivation therapy, APA: apalutamide plus ADT, DOX: docetaxel plus ADT, ERG: evidence review group, ICER: incremental cost-effectiveness ratio.				

9.6 ERG alternative medical resource use estimates

Table A nmHRPC: medical resource use suggested by the clinical experts advising the ERG [a]

Resource use	Apalutamide plus ADT			ADT alone		
	% use	Frequency (first 3 months)	Frequency per cycle (after 3 months)	% use	Frequency (first 1 year)	Frequency per cycle (after 1 year)
CT scan	**10%**	1 every 52 weeks	1 every 52 weeks	**10%**	**1 every 26 weeks**	**1 every 26 weeks**
Bone scan	**10%**	1 every 52 weeks	1 every 52 weeks	**10%**	**1 every 26 weeks**	**1 every 26 weeks**
PSA test	100%	1 every 4 weeks	1 every 12 weeks	100%	1 every 12 weeks	1 every 9 weeks
Testosterone	100%	1 every 52 weeks	1 every 52 weeks	100%	1 every 52 weeks	1 every 52 weeks
Liver function test	33%	1 every 4 weeks	1 every 12 weeks	33%	1 every 12 weeks	1 every 9 weeks
Kidney function test	33%	1 every 4 weeks	1 every 12 weeks	33%	1 every 12 weeks	1 every 9 weeks
FBC	33%	1 every 4 weeks	1 every 12 weeks	33%	1 every 12 weeks	1 every 9 weeks
Oncologist OP visit	100%	1 every 12 weeks	1 every 12 weeks	100%	1 every 12 weeks	1 every 12 weeks
MRI	5%	**1 every 26 weeks**	**1 every 26 weeks**	5%	1 every 12 weeks	1 every 12 weeks
GP visit	100%	1 every 12 weeks	1 every 12 weeks	100%	1 every 12 weeks	1 every 12 weeks
CNS	33%	1 every 26 weeks	1 every 26 weeks	33%	1 every 26 weeks	1 every 26 weeks
PSMA-PET	**50%**	1 every 52 weeks	1 every 52 weeks	**50%**	1 every 52 weeks	1 every 52 weeks
Urologist/ Oncologist	**0%**	1 every 4 weeks	1 every 4 weeks	**0%**	1 every 12 weeks	1 every 12 weeks
Nurse OP visit	**100%**	**1 every 12 weeks**	**1 every 12 weeks**	**100%**	**1 every 12 weeks**	**1 every 12 weeks**

[a] The changes between this table and CS Table 78 are underlined and in bold.
ADT: androgen deprivation therapy; CNS: central nervous system; CT: computed tomography; ERG: Evidence Review Group; FBC: full blood count; GP: general practitioner; MRI: magnetic resonance imaging; nmHRPC: nonmetastatic hormone resistant prostate cancer; OP: outpatient; PSA: prostate-specific antigen; PSMA-PET: prostate-specific membrane antigen positron emission tomography.

Table B mHSPC: medical resource use suggested by the clinical experts advising the ERG [a]

Resource use	Apalutamide plus ADT			ADT alone			Docetaxel plus ADT	
	% use	Frequency (first 3 months)	Frequency per cycle (after 3 months)	% use	Frequency (first 1 year)	Frequency per cycle (after 1 year)	% use	Frequency
CT scan	100 %	1 every 52 weeks	1 every 52 weeks	100 %	1 every 52 weeks	1 every 52 weeks	100 %	1 every 18 weeks
Bone scan	100 %	1 every 52 weeks	1 every 52 weeks	100 %	1 every 52 weeks	1 every 52 weeks	100 %	1 every 52 weeks
PSA test	100 %	**1 every 4 weeks**	1 every 12 weeks	100 %	1 every 12 weeks	1 every 12 weeks	100 %	1 every 3 weeks
Testosterone	**0%**	1 every 12 weeks	1 every 12 weeks	**0%**	1 every 12 weeks	1 every 12 weeks	**0%**	1 every 3 weeks
Liver function test	100 %	**1 every 26 weeks**	**1 every 26 weeks**	100 %	**1 every 26 weeks**	**1 every 26 weeks**	100 %	1 every 3 weeks
Kidney function test	100 %	**1 every 4 weeks**	1 every 12 weeks	100 %	1 every 12 weeks	1 every 12 weeks	100 %	1 every 3 weeks
FBC	100 %	**1 every 4 weeks**	1 every 12 weeks	100 %	1 every 12 weeks	1 every 12 weeks	100 %	1 every 3 weeks
Oncologist visit	100 %	**1 every 26 weeks**	**1 every 26 weeks**	100 %	**1 every 26 weeks**	**1 every 26 weeks**	100 %	**1 every 6 weeks**
GP visit	**100 %**	**1 every 26 weeks**	**1 every 26 weeks**	**100 %**	**1 every 26 weeks**	**1 every 26 weeks**	**100 %**	**1 every 6 weeks**

[a] The changes between this table and CS Table 77 are underlined and in bold.
ADT: androgen deprivation therapy; CT: computed tomography; ERG: Evidence Review Group; FBC: full blood count; GP: general practitioner; mHSPC: metastatic hormone sensitive prostate cancer; PSA: prostate-specific antigen.