Committee Papers

Enzalutamide for treating non-metastatic hormone-relapsed prostate cancer [ID1359]

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HIGHLY CONFIDENTIAL

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Enzalutamide for treating non-metastatic hormone-relapsed prostate cancer [ID1359]

Appraisal Committee Meeting – 4 December 2018

The following documents are made available to the company:

Pre-Meeting Briefing (PMB)

Final Scope and **Final Matrix**

1. **Company submission summary** from Astellas Pharma Ltd

2. **Clarification letters**
   - Company response to NICE's request for clarification

3. **Patient group, professional group and NHS organisation submission** from:
   - Prostate Cancer UK
   - NCRI-ACP-RCP-RCR

4. **Expert personal perspectives from:**
   Professor Gerhardt Attard – clinical expert, nominated by [Astellas Pharma Ltd. – to follow
   - Dr Alison Tree – clinical expert, nominated by NCRI- ACP- RCP- RCR – to Folow
     Dr Tree has stated that she agrees with the statement from the NCRI-ACP-RCP-RCR
   - Anthony Good – patient expert, nominated by Prostate Cancer UK
     Anthony Good stated that he agreed with the statement from the Prostate Cancer UK
   - Ron Keats – patient expert, nominated by Prostate Cancer UK
     Ron Keats stated that he agreed with the statement from the Prostate Cancer UK

5. **Evidence Review Group** report prepared by Aberdeen HTA Group
   - Evidence Review Group report
   - Erratum

6. **Evidence Review Group report – factual accuracy check**

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Enzalutamide for treating non-metastatic hormone-relapsed prostate cancer [ID1359]

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Enzalutamide for treating non-metastatic hormone-relapsed prostate cancer [ID1359]

Contents:

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

NICE National Institute for Health and Care Excellence

Enzalutamide for non-metastatic hormone-relapsed prostate cancer

Pre-meeting briefing

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

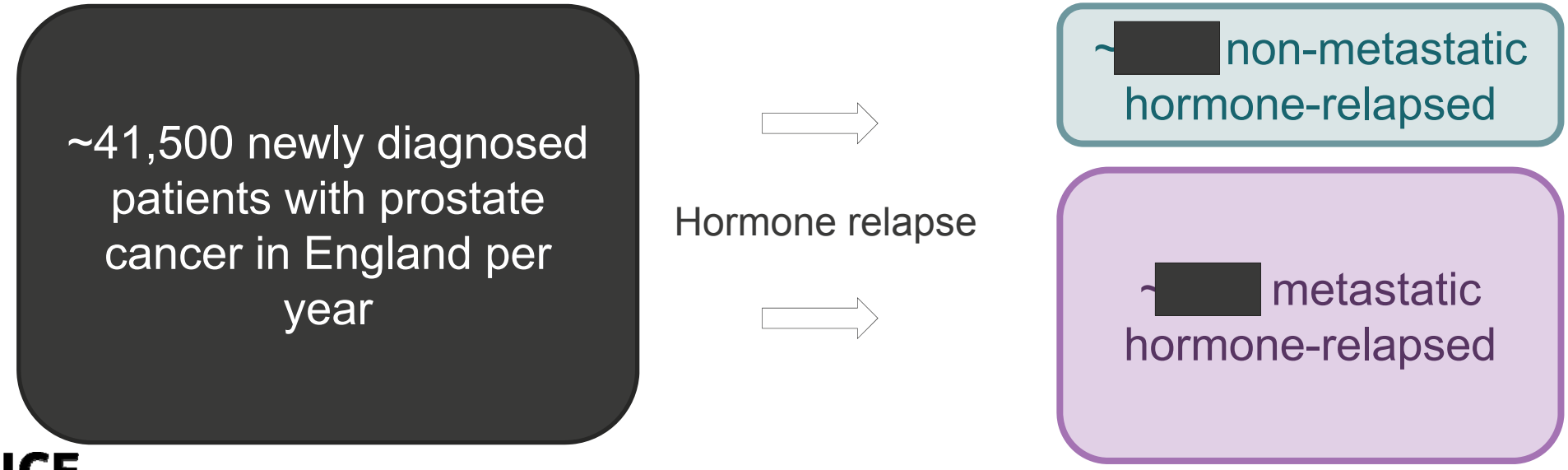
It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

Disease Background

- Prostate cancer is the 4th most common cancer in the UK
- Median age at diagnosis: ~66 years
- 85% of people diagnosed with prostate cancer survive for at least 5 years.
- Initial treatment involves androgen deprivation therapy (**ADT**)
- There are two independent events that change treatment options:
  - ADT becomes less effective – cancer changes from 'hormone sensitive' to 'hormone-relapsed' and/or
  - Development of prostate cancer at secondary sites 'metastatic'



Patient perspective

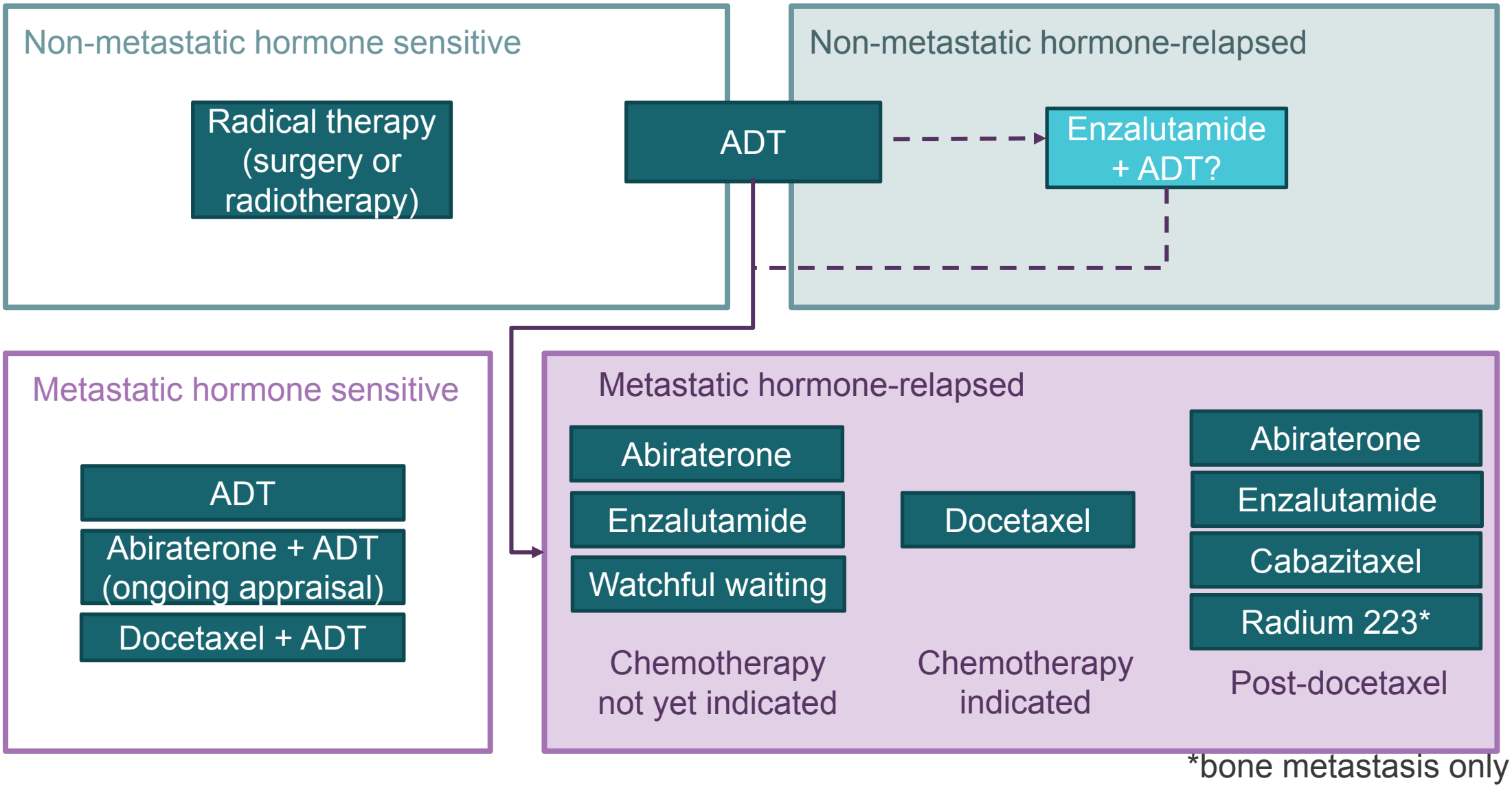
Symptoms

- Low symptom burden in early stages of prostate cancer, symptoms may include urinary difficulties, depending on location and extent of localised disease
- Disease burden likely increases upon progression to metastatic prostate cancer
- Symptoms depend on site of metastases but commonly include pain, fatigue, urinary and bowel problems
- Many people develop bone metastases, these can result in severe bone pain and potential for skeletal-related events such as spinal cord compression
- Anxiety over lack of treatments before progression

Current experience of treatment

- Androgen deprivation therapy (ADT) causes sexual side effects such as loss of libido and erectile dysfunction, less common symptoms include skeletal morbidity, anaemia, metabolic syndrome and cognitive side effects
- Chemotherapy is associated with substantial decrease in quality of life with serious side effects such as extreme fatigue, nausea and hair loss

Treatment Pathway



*bone metastasis only

NHS England: Enzalutamide cannot be taken before or after abiraterone and each can only be used once in the treatment pathway

Enzalutamide (XTANDI®, Astellas)

Mechanism	• Enzalutamide is an androgen receptor signalling inhibitor, which inhibits the main driver of prostate cancer
Marketing authorisation	• September 2018 - “treatment of adult men with non-metastatic castration-resistant* cancer”
Administration and dose	• 40mg taken orally four times daily (160mg)
List price	• £2734.67 per pack of 112 units (28 daily doses at £97.64 per day), a confidential discount to the list price has been agreed.
Other indications	• “Treatment of adult men with metastatic castration resistance prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated” • “Treatment of adult men with metastatic castration resistance prostate cancer whose disease has progressed on or after docetaxel therapy”

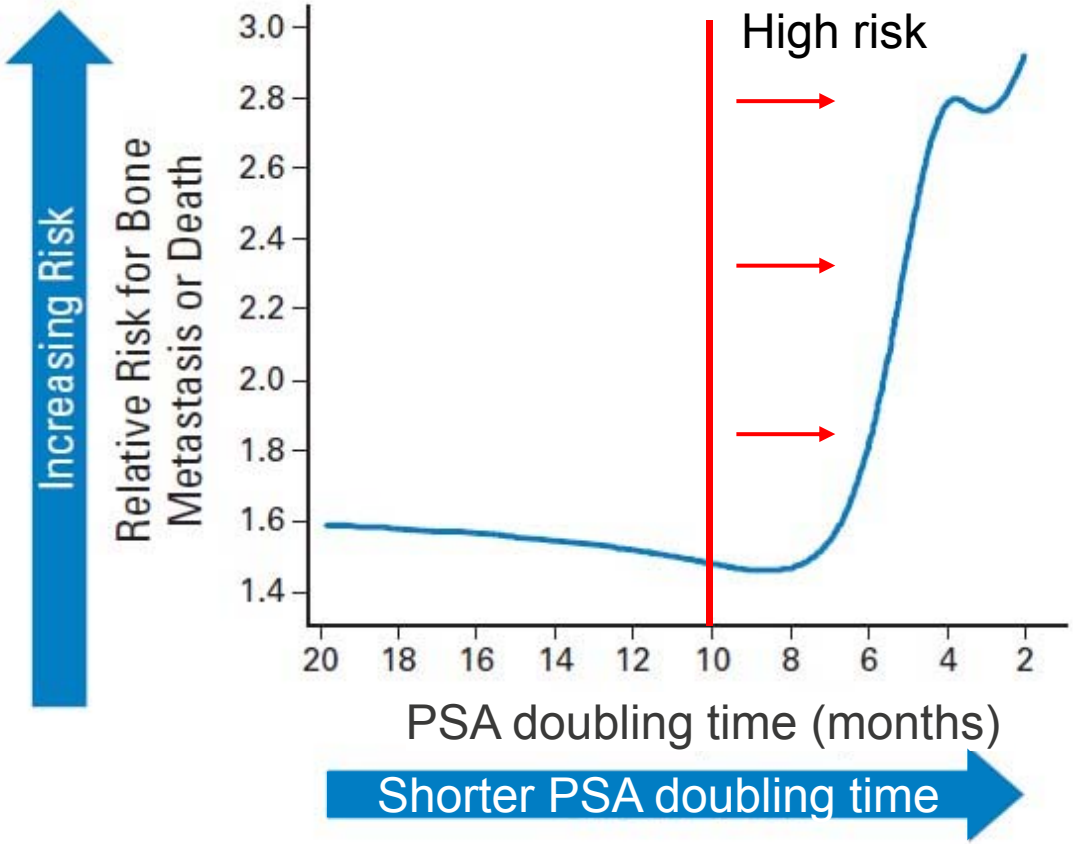
*Note: hormone-relapsed is updated terminology

Decision Problem

	Final scope issued by NICE	Decision problem addressed in the company submission
Population	Non-metastatic hormone-relapsed prostate cancer	High risk (see next slide) non-metastatic hormone-relapsed prostate cancer
Intervention	Enzalutamide with androgen deprivation therapy	As per final scope
Comparator	Androgen deprivation therapy	As per final scope
Outcomes	The outcome measures to be considered include: - Metastasis-free survival* - Time to prostate-specific antigen progression - Overall survival* - Adverse effects of treatment* - Health-related quality of life*	Additionally: - Time to next therapy for prostate cancer - Time to treatment discontinuation* - Time to chemotherapy - Time to pain progression - PSA response rates

NICE *Used in the economic model

Company definition of high risk



- Key predictors for risk of metastases include absolute prostate specific antigen (**PSA**) levels and PSA doubling time – the time it takes for PSA levels to double.
- For this appraisal, high risk is defined as an absolute PSA level ≥2 ng/mL and a PSADT of ≤10 months.
- An estimated 60% of total non-metastatic hormone resistant prostate cancer patients are defined as high risk.
- This sub-population definition was prescribed in line with the expected management of the disease and the pivotal trial population (PROSPER, see slide 11)

Professional group comments

Aims of treatment

- Prolong overall survival
- Delay onset of metastases
- Stabilisation of PSA for patients with fast PSADT
- Maintain quality of life
- Reduce skeletal related events

Current treatment options

- Clinicians continue to offer ADT even after hormone-relapse because stopping would increase testosterone and decrease time to metastasis
- Sometimes offered unproven therapies such as bicalutamide and dexamethasone

Clinical need

- Unmet need for treatment that improves metastasis free survival but there are very few patients in this group and the number is reducing because:
  - Clinicians start ADT later, meaning fewer patients develop hormone-relapsed disease before metastasis
  - Improved imaging diagnose metastatic disease earlier, meaning patients progress to the metastatic disease and different treatment options

Treatment benefit

- Enzalutamide delays onset of metastasis but does not increase overall survival
- Does not show that enzalutamide delays decrease in quality of life
- No clear benefit from moving enzalutamide from the metastatic to non-metastatic setting

Clinical evidence overview

PROSPER

Pivotal phase III randomised, blinded, placebo-controlled trial

Total target population n=1401

Enzalutamide vs. Placebo

Used in economic model
Used for safety data

STRIVE

Supportive evidence from phase II randomised placebo-controlled trial

Total target population n=139

Enzalutamide vs. Bicalutamide

Not used in economic model

Network meta-analysis

Evidence network includes only PROSPER and STRIVE
Assesses relative effectiveness for 2 outcomes in the 3 available treatment arms (enzalutamide, bicalutamide and placebo) in these studies

PROSPER study design

- Phase III multinational study, 254 study sites from 2013-present
- Patients with confirmed diagnosis of non-metastatic prostate cancer, progressive disease despite being on ADT, 3 consecutive rising PSA levels
- Prostate specific antigen doubling time of ≤10 months (high-risk)

Randomised

Enzalutamide + ADT (n=933)	Placebo + ADT (n=468)

Median follow-up 18.5 months

Follow up every 16 weeks until radiographic progression

Median follow-up 15.1 months

1º outcome: Metastasis-free survival (time to radiographic progression or death)

2º outcomes:

- Overall Survival* (two interim analyses)
- Time to PSA progression
- Quality of Life*
- Time to treatment discontinuation*
- Time to pain progression
- Time to chemotherapy
- PSA response rates
- Safety data*

NICE

*used in economic modelling

STRIVE study design – not used in model

- Phase II USA study, 62 sites from 2012-2015
- Total 396 patients with progressive hormone-relapsed prostate cancer, 2 consecutive rising PSA levels or presence of metastases
- 139 non-metastatic hormone relapsed patients included in this appraisal

Randomised

Enzalutamide + ADT (n=70)	Bicalutamide + ADT (n=69)
Median follow-up 16.7 months	Median follow-up 16.8 months

Follow up until initiation of next therapy or end of last dose

- **1º outcome: progression-free survival**
- Radiographic progression-free survival
- Time to PSA progression
- Quality of life
- Best overall soft-tissue response

Baseline characteristics

Baseline Characteristic	PROSPER		STRIVE	
	Enzalutamide	Placebo	Enzalutamide	Bicalutamide
Median age (range)	74 (50-95)	73 (53-92)	74 (50-92)	77 (58-91)
Baseline ECOG performance status	0: 80.1% 1: 19.8%	0: 81.6% 1: 18.2%	0: 80.0% 1: 20.0%	0: 76.8% 1: 23.2%
Median PSA doubling time (months, range)	3.8 (0.4-37.4)	3.6 (0.5-71.8)	NA	NA
Median serum PSA (ng/mL range)	11.1(0.8-1071)	10.2(0.2-467.5)	NA	NA
Gleason Score	Low (2-4): 2.3% Med (5-7): 52.6% High (8-10): 40.8%	Low (2-4): 2.6% Med (5-7): 49.1% High (8-10): 44.2%	NA	NA
Pain Score (Brief Pain Inventory- Short Form)	Low 0-1: 68.5% Med 2-3:11.4% High >3:15.2%	Low 0-1: 71.8% Med 2-3: 11.1% High >3: 10.9%	NA	NA

Statistical analyses

- From the statistical plan ‘The analysis of overall survival will be performed using a stratified log-rank test to compare the 2 treatment groups. This analysis will not be performed until at least 480 deaths are observed.’
- Then Protocol Amendment 3, 11 August 2017

Analysis	Number of death events	Significance level	
		Error rate: 0.03	Error rate: 0.05
First interim	135	0.001	0.001
Second interim	285	0.001	0.002
Third interim	440	0.009	0.018
Final	596	0.026	0.044

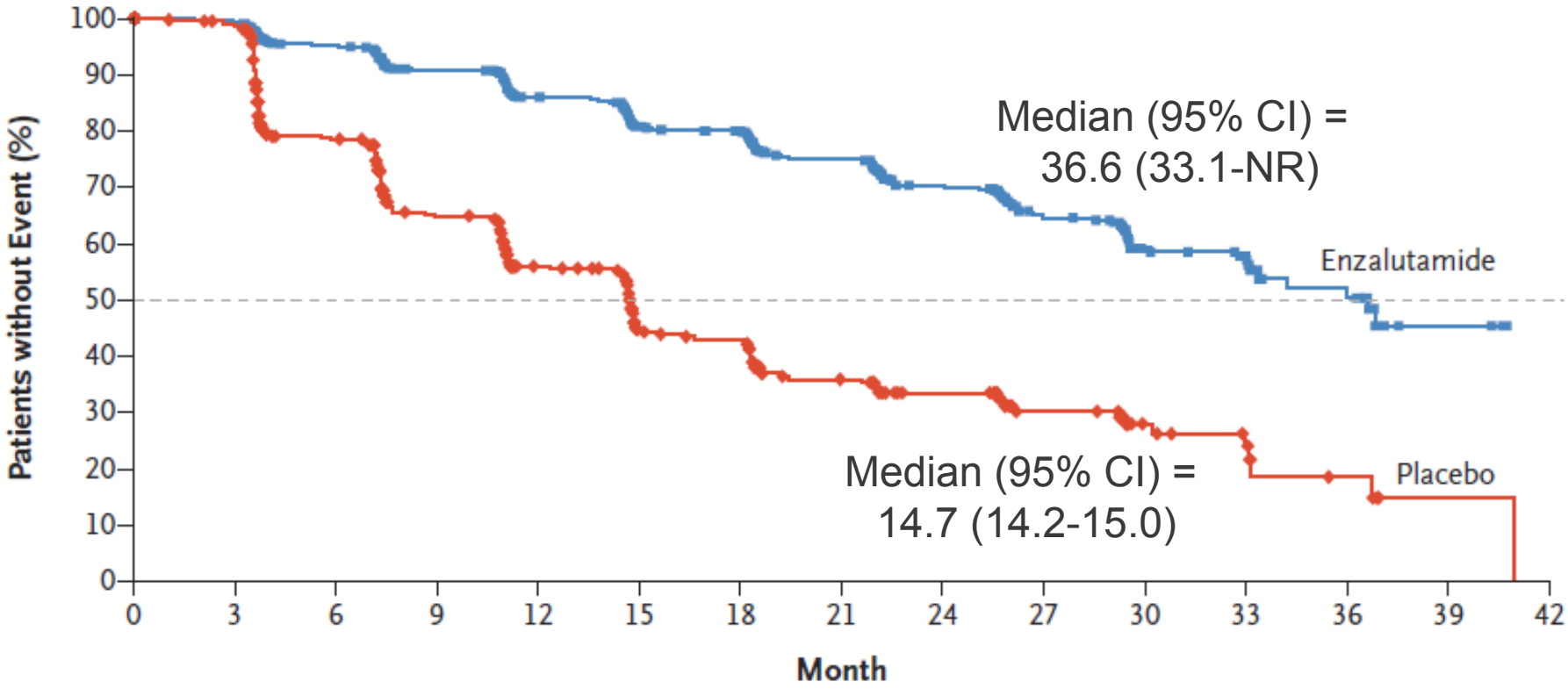
PROSPER - results summary

Outcome		Enzalutamide (n=933)	Placebo (n=468)
Metastasis-free survival*	Events, n	219 (23.5%)	228 (48.7%)
	Median, months (95% CI)	36.6 (33.1, NR)	14.7 (14.2, 15)
	Hazard ratio (95% CI)	0.29 (0.24, 0.35) [p<0.0001]	
Overall survival (Interim analysis 2)*	Events, n		
	Median, months (95% CI)		
	Hazard ratio (95% CI)		
Time to PSA progression	Events, n	208 (22.3%)	324 (69.2%)
	Median, months (95% CI)	37.2 (33.1, NR)	3.9 (3.8, 4.0)
	Hazard ratio (95% CI)	0.07 (0.05, 0.08) [p<0.0001]	
Time to first use of antineoplastic therapy	Events, n		
	Median, months (95% CI)		
	Hazard ratio (95% CI)		
Time to treatment discontinuation*	Events, n		
	Median, months (95% CI)		
	Hazard ratio (95% CI)		

NICE *used in economic modelling

PROSPER: Metastasis free survival

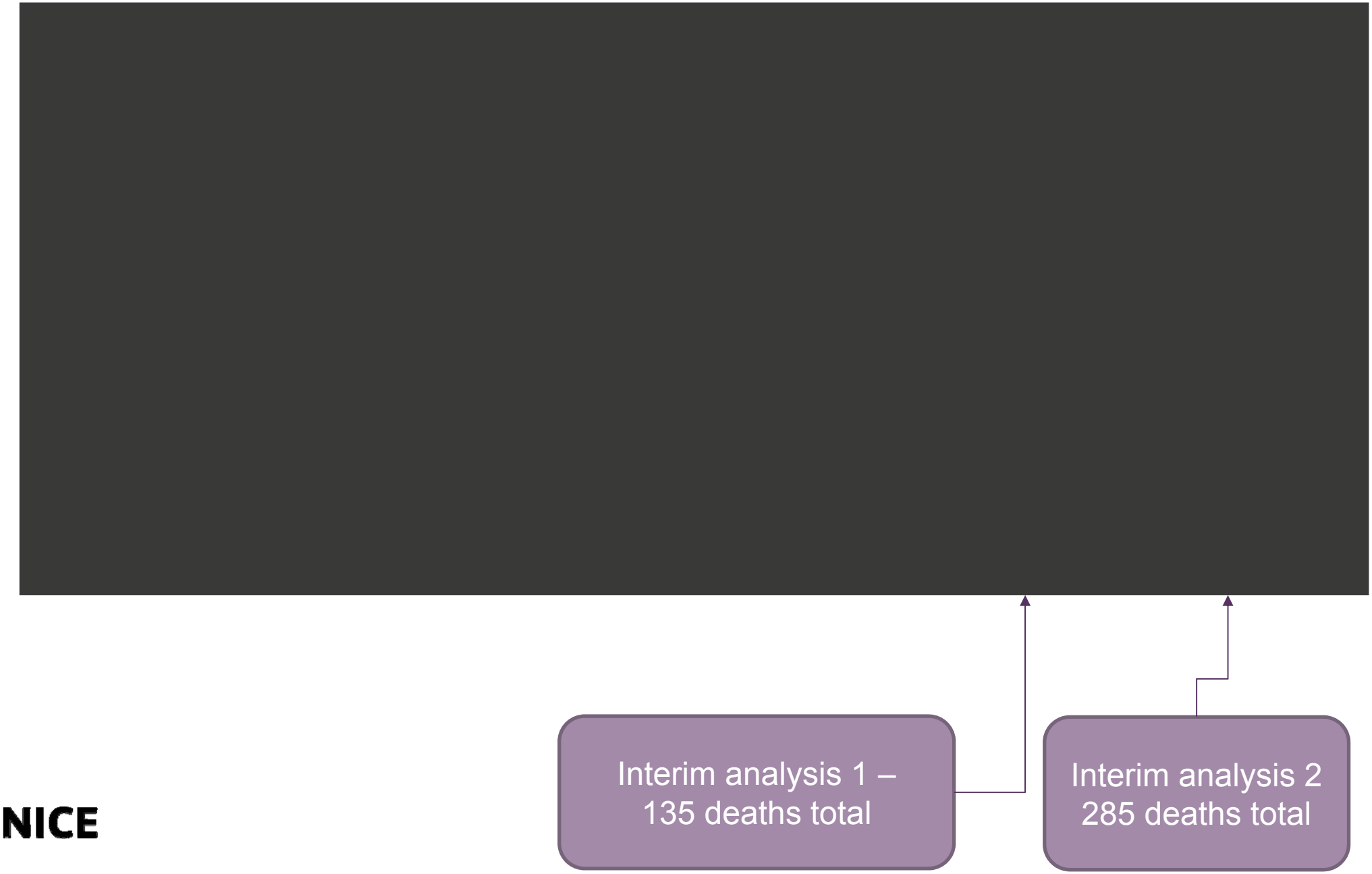
(progression-free survival, as measured by radiographic progression)



No. at Risk															
Enzalutamide	933	865	759	637	528	431	418	328	237	159	87	77	31	4	0
Placebo	468	420	296	212	157	105	98	64	49	31	16	11	5	1	0

NICE

PROSPER: Overall survival



NICE

PROSPER: Time to treatment discontinuation

Subsequent treatments – PROSPER

- ERG notes that treatments received after stopping treatment are not seen in UK practice (abiraterone and enzalutamide twice in same patient)
- Information reported for all subsequent treatments combined, not separated by line of therapy

All subsequent treatments:

Health-related quality of life

- PROPSER measured quality of life using multiple instruments: Brief Pain inventory (BPI), European Organisation for Research and Treatment of Cancer prostate cancer module (EORTC), Functional Assessment of Cancer Therapy – Prostate (FACT-P) and EQ-5D
- No significant difference between enzalutamide and placebo group, except hormonal treatment-related symptoms (EORTC) and social well-being (FACT-P) at 22 months

Instrument	Least squares mean change from baseline at 22 months (SE)		Least squares mean difference [95% CI]
	Enzalutamide	Placebo	Enzalutamide vs placebo
BPI-SF Pain severity	0.49 (0.10)	0.55 (0.16)	-0.06 [-0.40, 0.29]
BPI-SF Pain interference	0.65 (0.10)	0.85 (0.16)	-0.20 [-0.53, 0.13]
EORTC QLQ-PR25: Hormonal treatment-related symptoms	1.55 (0.66)	-1.83 (1.04)	3.38 [1.24, 5.51]
FACT-P Social well-being	0.30 (0.28)	-0.64 (0.44)	0.94 [0.02, 1.85]
FACT-P total	-7.17 (0.92)	-9.20 (1.45)	2.04 [-0.97, 5.04]
EQ-VAS*	-4.57 (0.91)	-5.29 (1.47)	0.72 [-2.30, 3.75]

NICE

*used in economic modelling

Positive values favour enzalutamide

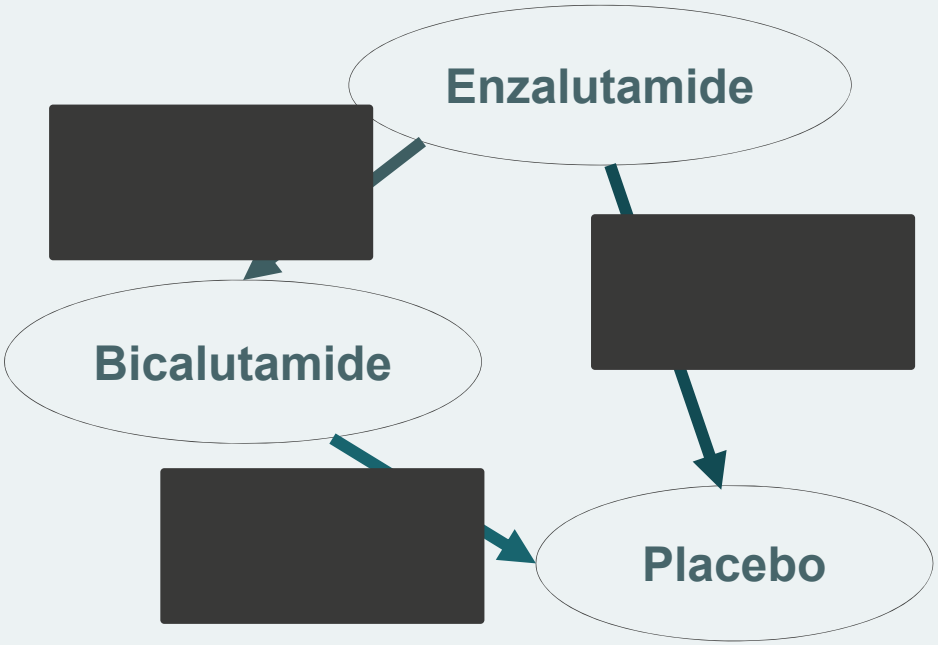
STRIVE: results summary

Outcome		Enzalutamide (n=70)	Bicalutamide (n=69)
Progression-free survival	Events, n	19 (27.1%)	49 (71.0%)
	Median, months (95% CI)	NR (19.4, NR)	8.6 (8.1, 11.1)
	Hazard ratio (95% CI)	0.243 (0.142, 0.416)	
Time to PSA progression	Events, n	13 (18.6%)	45 (65.2%)
	Median, months (95% CI)	NR (NR, NR)	11.1 (8.4, 13.9)
	Hazard ratio (95% CI)	0.182 (0.098, 0.341)	

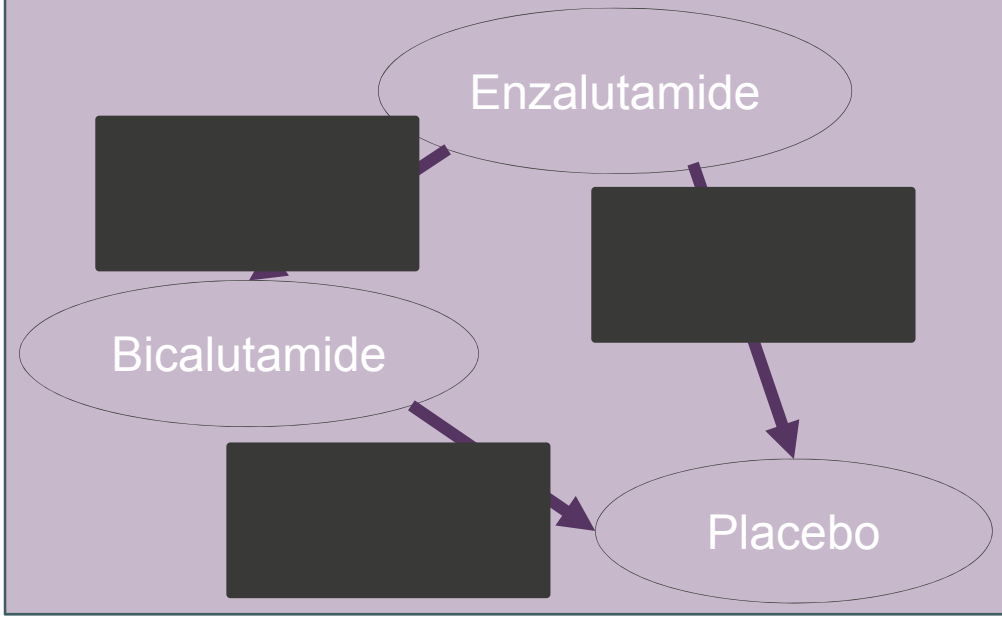
Network meta-analysis

- The company performed a fixed effect network meta-analysis using the PROSPER and STRIVE studies
- Disease progression definition differed between STRIVE (radiographic progression free survival) and PROSPER (metastasis-free survival) but were considered equivalent for the network outcomes

Metastasis-free survival (PROSPER)/ radiographic progression free survival (STRIVE)



Time to PSA progression



- ERG: NMA performed appropriately, however bicalutamide is not a comparator in scope

Adverse events - overview

Outcome	Enzalutamide (n=930)	Placebo (n=465)
Patients with any treatment emergent adverse event	808 (86.9%)	360 (77.4%)
Any TEAE Grade 3 or higher	292 (31.4%)	109 (23.4%)
Any TEAE leading to death	32 (3.4%)	3 (0.6%)
Any serious TEAE	226 (24.3%)	85 (18.3%)
Any TEAE leading to study drug discontinuation	96 (10.3%)	35 (7.5%)
Any TEAE leading to dose reduction of study drug		
Any TEAE leading to dose interruption of study drug		
Patients with any TEAE related to study drug		
Any TEAE Grade 3 or higher related to study drug		
Any serious TEAE related to study drug		

Adverse events

Adverse event of special interest	Enzalutamide (n=930)	Placebo (n=465)
Convulsion	3 (0.3%)	0 (0.0%)
Hypertension	114 (12.3%)	25 (5.4%)
Neutropenia	9 (1.0%)	1 (0.2%)
Memory impairment	48 (5.2%)	9 (1.9%)
Hepatic impairment	11 (1.2%)	9 (1.9%)
Major adverse cardiovascular event (MACE)	48 (5.2%)	13 (2.8%)
Posterior reversible encephalopathy syndrome (PRES)	0 (0.0%)	0 (0.0%)

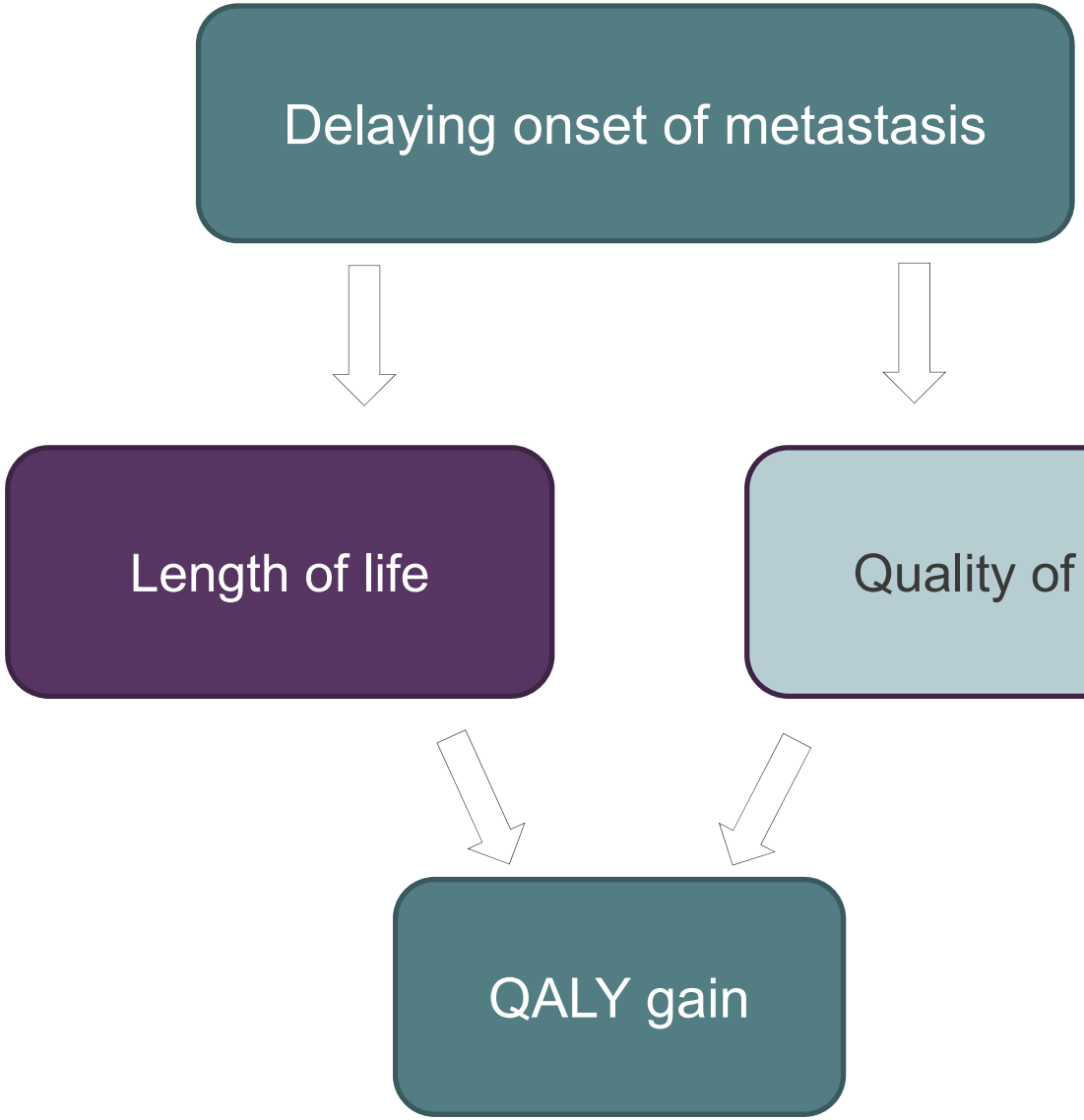
- ERG: company identified known risks of enzalutamide from previous appraisals
- Adverse event incidence is consistent with previous studies of metastatic hormone-resistant prostate cancer appraisals.
- Higher incidence of treatment-emergent adverse events in enzalutamide arm compared to placebo was primarily driven by increased rates of hypertension, memory impairment and major adverse cardiovascular events.

Key issues – clinical effectiveness

- When would patients choose to have enzalutamide – before or after metastasis?
- Is the narrowing of marketing authorisation to ‘high risk’ appropriate?
- Are PSA levels and PSA doubling time measured in routine clinical practice? Is the company definition of high risk used in clinical practice?
- Are the results from PROSPER generalisable to the NHS?
- Which interim analysis should be used in the modelling?
- What treatments are appropriate as subsequent therapies?
- Are subsequent therapies likely to have confounded the results for overall survival? How should the company address this?

Cost-effectiveness

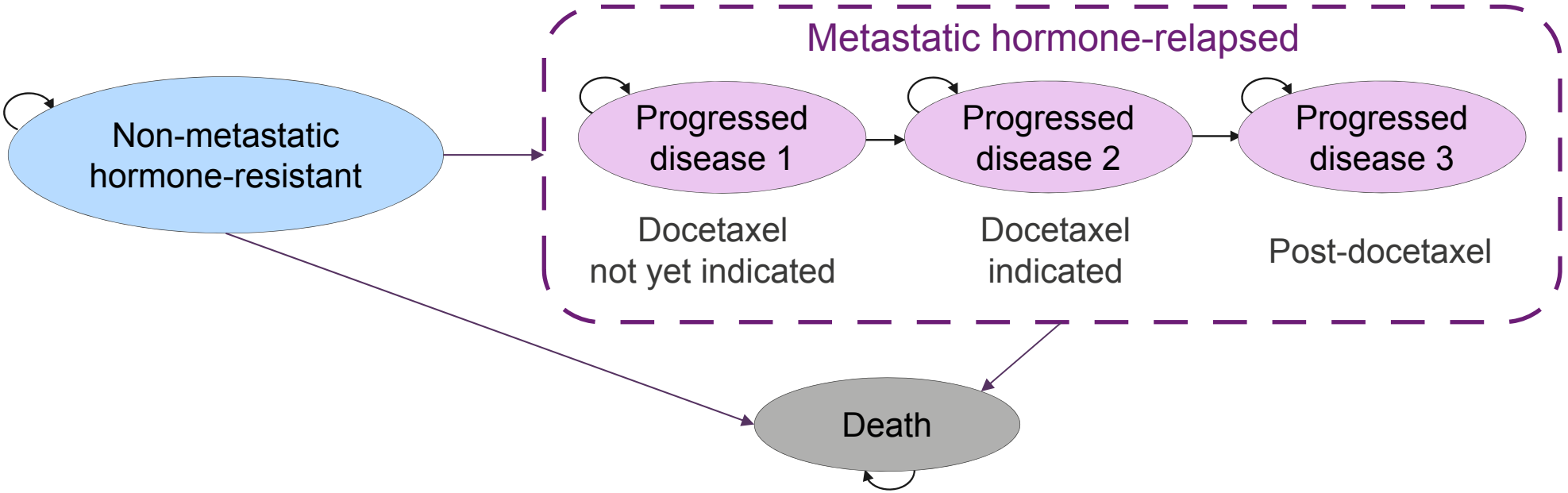
Conceptual model



Company assumes that delaying the onset of metastasis will increase both length of life (longer overall survival) and quality of life (higher utility in non-metastatic state).

Increase in QALY for enzalutamide is associated with both length and quality of life.

Company model structure

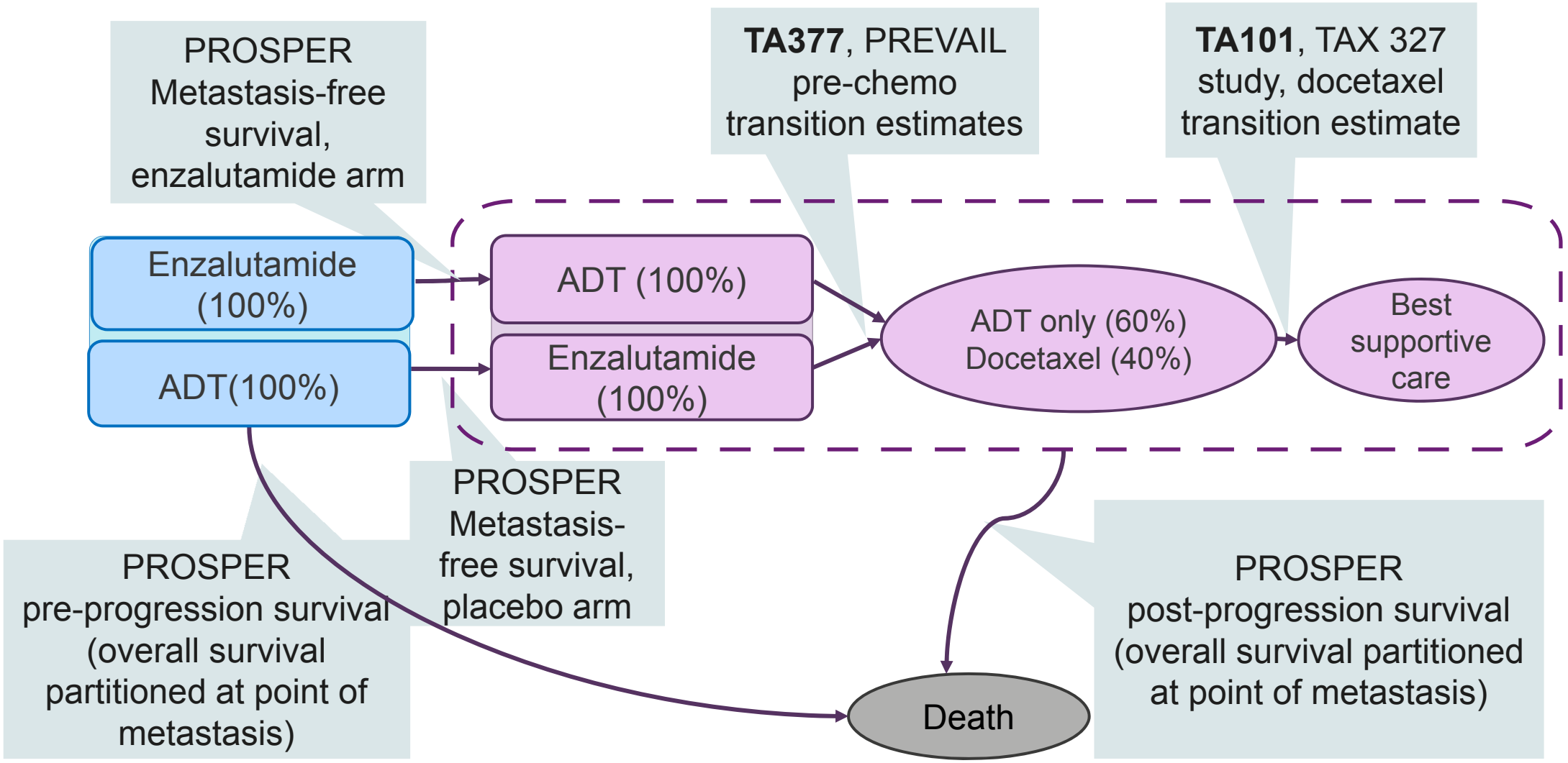


- Semi-Markov combined with partitioned survival model
- Survival is partitioned between pre-progression in the non-metastatic state and post-progression in metastatic state, using the moment of metastasis as the point of progression
- Markov model is used for the metastatic hormone-relapsed state and uses transition probabilities based on treatment durations in other trials for progressed disease states (1-3)

- Monthly cycle length
- Life-time horizon: 20 years starting at age 73.5
- Discount rate of 3.5%
- NHS perspective
- Adverse events modelled

- ERG: the model captures the progressive nature of the disease
- However, post-progression survival does not vary across progressed disease states – underestimates survival in progressed disease 1, favours enzalutamide

Summary of base-case treatment sequence and transitions

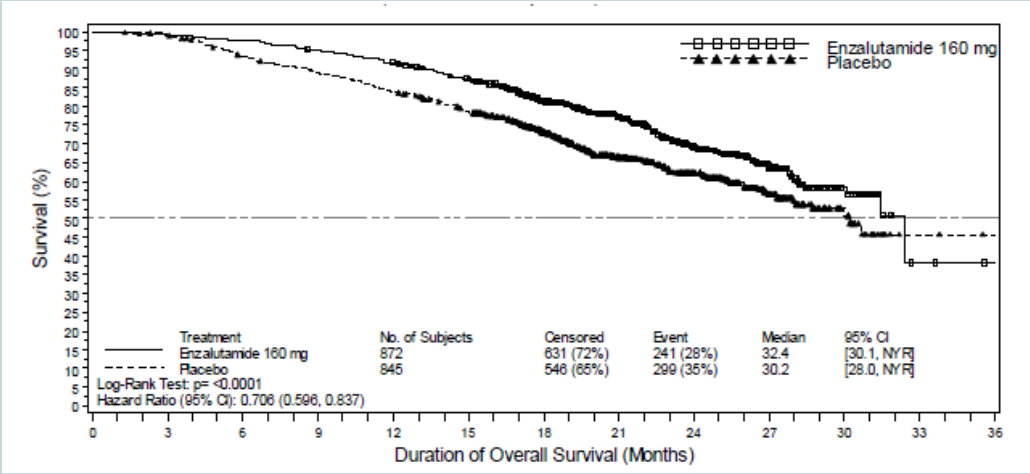


ERG has concerns about proposed sequence (slide 45) and PD1-2 transition estimate (slide 31)

Other trials used to populate transition estimates and utilities in model

PREVAIL

- TA377 appraised this study for enzalutamide in the pre-chemotherapy metastatic setting
- Used to:
  - Estimate time to transition between progressed disease states 1 and 2
  - Validate enzalutamide safety data
  - Source of utility value for progressed disease state 2
  - Overall survival curve (below) used to validate post-progression survival in PROSPER



TAX-327

- TA101 appraised this study for docetaxel in the metastatic setting
- Used to estimate time to transition between progressed disease states 2 and 3 for both docetaxel and ADT trial arms

AFFIRM

- TA316 appraised this study for enzalutamide in the post-docetaxel setting
- Used to validate safety data and as the source of utility value for progressed disease state 3

ERG comment – progressed disease state 1 → state 2 transition

- Model assumes that people stay on ADT following stopping enzalutamide
- Company assumed a constant probability of transition between progressed disease states
- Company based transition estimates between state 1 and state 2 on data from enzalutamide and placebo arms in PREVAIL
- ERG concerned about the generalising PREVAIL to the PROSPER population because PROSPER population has high risk of progression to metastasis at baseline
- ERG requested scenario analysis including median time to starting another antineoplastic therapy observed in PROSPER for the enzalutamide arm ★1
- Median time from radiographic progression to first antineoplastic treatment: **3.8 months**
- Shorter time in state 1 results in faster time to starting docetaxel in state 2

NICE ★ = ERG scenario analysis

Metastasis-free survival extrapolation

- Company performed a spline-based extrapolation (2 knots, hazard scale)
- Spline-based extrapolation involves using standard extrapolation piecewise curves around fixed points (knots)
- ERG considers the model to provide a good visual fit for relatively mature data and that it is appropriate for extrapolation

Pre-progression survival extrapolation

- Company chose separate curves to fit pre-progression survival [redacted]
- Scenario that uses age specific general mortality minimally impacts the ICER because most people on placebo develop metastatic disease before the curves diverge

Post-progression survival extrapolation

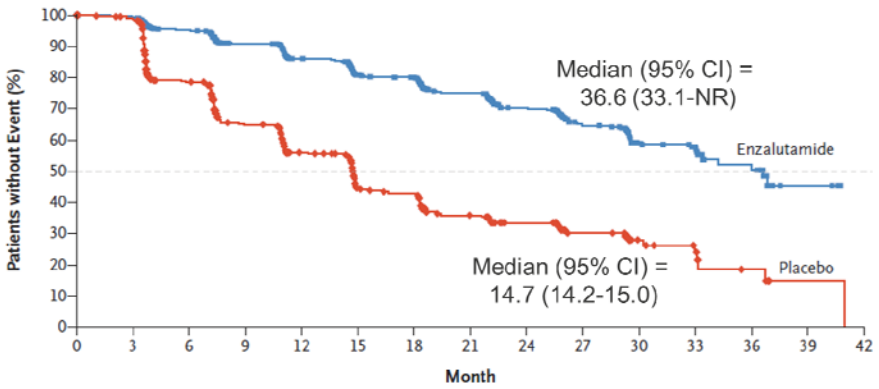
- ERG recognises a significant benefit in favour of placebo because this is when the placebo arm receives active treatment and enzalutamide arm cease treatment
- Fitted curves may overestimate observed difference in overall survival compared to PREVAIL

Model output – overall survival

- ERG comment: Approach that combines pre/post-progression survival creates divergence in overall survival that favours enzalutamide which does not match observed overall survival data at 2nd interim analysis
- ERG attributes this problem to long-term projection from 1st interim analysis
- ERG considers the use of 2nd interim analysis data to be most relevant (see slide 37)
- However, the post-progression survival has been externally validated against the PREVAIL trial which included patients equivalent to the PD1 state.

Model output- increasing hazard over time

Metastasis-free survival vs time to treatment discontinuation as point of progression in interim analysis 2



[redacted]

- Metastasis-free survival is measured at interim analysis 1 only
- Time to treatment discontinuation is measured at both interim analyses 1 and 2
- Company provided 2 scenario analyses using updated survival data from interim analysis 2:
  - Using point of metastasis as point of progression from interim analysis 1
  - Using point of treatment discontinuation as a proxy for point of metastasis as point of progression from interim analysis 2
- ERG are uncertain to what extent patients may have remained on treatment after metastases occurrence until a decision on next subsequent treatment and therefore prefer using metastasis-free survival as the point of progression
- However, ERG presents both of these options within scenario analyses 2 3

Utility values used in the economic model

- Company derived utility values from EQ-5D data in PROSPER for the non-metastatic state and the 1st progressed state of the model
- Other progressed state utility values came from PREVAIL and AFFIRM trial EQ-5D data
- Mapped to utility values using UK valuation sets
- End-of-life utility of 0.590 applied for 3 month period prior to death (from PREVAIL trial)

[redacted]

- ERG is concerned that utility value for 1st progressed state represents mean value at first assessment following progression which was infrequent (every 16 weeks) and that it was not adjusted for baseline utility before progression
- Non-metastatic state measures at baseline before any treatment is initiated
- ERG explores a scenario where baseline utility from PREVAIL (**0.844**) is used for 1st progressed state, which is equivalent position in the pathway used in previous appraisal (TA377)

Cost and resource use

Cost/resource	Source	ERG approved
Health state specific resource use	Largely based on values in TA377 appraisal and validated by UK clinical expert	X
Drug unit costs	Concomitant medication was measured in PROSPER and costs sourced from BNF and eMIT	✓
Administration and monitoring costs	NHS reference costs and PSSRU	✓
Adverse reaction costs	Resource use from PROSPER, cost from NHS reference costs and TA259 ERG report, includes skeletal related events	X
End-of-life costs	One-off cost of £3,958 for all deaths to capture increased cost of end-of-life treatment, adopted from TA387 submission	✓

ERG comments – cost and resource use

Health state specific costs

- Company have assumed monitoring and visits are more frequent in the placebo arm than the enzalutamide arm without justification
- Previous appraisal (TA377) discussed this issue and concluded that frequency of long-term monitoring would be similar due to monitoring for adverse events
- ERG clinical expert agrees with previous appraisal decision
- ERG explored scenario analysis where the monitoring and visit frequency are equalised between treatment arms

Adverse event costs

- Most adverse event costs are appropriate and consistent with TA377
- Cost applied to major adverse cardiovascular events (MACE) was lower than expected at £759
- Company used costs for non-elective short stay rather than long stay
- A majority (63%)of events are coded as long stay, assumption is inappropriate
- ERG explored scenario based on total activity which increased cost of MACE to £3,279

Base case cost-effectiveness results

		Total		Incremental		
	Treatment	Costs	QALYs	Costs	QALYs	CE ratio
Deterministic	Enzalutamide	XXXXX	XXXXX	XXXXX	XXXX X	£28,853
	ADT	XXXXX	XXXXX			
Probabilistic	Enzalutamide	XXXXX	XXXXX	XXXXX	XXXX X	£30,175
	ADT	XXXXX	XXXXX			

Deterministic sensitivity analysis

Probabilistic sensitivity analysis

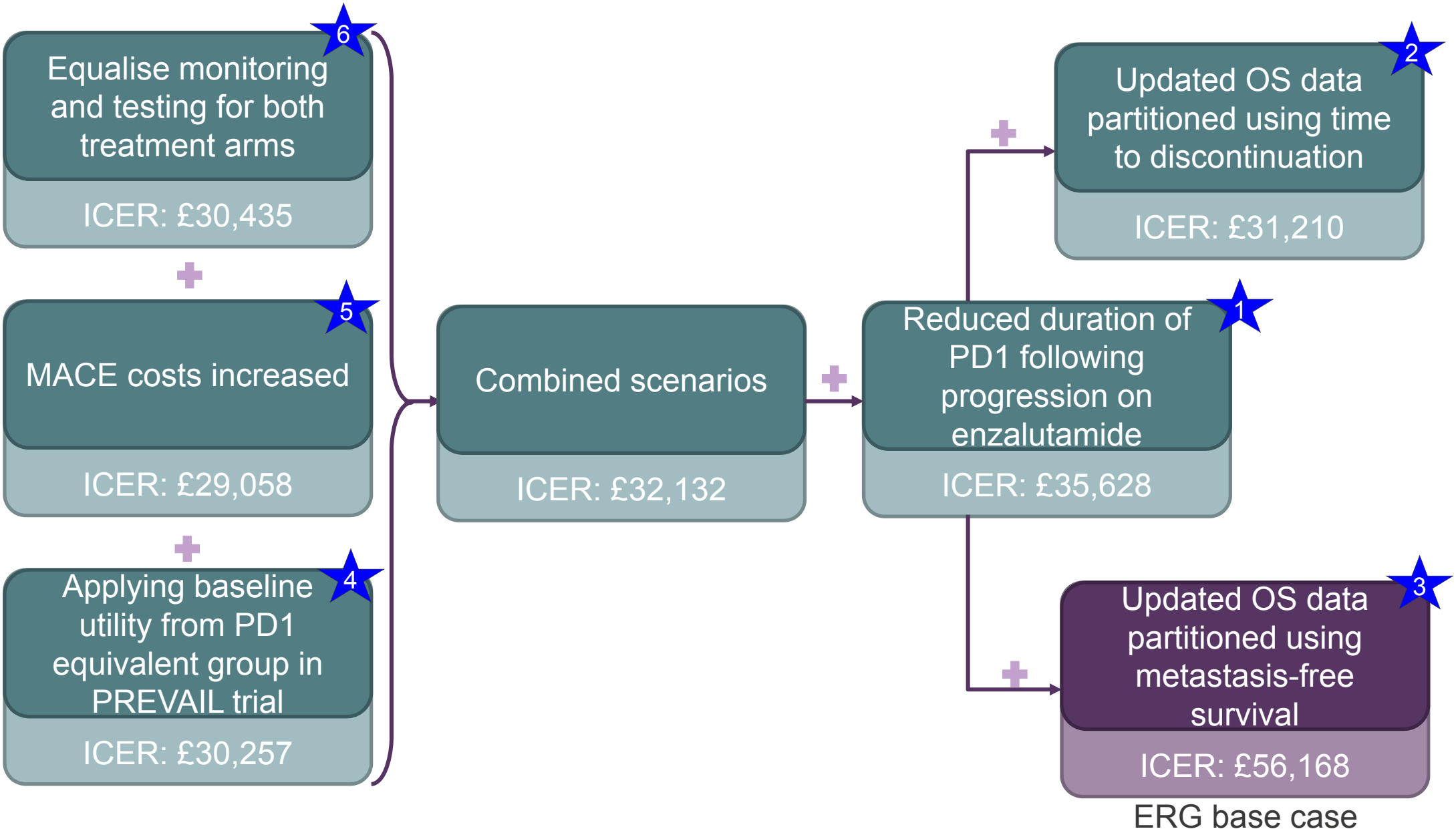
Company scenario analyses

Model scenario	Cost ENZA	Cost ADT	QALY ENZA	QALY ADT	ICER
Company base-case	XXXXX	XXXXX	XXXX	XXXX	£28,853
Updated overall survival data from 2nd IA, survival partitioned by 2nd IA time to treatment discontinuation	XXXXX	XXXXX	XXXX	XXXX	£24,874
Updated overall survival data from 2nd IA, survival partitioned by 1st IA metastasis-free survival	XXXXX	XXXXX	XXXX	XXXX	£38,918
Survival partitioned by IA1 time to treatment discontinuation	XXXXX	XXXXX	XXXX	XXXX	£30,456
General population mortality for pre-progression	XXXXX	XXXXX	XXXX	XXXX	£28,859
PREVAIL post progression survival reference curve	XXXXX	XXXXX	XXXX	XXXX	£26,237
Chemotherapy received in PD1 in enzalutamide arm	XXXXX	XXXXX	XXXX	XXXX	£30,937
Abiraterone received in PD1 in placebo arm	XXXXX	XXXXX	XXXX	XXXX	£24,303
Enzalutamide arm in PD1 for 3.7 months (observed)	XXXXX	XXXXX	XXXX	XXXX	£31,671
Treatment costs of observed treatments used in PD1	XXXXX	XXXXX	XXXX	XXXX	£33,863
No skeletal related events	XXXXX	XXXXX	XXXX	XXXX	£28,878

Additional ERG scenario analysis

Description	Inc. Cost	Inc. QALY	Deterministic ICER	% change in the ICER
Company base case	XXXX	XXXX	£28,853	0%
ERG exploratory treatment pathway	XXXX	XXXX	£46,198	+60.12%
Equalise monitoring and testing frequency for both arms.	XXXX	XXXX	£30,435	+5.49%
Apply health care visit and testing frequencies as presented in Table 49 of the company submission	XXXX	XXXX	£28,207	-2.24%
MACE cost = overall reference cost (£3,279)	XXXX	XXXX	£29,058	+0.71%
Baseline utility value for PD1 equivalent patients from NICE TA377 (0.844)	XXXX	XXXX	£30,257	+4.87%

ERG base case – additive scenarios



ERG base case

Summary of distributions in subsequent treatments

Treatment options	Non-metastatic	PD1	PD2	PD3
PROPSER enzalutamide arm	100	*	Not reported	Not reported
PROSPER ADT/placebo arm	100	*	Not reported	Not reported
Company model enzalutamide arm	100	100	40 / 60	100
Company model ADT/placebo arm	100	100	40 / 60	100
ERG scenario enzalutamide arm	100	60 / 40	40 / 60	10 / 90
ERG scenario ADT/placebo arm	100	100	50 / 50	60 / 40

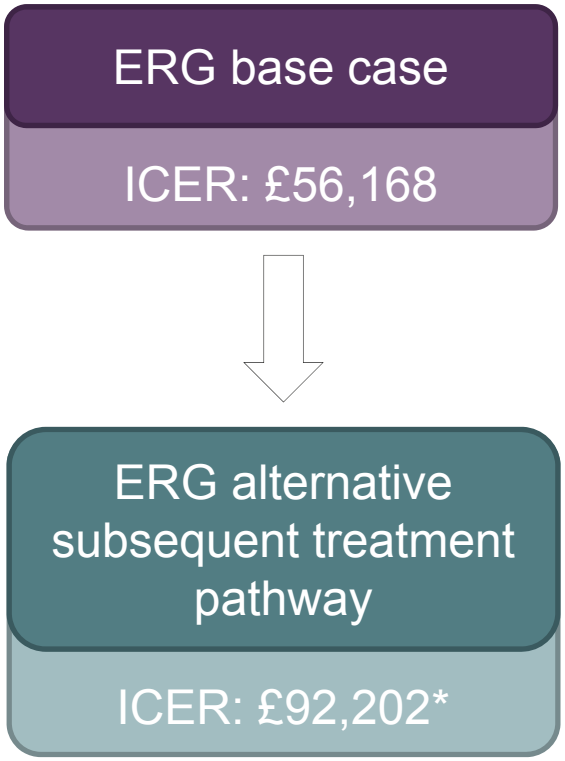
% Enzalutamide % ADT % Docetaxel % Abiraterone % BSC % Radium-223 % Other

NICE *first subsequent treatment received (not necessarily in 1st progressed state)

Alternative treatment pathway scenario

- Subsequent treatments observed in trials do not match those modelled by the company
- Treatment distributions in company model justified by previous appraisal (TA377) and supported by clinical expert opinion
- Radium-223 and cabazitaxel treatments are disregarded by company using evidence from market research questionnaire

- ERG concerned that the costs of radium-223 and cabazitaxel as downstream treatments are disregarded
- ERG suggests that moving enzalutamide up the treatment pathway would lead to a shift in subsequent treatments up the treatment pathway
- Scenario using above treatment sequence **for costs only** was included to explore this uncertainty
- Justification for proportions in each state (awaiting response from FAC)
- PAS discounts are available for radium-223 and cabazitaxel and these are included in a confidential appendix



*no PAS included

Innovation

Company comments:

- Enzalutamide is the first treatment to obtain a marketing authorisation in the non-metastatic hormone-resistant population
- Delaying the development of metastases would give considerable benefit by delaying skeletal related events and visceral metastases which increase symptom burden

Equality

- The company and ERG are not aware of any issues relating to equality for this appraisal

Key issues – cost effectiveness

- How does the company base case model structure relate to the decision problem?
- Which point of progression should be used to partition survival?
  - Time to treatment discontinuation
  - Metastasis-free survival
- What is the expected utility of people in the PD1 progression state?
- What is the most likely treatment pathway following treatment with enzalutamide?

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Enzalutamide for treating non-metastatic hormone-relapsed prostate cancer [ID1359]

Document B

Company evidence submission

September 2018

File name	Version	Contains confidential information	Date
Astellas_Document B_Enzalutamide for treating non-metastatic hormone-relapsed prostate cancer [ID1359]	**1.0**	**Yes**	**10 September 2018**

Contents

List of tables

List of figures

List of abbreviations and definitions

Abbreviation	Full name or description
ABI	Abiraterone
ADT	Androgen deprivation therapy
AE	Adverse event
AiC	Akaike information criterion
ALT	Alanine aminotransferase
APA	Apalutamide
AR	Androgen receptor
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
ATR	Atrasentan
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
BC	Base-case
BiC	Bayesian information criterion
BIC	Bicalutamide
BICR	Blinded independent central review
BID	Twice daily
BNF	British national formulary
BPI-SF	Brief Pain Inventory-short form
BSC	Best supportive care
BTA	Bone-targeting agent
CE	Cost-effectiveness
CI	Confidence interval
CR	Complete response
CRF	Case report form
CrI	Credible interval
CRPC	Castration-resistant prostate cancer
CSR	Clinical study report
CT	Computer tomography
CTCAE	Common Terminology Criteria for Adverse Events
Cum	Cumulative
DAR	Darolutamide
DB	Double blinded
dl	decilitre
DOC	Docetaxel
DSU	Decision support unit

Abbreviation	Full name or description
DT	Doubling time
DUT	Dutasteride
EAU	European Association of Urology
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group performance status
EMA	European Medicines Agency
ENZA	Enzalutamide
EORTC QLQ PR25	European Organisation for Research and Treatment of Cancer Quality of life Questionnaire
EQ VAS	European Quality of Life-Visual Analogue Scale
EQ-5D-3L	European Quality of Life-5 Dimensions-3 Levels health questionnaire
EQ-5D-5L	European Quality of Life-5 Dimensions-5 Levels health questionnaire
ER	Emergency room
ERG	Evidence review group
ESMO	European Society for Medical Oncology
EST	Estramustine
EU5	France, Germany, Italy, Spain and the United Kingdom
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FDA	Food and Drug Administration
FE	Fixed effect
FLU	Flutamide
GCSF	Granulocyte colony-stimulating factor
GnRH	Gonadotropin-releasing hormone
HE	Health economic
HEOR	Health economics and outcomes research
HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health-related quality of life
HRPC	Hormone-relapsed prostate cancer Definition of HRPC used in this submission is aligned with that of European Association of Urology guidelines, i.e., castrate serum testosterone ≤50 ng/dL or 1.7 nmol/L plus either: a) Biochemical progression: Three consecutive rises in PSA 1 week apart resulting in two 50% increases over the nadir, and a PSA >2 ng/mL or,

Abbreviation	Full name or description
	b) b) Radiological progression: The appearance of new lesions: either two or more new bone lesions on bone scan or a soft tissue lesion using RECIST.
HRU	Health resource utilisation
HSPC	Hormone-sensitive prostate cancer
HTA	Health technology assessment
IA1	First interim OS analysis
IA2	Second interim OS analysis
ICECaP	Intermediate Clinical Endpoints in Cancer of the Prostate
IL2	Interleukin 2
ITC	Indirect treatment comparison
ITT	Intent-to-treat
IV	Intravenous
IXRS	Interactive voice / web recognition system
LDH	Lactate dehydrogenase
log HR	Logarithm of the hazard ratio
KM	Kaplan Meier
LCI	Lower confidence interval
LS	Least square
LYG	Life years gained
m	Metastatic
M0	No distant metastasis
M1	Presence of distant metastasis
MACE	Major adverse cardiovascular event
mCRPC	Metastatic castration-resistant prostate cancer
mHRPC	Metastatic hormone-relapsed prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MFS	Metastasis-free survival
mg	Milligram
MIT	Mitoxantrone
mmHg	Millimetres of mercury
MMRM	Mixed model repeated measures
MRI	Magnetic resonance imaging
n	Number of patients
NA	Not available/applicable
NCI	National Cancer Institute
NEJM	New England Journal of Medicine
NEL	Non-elective long stay

Abbreviation	Full name or description
NES	Non-elective short stay
NIL	Nilutamide
NHS	National Health Service
ng	Nanogram
NICE	National Institute for Health and Care Excellence
nm	Non-metastatic
NMA	Network meta-analysis
nmCRPC	Non-metastatic castration-resistant prostate cancer
nmHRPC	Non-metastatic hormone-relapsed prostate cancer
NR	Not reached
OD	Once daily
OL	Open label
OS	Overall survival
OWSA	One way sensitivity analysis
PAS	Patient access scheme
PCa	Prostate cancer
PCWG	Prostate Cancer Clinical Trials Working Group
PD	Progressive disease
PFS	Progression free survival
PICOS	Population, intervention, comparator, outcomes, study design
PLA	Placebo
PostTD	Post-treatment discontinuation survival
PPS	Post-progression survival
PR	Partial response
PrePS	Pre-progression survival
PreTD	Pre-treatment discontinuation survival
PRES	Posterior reversible encephalopathy syndrome
PRO	Patient-reported outcomes
Prob	Probability
PSA	Prostate-specific antigen
PSADT	PSA doubling time
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
pts	Patients
QALYs	Quality-adjusted life years
QLQ-PR25	Prostate cancer module
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours

Abbreviation	Full name or description
RMP	Risk management plan
RoW	Rest of world
rPFS	Radiographic progression free survival
SD	Standard deviation
SA	Sensitivity analysis
SAP	Statistical analysis plan
SC	Subcutaneous
SE	Standard error
SLR	Systematic literature review
SMQ	Standardised MedDRA query
SoC	Standard of care
SmPC	Summary of Product Characteristics
SRE	Skeletal-related event
StDev	Standard deviation
TA	Technology appraisal
TDP	Time to disease progression
TEAE	Treatment-emergent adverse event
TID	Three times daily
TSD2	Technical support decision unit document 2
TTD	Time to treatment discontinuation
TTFAnti	Time to first use of new antineoplastic therapy
TTPSA	Time to prostate-specific antigen progression
Tx	Treatment
UCI	Upper confidence interval
UK	United Kingdom
ULN	Upper limit of normal
USA	United States of America
VAS	Visual analogue scale
WTP	Willingness to pay
ZIB	Zibotentan

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

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for the intended indication which is "*Xtandi is indicated in the treatment of adult men with non-metastatic CRPC*"[1]. However, in this submission, these patients will be described as adults with high risk non-metastatic (nm) hormone-relapsed prostate cancer (HRPC) in line with the description preferred by NICE.

In this submission HRPC should be considered synonymous to "castration-resistant prostate cancer (CRPC)", i.e., prostate cancer with rising prostate specific antigen (PSA) despite castration levels of testosterone (≤50 ng/dL; 1.7 nmol/L). HRPC does not relate to patients with increasing PSA levels but with testosterone levels >50 ng/dL.

Despite HRPC and CRPC being synonymous in this submission, when we refer to the indication in the European Summary of Product Characteristics (SmPC) or other labels, we refer to the exact wording which is CRPC.

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with non-metastatic hormone-relapsed prostate cancer	Adults with high risk non-metastatic hormone-relapsed prostate cancer (nmHRPC). High risk is defined as PSA doubling time (DT) being ≤10 months and a PSA ≥2 ng/mL	Astellas has applied for marketing authorization for enzalutamide (Xtandi™) in the treatment of adult men with high-risk on-metastatic castration-resistant prostate cancer (CRPC)[1]. This is in line with the expected management of nmHRPC patients in the UK clinical practice and the study population in the pivotal phase III trial PROSPER[2].
Intervention	Enzalutamide with androgen deprivation therapy (ADT)	As per final scope	NA
Comparator(s)	ADT	As per final scope	NA
Outcomes	The outcome measures to be considered include: - Metastasis-free survival (MFS) - Time to prostate-specific antigen (PSA) progression - Overall survival (OS) - Adverse effects of treatment - Health-related quality of life (HRQoL)	The list of outcomes presented in this submission is as follows: - Metastasis-free survival (MFS) - Time to PSA progression - OS - Adverse effects of treatment - HRQoL - Time to next therapy for prostate cancer - Time to treatment discontinuation - Time to first use of cytotoxic chemotherapy - Chemotherapy-free disease specific survival - Chemotherapy-free survival - Time to pain progression - PSA response rates	The list of outcomes in the final scope is not exhaustive. Given the disease evolution of patients with high risk nmHRPC and proposed positioning of enzalutamide in this setting, additional outcomes such as time to discontinuation, time to next therapy for prostate cancer, or time to first use of cytotoxic chemotherapy are relevant for the enzalutamide health economic model

Abbreviations: ADT: androgen deprivation therapy; HRQoL: health-related quality of life; MFS: metastasis-free survival; NA: not applicable; nmHRPC: non-metastatic-hormone relapsed prostate cancer; OS: overall survival; PSA: prostate specific antigen.

B.1.2 Description of the technology being appraised

An overview of enzalutamide is provided in Table 2.

Table 2 Technology being appraised

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

	July 2018, the Food and Drug Administration (FDA) approved enzalutamide for nmCRPC patients[7].
Indications and any restriction(s) as described in the Summary of product characteristics (SmPC)	At time of submission, in Europe enzalutamide has market authorisation for the following indications[1]: • "*Treatment of adult men with mCRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated*" • "*Treatment of adult men with mCRPC whose disease has progressed on or after docetaxel therapy*" EMA authorisation for the indication of relevance here (i.e., high risk nmCRPC) is expected by November 2018. A risk management plan (RMP) was developed for enzalutamide in the post-chemotherapy setting and extended to include the treatment of chemotherapy-naïve mCRPC patients. This RMP is expected to be further extended to include the treatment of high risk nmHRPC patients. Based on this RMP, safety information on enzalutamide has been included in its Summary of product characteristics. In addition, Astellas is undertaking active pharmacovigilance for the following safety concerns: seizures, hypertension, falls, hallucination, neutrophil count decreased, non-pathologic fracture, interactions with strong inhibitors or inducers of CYP2C8 and interactions with medicinal products that are substrates of CYP3A4, CYP2C9 or CYP2C19.
Method of administration and dosage	Enzalutamide is formulated as both 40 mg soft capsules and tablets. The tablet formulation is licensed in Europe and will be made available in coming months. The enzalutamide dose for high risk nmCRPC in the licence applications is a single daily oral dose of 160 mg (as four × 40 mg soft capsules[1])
Additional tests or investigations	This indication for enzalutamide does not require any additional tests beyond what is currently done for patients with prostate cancer e.g. PSA levels[1]. Identification of patients eligible for enzalutamide does not require any additional tests either. The PSA monitoring test needed for their identification is in line with UK clinical practice[8].
List price and average cost of a course of treatment	The current UK list price is £2,734.67 per pack (112 units of 40 mg)[9]. With a daily dose of 160 mg, daily UK treatment costs are £97.64, based on the UK list price. Based on the PROSPER median treatment duration, a course of treatment would be [redacted] which would result in a total costs of £[redacted] for an entire course of enzalutamide in nmHRPC (without applying patient access scheme and excluding additional costs).
Patient access scheme (if applicable)	[redacted].

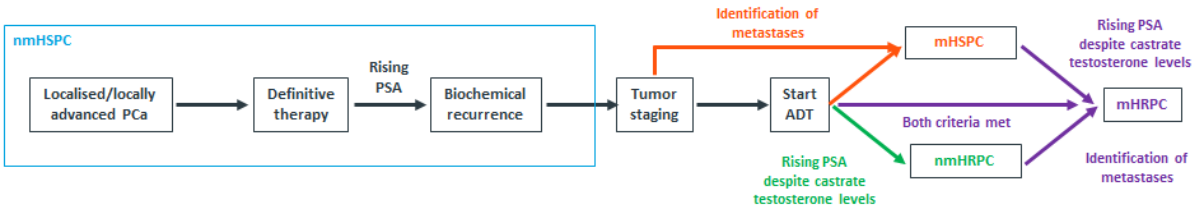
Abbreviations: AR: androgen receptor; CRPC: castration-resistant prostate cancer; PSA: prostate-specific antigen.

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

Prostate cancer is the second most commonly diagnosed cancer and the sixth most common cancer-related cause of death in men worldwide[10]. Prostate cancer progresses through a series of characteristic and well-described clinical stages (Figure 1). Disease progression during prostate cancer is usually signalled by rising PSA levels. This is also known as biochemical failure or recurrence[11, 12].

Prostate cancer is androgen-dependent which forms the basis for several treatment options. Patients with localised prostate cancer may receive radical prostatectomy or radiotherapy (definitive therapy in Figure 1). If the cancer is not eligible for these therapeutic options, patients may receive androgen deprivation therapy (ADT)[11, 13]. Stages that are responsive to ADT are referred to as hormone-sensitive prostate cancer (HSPC)[14]. However, as prostate cancer progresses, further genetic mutations can affect the androgen receptors and allow increasing numbers to function without androgen[5]. At this moment, ADT becomes less effective, at which point serum PSA levels begin to rise again. This stage is known as HRPC[11] and is defined as a minimum PSA level of 1.0 ng/mL, a rising PSA that is ≥2 ng/mL higher than the nadir PSA with this rise being ≥25% over the nadir PSA and castrate levels of testosterone ≤50 ng/dL; 1.7 nmol/L)[25]. It has been estimated that 10–20% of patients with prostate cancer develop HRPC within approximately 5 years of follow-up[15]. At the point of diagnosis of HRPC, most patients will also have metastatic disease[15]. In the UK it has been estimated that 16%[15]-25%[16] of HRPC patients are non-metastatic. The low proportion of HRPC patients with non-metastatic disease is partly due to nmHRPC patients developing metastases rapidly once they become HRPC.

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



Source: Adapted from Anantharaman & Small 2017[17].
Abbreviations: ADT: androgen deprivation therapy; HRPC: hormone-relapsed prostate cancer; HSPC: hormone-sensitive prostate cancer; m: metastatic; nm: non-metastatic; PCa: prostate cancer; PSA: prostate-specific antigen.

There is no clear relationship between the development of metastases and hormonal relapse – either can occur first. It is estimated that 33% of nmHRPC patients will develop metastases within 2 years[15]; and in one study approximately 56% of nmHRPC patients developed metastases over a median follow-up of 36 months[18].

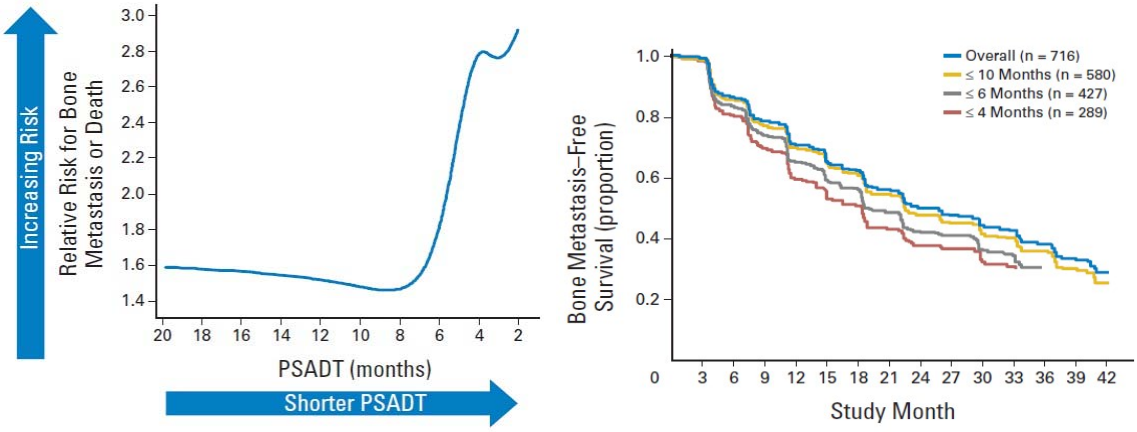
Development of metastases has is associated with potentially serious complications for patients. Health-related quality of life (HRQoL) of patients deteriorate upon the development of metastases and the symptom burden which is initially low in these patients increases[19]. Patients with bone metastases are at high risk of skeletal-related events (SREs), including spontaneous fracture and spinal cord compression, that are a source of significant pain and decreased HRQoL[20]. In line with this, in a 1-year observational, cross-sectional, prospective study conducted in Germany in 101 patients with mHRPC showed that these patients

experienced impairments in HRQoL with 67.3% of patients exhibiting pain or discomfort, 58.1% problems to perform usual activities, 53.1% mobility problems, 37.7% anxiety/depression troubles and 32.7% self-care problems[21].

In addition to bone, metastases can also occur to other sites including lymph nodes and internal organs (visceral metastases). Visceral disease, commonly including liver and lung metastases, is a negative prognostic factor[22]. Not only it is associated with an increase in the symptom burden but visceral disease is also associated with poor survival[23]. Therefore, there is a pressing need for a treatment option for men with high risk nmHRPC to delay the onset of metastases and delay disease progression[24].

For all stages of prostate cancer, clinical management decisions and the design of clinical trials are primarily based on a determination of risk. Studies in men with nmHRPC[25-27] indicate that the key predictors for metastases are absolute PSA levels and PSA doubling time (PSADT, i.e. the length of time in months needed for PSA levels to double in a given patient). As shown by data obtained in the placebo group of a phase III study in patients with nmHRPC (Figure 2), the risk of bone metastasis or death increases considerably when the PSADT becomes shorter than 8-9 months[27]. The mortality risk for nmHRPC patients with a PSADT of ≤10 months increased with a median overall survival (OS) of 42.2 months (~3.5 years)[27]. Other risk factors include absolute baseline PSA levels, tumour stage (T-stage), and pathology findings (including Gleason score, surgical margin status, and lymph node status)[28].

Figure 2 Relationship between PSADT and risk for bone metastasis and death in nmHRPC



Source: Smith et al[27]
Abbreviations: nmHRPC: non-metastatic hormone-relapsed prostate cancer; PSADT: prostate-specific antigen doubling time

NICE does not provide any specific guidance for management of nmHRPC patients[8, 29]. Specific guidance for management of these patients is not provided in other European guidelines either. This is unsurprising given that no treatment has demonstrated any significant survival benefit in this setting[30]. The use of ADT in nmHRPC patients is not clearly supported by robust evidence. However, European guidelines highlight that there are no data that would support discontinuing ADT in these patients. The European Association of Urology (EAU) guidelines highlight that the modest potential benefits of continuing castration with ADT outweigh the minimal risks of treatment and that all treatments for HRPC have

been studied in men with ongoing androgen suppression[30]. Therefore, European guidelines recommend ADT to be continued indefinitely in HRPC patients[30]. In addition, an UK clinical expert confirmed that ADT is frequently being used for men with locally advanced, non-metastatic disease in clinical practice[16].

This submission aims to introduce enzalutamide as a treatment option for high risk nmHRPC in UK practice.

B.1.4 Equality considerations

Astellas are not aware of any issues relating to equality or equalities in NICE guidance or protocols of the treatment of patients with high risk nmHRPC.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR)[31] was conducted to identify clinical evidence regarding the efficacy and safety of enzalutamide plus ADT and of ADT alone (i.e., the standard of care in Europe) in nmHRPC. The scope of the SLR undertaken by Astellas also included drugs that were being assessed in the nmHRPC setting in phase 3 randomised clinical trials at the time of the initial SLR[31]. The SLR was not restricted to high risk nmHRPC. However, in line with the intended indication of enzalutamide (section B.1.1), only those studies conducted in high risk nmHRPC patients and including the intervention/comparators and outcomes relevant to the decision problem are presented in this submission.

The methodology used for the SLR including the search strategy, databases searched and selection criteria is detailed in appendix D. However, a summary of the inclusion and exclusion criteria is provided in Table 3. In line with the final scope, of the comparators included in the SLR, only ADT has been considered as relevant for this submission.

An initial SLR was conducted on November 2016 with searches in Cochrane, PubMed and relevant congresses websites. An update of this SLR was conducted in July 2018. In line with NICE guidance[32], the databases searched were expanded to include also Medline and Medline in Process and Embase. PubMed was not searched in the SLR update. Thus, searches in PubMed were only up to 24th of November 2016. All other databases (Cochrane, Medline and Medline in Process, Embase and congresses) were searched for up to July 2018 (see appendix D for further information). Overall, 27 publications (11 studies) met the SLR selection criteria[31] (Figure 3) but only 9 publications covering 2 studies (PROSPER[33] and STRIVE[34]) were deemed relevant for this submission. Identification of relevant studies was conducted by two experienced information specialists. Any discrepancies were discussed with a third specialist.

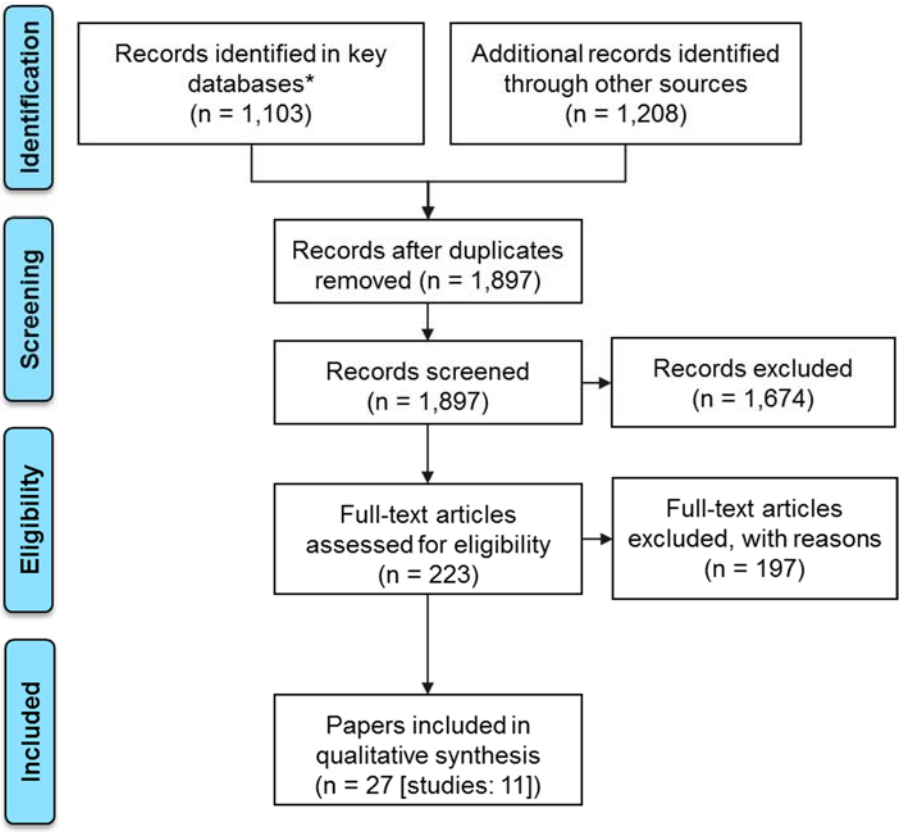
Table 3 Selection criteria in the systematic literature review

PICOS	Inclusion criteria	Exclusion criteria
Population of interest	Adult patients (≥18 year) with nmHRPC	Children
Interventions of interest	Enzalutamide	
Comparators of interest	ADT Anti-androgens: bicalutamide, flutamide, abiraterone, apalutamide, ODM-201 Docetaxel Sipuleucel-T Placebo/ active surveillance Denosumab	Therapies not yet at phase III setting in the nmHRPC setting
Outcomes of interest	Overall survival Progression-free survival Metastasis-free survival PSA response Time to PSA progression Time to chemotherapy initiation	

PICOS	Inclusion criteria	Exclusion criteria
	Time to opiate use for prostate cancer pain Time to pain progression Time to treatment discontinuation Adverse effects of treatment	
Study design of interest	Meta-analyses, systematic literature reviews, randomised controlled trials (RCTs), non-randomised studies, observational studies, case-cohort studies, registries	Preclinical and phase I studies, prognostic studies, case reports, reviews/ expert opinion, commentaries/ letters

Source: PROSPER SLR report[31]
Abbreviations: ADT: androgen deprivation therapy; nmHRPC: non-metastatic hormone-relapsed prostate cancer; PICOS: population; intervention; comparator, outcome, study design; PSA: prostate-specific antigen.

Figure 3 PRISMA flow diagram with the identified studies



Source: PROSPER SLR report[31]
*Key databases included PubMed (n=385; search included only until 24th of November 2016; PubMed was searched through Medline between that date and July 2018), Cochrane (n=118), and Medline, Medline in Process and Embase (n=600).

B.2.2 List of relevant clinical effectiveness evidence

The SLR[31] identified one comparative trial conducted with enzalutamide in adults with high risk nmHRPC:

- PROSPER (NCT02003924), a randomised, double-blinded, placebo-controlled phase III trial that compared the safety and efficacy of enzalutamide and placebo in

high risk nmHRPC patients[33]. This study enrolled 1,401 high risk nmHRPC patients, defined as PSADT ≤10 months with a PSA ≥2 ng/mL.

The SLR identified an additional comparative study with enzalutamide in a heterogeneous HRPC population that included metastatic (m) and (high- and non-high risk) non-metastatic HRPC patients[31]:

- STRIVE (NCT01664923), a randomised, double-blind, placebo-controlled phase II trial that compared the safety and efficacy of enzalutamide and bicalutamide in HRPC patients[34]. This study enrolled both non-metastatic (n=139/396; 35.1%) and metastatic (n=257/396; 64.9%) HRPC patients but the protocol pre-specified subgroup analyses in patients with non-metastatic disease. Overall, 82.96% of nmHRPC patients had a PSADT ≤10 months (i.e., were at high risk).

The designs of the PROSPER and STRIVE trials are summarised in Table 4.

PROSPER is a head-to-head randomised, double-blind placebo-controlled phase III study comparing enzalutamide 160 mg once daily to placebo, while continuing ADT. Management of patients in the placebo arm is considered the equivalent to standard of care[30]. PROSPER data presented in this submission are drawn from both published and unpublished sources:

- Published articles: Hussain et al in the New England Journal of Medicine (NEJM)[33] is the main publication. In addition, PROSPER-related data (either clinical or health-related quality of life [HRQoL] have been presented presentations at different congresses: Hussain et al presented at ASCO 2018[35], Attard et al presented at ASCO 2018[36], a second presentation of Attard et al at ASCO 2018[37], Shore et al at American Urological Association (AUA) 2018[38] and Stenberg et al presented at the European Association of Urology 2018[39].
- Unpublished: PROSPER Clinical Study Report[2], PROSPER PRO analysis report[40].

STRIVE is a head-to-head randomised, double-blind placebo-controlled phase II study comparing enzalutamide 160 mg once daily to bicalutamide 50 mg once daily both in addition to ADT and placebo. STRIVE data presented in this submission originate from both published and non-published sources:

- Published articles: Penson et al in Journal of Clinical Oncology[34]
- Unpublished: STRIVE Clinical Study Report[41].

The evidence of the efficacy and safety of enzalutamide in the high risk nmHRPC setting originates primarily from the PROSPER trial. The treatment benefit of enzalutamide observed in the nmHRPC cohort of STRIVE is provided in this submission as supportive evidence for enzalutamide in this setting. STRIVE is a phase II trial, with smaller sample size than PROSPER and conducted in a single country (the USA). Given these limitations and the fact that bicalutamide is not within the remit of the final scope, enzalutamide-related input parameters for high risk nmHRPC patients in the health economic model (HE model) presented in section B.3 relate to PROSPER only. An additional reason for not including STRIVE in the model is that the endpoints assessed in this trial differed from those in PROSPER and no OS data were collected. However, the results for nmHRPC patients in STRIVE are in line with the PROSPER findings for radiographic and PSA progression.

In this document, the intervention arm of PROSPER and STRIVE is referred to as the “enzalutamide” arm however, the treatment in this arm includes:

- Enzalutamide and ADT in PROSPER
- Enzalutamide, ADT and bicalutamide placebo in STRIVE.

In addition, in this document the comparator arm of these two studies are referred to as “placebo” and “bicalutamide” arm, respectively. The treatment in these arms include:

- Enzalutamide placebo and ADT in PROSPER
- Bicalutamide, ADT and enzalutamide placebo in STRIVE.

Table 4 PROSPER and STRIVE trial design

Study	PROSPER		STRIVE
Study design	Multinational, phase III, randomised, double-blind, placebo-controlled, efficacy and safety study		Multicentre, phase II, single country, l randomised, double-blind placebo-controlled, efficacy and safety study of enzalutamide versus bicalutamide in the United States
Population	nmHRPC with PSA doubling time ≤10 months (i.e., high risk)		Metastatic and nmHRPC. In the nmHRPC cohort, 83.0% had PSA doubling time ≤10 months (i.e., high risk)
Intervention(s)	The intervention was enzalutamide plus ADT Enzalutamide orally was given as a daily dose of 160 mg/day in 4 capsules (40 mg each) by mouth once daily Patients remained on ADT (by either receiving a GnRH agonist/antagonist or having a history of bilateral orchiectomy)		The intervention was enzalutamide, ADT and bicalutamide placebo Enzalutamide was given orally as 160 mg per day as four 40-mg capsules The bicalutamide placebo was administered orally as one placebo capsule ADT was maintained throughout the study; concurrent use of bisphosphonates and denosumab was permitted
Comparator(s)	The comparator was an enzalutamide-matched placebo plus ADT Placebo was administered orally as 4 capsules once daily Patients remained on ADT (by either receiving a GnRH agonist/antagonist or having a history of bilateral orchiectomy)		The comparator was bicalutamide, ADT and enzalutamide placebo Bicalutamide was given orally 50 mg per day as one capsule Enzalutamide placebo was given orally as four placebo capsules ADT was maintained throughout the study, and concurrent use of bisphosphonates and denosumab was permitted
Indicate if trial supports application for marketing authorisation	Yes	X	X
	No		
Indicate if trial used in the economic model	Yes	X	
	No		X

Study	PROSPER	STRIVE
Rationale for use/non-use in the model	The study provides evidence of efficacy and safety of enzalutamide plus ADT vs standard of care (i.e., ADT alone) in high risk nmHRPC patients	This study provides evidence of efficacy and safety of enzalutamide plus ADT vs ADT plus bicalutamide. However, the study included only 139 (35.1%) nmHRPC patients of which 112 (83.0%; missing data: n=4) were high risk. No STRIVE-related data are used in the economic model
Reported outcomes specified in the decision problem	**MFS (primary objective)** Time to PSA progression **Overall survival** **Quality of life** **Safety**	PFS (primary objective) Time to PSA progression Radiographic progression-free survival (metastatic only)
All other reported outcomes	Time to pain progression Chemotherapy-free disease-specific survival Chemotherapy-free survival Time to first use of new antineoplastic therapy Time to first use of cytotoxic chemotherapy PSA response rates **Time to treatment discontinuation**	PSA Response rates

Source: PROSPER Clinical Study Report[2], STRIVE Clinical Study Report[41]. Outcomes highlighted in the bold have been used in the cost effectiveness model.
Abbreviations: ADT: androgen deprivation therapy; GnRH: gonadotropin-releasing hormone; MFS: metastasis-free survival; nmHRPC: non-metastatic hormone-relapsed prostate cancer; PFS: progression-free survival; PSA: prostate-specific antigen.

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

B.2.3.1 Methodology

B.2.3.1.1 PROSPER

The study design of PROSPER and STRIVE are summarised in Table 5.

Table 5 PROSPER and STRIVE methodology

Trial no. (acronym)	MDV3100-14 (PROSPER)	MDV3100-09 (STRIVE)
Location	The study was conducted at a total of 254 study sites in 32 countries in North and South America, Europe, Australia, New Zealand, and Asia. Overall, 70 patients were recruited in 10 UK sites.	The study was conducted at a total of 62 sites in the United States.
Design	PROSPER was a multinational, randomised, double-blind, placebo-controlled, phase III study, comparing oral enzalutamide with placebo for efficacy and safety in adults with high risk nmHRPC, while maintaining ADT. High risk was defined as PSADT ≤10 months and a PSA ≥2 ng/mL.	STRIVE was a multicentre, randomised, double-blind placebo-controlled phase II trial of enzalutamide versus bicalutamide for efficacy and safety in adults with HRPC, while maintaining ADT. The protocol pre-specified subgroup analyses for patients with nmHRPC. In total, 83.0% of patients with nmHRPC were at high risk, i.e., with a PSADT ≤10 months.
Duration of study	The first subject first visit was on 26 November 2013. The data presented here corresponds to the cut-off date of June 28, 2017 when the study was read-out. However, patients are still being followed-up and data collected.	Patients were randomly assigned between August 2012 and March 2014. The data cut-off date was February 9, 2015.
Method of randomisation	The study was centrally randomised by IXRS. Patients were randomised to enzalutamide (160 mg orally once daily as four 40-mg capsules) or matched placebo capsules in a 2:1 ratio. Randomisation was stratified by PSADT (<6 months versus ≥6 months) and baseline use of a bone targeting agent (yes versus no)	Patients were randomly assigned 1:1 to enzalutamide or bicalutamide, stratified by disease stage (M0/N0, M0/N1, or M1). M1 was defined as bone metastases on bone scan or soft-tissue metastases, N1 as absence of bone metastases on bone scan and distant soft-tissue metastases but with nodal metastases below the aortic bifurcation
Method of blinding (care provider, patient and outcome assessor)	All patients, study site personnel (including investigators), and Sponsor staff and its representatives were blinded to treatment assignment. An emergency procedure for breaking the blind was built into the IXRS but was not required during the study. The Sponsor, sites, and patients remained blinded to study drug until database lock. An independent Data Monitoring Committee monitored and reviewed the accumulated safety data on an ongoing basis	Patients, investigators, site personnel, and sponsor personnel involved in the conduct of the study were blinded to treatment assignment. All investigators and medical monitors were provided with codes that allowed immediate and direct unblinding through the interactive response system if necessary. Unblinding was to occur only if the knowledge of treatment assignment would materially change the planned management of a patient in the event of a medical emergency. Emergency unblinding was not needed.
Intervention(s) (n=) and	Randomised/ITT (n=1,401):	Randomised/ITT (n=396 [nmHRPC=139]): • Enzalutamide: n=198 (nmHRPC=70)

Trial no. (acronym)	MDV3100-14 (PROSPER)	MDV3100-09 (STRIVE)
comparator(s) (n=)	• Enzalutamide: n=933 patients • Placebo: n=468 Safety (n=1,395): • Enzalutamide: n=930 patients • Placebo: n=465	• Bicalutamide: n=198 (nmHRPC=69) Safety population consisted of n=395 patients as one patient in the enzalutamide group did not receive the allocated intervention. No separate safety analysis was conducted for nmHRPC patients.
Primary outcomes (including scoring methods and timings of assessments)	The primary efficacy endpoint of the study was **MFS** in the ITT population. MFS was defined as the time from randomisation to the first date of radiographic progression (assessed by BICR) at any time or death within 112 days of treatment discontinuation without evidence of radiographic progression. Radiographic progression for bone disease was defined as the appearance of 1 or more metastatic lesions on radionuclide bone scan of the skull, thorax, spine, pelvis, and extremities. Assessment of soft tissue metastases was performed by CT or MRI. Radiographic progression for soft tissue disease was defined by RECIST 1.1.[42] A blinded independent third-party core imaging laboratory performed a review of radiographic images and clinical information collected on study to assess metastases in support of the primary endpoint MFS. A single MFS analysis was to be performed after approximately 440 MFS BICR-assessed events occurred. All secondary endpoints were also evaluated at this time. Radiographic assessments were conducted at baseline, at week 17 and every 16 weeks thereafter. They were also conducted at any unscheduled visit that took place during the study.	The primary end point was **PFS** in the ITT population. PFS was defined as the time from random assignment to the earliest objective evidence of PSA progression, radiographic disease progression, or death on study (death as a result of any cause up to and including 30 days after treatment discontinuation), whichever occurred first. PSA progression was defined according to PCWG2 guidelines, as the date that a ≥25% increase in PSA with an absolute increase of ≥2 ng/mL above the nadir (or baseline for patients with no PSA decline at week 13) was documented. Radiographic disease progression included soft-tissue disease progression as defined by RECIST 1.1[42] and bone disease progression per PCWG2 guidelines[24]. Generally, patients who had not progressed or died by the data cut-off date were censored on the date of the last available PSA or radiographic assessment. A single PFS analysis was to be performed after a minimum of 231 PFS events had occurred. All secondary endpoints were also to be evaluated for efficacy at this time. Abdominopelvic CT/MRI and bone scan were conducted at screening, week 13, week 25 and every 12 weeks thereafter. They were also conducted at any unscheduled visit that took place during the study but not at the safety follow-up visit. PSA was assessed at screening, week 1, week 13, week 25 and every 12 weeks thereafter. It was also monitored at the safety follow-up visit and all unscheduled visits.
Key secondary outcomes (including scoring	Key secondary endpoints were: • **Time to PSA progression** where PSA progression was defined according to PCWG2 guidelines[24]. PSA was	The secondary endpoints were: • **Time to PSA progression**, defined as the time from random assignment to the earliest evidence of PSA

Trial no. (acronym)	MDV3100-14 (PROSPER)	MDV3100-09 (STRIVE)
methods and timings of assessments)	assessed at the central laboratory throughout the study. PSA values considered undetectable for this study were those below the limit of quantification of centrally assessed PSA results. • **Time to first use of new antineoplastic therapy** and cytotoxic chemotherapy. It was assessed via treatment modalities study participants received documented in the Case Report Forms (CRFs). Prior to unblinding, the study medical monitor independently reviewed each concomitant medication and determined whether they belonged to one of these categories. No changes to this classification were allowed after study unbinding. • **OS** which was defined as the time from randomisation to death from any cause. A survival sweep (i.e., a recording of the status [alive or death] of recruited patients) was conducted prior to the primary completion date in order to obtain an accurate number of deaths across the study PSA was monitored at baseline, at week 17 and every 16 weeks thereafter. It was also assessed at any unscheduled visit that took place during the study. New treatment prescribed to patients was collected at each visit.	progression per PCWG2 guidelines[24]. The PSA progression date was defined as the date that a ≥25% increase in PSA with an absolute increase of ≥2 ng/mL above the nadir (or baseline for patients with no PSA decline at week 13) was documented, which was confirmed by a second consecutive value obtained at least 3 weeks later. A log-rank test stratified by disease stage at study entry (M0 or M1) was used to compare the time to PSA progression between the treatment groups. Confirmed PSA responses, defined as ≥50% and ≥90% reductions in PSA from baseline at any post-baseline assessment, were calculated by treatment group for patients with a baseline PSA value and at least one post-baseline PSA value. Confirmation of these PSA responses was required at a consecutive assessment obtained at least 3 weeks later. • **Radiographic progression-free survival** was defined as the time from randomisation to the first objective evidence of radiographic disease progression or death on study (death as a result of any cause up to and including 30 days after treatment discontinuation), whichever occurred first. Radiographic disease progression included soft-tissue disease progression as defined by RECIST 1.1[42] and bone disease progression per PCWG2 guidelines [24]. Abdominopelvic CT/MRI and bone scan were conducted at screening, week 13, week 25 and every 12 weeks thereafter. They were also conducted at any unscheduled visit that took place during the study but not at the safety follow-up visit. PSA was assessed at screening, week 1, week 13, week 25 and every 12 weeks thereafter. It was also monitored at the safety follow-up visit and all unscheduled visits.
Other secondary outcomes	Other secondary endpoints were: • **Time to pain progression** determined by the BPI-SF, a questionnaire that uses a self-reported scale to assess	Other secondary endpoints were: • **Time to degradation of FACT-P** was defined as the time from random assignment to the date of the first

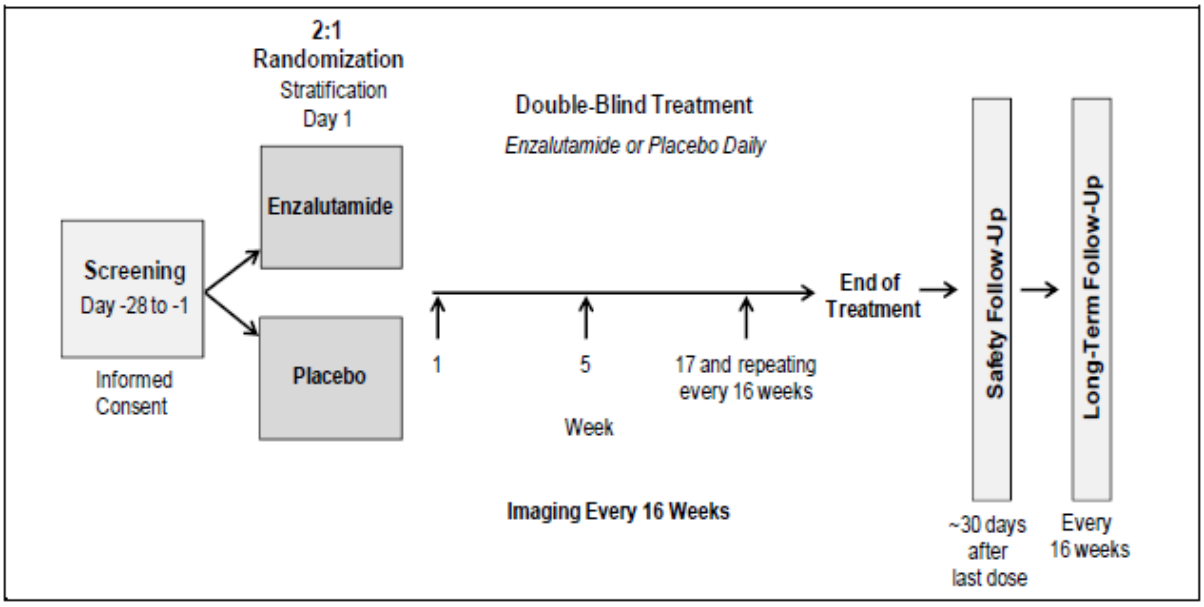
Trial no. (acronym)	MDV3100-14 (PROSPER)	MDV3100-09 (STRIVE)
	level of pain, its effect on activities of daily living, and analgesic medication use • **Quality of life** as assessed by: - FACT-P questionnaire - EQ-5D-5L questionnaire - The EORTC QLQ-PR25 module • **Time to first use of cytotoxic chemotherapy** • **Chemotherapy-free disease-specific survival**, defined as the time from randomisation to first use of cytotoxic chemotherapy for prostate cancer or death due to prostate cancer as assessed by the investigator • **Chemotherapy-free survival** defined as the time from randomisation to first use of cytotoxic chemotherapy for prostate cancer or death due to any cause • **PSA response rates**, defined as a decline of 50% and 90% from baseline or undetectable PSA levels • **Time to treatment discontinuation**	assessment with at least a 10-point decrease from baseline in the global score. • **Best overall soft-tissue response**, assessed by using RECIST 1.1[42] was defined as a best overall soft-tissue response of CR or PR. Only patients with measurable (at least one target lesion) M1 soft-tissue disease at screening were included in the analysis.
Duration of follow-up	Patients were expected to remain on study treatment until radiographic progression. Patients were to have a safety follow-up visit approximately 30 days after the last dose of study drug, and then have long-term follow-up until the patient died. At the cut-off date of June 28, 2017, the median follow-up time for all patients based on reverse Kaplan-Meier estimation was 18.5 months in the enzalutamide group and 15.1 months in the placebo group.	Follow-up continued up until approximately 30 days after last dose of study drug or prior to initiation of cytotoxic or investigational therapy, whichever was first. At the cut-off date of February 09, 2015, the median follow-up time based on reverse Kaplan-Meier estimation were 16.7 months for the enzalutamide group and 16.8 months for the bicalutamide group (for the nmHRPC cohort).

Source: PROSPER Clinical Study Report[2]; STRIVE Clinical Study Report[41]

Abbreviations: BICR: blinded independent central review; BPI-SF: Brief Pain Inventory-Short Form; CR: complete response; CRFs: case report forms; DT: doubling time; EQ-5D-5L: European Quality of Life-5 Dimensions-5 Levels; FACT-P: Functional Assessment of Cancer Therapy-Prostate; ITT: intent-to-treat; IXRS: interactive voice / web recognition system; M0: no distant metastasis (could have regional nodal metastasis); M1: presence of distant metastasis; MFS: metastasis-free survival; nmHRPC: non-metastatic hormone-relapsed prostate cancer; OS: overall survival; PCWG2: Prostate Cancer Clinical Trials Working Group 2; PR: partial response; PSA: prostate-specific antigen; RECIST: Response Evaluation Criteria in Solid Tumours.

The study schematic for PROSPER is provided in Figure 4. After screening, patients were randomised 2:1 to enzalutamide or placebo on Day 1. Study visits were scheduled for weeks 5, 17, and every 16 weeks thereafter. Efficacy assessments were conducted at Week 17 and every 16 weeks thereafter until treatment discontinuation. Safety-related data were collected at these visits as well as at Weeks 1 and 29. Patients had safety follow-up approximately 30 days after the last dose of study drug. If a new antineoplastic treatment was initiated before 30 days after the last dose of study drug, then safety follow-up occurred immediately before starting the new treatment. Long-term follow-up assessments included monitoring for survival status, new antineoplastic therapies for prostate cancer, opiate medications, skeletal-related events, and interventions due to locoregional progression (e.g., radiation, transurethral resection of the prostate, nephrostomy tube placement). At Week 17 and every 16 weeks thereafter until treatment discontinuation, general activities included radiographic assessments, completion of health-related quality of life (HRQoL) questionnaires, study drug dispensing, and central laboratory evaluations (haematology, serum chemistry, and PSA) in addition to the activities performed at Week 5. Safety follow-up after permanent treatment discontinuation occurred approximately 30 days after the last dose of study drug or occurred immediately before starting a new antineoplastic treatment if before 30 days after the last dose of study drug.

Figure 4 PROSPER study schematic



Source: PROSPER Clinical Study Report[2]

B.2.3.2 Participants

Study selection criteria in PROSPER and STRIVE are listed in Table 6. Briefly, in PROSPER patients were eligible for enrolment if they had histologically or cytologically confirmed diagnosis of non-metastatic prostate cancer, castrate levels of testosterone (≤50 ng/dL or ≤1.73 nmol/L), progressive disease despite being on ADT based on 3 consecutive rising PSA values and a PSADT of ≤10 months.

In STRIVE, patients were eligible for enrolment if they had histologically or cytologically confirmed adenocarcinoma of the prostate, castrate levels of testosterone (≤50 ng/dL or ≤1.73 nmol/L), and progressive disease, defined as:

- PSA progression defined by a minimum of two increasing PSA values (one of which could be the screening PSA value) with an interval of ≥1 week between each determination and a PSA value at the screening visit of ≥5 µg/L (5 ng/mL) or a PSADT of ≤10 months if screening PSA was ≥2 µg/L (2 ng/mL)
- Soft-tissue disease progression based on CT or MRI
- Bone disease progression based on bone scan.

STRIVE included both mHRPC and nmHRPC patients.

Table 6 Eligibility criteria in PROSPER and STRIVE

PROSPER		STRIVE	
Inclusion criteria	**Exclusion criteria**	**Inclusion criteria**	**Exclusion criteria**
Patients had to meet all of the following criteria: 1. Age 18 years or older and willing and able to provide informed consent. 2. Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation, signet cell, or small cell features. 3. Ongoing ADT with a GnRH agonist/antagonist or prior bilateral orchiectomy (medical or surgical castration). 4. Testosterone ≤50 ng/dL (≤1.73 nmol/L) at screening. 5. For patients receiving bisphosphonates or denosumab, dose must have been stable for at least 4 weeks before randomisation. 6. Progressive disease on ADT at enrolment defined as a minimum of 3 rising PSA values (PSA1 <PSA2 <PSA3) assessed by a local laboratory (local PSA) with an interval of ≥1 week between each determination. 7. The most recent local PSA and the screening PSA assessed by the central laboratory (central PSA) should have been ≥2 µg/L	Patients could not meet any of the following criterion: 1. Prior cytotoxic chemotherapy, aminoglutethimide, ketoconazole, abiraterone acetate, or enzalutamide for the treatment of prostate cancer or participation in a clinical trial of an investigational agent that inhibits the androgen receptor or androgen synthesis (unless treatment was placebo). 2. Treatment with hormonal therapy or biologic therapy for prostate cancer other than approved BTAs and GnRH agonist/antagonist therapy within 4 weeks of randomisation. 3. Use of an investigational agent within 4 weeks of randomisation. 4. Known or suspected brain metastasis or active leptomeningeal disease. 5. History of another invasive cancer within 3 years of randomisation, with the exception of fully treated cancers with a remote probability of recurrence in the opinion of both the medical monitor and investigator. 6. Absolute neutrophil count <1000/µL, platelet count <100,000/µL, or haemoglobin <10 g/dL (6.2 mmol/L) at screening.	Patients had to meet all of the following criteria: 1. Males age 18 years or older and willing and able to provide informed consent 2. Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation, signet-cell, small-cell, or ductal features 3. Ongoing androgen deprivation therapy for prostate cancer with a GnRH analogue at a stable dose and schedule as of 4 weeks immediately before day 1, or bilateral orchiectomy (i.e., medical or surgical castration). Prior intermittent therapy with a GnRH analogue was allowed. 4. Patients who did not have a bilateral orchiectomy must maintain effective continuous GnRH analogue therapy for the duration of the trial. 5. Serum testosterone level ≤50 ng/dL (1.73 nmol/L) at the screening visit 6. Progressive disease at study entry defined as one or more	Patients could not meet any of the following criterion: 1. Prior cytotoxic chemotherapy, aminoglutethimide, ketoconazole, abiraterone acetate, or enzalutamide for the treatment of prostate cancer or participation in a clinical trial of an investigational agent that inhibits the androgen receptor or androgen synthesis (unless treatment was placebo). 2. Treatment with hormonal therapy or biologic therapy for prostate cancer other than approved BTAs and GnRH agonist/antagonist therapy within 4 weeks of randomisation. 3. Use of an investigational agent within 4 weeks of randomisation. 4. Known or suspected brain metastasis or active leptomeningeal disease. 5. History of another invasive cancer within 3 years of randomisation, with the exception of fully treated cancers with a remote probability of recurrence in

PROSPER		STRIVE	
Inclusion criteria	**Exclusion criteria**	**Inclusion criteria**	**Exclusion criteria**
(2 ng/mL). In the event of prior androgen receptor inhibitor use, the most recent local PSA and the central PSA assessed at screening was obtained at least 4 weeks after the last dose of the androgen receptor inhibitor. 8. PSADT ≤10 months calculated by the Sponsor using the method of Pound et al[43]. 9. No prior or present evidence of metastatic disease as assessed by CT/MRI for soft tissue disease and whole-body radionuclide bone scan for bone disease. If the screening bone scan showed a lesion suggestive of metastatic disease, the patient was eligible only if a second imaging modality (plain film, CT, or MRI) did not show bone metastasis. If the imaging results were equivocal or consistent with metastasis, the patient was not eligible for enrolment. Patients with soft tissue pelvic disease may have been eligible if lesions did not qualify as target lesions (e.g., lymph nodes below aortic bifurcation were permissible if the short axis of the largest lymph node was <15 mm). 10. Asymptomatic prostate cancer. 11. ECOG performance status of 0 or 1. 12. Estimated life expectancy ≥12 months.	NOTE: may not have received growth factors or blood transfusions within 7 days before obtaining the haematology values at screening. 7. Total bilirubin ≥1.5 times the ULN (except patients with a diagnosis of Gilbert's disease); ALT or AST ≥2.5 times ULN at screening. 8. Creatinine >2 mg/dL (177 µmol/L) at screening. 9. Albumin <3.0 g/dL (30 g/L) at screening 10. History of seizure or any condition that may have predisposed the patient to seizure (e.g., prior cortical stroke or significant brain trauma). History of loss of consciousness or transient ischemic attack within 12 months of randomisation. 11. Clinically significant cardiovascular disease including myocardial infarction within 6 months before screening, uncontrolled angina within 3 months before screening, congestive heart failure New York Heart Association class 3 or 4, or a history of congestive heart failure New York Heart Association class 3 or 4, unless a screening echocardiogram or mitigated acquisition scan performed within 3 months before randomisation demonstrated a left ventricular ejection fraction ≥50%, history of clinically significant ventricular	of the following three criteria that occurred while the patient was receiving primary androgen deprivation therapy as defined in inclusion criterion No. 3: 1. PSA progression defined by a minimum of two increasing PSA values (one of which could be the screening PSA value) with an interval of ≥1 week between each determination and a PSA value at the screening visit of ≥5 µg/L (5 ng/mL) or a PSADT ≤10 months if screening PSA was ≥2 µg/L (2 ng/mL) 2. Soft-tissue disease progression based on CT or MRI 3. Bone disease progression based on bone scan 7. Asymptomatic or mildly symptomatic as a result of prostate cancer (i.e., the score on Brief Pain Inventory–Short Form question 3 must be <4) 8. ECOG PS of 0 or 1 at screening and on day 1 visit	the opinion of both the medical monitor and investigator. 6. Absolute neutrophil count <1,000/µL, platelet count <100,000/µL, or haemoglobin <10 g/dL (6.2 mmol/L) at screening. NOTE: may not have received growth factors or blood transfusions within 7 days before obtaining the haematology values at screening. 7. Total bilirubin ≥1.5 times the ULN (except patients with a diagnosis of Gilbert's disease); ALT or AST) ≥2.5 times ULN at screening. 8. Creatinine >2 mg/dL (177 µmol/L) at screening. 9. Albumin <3.0 g/dL (30 g/L) at screening 10. History of seizure or any condition that may have predisposed the patient to seizure (e.g., prior cortical stroke or significant brain trauma). History of loss of consciousness or transient ischemic attack within 12 months of randomisation. 11. Clinically significant cardiovascular disease including myocardial infarction within 6 months before

PROSPER		STRIVE	
Inclusion criteria	**Exclusion criteria**	**Inclusion criteria**	**Exclusion criteria**
13. Able to swallow the study drug and comply with study requirements. 14. Male patient and his female partner who was of childbearing potential must have used 2 acceptable methods of birth control (1 of which must have included a condom as a barrier method of contraception) starting at screening and continuing throughout the study period and for 3 months after final study drug administration. 15. Male patient must have used a condom if having sex with a pregnant woman.	arrhythmias, history of Mobitz II second-degree or third-degree heart block without a permanent pacemaker in place, hypotension as indicated by systolic blood pressure <86 mm Hg at screening, bradycardia as indicated by a heart rate of <45 beats per minute on the screening electrocardiogram and on physical examination, uncontrolled hypertension as indicated by systolic blood pressure >170 mm Hg or diastolic blood pressure >105 mm Hg at screening 12. Gastrointestinal disorder that affected absorption (e.g., gastrectomy, active peptic ulcer disease within 3 months before randomisation). 13. Major surgery within 4 weeks of randomisation. 14. Hypersensitivity reaction to the active pharmaceutical ingredient or any of the capsule components, including Labrasol, butylated hydroxyanisole, and butylated hydroxytoluene. 15. 15. Any concurrent disease, infection, or comorbid condition that interfered with the ability of the patient to participate in the trial, which placed the patient at undue risk, or complicated the interpretation of data, in the opinion	9. Estimated life expectancy of ≥12 months 10. Able to swallow the study drug and comply with study requirements 11. Must use a condom if having sex with a pregnant woman 12. Male patient and his female partner of childbearing potential must use two acceptable methods of birth control (one of which must include a condom as a barrier method of contraception) starting at screening and continuing throughout the study period and for 3 months after final study drug administration.	screening, uncontrolled angina within 3 months before screening, congestive heart failure New York Heart Association class 3 or 4, or a history of congestive heart failure New York Heart Association class 3 or 4, unless a screening echocardiogram or mitigated acquisition scan performed within 3 months before randomisation demonstrated a left ventricular ejection fraction ≥50%, history of clinically significant ventricular arrhythmias, history of Mobitz II second-degree or third-degree heart block without a permanent pacemaker in place, hypotension as indicated by systolic blood pressure <86 mm Hg at screening, bradycardia as indicated by a heart rate of <45 beats per minute on the screening electrocardiogram and on physical examination, uncontrolled hypertension as indicated by systolic blood pressure >170 mm Hg or diastolic blood pressure >105 mm Hg at screening 12. Gastrointestinal disorder that affected absorption (e.g.,

PROSPER		STRIVE	
Inclusion criteria	**Exclusion criteria**	**Inclusion criteria**	**Exclusion criteria**
	of the investigator or medical monitor.		gastrectomy, active peptic ulcer disease within 3 months before randomisation). 13. Major surgery within 4 weeks of randomisation 14. Hypersensitivity reaction to the active pharmaceutical ingredient or any of the capsule components, including Labrasol, butylated hydroxyanisole, and butylated hydroxytoluene. 15. Any concurrent disease, infection, or comorbid condition that interfered with the ability of the patient to participate in the trial, which placed the patient at undue risk, or complicated the interpretation of data, in the opinion of the investigator or medical monitor.

Source: PROSPER Clinical Study Report[2]; STRIVE Clinical Study Report[41]

Abbreviations: ADT: Androgen deprivation therapy; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BTA: bone-targeting agent; CT: computer tomography; DT: doubling time; ECOG: Eastern Cooperative Oncology Group; GnRH: gonadotropin-releasing hormone, MRI: magnetic resonance imaging; PSA: prostate-specific antigen; ULN: the upper limit of normal.

Demographics and baseline characteristics of patients in PROSPER and STRIVE

In PROSPER, both treatment arms were well balanced in terms of demographics, baseline disease characteristics and medical history (Table 7). The majority of patients in both arms had a PSADT less than 6 months (enzalutamide: 76.6%; placebo: 77.2%) and had non-metastatic disease (enzalutamide: 97.5%; placebo: 97.0%). In addition, the majority of patients (enzalutamide: 88.7%; placebo: 89.7%) had not received any bone-targeting agent prior to or at study entry. The majority of patients in both arms had an ECOG performance of 0 (enzalutamide: 80.1%; placebo: 81.6%) and either medium (i.e., score of 5-7; enzalutamide: 52.6%; placebo: 49.1%) or high (i.e., score of 8-10; enzalutamide: 40.8%; placebo: 44.2%) Gleason score at diagnosis.

Overall, 55.0% and 57.7% of patients in the enzalutamide and placebo arms had been exposed to bicalutamide prior to study entry.

[redacted]

Table 7 Demographic and baseline disease characteristics in PROSPER (ITT population)

Outcomes	Enzalutamide (n=933)	Placebo (n=468)	Total (n=1,401)
Age (years)			
<65	121 (13.0%)	69 (14.7%)	190 (13.5%)
65 to <75	368 (39.4%)	198 (42.3%)	566 (40.4%)
≥75	444 (47.6%)	201 (42.9%)	645 (46.0%)
Median (range)	74.0 (50.0, 95.0)	73.0 (53.0, 92.0)	74.0 (50.0, 95.0)
Race			
American Indian or Alaskan Native	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asian	142 (15.2%)	88 (18.8%)	230 (16.4%)
Black or African American	21 (2.3%)	10 (2.1%)	31 (2.2%)
Native Hawaiian or Other Pacific Islander	3 (0.3%)	2 (0.4%)	5 (0.4%)
White	671 (71.9%)	320 (68.4%)	991 (70.7%)
Multiple	4 (0.4%)	4 (0.9%)	8 (0.6%)
Other	15 (1.6%)	5 (1.1%)	20 (1.4%)
Missing	77 (8.3%)	39 (8.3%)	116 (8.3%)
Weight (kg)			
Mean (SD)	84.0 (15.87)	83.6 (16.21)	83.9 (15.98)
Median (min, max)	82.0 (43.1, 149.8)	82.0 (38.0, 167.0)	82.0 (38.0, 167.0)
Missing	0	1	1
Baseline ECOG performance status			
0	747 (80.1%)	382 (81.6%)	1,129 (80.6%)
1	185 (19.8%)	85 (18.2%)	270 (19.3%)
>1	0 (0.0%)	0 (0.0%)	0 (0.0%)

Outcomes	Enzalutamide (n=933)	Placebo (n=468)	Total (n=1,401)
Missing	1 (0.1%)	1 (0.2%)	2 (0.1%)
Disease status (by blinded independent central review)			
Non-metastatic	910 (97.5%)	454 (97.0%)	1,364 (97.4%)
Metastatic[a]	23 (2.5%)	14 (3.0%)	37 (2.6%)
Baseline prior or concurrent use of BTA[b]			
No (0)	828 (88.7%)	420 (89.7%)	1,248 (89.1%)
Yes	105 (11.3%)	48 (10.3%)	153 (10.9%)
1	103 (11.0%)	47 (10.0%)	150 (10.7%)
2	2 (0.2%)	1 (0.2%)	3 (0.2%)
PSADT category[b]			
<6 months	715 (76.6%)	361 (77.1%)	1,076 (76.8%)
≥6 months	217 (23.3%)	107 (22.9%)	324 (23.1%)
Missing	1 (0.1%)	0 (0.0%)	0 1 (<0.1%)
Stratification			
PSADT <6 months and no baseline BTA	642 (68.8%)	327 (69.9%)	969 (69.2%)
PSADT <6 months and baseline BTA	73 (7.8%)	34 (7.3%)	107 (7.6%)
PSADT ≥6 months and no baseline BTA	185 (19.8%)	93 (19.9%)	278 (19.8%)
PSADT ≥6 months and baseline BTA	32 (3.4%)	14 (3.0%)	46 (3.3%)
Missing	1 (0.1%)	0 (0.0%)	1 (<0.1%)
PSADT (months)			
Mean (SD)	4.3 (2.8)	4.3 (3.9)	4.3 (3.2)
Median (range)	3.8 (0.4, 37.4)	3.6 (0.5, 71.8)	3.7 (0.4, 71.8)
Missing	1 (0.1%)	0 (0.0%)	1 (<0.1%)
Serum PSA (ng/mL)			
Mean (SD)	22.2 (46.1)	22.1 (41.1)	22.2 (44.5)
Median (range)	11.1 (0.8, 1071.1)	10.2 (0.2, 467.5)	10.7 (0.2, 1071.1)
Missing	0 (0.0%)	1 (0.2%)	1 (<0.1%)
Gleason Score			
Low (2-4)	21 (2.3%)	12 (2.6%)	33 (2.4%)
Medium (5-7)	491 (52.6%)	230 (49.1%)	721 (51.5%)
High (8-10)	381 (40.8%)	207 (44.2%)	588 (42.0%)
Unknown	40 (4.3%)	19 (4.1%)	59 (4.2%)
Pain score as assessed by BPI-SF Question #3			
0-1	639 (68.5%)	336 (71.8%)	975 (69.6%)
2-3	106 (11.4%)	52 (11.1%)	158 (11.3%)
>3	142 (15.2%)	51 (10.9%)	193 (13.8%)
Missing	46 (4.9%)	29 (6.2%)	75 (5.4%)

Source: PROSPER Clinical Study Report[2]

a. Patients may have been determined by the blinded independent central review to be metastatic following entry into the study.

b. Baseline use of BTA and PSADT categories were summarised based on data collected in study case report

form pages.
Abbreviations: BPI-SF: Brief Pain Inventory-Short Form; BTA: bone-targeting agent; DT: doubling time; ECOG: Eastern Cooperative Oncology Group; ITT: intent-to-treat; n: number of patients; PSA: prostate-specific antigen; SD: standard deviation. Percentages were based on the number of patients in the ITT population.

In STRIVE, both treatment arms were also well balanced in terms of demographics, baseline disease characteristics and medical history (Table 8). The majority of patients in both arms had an ECOG performance of 0 (enzalutamide: 74.7%; bicalutamide: 73.2%) and either medium (i.e., score of 5-7; enzalutamide: 45.5%; bicalutamide: 47.0%) or high (i.e., score of 8-10; enzalutamide: 50.5%; bicalutamide: 49.0%) Gleason score at diagnosis. Overall, 35.1% of patients had nmHRPC at baseline and of these, 82.96% (enzalutamide: n=62/70, 88.6%; bicalutamide: n=50/65, 76.9%) had a PSADT ≤10 months.

Table 8 Baseline patient and disease characteristics in STRIVE (ITT population)

Baseline Characteristic	mHRPC and nmHRPC		nmHRPC only	
	Enzalutamide (n=198)	Bicalutamide (n=198)	Enzalutamide (n=70)	Bicalutamide (n=69)
Age, years				
<65	39 (19.7%)	25 (12.6%)	[redacted]	[redacted]
65-74	82 (41.4%)	76 (38.4%)	[redacted]	[redacted]
≥75	77 (38.9%)	97 (49.0%)	[redacted]	[redacted]
Median (range)	72 (46-92)	74 (50-91)	[redacted]	[redacted]
Race				
Black or African American	29 (14.6%)	24 (12.1%)	[redacted]	[redacted]
White	160 (80.8%)	169 (85.4%)	[redacted]	[redacted]
Other	9 (4.5%)	5 (2.5%)	[redacted]	[redacted]
Baseline weight, kg				
Median (range)	91.4 (58.5-249.7)	89.1 (45.8-181.8)	[redacted]	[redacted]
Baseline ECOG PS				
0	148 (74.7%)	145 (73.2%)	[redacted]	[redacted]
1	50 (25.3%)	53 (26.8%)	[redacted]	[redacted]
Baseline pain score as assessed by Brief Pain Inventory–Short Form question 3				
0-1	165 (83.3%)	158 (79.8%)	[redacted]	[redacted]
2-3	33 (16.7%)	40 (20.2%)	[redacted]	[redacted]
Baseline serum PSA, µg/L				
Median (range)	11.0 (0.0-1499.7)	13.2 (0.2-2849.7)	[redacted]	[redacted]
Baseline FACT–P global score				
Median (range)	125.7 (37.0-154.0)	124.0 (51.0-156.0)	[redacted]	[redacted]

Baseline Characteristic	mHRPC and nmHRPC		nmHRPC only	
	Enzalutamide (n=198)	Bicalutamide (n=198)	Enzalutamide (n=70)	Bicalutamide (n=69)
Total Gleason score category at initial diagnosis				
Low (2-4)	0	2 (1.0%)	[redacted]	[redacted]
Medium (5-7)	90 (45.5%)	93 (47.0%)	[redacted]	[redacted]
High (8-10)	100 (50.5%)	97 (49.0%)	[redacted]	[redacted]
Missing[a]	8 (4.0%)	6 (3.0%)	[redacted]	[redacted]
Disease stage at study entry per CRF				
M0	70 (35.4%)	69 (34.8%)	[redacted]	[redacted]
M0/N0 (non-nodal)	61 (30.8%)	60 (30.3%)	[redacted]	[redacted]
M0/N1 (nodal)	9 (4.5%)	9 (4.5%)	[redacted]	[redacted]
M1	128 (64.6%)	129 (65.2%)	[redacted]	[redacted]
Disease localisation at screening				
Bone only	61 (30.8%)	66 (33.3%)	[redacted]	[redacted]
Soft tissue only	29 (14.6%)	30 (15.2%)	[redacted]	[redacted]
Both bone and soft tissue	48 (24.2%)	42 (21.2%)	[redacted]	[redacted]
None	60 (30.3%)	60 (30.3%)	[redacted]	[redacted]
Soft-tissue disease at screening				
Measurable disease[b]	41 (20.7%)	50 (25.3%)	[redacted]	[redacted]
Target only	16 (8.1%)	18 (9.1%)	[redacted]	[redacted]
Target and non-target	25 (12.6%)	32 (16.2%)	[redacted]	[redacted]
Non-target only	36 (18.2%)	22 (11.1%)	[redacted]	[redacted]
Distribution of disease at screening[c]				
Bone	109 (55.1%)	108 (54.5%)	[redacted]	[redacted]
Lymph node	63 (31.8%)	61 (30.8%)	[redacted]	[redacted]
Visceral disease (lung or liver)	11 (5.6%)	13 (6.6%)	[redacted]	[redacted]
Liver	4 (2.0%)	3 (1.5%)	[redacted]	[redacted]

Baseline Characteristic	mHRPC and nmHRPC		nmHRPC only	
	Enzalutamide (n=198)	Bicalutamide (n=198)	Enzalutamide (n=70)	Bicalutamide (n=69)
Lung	7 (3.5%)	10 (5.1%)	[redacted]	[redacted]
Lung and liver	0	0	[redacted]	[redacted]
Other soft tissue	18 (9.1%)	11 (5.6%)	[redacted]	[redacted]
Bone metastases at screening				
0	89 (44.9%)	90 (45.5%)	[redacted]	[redacted]
1	23 (11.6%)	21 (10.6%)	[redacted]	[redacted]
2-4	35 (17.7%)	18 (9.1%)	[redacted]	[redacted]
5-9	26 (13.1%)	25 (12.6%)	[redacted]	[redacted]
10-20	14 (7.1%)	22 (11.1%)	[redacted]	[redacted]
>20	11 (5.6%)	22 (11.1%)	[redacted]	[redacted]

Source: STRIVE Clinical Study Report[41]

a. Missing, patients with missing primary, secondary, and total Gleason scores.

b. Measurable soft-tissue disease was defined as at least one target lesion identified per Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1).

c. Patients could be summarised for more than one category, but only counted once for each category.

Abbreviations: CRF: case report form; ECOG PS: Eastern Cooperative Oncology Group performance status; FACT–P: Functional Assessment of Cancer Therapy–Prostate; M0: non-metastatic; M1: metastatic; NA: not available; PSA: prostate-specific antigen.

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

B.2.4.1 Primary hypothesis

In PROSPER, the null hypothesis was that the hazard of MFS with enzalutamide plus ADT would be the same as with ADT alone and thus, the hazard ratio would be 1. In STRIVE, the null hypothesis was that the hazard of progression-free survival (PFS) with enzalutamide plus ADT is the same as with bicalutamide plus ADT and thus, the hazard ratio would be 1.

B.2.4.2 Patient population

In PROSPER, the intent-to-treat (ITT) population, defined as all randomised patients, was used for all efficacy analyses, and analyses of disposition, demographics, and baseline disease characteristics. Safety analyses were conducted using the safety population (i.e., all patients in the randomised population who received any study medication) and summarised by treatment group.

Similarly in STRIVE, the ITT population, defined as all randomised patients, was used for all efficacy analyses. However, the protocol pre-specified subgroup analyses for the ITT mHRPC and ITT nmHRPC populations. In this submission we only provide efficacy data for the ITT nmHRPC cohort. The safety population included all patients randomly assigned to treatment who received at least 1 partial dose of study drug (enzalutamide or bicalutamide). No safety population was defined for the nmHRPC cohort.

B.2.4.3 Sample size, power calculations

In PROSPER, the following assumptions were used to determine the sample size calculation for the MFS endpoint:

- 2:1 enzalutamide to placebo treatment allocation;
- An increasing non-uniform accrual of 0.25 patients per month per site with maximum accrual of 63 patients per month;
- For MFS, a target HR of 0.72 at a 2-sided significance level of 5% with 90% power. Under an exponential model assumption, the target difference in Kaplan-Meier estimated medians was 9 months (control median of 24 months versus treatment median of 33 months[2]). The median MFS of 24 months for the placebo group was based on published data[44].

A total of 440 MFS events provided 90% power to detect a target HR of 0.72 based on a two-sided log-rank test and the overall significance level of 0.05. A sample size of approximately 1,305 patients (870 enzalutamide and 435 placebo) was expected to achieve 440 events in approximately 43 months. Approximately 10% of patients enrolled were expected to be lost to follow-up, found to have metastatic disease at study entry, or have events censored due to required analytical methods, so approximately 1,440 patients (960 enzalutamide and 480 placebo) were targeted to be randomised. The time from date of first

randomisation until 440 MFS events were observed was estimated to be approximately 43 months.

In STRIVE, a minimum of 231 PFS events provided 90% power to detect a HR of 0.65 based on a two-sided log-rank test with a significance level of 0.05.

B.2.4.4 Handling of dropouts or missing data

In PROSPER, the primary endpoint data (MFS) was censored for missing data, patient ineligibility and non-occurrence of MFS event at data cut-off date. The censoring criteria for each of the analysis steps are listed in Table 10.

No imputations of missing efficacy data were performed; full dates were known for survival (i.e., death or last known alive) and for all MFS imaging time points. Missing data were excluded from analysis.

The treatment-emergent period was defined as the period of time from the date and time of the first dose of study drug through the date of last dose + 30 days (or the day before initiation of a new antineoplastic treatment, whichever occurred first). For incomplete dates of last dose of study drug that were missing the day of the month, the 15th of the month was assumed in determining the treatment-emergent period.

In STRIVE, missing data were not imputed and only the observed records were included.

B.2.4.5 Interim analyses and stopping guidelines

In PROSPER, no interim analysis and associated stopping guidelines were pre-specified in the protocol for any endpoints, with the exception of OS. For OS, three interim and one final analyses were pre-specified (Table 9). Only the first two interim OS analyses were available at the time of writing this dossier. OS was immature in both interim analysis with only 28% and 48% of the expected deaths (i.e., 596) had occurred in the first and second interim analyses, respectively (see section B.2.4.6).

In STRIVE, no interim analysis was planned.

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

Three interim and one final analyses were to be conducted for OS (Table 9)[2]. The single MFS analysis was to be performed after approximately 440 MFS blinded independent central review (BICR)-assessed events occurred. All other secondary endpoints were also evaluated at this time along with an interim analysis of OS. Two additional interim analyses and the final analysis of OS are planned after approximately 285, 440, and 596 death events occur, respectively. If an interim analysis of OS was statistically significant, it was to be reported as the final analysis and no subsequent analyses were to be performed.

Table 9 Protocol pre-specified analysis for OS and type I error

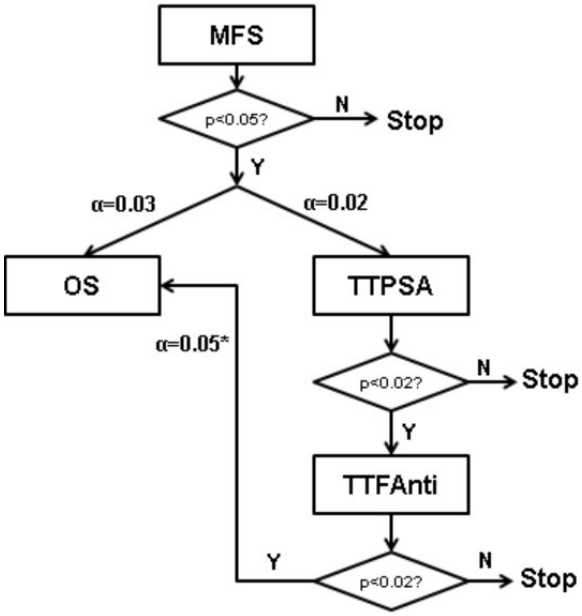
Analysis	Number of death events	Significance level	
		Error rate: 0.03	Error rate: 0.05
First interim	135	0.001	0.001
Second interim	285	0.001	0.002
Third interim	440	0.009	0.018
Final	596	0.026	0.044

Source: PROSPER Clinical Study Report[2]

Significance for all primary and secondary end-points was tested with a stratified log-rank test on the ITT population to compare the 2 treatment groups. The strata used were: PSADT (<6 months vs ≥6 months) and prior or current bone targeting agent (BTA) (yes vs no).

Adjustment for multiplicity was considered for MFS based on BICR assessment, and the key secondary endpoints of time to PSA progression, time to first use of new antineoplastic therapy, and OS. All secondary endpoint analyses were performed at the time of the single MFS analysis. To maintain the family-wise two-sided type I error rate at 0.05, a parallel testing strategy between OS (with allocated type I error rate 0.03) and remaining key secondary endpoints time to PSA progression and time to first use of new antineoplastic therapy with allocated type I error rate 0.02) was performed Figure 5.

Figure 5 Testing strategy for primary and key secondary endpoints



Source: PROSPER Clinical study report[2]
*OS was tested at 0.05 only if both time to PSA progression and time to first use of new antineoplastic therapy endpoints were significant. If either time to PSA progression or time to first use of new antineoplastic therapy endpoints failed to show significance, OS was tested at 0.03
Abbreviations: MFS: metastasis-free survival; OS: overall survival; TTPSA: time to prostate-specific antigen progression; TTFAnti: time to first use of new antineoplastic therapy.

MFS was tested at an overall significance level of 0.05. If p-value <0.05, MFS difference was declared statistically significant, and time to PSA progression and time to first use of new antineoplastic therapy were tested at a significance level of 0.02. If both would to be declared significant, each sequential OS interim analysis had to be tested at a significance level of 0.05, otherwise it had to be tested at 0.03. All other efficacy analyses (including sensitivity analysis to primary, and other secondary endpoints) and associated p-values were deemed exploratory, for which no adjustment for multiplicity was used. For the interim OS analyses, the significance levels will be lower due to the lower number of events and recalculated using the O'Brien-Fleming method.

In STRIVE, time-to-event end points, including the primary end point of PFS as well as time to PSA progression and rPFS, were compared between the two treatment arms by using a two-sided log-rank test stratified by disease stage (non-metastatic [M0N0 and M0N1] or metastatic) where applicable. Kaplan-Meier curves and medians were calculated for these end points, and HRs were estimated by using a Cox regression model stratified by disease stage where applicable. A two-sided Cochran-Mantel-Haenszel test was used to compare PSA response rates for enzalutamide and bicalutamide.

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

In PROSPER, radiographic assessments from both scheduled and unscheduled visits were used to determine events in the primary analysis. For patients not known to have had radiographic progression or death at the time of the analysis data cut-off, MFS time was censored at the date of the last available scan before the analysis data cut-off date. Patients who were randomised but later confirmed to have metastatic disease before randomisation by BICR or patients with no post-baseline tumour assessment information were censored on the date of randomisation. Patients who initiated antiandrogen receptor agents (e.g., bicalutamide, flutamide, or nilutamide) without evidence of metastasis as per BICR were not censored for the primary MFS analysis. The details of the censoring rules for the primary analysis of MFS, as well as the sensitivity, are provided in Table 10.

Table 10 Censoring rules

Analysis	Censoring rules	Date of censoring
Primary analysis of MFS	Patients with no baseline or no post-baseline assessments	Date of randomisation
	Patients who were randomised but confirmed metastatic at baseline by BICR	Date of randomisation
	Patients who had no confirmed metastasis as per BICR or did not die prior to data cut-off date	Date of the last radiographic assessment prior to data cut-off date
	Patients who had no confirmed metastasis as per BICR but died after 112 days following last dose of study drug	Date of the last radiographic assessment prior to data cut-off date
	Patients who initiated cytotoxic chemotherapy, abiraterone acetate, or nonradioactive bone-targeting agents without evidence of metastasis as per BICR	Date of the last radiographic assessment prior to first use of any such therapy

Analysis	Censoring rules	Date of censoring
	Patients who experienced a skeletal-related event without evidence of metastasis as per BICR	Date of the last radiographic assessment prior to the earliest skeletal-related event
	Patients with radiation therapy performed for prostate cancer-related lesions without evidence of metastasis as per BICR	Date of the last radiographic assessment prior to the earliest use of radiation therapy
	Patients with 2 or more consecutive missed tumour assessment visits without evidence of metastasis as per BICR	Date of the last radiographic assessment prior to the missed visit date
MFS based on investigator assessment	Same as censoring rules for primary analysis of MFS as per investigator	Same as dates of censoring for primary analysis of MFS as per investigator
Impact of antineoplastic therapies	All censoring rules for the primary analysis of MFS	Same as the primary analysis of MFS
	Patients who initiated any antineoplastic therapy without evidence of metastasis as per BICR	Date of the last radiographic assessment prior to first antineoplastic therapy use
Modified MFS1 (including progression after alternative therapy as event)	Patients with no baseline or no post-baseline assessments	Date of randomisation
	Patients who had no confirmed metastasis as per BICR but died after 112 days following last dose of study drug	Date of the last radiographic assessment prior to data cut-off date
	Patients who experienced a skeletal-related event without evidence of metastasis as per BICR	Date of the last radiographic assessment prior to the earliest skeletal-related event
	Patients with 2 or more consecutive missed tumour assessment visits without evidence of metastasis as per BICR	Date of the last radiographic assessment prior to the missed visit date
Modified MFS2 (including post-treatment deaths as event)	Patients with no baseline or no post-baseline assessments	Date of randomisation
	Patients who were randomised but confirmed metastatic at baseline by BICR	Date of randomisation
	Patients who had no confirmed metastasis as per BICR or did not die prior to data cut-off date	Date of the last radiographic assessment prior to data cut-off date
	Patients who initiated cytotoxic chemotherapy, abiraterone acetate, or nonradioactive bone-targeting agents without evidence of metastasis as per BICR	Date of the last radiographic assessment prior to first use of any such therapy
	Patients who experienced a skeletal-related event without evidence of metastasis as per BICR	Date of the last radiographic assessment prior to the earliest skeletal-related event
	Patients with radiation therapy performed for prostate cancer-related lesions without evidence of metastasis as per BICR	Date of the last radiographic assessment prior to the earliest use of radiation therapy
	Patients with 2 or more consecutive missed tumour assessment visits without evidence of metastasis as per BICR	Date of the last radiographic assessment prior to the missed visit date

Source: PROSPER Clinical Study Report[2]

Abbreviations: BICR: blinded independent central review; MFS; metastasis-free survival.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

A quality assessment of the relevant clinical effectiveness evidence is included in appendix D. The quality assessment was conducted on the main publication for PROSPER (i.e., Hussain et al[33]) and STRIVE (i.e., Penson et al[34]). This appraisal was conducted using the quality elements suggested by NICE to assess the risk of bias and generalisability in parallel groups RCTs[32]. Both PROSPER and STRIVE met all of the quality assessment criteria, with the exception of 'Was the outcome data complete?'. The main publication reported only the key PROSPER and STRIVE endpoints. However, the corresponding CSRs report all complete data.

Overall the quality assessment indicated that PROSPER and STRIVE were of high quality with little risk of bias.

B.2.6 Clinical effectiveness results of the relevant trials

Unless stated otherwise, all data in this section originate from the PROSPER[2, 33] or STRIVE[34, 41] clinical study reports or key publications. The clinical effectiveness results are provided separately for PROSPER and STRIVE.

As mentioned in section B.2.2, the evidence of the efficacy and safety of enzalutamide in the high risk nmHRPC setting originates primarily from the PROSPER trial. The treatment benefit of enzalutamide observed in the nmHRPC cohort of STRIVE is provided in in this submission as supportive evidence for enzalutamide in this setting.

B.2.6.1 PROSPER Clinical effectiveness results of the relevant trials

B.2.6.1.1 Primary outcome: MFS

The protocol pre-specified primary efficacy analysis was to be performed after 440 MFS events occurred. As of the data analysis cut-off date (28 June 2017), a total of 447 patients (31.9% of the total randomised population) had an event (metastasis or death), with 219 patients (23.5%) in the enzalutamide group and 228 patients (48.7%) in the placebo group[2] (Figure 6).

The study met its primary objective and showed a substantial improvement of BICR-assessed MFS in the enzalutamide group compared with the placebo group. The median MFS (95% confidence interval [CI]) was 36.6 months (95% CI: [33.1; not reached]) in the enzalutamide group and 14.7 months (95% CI: [14.2; 15.0]) in the placebo group, with a difference of 21.9 months. The median follow-up time for all patients based on reverse Kaplan-Meier estimation was 18.5 months in the enzalutamide group and 15.1 months in the placebo group. The analysis results demonstrated a statistically significant and a clinically meaningful 70.8% reduction in the risk of an MFS event (HR: 0.292, 95% CI: [0.241; 0.352], p<0.0001) in favour of the enzalutamide group.

Table 11 MFS - Primary efficacy analysis based on BICR assessment (ITT population)

Outcome	Enzalutamide (n=933)	Placebo (n=468)
Status of MFS follow-up		
Events[a]	219 (23.5%)	228 (48.7%)
Progression by BICR	187 (20.0%)	224 (47.9%)
Bone progression	71 (7.6%)	79 (16.9%)
Soft tissue progression	109 (11.7%)	132 (28.2%)
Concurrent bone and soft tissue progression	7 (0.8%)	13 (2.8%)
Death without documented radiographic progression	32 (3.4%)	4 (0.9%)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
MFS (months)		
[redacted]	[redacted]	[redacted]
Median [95% CI]	36.6 [33.1; NR]	14.7 [14.2; 15.0]
[redacted]	[redacted]	[redacted]
Probability of being event-free at:[c]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Treatment comparison: enzalutamide versus placebo		
Hazard ratio [95% CI][d]	0.292 [0.241; 0.352]	
p-value[d]	<0.0001	
Median follow-up time based on reverse Kaplan-Meier estimates for all patients (months)	18.5	15.1

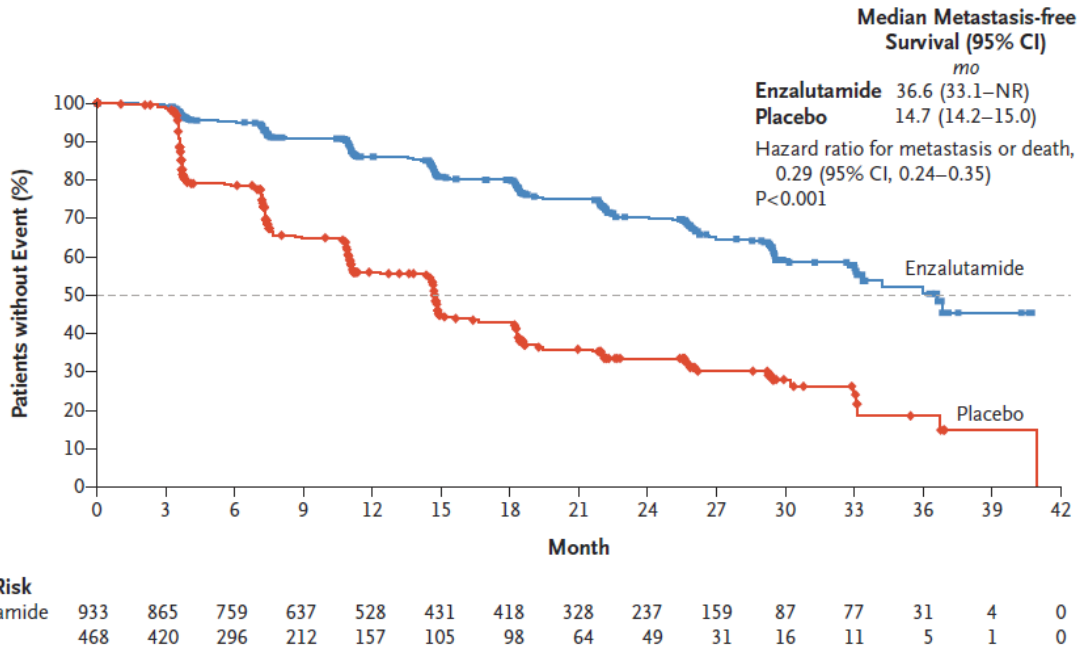
Source: PROSPER Clinical Study Report[2]

a. Based on earliest contributing event (radiographic progression or death due to any cause within 112 days after treatment discontinuation).

b. Patients who were not known to have had an MFS event at the time of analysis data cut-off were censored at date of last assessment showing no objective evidence of radiographic progression prior to initiation of cytotoxic chemotherapy, abiraterone acetate, nonradioactive bone-targeting agent, radiation therapy for prostate cancer, skeletal-related event, or ≥2 consecutive missed tumour assessments. Patients who were randomised but later confirmed to have metastatic disease before randomisation were censored on the date of randomisation.

c. Based on Kaplan-Meier estimates. Kaplan-Meier curves are provided in Figure 6.
d. P-value was based on a stratified log-rank test by PSA doubling time (<6 months, ≥6 months) and prior or concurrent use of a bone-targeting agent (yes, no) as per interactive voice/web recognition system. Hazard ratio was based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and was relative to the placebo group with <1 favouring the enzalutamide group.
Abbreviations: BICR: blinded independent central review; BTA: bone-targeting agent; CI: confidence interval; ITT: intent-to-treat; n: number of patients; MFS: metastasis-free survival; NR: not reached; PD: progressive disease.

Figure 6 Kaplan-Meier curves for MFS (ITT population)



Source: Hussain et al[33]
Note: p-value was based on a log-rank test stratified by PSADT (<6 months, ≥6 months) and prior or concurrent use of a bone-targeting agent (yes, no) as per IXRS.
Hazard ratio was based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and was relative to placebo with <1 favouring the enzalutamide group.
Abbreviations: ITT: intent-to-treat; IXRS: Interactive voice/web recognition system; MFS: metastasis-free survival; PSADT: prostate-specific antigen doubling time.

The robustness of the MFS results was demonstrated through pre-specified sensitivity analyses evaluating the effect of various censoring rules on the MFS of enzalutamide versus placebo. The different censoring rules were the following[2]:

- Sensitivity 1: Inclusion of progression after alternative therapy as an event
- Sensitivity 2: Inclusion of any post-treatment death as an event
- Sensitivity 3: Assessment of impact of antineoplastic therapies by censoring patients who received any antineoplastic therapy without evidence of metastasis
- Sensitivity 4: MFS based on investigator assessment
- Sensitivity 5: Impact of clinical deterioration for patients who discontinued study drug primarily due to treatment-emergent adverse events (TEAEs) defined by investigator prior to protocol-defined evidence of radiographic deterioration.

[redacted]

[redacted]7[redacted]

[redacted]

Source: PROSPER Clinical Study Report[2].
Note: Numbers of patients included in this analysis were 933 for the enzalutamide group and 468 for the placebo group. Hazard ratios for all analyses were based on a Cox regression model (with treatment as the only covariate) stratified by PSADT (<6 months, ≥6 months) and prior or concurrent use of a bone-targeting agent (yes, no) as per IXRS.
Abbreviations. CI: confidence interval; ITT: intent-to-treat; IXRS: interactive voice/web recognition system; MFS: metastasis-free survival; PSADT: prostate-specific antigen doubling time.

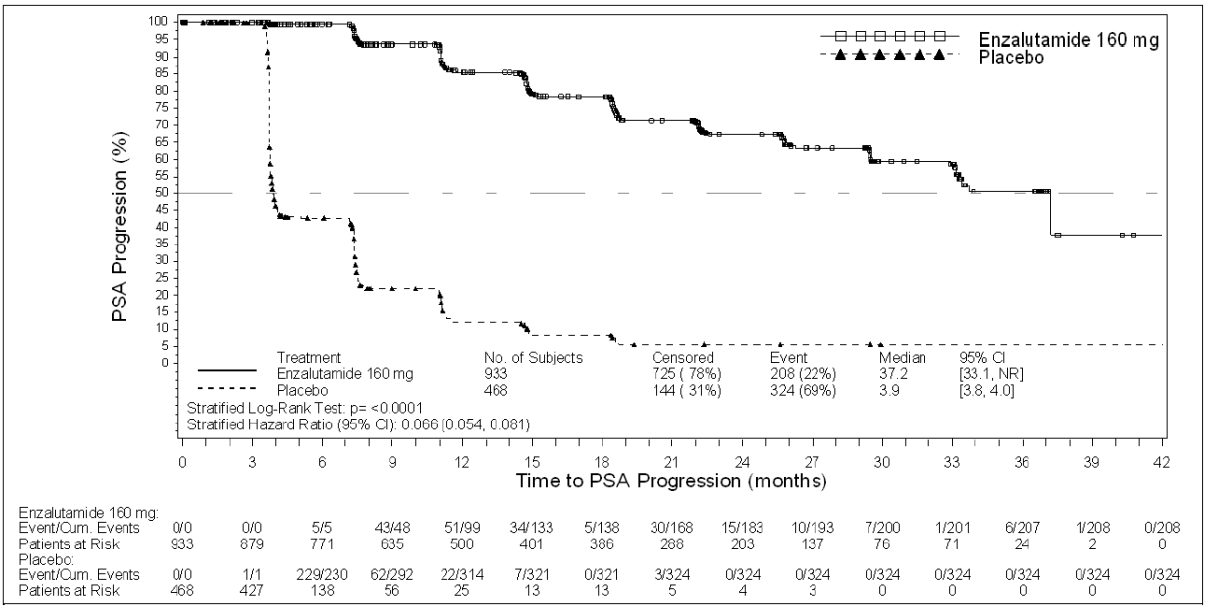
B.2.6.1.2 Key secondary endpoints

As per protocol, all key and additional secondary endpoints were also evaluated at the data cut-off point of approximately 440 MFS events, 28 June 2017. These evaluations were final for all endpoints except for OS for which only 165 events had occurred. The final OS analysis is expected to take place at 596 events with additional planned interim analyses at 285 and 440 deaths.

B.2.6.1.2.1 Time to PSA progression

A total of 208 patients (22.3%) in the enzalutamide group and 324 patients (69.2%) in the placebo group experienced PSA progression as of the data cut-off date. Treatment with enzalutamide was associated with a statistically significant 93.4% reduction in the risk of PSA progression (HR: 0.066, 95% CI: [0.054; 0.081], p<0.0001). The median [95% CI] time to PSA progression was 37.2 months [33.1; not reached (NR)] in the enzalutamide group versus 3.9 months [3.8; 4.0] in the placebo group, with a treatment difference of 33.3 months.

Figure 8 Kaplan-Meier curves for time to PSA progression (ITT population)



Source: PROSPER Clinical Study Report[2]. Note: p-value was based on a log-rank test stratified by PSADT (<6 months, ≥6 months) and prior or concurrent use of a bone-targeting agent (yes, no) as per IXRS.
Hazard ratio was based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and was relative to placebo with <1 favouring the enzalutamide group.
Abbreviations: CI: confidence interval; ITT: intent-to-treat; IXRS: interactive voice/web recognition system; PSADT: prostate-specific antigen doubling time.

B.2.6.1.2.2 Time to first use of new antineoplastic therapy

A total of 142 patients (15.2%) in the enzalutamide group and 226 patients (48.3%) in the placebo group initiated first use of a new antineoplastic therapy (e.g., cytotoxic, hormonal except GnRH agonist/antagonist, or investigational; Table 12). Abiraterone and docetaxel were the most frequently reported post-baseline antineoplastic therapy. Overall, 15 (1.6%) and 29 (6.2%) patients in the enzalutamide and placebo arms, respectively received bicalutamide post-baseline. Enzalutamide significantly delayed by 21.9 months median time to first use of new antineoplastic therapy (HR: 0.208, 95% CI: [0.168; 0.258], p-value<0.0001; Figure 9).

Table 12 Time to first use of new antineoplastic therapy (ITT population)

Outcome	Enzalutamide (n=933)	Placebo (n=468)
Status of antineoplastic therapy follow-up		
Event[a]	142 (15.2%)	226 (48.3%)
Censored[b]	791 (84.8%)	242 (51.7%)
Time to first use of antineoplastic therapy[c] (months)		
n	933	468
25th percentile	30.9	8.8
Median [95% CI]	39.6 [37.7; NR]	17.7 [16.2; 19.7]
75th percentile	NR	35.3
Treatment comparison: enzalutamide versus placebo		
Hazard ratio [95% CI][d]	0.208 [0.168; 0.258]	
p-value[d]	<0.0001	
Median follow-up time based on reverse Kaplan-Meier estimates for all patients (months)	22.1	22.0

Source: PROSPER Clinical Study Report[2]

a. Based on the first post-baseline use of antineoplastic therapy for prostate cancer.

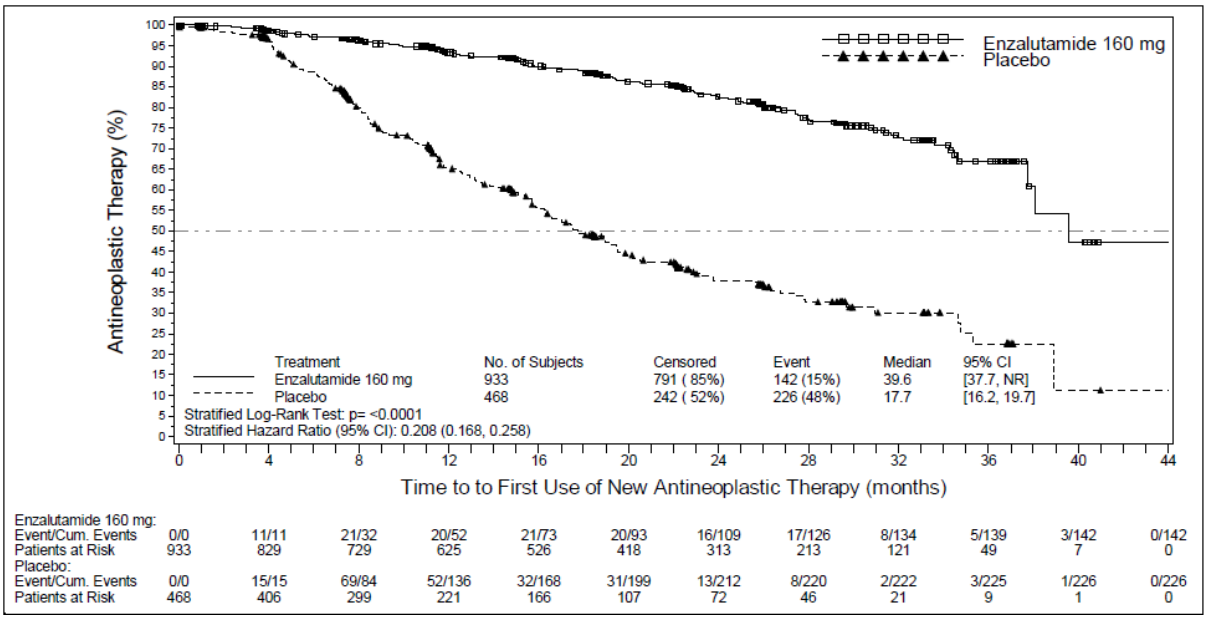
b. Patients who have not initiated antineoplastic therapy for prostate cancer at the time of analysis data cut-off were censored at date of last assessment prior to the analysis data cut-off date.

c. Based on Kaplan-Meier estimates. Kaplan-Meier curves are provided in Figure 9

d. p-value was based on a stratified log-rank test by PSADT (<6 months, ≥6 months) and prior or concurrent use of a bone-targeting agent (yes, no) as per IXRS. Hazard ratio was based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and was relative to the placebo group with <1 favouring the enzalutamide group.

Abbreviations. CI: confidence interval; ITT: intent-to-treat; IXRS: interactive voice/web recognition system; n: number of patients NR: not reached; PSADT: prostate-specific antigen doubling time.

Figure 9 Kaplan-Meier curves for time to first use of new antineoplastic therapy (ITT population)



Source: PROSPER Clinical Study Report[2]
Note: p-value was based on a log-rank test stratified by PSADT (<6 months, ≥6 months) and prior or concurrent use of a bone-targeting agent (yes, no) as per IXRS.
Hazard ratio was based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and was relative to placebo with <1 favouring the enzalutamide group.
Abbreviations: CI: confidence interval; ITT: intent-to-treat; IXRS: interactive voice/web recognition system; PSADT: prostate-specific antigen doubling time.

B.2.6.1.2.3 Overall Survival

As already mentioned in Section B.2.4.6 (Table 9), the protocol pre-specified three interim analyses and one final analysis for OS data. Data from the first two interim OS analyses are currently available. As of the data cut-off date for the formal analysis of the primary endpoint of MFS (28 June 2017), a total of 165 deaths (approximately 30% of the 596 deaths specified for the final OS analysis) occurred and included 103 deaths (11.0%) in the enzalutamide group and 62 deaths (13.2%) in the placebo group (Table 13). This first interim analysis (IA1) of OS did not show a statistically significant decrease in the risk of death in patients treated with enzalutamide versus placebo (HR: 0.795, 95% CI: 0.580; 1.089; p-value=0.1519; Figure 10); however, OS data are not yet mature, and the median OS was not reached in either treatment group. The patients continue to be followed for survival, and a second interim OS analysis was planned for when 285 deaths had occurred.

Table 13 Overall survival IA1 (ITT population)

Outcome	Enzalutamide (n=933)	Placebo (n=468)
Survival status		
Death	103 (11.0%)	62 (13.2%)
Censored[a]	830 (89.0%)	406 (86.8%)
Alive at data analysis cut-off date	808 (86.6%)	387 (82.7%)
Withdrew consent	19 (2.0%)	17 (3.6%)

Outcome	Enzalutamide (n=933)	Placebo (n=468)
Lost to follow-up	2 (0.2%)	0 (0.0%)
Other	1 (0.1%)	2 (0.4%)
Overall survival[b] (months)		
n	933	468
25th percentile	NR	34.0
Median [95% CI]	NR [NR; NR]	NR [NR; NR]
75th percentile	NR	NR
Treatment comparison: enzalutamide versus placebo		
Hazard ratio [95% CI][c]	0.795 [0.580; 1.089]	
p-value[c]	0.1519	
Probability of being event-free at:[b]		
Year 1 [95% CI]	0.98 [0.96; 0.98]	0.97 [0.95; 0.98]
Year 2 [95% CI]	0.91 [0.88; 0.93]	0.87 [0.82; 0.90]
Year 3 [95% CI]	0.77 [0.71; 0.81]	0.71 [0.62; 0.78]
Median follow-up time based on reverse Kaplan-Meier estimates for all patients (months)	[redacted]	[redacted]

Source: PROSPER Clinical Study Report

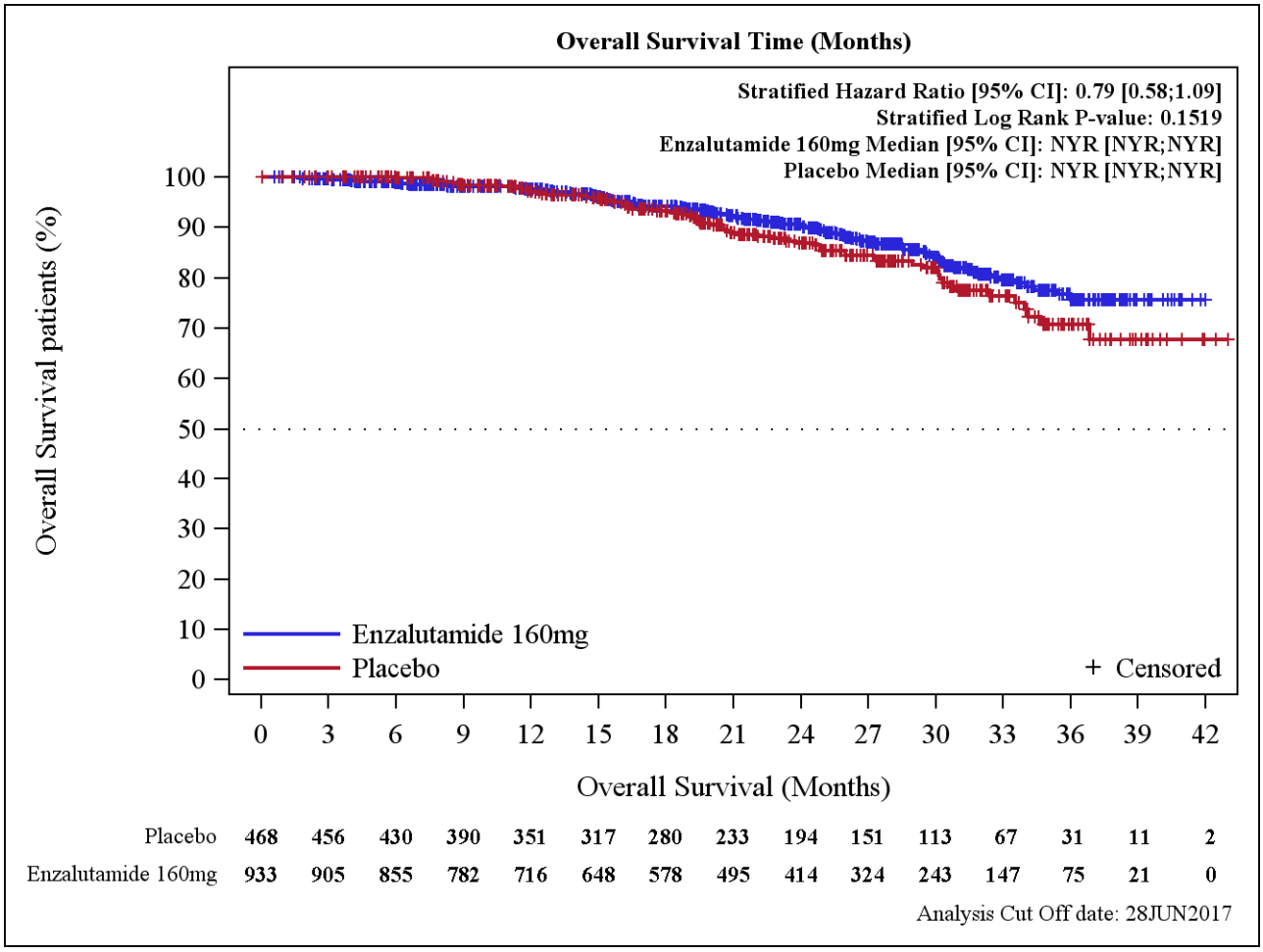
a. Patients who were not known to have died at the analysis date were censored at the date last known alive or data analysis cut-off date, whichever occurred first.

b. Based on Kaplan-Meier estimates. Kaplan-Meier curves are provided in Figure 10.

c. P-value was based on a stratified log-rank test by PSADT (<6 months, ≥6 months) and prior or concurrent use of a bone-targeting agent (yes, no) as per IXRS. Hazard ratio was based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and was relative to the placebo group with <1 favouring the enzalutamide group.

Abbreviations: CI: confidence interval; IA1: interim analysis 1; ITT: intent-to-treat; IXRS: interactive voice / web recognition system; n: number of patients; NR: not reached; PSA: prostate-specific antigen.

Figure 10 Kaplan-Meier curves for duration of OS IA1 (ITT population)



Source: PROSPER Clinical Study Report[2].
Note: p-value was based on a log-rank test stratified by PSA doubling time (<6 months, ≥6 months) and prior or concurrent use of a bone-targeting agent (yes, no) as per IXRS.
Hazard ratio was based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and was relative to placebo with <1 favouring the enzalutamide group.
Abbreviations: IA1: interim analysis 1; ITT: intent-to-treat; IXRS: interactive voice/web recognition system; OS: overall survival; PSADT: prostate-specific antigen doubling time.

As per protocol, the IA2 was performed at approximately 285 deaths. The data cut-off date for this analysis was 31 May 2018 when 288 deaths had occurred (approximately 48% of the 596 deaths specified for the final OS analysis).
[redacted] The IA2 data included [redacted] deaths ([redacted] in the enzalutamide group and [redacted] deaths ([redacted] in the placebo group (Table 14).

Overall,
[redacted], *** [redacted] 11).

Table 14 IA2 overall survival (ITT population)

Outcome	Enzalutamide (n=933)	Placebo (n=468)
Survival status		
Death	[redacted]	[redacted]
Censored[a]	[redacted]	[redacted]
Alive at data analysis cut-off date	[redacted]	[redacted]
Withdrew consent	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Other	[redacted]	[redacted]
Overall survival[b] (months)		
n	[redacted]	[redacted]
25th percentile	[redacted]	[redacted]
Median [95% CI]	[redacted]	[redacted]
75th percentile	[redacted]	[redacted]
Treatment comparison: enzalutamide versus placebo		
Hazard ratio [95% CI][c]	[redacted]	
p-value[c]	[redacted]	
Probability of being event-free at:[b]		
Year 1 [95% CI]	[redacted]	[redacted]
Year 2 [95% CI]	[redacted]	[redacted]
Year 3 [95% CI]	[redacted]	[redacted]
Median follow-up time based on reverse Kaplan-Meier estimates for all patients (months)	[redacted]	[redacted]

Source: PROSPER extrapolation report[45]

a. P-value is based on a stratified log-rank test.

b. Hazard ratio is based on a stratified Cox regression model (with treatment as the only covariate) and is relative to placebo with < 1 favouring enzalutamide. The 2 randomisation factors are PSA doubling time (< 6 months vs. >= 6 months) and prior or current use of a bone targeting agent.

Abbreviations: CI: Confidence interval; HR: Hazard ratio; n: number of patients; NR: Not reached; SE: standard error.

11

Source: PROSPER extrapolation report[46]
Abbreviations: IA2: interim analysis 2; ITT: intention to treat; OS: overall survival.

B.2.6.1.2.4 Antineoplastic therapy administered after treatment discontinuation

Patients who progressed while being on study drug, received second-line therapy. In IA1, [redacted] and [redacted] of patients in the enzalutamide and placebo arms respectively received at least one antineoplastic therapy after discontinuation of study treatment. In IA2, this percentage was [redacted] and [redacted] for enzalutamide and placebo, respectively (Table 15). Of these therapies, docetaxel and abiraterone have been shown to have an OS benefit. A higher proportion of patients in the placebo arm had received second line docetaxel and abiraterone at the time of IA1 and IA2 OS analyses (Table 15).

Table 15 Antineoplastic therapy administered to at least 1% of patients in either treatment group after treatment discontinuation in IA1 or IA2 (safety population)

	IA1		IA2	
	ENZA 160 mg (N=930)	PLA (N=465)	ENZA 160 mg (N=930)	PLA (N=465)
Number of patients taking at least one posttreatment discontinuation antineoplastic	[redacted]	[redacted]	[redacted]	[redacted]
All other therapeutic products	[redacted]	[redacted]	[redacted]	[redacted]
Investigational drug	[redacted]	[redacted]	[redacted]	[redacted]

	IA1		IA2	
	ENZA 160 mg (N=930)	PLA (N=465)	ENZA 160 mg (N=930)	PLA (N=465)
Antineoplastic agents	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]
Estramustine	[redacted]	[redacted]	[redacted]	[redacted]
Corticosteroids for systemic use	[redacted]	[redacted]	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]
Prednisolone	[redacted]	[redacted]	[redacted]	[redacted]
Dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]
Drugs for treatment of bone diseases	[redacted]	[redacted]	[redacted]	[redacted]
Denosumab	[redacted]	[redacted]	[redacted]	[redacted]
Zoledronic Acid	[redacted]	[redacted]	[redacted]	[redacted]
Endocrine therapy	[redacted]	[redacted]	[redacted]	[redacted]
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]
Bicalutamide	[redacted]	[redacted]	[redacted]	[redacted]
Leuprorelin	[redacted]	[redacted]	[redacted]	[redacted]
Goserelin	[redacted]	[redacted]	[redacted]	[redacted]
Triptorelin	[redacted]	[redacted]	[redacted]	[redacted]
Flutamide	[redacted]	[redacted]	[redacted]	[redacted]
Immunostimulants	[redacted]	[redacted]	[redacted]	[redacted]
Sipuleucel-T	[redacted]	[redacted]	[redacted]	[redacted]
BCG-vaccine	[redacted]	[redacted]	[redacted]	[redacted]
Lentinan	[redacted]	[redacted]	[redacted]	[redacted]
Sex hormones and modulators of the genital system	[redacted]	[redacted]	[redacted]	[redacted]
Antiandrogens	[redacted]	[redacted]	[redacted]	[redacted]
Therapeutic Radiopharmaceuticals	[redacted]	[redacted]	[redacted]	[redacted]

Source: PROSPER Clinical Study Report[2].

Abbreviations: ENZA: enzalutamide; n: number of patients; OS: overall survival; PLA: placebo. Drugs were classified using the World Health Organisation Drug Dictionary.

B.2.6.1.3 Other secondary endpoints

B.2.6.1.3.1 Time to pain progression

Time to pain progression was assessed using the score from the Brief Pain Inventory-Short Form (BPI-SF) question 3, with pain progression defined as a ≥2-point increase from baseline. As of the data analysis cut-off date, [redacted] in the enzalutamide group and [redacted] in the placebo group had pain progression. Time to pain progression was comparable between enzalutamide and placebo ([redacted]). The median (95% CI) time to pain progression was [redacted] in the enzalutamide group versus [redacted] in the

placebo group at the data analysis cut-off date.
[redacted] median MFS was 36.6 months (95% CI: [33.1; not reached]) in the enzalutamide group and 14.7 months (95% CI: [14.2; 15.0]) in the placebo group. It cannot be ruled out that many of the pain events reported in PROSPER would be due to the advanced age of patients rather than to bone metastases-related pain.
[redacted].

B.2.6.1.3.2 Time to first use of cytotoxic chemotherapy, chemotherapy-free survival and chemotherapy-free disease specific survival

The definitions of time to first use of cytotoxic chemotherapy, chemotherapy-free disease specific survival and chemotherapy-free survival all included time to chemotherapy initiation (Table 16). Therefore, these three endpoints are reported together.

Table 16 Definition of time to chemotherapy initiation-related endpoints in PROSPER

Endpoint	Definition
Time to first use of cytotoxic chemotherapy	time from randomisation to the first use of cytotoxic chemotherapy for prostate cancer
Chemotherapy-free disease specific survival	time from randomisation to first use of cytotoxic chemotherapy for prostate cancer or death due to prostate cancer as assessed by the investigator
Chemotherapy-free survival	Time from randomisation to first use of cytotoxic chemotherapy for prostate cancer or death due to any cause

As of the data analysis cut-off date, a total of [redacted] patients ([redacted] in the enzalutamide group and [redacted] patients ([redacted]%) in the placebo group initiated a cytotoxic chemotherapy agent. In addition, there were [redacted] deaths ([redacted] of which [redacted] due to prostate cancer ([redacted]%) in the enzalutamide group and [redacted] deaths in the placebo group, of which [redacted] were prostate cancer specific (Table 17).
[redacted] (Table 17).

Table 17 Time to first use of cytotoxic chemotherapy, chemotherapy-free disease specific survival and chemotherapy-free survival (ITT population)

Outcome	Enzalutamide (n=933)	Placebo (n=468)
Status of chemotherapy and survival follow-up		
Event[a]	[redacted]	[redacted]
Initiated chemotherapy	[redacted]	[redacted]
Death	[redacted]	[redacted]
Death due to prostate cancer	[redacted]	[redacted]
Censored[b]	[redacted]	[redacted]

Outcome	Enzalutamide (n=933)	Placebo (n=468)
Treatment comparison: First Cytotoxic Therapy		
Hazard ratio [95% CI][c]	[redacted]	
p-value[c]	[redacted]	
Treatment comparison: Chemotherapy-Free Disease-Specific Survival		
Hazard ratio [95% CI][c]	[redacted]	
p-value[c]	[redacted]	
Treatment comparison: Chemotherapy-Free Survival		
Hazard ratio [95% CI][c]	[redacted]	
p-value[c]	[redacted]	

Source: PROSPER Clinical Study Report[2]

a. Based on the first post-baseline use of cytotoxic chemotherapy for prostate cancer.

b. Patients who had not initiated cytotoxic chemotherapy for prostate cancer at the time of analysis data cut-off were censored at date of last assessment prior to the analysis data cut-off date.

c. P-value was based on a stratified log-rank test by PSADT (<6 months, ≥6 months) and prior or concurrent use of a bone targeting agent (yes, no) as per IXRS. Hazard ratio was based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and was relative to the placebo group with <1 favouring the enzalutamide group.

Abbreviations: CI: confidence interval; ITT: intent-to-treat; IXRS: interactive voice / web recognition system; n: number of patients; PSADT: prostate-specific antigen doubling time.

B.2.6.1.3.3 PSA response

PSA response rate is summarised in Table 18. Three different PSA-response rate were assessed: ≥50% decrease from baseline, ≥90% decrease and decrease to an undetectable level. The differences in rates were compared between treatment groups using a Cochran-Mantel-Haenszel mean score test stratified by PSADT and prior or concurrent use of a BTA. The difference in response rates consistently favoured enzalutamide being significant for all levels of PSA reduction (p-value<0.0001).

Table 18 PSA response rates (ITT population)

Outcome	Enzalutamide (n=933)	Placebo (n=468)
Patients with baseline PSA values	933 (100.0%)	467 (99.8%)
With at least 1 post-baseline PSA assessment	887 (95.1%)	439 (93.8%)
No post-baseline assessment	46 (4.9%)	28 (6.0%)
Number of evaluable patients[a]	887	439
Confirmed responders (≥50% reduction)[b]	712 (76.3%)	11 (2.4%)
95% CI for response rate[c]	73.5%;79.0%	1.2%;4.2%
Difference in response rate [95% CI][d]	73.96% [70.91%;77.02%]	
p-value[e]	<0.0001	
Confirmed responders (≥90% reduction)[b]	522 (55.9%)	2 (0.4%)
95% CI for response rate[c]	52.7%;59.2%	0.1%;1.5%
Difference in response rate [95% CI][d]	55.52% [52.28%;58.76%]	
p-value[e]	<0.0001	

Outcome	Enzalutamide (n=933)	Placebo (n=468)
Confirmed responders (decrease to undetectable level)[b]	90 (9.6%)	0 (0.0%)
95% CI for response rate[c]	7.8%-11.7%	99.2%-100.0%
Difference in response rate [95% CI][d]	9.65% [7.75%;11.54%]	
p-value[e]	<0.0001	

Source: PROSPER Clinical Study Report[2]

a. Evaluable patients for PSA response were patients with a baseline PSA value and at least 1 post-baseline PSA value.

b. Confirmation required a subsequent assessment that was consecutive and conducted at least 3 weeks later.

c. Clopper-Pearson exact binomial CI.

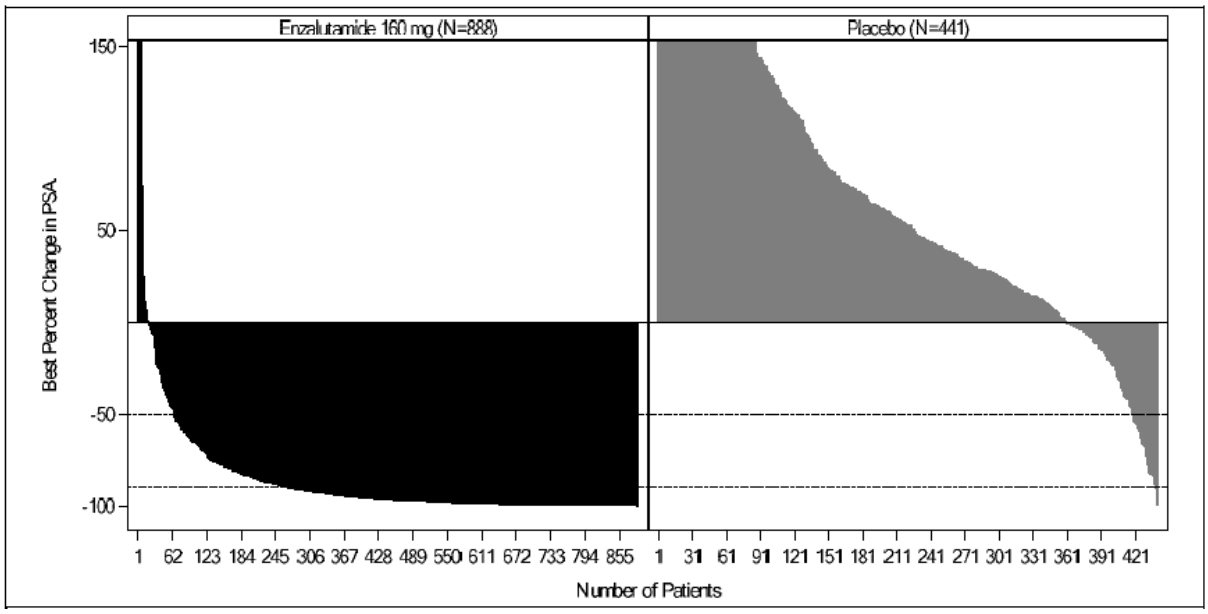
d. Enzalutamide rate minus placebo rate.

e. p-value was based on Cochran-Mantel-Haenszel mean score test stratified by PSA doubling time (<6 months, ≥6 months) and prior or concurrent use of a bone-targeting agent (yes, no) as per IXRS.

Abbreviations: CI: confidence interval; ITT: intent-to-treat; IXRS: interactive voice/web recognition system; n: number of patients; PSA: prostate-specific antigen.

A waterfall plot of the best PSA response on study (percent PSA change) for all evaluable patients is shown in Figure 12. The results showed that most patients treated with enzalutamide in this study had substantial decreases in PSA compared with few patients treated with placebo who had decreases in PSA.

Figure 12 Waterfall plot of PSA best responses (ITT population)



Source: PROSPER Clinical Study Report[2]

Only patients who had both baseline and post-baseline assessments were included in this analysis. Each vertical bar represented a patient. The length of the bar was sorted in a descending order of the best percent change of PSA levels.

Abbreviations: ITT: intent-to treat; n: number of patients; PSA: prostate-specific antigen.

B.2.6.1.3.4 Health-related quality of life and other patient-reported outcomes

Patient reported outcomes (PROs) were assessed using the Brief Pain Inventory short-form (BPI-SF), Functional Assessment of Cancer Therapy-Prostate (FACT-P), the prostate

cancer module (QLQ-PR25) of the European Organisation for Research and Treatment of Cancer (EORTC), and the European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L). PROs were collected at the randomisation visit (baseline), at week 17, every 16 weeks thereafter, and at the safety follow-up (approximately 30 days after the last dose of study drug). PROs were to be collected after disease progression.

Baseline scores for all instruments were comparable between treatment arms and showed that high risk nmHRPC patients were either asymptomatic or had a low symptom burden, had good HRQoL and were high functioning (Table 19). For BPI-SF, 65.4% and 69.0% of patients in the enzalutamide and placebo groups, respectively, had a baseline score of 0 denoting no pain. According to the baseline EORTC QLQ-PR25 scores, symptom burden was low across all domains, except for sexual activity and sexual functioning.

Table 19 Baseline PRO scores in PROSPER (ITT population)

Outcome	Enzalutamide (n=933)		Placebo (n=468)	
BPI-SF scores, mean (SD)				
Item 3: pain at its worst	887	1.24 (2.09)	439	1.01 (1.94)
Pain severity	887	0.93 (1.50)	439	0.71 (1.35)
Pain interference	887	0.75 (1.47)	439	0.59 (1.43)
EORTC QLQ-PR25, mean (SD)				
Sexual activity*	[redacted]	[redacted]	[redacted]	[redacted]
Sexual functioning*	49	53.40 (23.44)	24	48.26 (26.35)
Bowel symptoms and function	884	5.14 (8.39)	439	4.65 (7.70)
Hormonal treatment-related symptoms	884	14.92 (12.50)	439	15.79 (13.30)
Urinary symptoms and problems	884	20.69 (17.55)	439	20.02 (17.68)
FACT-P, mean (SD)				
Physical well-being	887	25.02 (3.32)	439	25.28 (3.23)
Functional well-being	887	19.99 (5.17)	439	20.14 (5.15)
Emotional well-being	887	19.18 (3.54)	439	19.16 (3.64)
Social/family well-being	887	20.69 (5.57)	439	20.73 (5.12)
Prostate cancer scale	887	34.67 (6.13)	439	35.47 (5.73)
Prostate cancer pain scale	887	13.16 (3.44)	439	13.56 (3.15)
FACT-P total score	887	119.54 (17.75)	439	120.79 (16.73)
EQ-5D-5L, mean (SD)				
EQ-VAS	884	76.17 (16.92)	439	77.53 (15.97)

Source: PROSPER PRO report[40]. **Lower score meaning worse functioning.
Abbreviations: BPI-SF: Brief Pain Inventory Short Form; EORTC QLQ-PR25: European Organisation for Research and Treatment of Cancer Quality of life Questionnaire; EQ-5D-5L: European Quality of Life-5 Dimensions-5 Levels health questionnaire; EQ-VAS: European Quality of Life-Visual Analogue Scale; FACT-P: Functional Assessment of Cancer Therapy-Prostate; SD: standard deviation.

The PRO findings in PROSPER show that enzalutamide does not increase symptom burden in high risk nmHRPC subjects and that subjects maintain their HRQoL.

Regarding pain, BPI-SF scores remained stable (changes <2 points) in both treatment groups up to week 97 (data not shown). Longitudinal changes from baseline in BPI-SF scores were analysed using a mixed model for repeated measures (MMRM, Table 20). No statistically significant differences were observed between arms but the difference between treatment arms in change from baseline in all BPI SF scores numerically favoured enzalutamide at most time points. At week 97, both treatment arms showed increases in pain scores from baseline but they did not meet the clinically meaningful threshold and no significant differences were observed between the groups (Table 20). However, the median time to first confirmed pain progression was longer for patients receiving enzalutamide compared with placebo for the BPI-SF item 3 and pain interference scores, with a significantly lower hazard in favour of enzalutamide in the BPI-SF severity composite score ([redacted]; Table 21).

Pain was also assessed using the FACT-P prostate cancer subscale – pain related (PCS-Pain). Similar results were observed on the PCS-pain, with no significant difference between the groups (Table 20) and a numerically longer median time to worsening of pain symptoms with enzalutamide compared to placebo (Table 21).

Table 20 Mean changes in PRO scores from baseline to week 97 (MMRM)

Instrument	LS mean (SE)		LS mean difference [95% CI]
	Enzalutamide	Placebo	Enzalutamide vs placebo
BPI-SF			
Item 3: pain at its worst	0.52 (0.13)	0.73 (0.22)	-0.21 [-0.66, 0.24]
Pain severity	0.49 (0.10)	0.55 (0.16)	-0.06 [-0.40, 0.29]
Pain interference	0.65 (0.10)	0.85 (0.16)	-0.20 [-0.53, 0.13]
EORTC QLQ-PR25			
Bowel symptoms and function	[redacted]	[redacted]	[redacted]
Hormonal treatment-related symptoms	[redacted]	[redacted]	[redacted]
Urinary symptoms and problems	[redacted]	[redacted]	[redacted]
FACT-P			
Physical well-being	-2.26 (0.23)	-2.00 (0.36)	-0.26 [-1.00, 0.49]
Social well-being	0.30 (0.28)	-0.64 (0.44)	**0.94 [0.02, 1.85]**
Emotional well-being	-0.24 (0.20)	-0.58 (0.31)	0.34 [-0.30, 0.98]
Functional well-being	-2.44 (0.28)	-2.57 (0.44)	0.13 [-0.78, 1.05]
Prostate cancer scale	-2.61 (0.32)	-3.32 (0.51)	0.70 [-0.35, 1.75]
Prostate cancer pain scale	-0.93 (0.18)	-1.06 (0.28)	0.13 [-0.46, 0.71]
FACT-P total	-7.17 (0.92)	-9.20 (1.45)	2.04 [-0.97, 5.04]
EQ-5D-5L			
EQ-VAS	[redacted]	[redacted]	[redacted]

Source: PROSPER PRO report[40]. A negative contrast favours enzalutamide over placebo for BPI-SF scores and bowel symptoms and function, hormonal treatment-related symptoms, and urinary symptoms and problems, while a positive contrast favours enzalutamide over placebo for FACT-P scores, sexual activity and EQ-VAS. Bolded contrast is significant at the p<0.05 level.
Abbreviations: BPI-SF: Brief Pain Inventory Short Form; EORTC QLQ-PR25: European Organisation for Research and Treatment of Cancer Quality of life Questionnaire; EQ-5D-5L: European Quality of Life-5 Dimensions-5 Levels health questionnaire; EQ-VAS: European Quality of Life-Visual Analogue Scale; FACT-P: Functional Assessment of Cancer Therapy-Prostate; LS: least squares; MMRM: mixed model repeated measures; SE: standard error.

Table 21 Time to confirmed symptoms progression and HRQoL deterioration (ITT population)

Instrument	Median (95% CI) time, months		HR (95% CI)
	Enzalutamide	Placebo	
BPI-SF			
Item 3	34.69 [29.73, 36.86]	30.52 [22.11, NR]	0.82 [0.66, 1.03]
Pain severity	36.83 [34.69, NR]	NR	**0.75 [0.57, 0.97]**
Pain interference	33.15 [29.54, NR]	30.52 [22.11, NR]	0.94 [0.76, 1.18]
EORTC QLQ-PR25			
Bowel symptoms/function	33.15 [29.50, NR]	25.89 [18.43, 29.67]	**0.72 [0.59, 0.89]**
Hormonal treatment-related symptoms	33.15 [29.60, NR]	36.83 [29.47, NR]	**1.29 [1.02, 1.63]**
Urinary symptoms and problems	36.86 [33.35, NR]	25.86 [18.53, 29.47]	**0.56 [0.46, 0.72]**
FACT-P			
Physical well-being	18.56 [16.82, 22.18]	19.35 [18.33, 25.79]	1.15 [0.96, 1.38]
Social well-being	34.04 [29.60, NR]	29.50 [25.79, NR]	0.87 [0.71, 1.08]
Emotional well-being	36.73 [33.12, 38.21]	29.47 [22.18, 33.15]	**0.69 [0.55, 0.86]**
Functional well-being	18.60 [18.20, 22.14]	18.37 [14.78, 18.66]	0.94 [0.79, 1.13]
Prostate cancer scale	18.43 [14.85, 18.66]	14.69 [11.07, 16.20]	**0.79 [0.67, 0.93]**
Prostate cancer pain scale	25.76 [22.11, 29.47]	22.11 [18.40, 30.52]	0.94 [0.78, 1.14]
FACT-P total	22.11 [18.63, 25.86]	18.43 [14.85, 19.35]	**0.83 [0.69, 0.99]**
EQ-5D-5L			
EQ-VAS	[redacted]	[redacted]	**0.75 [0.63, 0.90]**

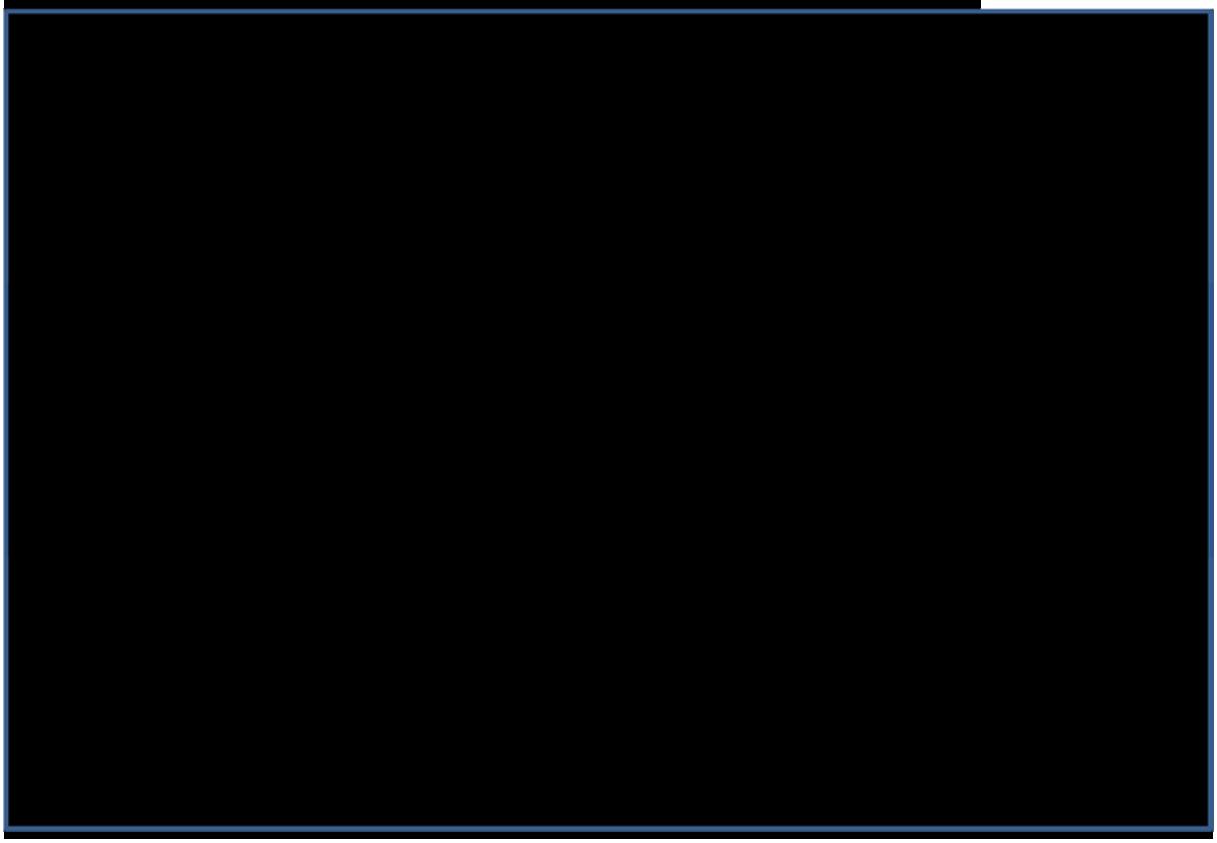
Source: PROSPER PRO report[40]; Attard et al[37]. Bolded contrast is significant at the p<0.05 level.
Abbreviations: BPI-SF: Brief Pain Inventory Short Form; CI=confidence interval; EORTC QLQ-PR25: European Organisation for Research and Treatment of Cancer Quality of life Questionnaire; EQ-5D-5L: European Quality of Life-5 Dimensions-5 Levels health questionnaire; EQ-VAS: European Quality of Life-Visual Analogue Scale; FACT-P: Functional Assessment of Cancer Therapy-Prostate; HR: hazard ratio; HRQoL: health-related quality of life; NR: not yet reached.

Mean EORTC QLQ-PR25 symptom scores also remained stable over the study (Table 20). No clinically meaningful difference between treatment arms was observed at week 97. However, compared with placebo, enzalutamide significantly delayed the time to first

confirmed worsening of urinary (36.86 vs 25.86 months; HR: 0.56, 95% CI [0.46, 0.72]) and bowel symptoms (33.15 vs 25.89 months; HR: 0.72, 95% CI [0.59, 0.89]). In contrast, time to first confirmed worsening in hormonal treatment-related symptoms favoured placebo (33.15 vs 36.83 months; HR: 1.29, 95% CI [1.02, 1.63]).

HRQoL also remained stable up to week 97 based on FACT-P scores (*** [redacted] 13). In the longitudinal analysis (MMRM), the difference between treatment arms in change from baseline in FACT-P total scores was less than 6 points, denoting no clinically meaningful difference (Table 20). At week 97, all scores decreased in both arms versus baseline, except for social well-being score among enzalutamide patients which increased (i.e., improved) by 0.30 (SD 0.28) points). This difference was statistically significant versus placebo (LS mean [95% CI 0.02, 1.85]; Table 20). Enzalutamide treatment was associated with a numerically, and for some outcomes statistically significant, lower decrease compared with placebo on all scores, except for physical wellbeing (Table 21). In line with the results observed for BPI-SF and EORTC QLQ-PR25, median time to first confirmed deterioration in FACT-P scores favoured enzalutamide versus placebo for all scores (18.43–36.73 vs 14.69–29.50) except for physical wellbeing (18.56 vs 19.35; Table 21). This difference in median time to deterioration reached statistical significance for emotional wellbeing (HR 0.69 [95% CI 0.55, 0.86]), physical composite score (HR 0.79 [95% CI 0.67, 0.93]) and FACT P total score (HR 0.83 [95% CI 0.69, 0.99]).

[redacted] 13



Source: PROSPER PRO report[40].
Abbreviations: FACT-P: functional assessment of cancer therapy – Prostate; MMRM: mixed model for repeated measures; SD: standard deviation.

Most patients maintained their baseline health status as assessed with EQ-5D utility and VAS scores over the observation period. The difference between arms in change from baseline for EQ-VAS numerically favoured enzalutamide at most time points. At week 97, patients receiving enzalutamide reported less decrease in EQ-VAS compared with placebo; the difference was not statistically significant (Table 20). However, enzalutamide significantly delayed median time to confirmed deterioration ([redacted]) versus placebo (Table 21).

B.2.6.1.4 Additional end points

Time to treatment discontinuation (TTD), pre-progression survival (PrePS), and post-progression survival (PPS) were calculated for modelling purposes. Of these, TTD is discussed here, and PrePS and PPS are discussed in Section B.3.3.3. Data included here originate from the PROSPER extrapolation report[46].

TTD was calculated as “treatment end date” – “treatment start date” + 1. It was calculated for both the IA1 and IA2. All patients were considered to have an event (discontinuation), unless their treatment was ongoing at the time of data cut-off, in which case these patients were censored (Table 22; *** [redacted] 14).

[redacted] than the delay in MFS (36.6 vs 14.7 months; HR: 0.292, 95% CI [0.241, 0.352]). In PROSPER, study drug administration continued at least until radiographic progression was assessed by the study site and BICR. Initiation of new therapy for prostate cancer (with the exception of cytotoxic chemotherapy, androgen receptor inhibitors, and investigational agents) at the time of radiographic progression did not mandate discontinuation of study drug if the investigator considered continuing study drug to be beneficial.

Table 22 Time to treatment discontinuation (IA1), post-progression survival and pre-progression survival (ITT population)

Outcome	Enzalutamide (n=933)	Placebo (n=468)
TTD (IA1)		
Total number of patients	[redacted]	[redacted]
Number of patients with events	[redacted]	[redacted]
Number of censored cases	[redacted]	[redacted]
Mean time to events, months (SE)	[redacted]	[redacted]
Q1 [95% CI]	[redacted]	[redacted]
Median [95% CI]	[redacted]	[redacted]
Q3 [95% CI]	[redacted]	[redacted]
p-value[a]	[redacted]	
HR [95% CI][b]	[redacted]	

Source: PROSPER extrapolation report[46]

a. p-value is based on a stratified log-rank test.

b. Hazard ratio is based on a stratified Cox regression model (with treatment as the only covariate) and is relative to placebo with <1 favouring enzalutamide. The 2 randomisation factors are PSA doubling time (<6 months vs. ≥6 months) and prior or current use of a bone-targeting agent.

Abbreviations: CI: Confidence interval; HR: Hazard ratio; IA1: interim analysis 1; NR: Not reached; PPS: post-progression survival; PrePS: pre-progression survival; SE: standard error; TTD: time to treatment discontinuation.

[redacted]

14

[redacted]

Source: PROSPER extrapolation report[46]

Note: p-value was based on a log-rank test stratified by PSADT (<6 months, ≥6 months) and prior or concurrent use of a bone-targeting agent (yes, no) as per IXRS.

Hazard ratio was based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and was relative to placebo with <1 favouring the enzalutamide group.

Abbreviations: ITT: intent-to-treat; IXRS: Interactive voice/web recognition system; TTD: time to treatment discontinuation; PSADT: prostate-specific antigen doubling time.

TTD was also analysed in the IA2 dataset. At IA2, a total of [redacted] patients had discontinued treatment in the enzalutamide arm versus [redacted] in the placebo arm (Table 23).

[redacted]

Table 23 PROSPER IA2 time to treatment discontinuation (ITT population)

Outcome	Enzalutamide (n=933)	Placebo (n=468)
Status		
Number of patients with events	[redacted]	[redacted]
Number of censored cases	[redacted]	[redacted]
Time to event (months)		
Mean (SE)	[redacted]	[redacted]
Q1 [95% CI]	[redacted]	[redacted]
Median [95% CI]	[redacted]	[redacted]
Q3 [95% CI]	[redacted]	[redacted]
Treatment comparison: enzalutamide versus placebo		
HR [95% CI][b]	[redacted]	
p-value[a]	[redacted]	

Source: PROSPER extrapolation report[46]
a. P-value is based on a stratified log-rank test.
b. Hazard ratio is based on a stratified Cox regression model (with treatment as the only covariate) and is relative to placebo with < 1 favouring enzalutamide. The 2 randomisation factors are PSA doubling time (< 6 months vs. >= 6 months) and prior or current use of a bone targeting agent.
Abbreviations: CI: Confidence interval; HR: Hazard ratio; n: number of patients; NR: Not reached; SE: standard error.

15

Source: PROSPER extrapolation report[46]
Abbreviations: ENZA: enzalutamide; IA2: interim analysis 2; ITT: intention to treat; PLA: placebo; TTD: time to treatment discontinuation.

B.2.6.1.5 Key conclusions

- PROSPER was a randomised double-blind placebo-controlled study comparing enzalutamide plus ADT to placebo plus ADT in adults with high risk nmHRPC.
- The primary endpoint of MFS was met, along with all key secondary endpoints, with the exception of OS. However, the OS analysis is immature with less than half of the total pre-specified number of expected events having occurred at time of this analysis.
- In men with nmHRPC and rapidly rising PSA, treatment with enzalutamide resulted in a substantial improvement in MFS over placebo as shown by:
    - A clinically meaningful and statistically significant 70.8% decrease in the risk of radiographic progression or death.
    - A 21.9 month delay in median time to an MFS event (36.6 months in the enzalutamide group versus 14.7 months in the placebo group).
    - The improvement in MFS was robust and consistent across all pre-specified sensitivity and subgroup analyses.
- Enzalutamide also led to:

- Significantly longer time to PSA progression for enzalutamide over placebo (HR: 0.066, 95% CI [0.054, 0.081]; p<0.0001)
- Significantly longer time to first use of new antineoplastic agent for enzalutamide over placebo (HR: 0.208, 95% CI [0.168, 0.258]; p<0.0001)

- [redacted] OS was still immature (with 28% and [redacted] of the pre-specified deaths at IA1 and IA2, respectively). At the time of this submission, [redacted] (HR for IA1: 0.795 [95% CI: 0.580, 1.089]; p-value=0.1519 and HR for IA2: [redacted]), despite a higher proportion of patients in the placebo arm being switched to therapies some of which with the potential to prolong survival, after discontinuation of the trial medication.
- Baseline scores for BPI-SF, EORTC QLQ-PR25, FACT-P and EQ-5D-5L show that high risk nmHRPC patients are either asymptomatic or have very low symptom burden, have good HRQoL and good functioning. Enzalutamide treatment maintained these baseline levels.
- Despite being active therapy, enzalutamide maintained the low symptom burden, high HRQoL and high functioning throughout the study with no clinically meaningful differences vs placebo. However, enzalutamide statistically significantly delayed time to symptom progression and HRQoL deterioration compared with placebo.

B.2.6.2 STRIVE Clinical effectiveness results

Unless stated otherwise, all data in this section originates from the STRIVE clinical study report (CSR)[41]. Given the indication of relevance, only the results for the nmHRPC population are discussed here.

B.2.6.2.1 Primary outcome: PFS

Among nmHRPC patients, [redacted] and [redacted] of patients in the enzalutamide and bicalutamide arms had a progression or death event (Table 24). Treatment with enzalutamide resulted in a statistically significant reduction in the risk of disease progression vs bicalutamide (HR: 0.24, 95% CI [0.14, 0.42]). The median PFS was not reached in the enzalutamide group versus 8.6 months in the bicalutamide group.

[redacted]

Table 24 PFS - Primary efficacy analysis (nmHRPC ITT population)

Outcome	Enzalutamide (n=70)	Bicalutamide (n=69)
PFS status		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Duration of PFS (months)[c]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Median (95% CI)	NR (19.4, NR)	8.6 (8.1, 11.1)
[redacted]	[redacted]	[redacted]
Treatment comparison[d]		
P-value	<0.0001	
Hazard ratio (95% CI)	0.243 (0.142, 0.416)	

Source: STRIVE Clinical Study Report[41]

a. Based on the earliest occurrence of PSA progression, radiographic progression, or death due to any cause on study and death up to and including 30 days after treatment discontinuation. The individual totals sum up to the total number of PFS events. Concurrent events occurred on the same date.

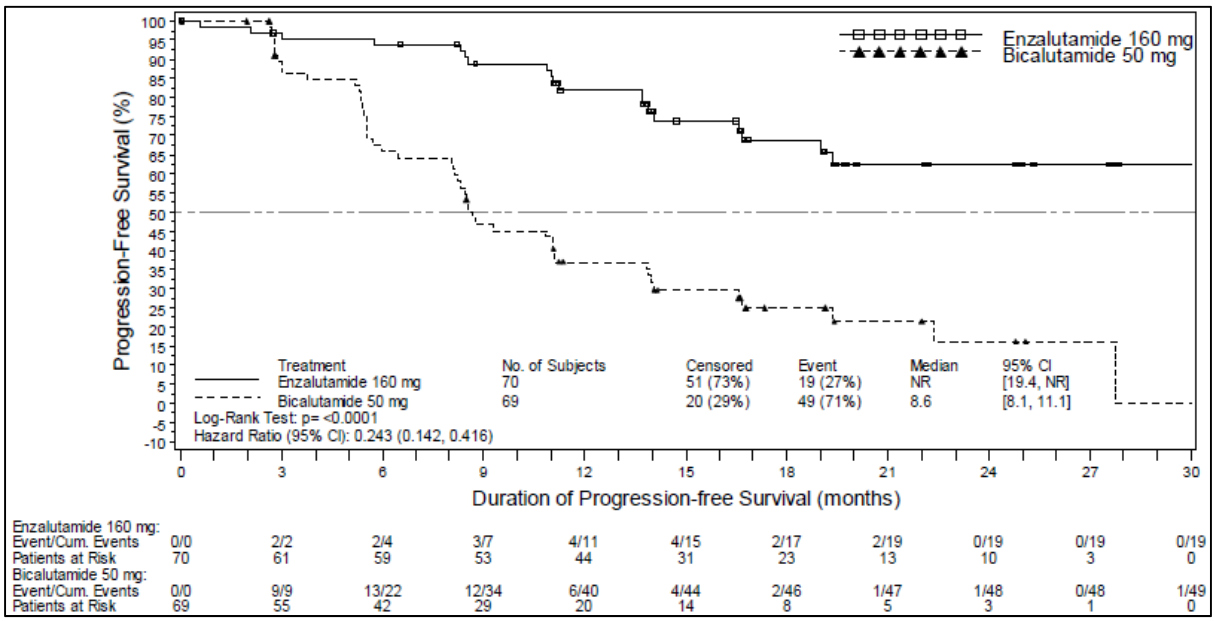
b. Patients not known to have had a PFS event at the time of the analysis data cut-off were censored at the date of last assessment (PSA or radiographic, whichever was later) prior to scan modality change, new antineoplastic treatment, initiation of radiation therapy for prostate cancer, treatment discontinuation, and 2 or more consecutive missed PSA or tumour assessments.

c. Based on Kaplan-Meier estimates.

d. p-value is based on an unstratified log-rank test. Hazard ratio is based on an unstratified Cox regression model (with treatment as the only covariate) and is relative to bicalutamide with <1 favouring enzalutamide.

Abbreviations: ITT: intent-to-treat; NR: not reached; PFS: progression-free survival; PSA: prostate-specific antigen.

Figure 16 Kaplan-Meier curve for PFS (nmHRPC ITT population)



Source: STRIVE Clinical Study Report[41]

P-value is based on an unstratified log-rank test. Hazard ratio is based on an unstratified Cox regression model (with treatment as the only covariate) and is relative to bicalutamide with <1 favouring enzalutamide.

Abbreviations: Cum: cumulative; ITT: intent-to-treat; nmHRPC: non-metastatic hormone-relapsed prostate cancer; NR: not reached; PFS: progression-free survival.

B.2.6.2.2 Secondary outcomes

B.2.6.2.2.1 Time to PSA progression

Enzalutamide reduced time to PSA progression compared with bicalutamide (HR: 0.182, 95% CI [0.098; 0.341]).

[redacted]. Median time to PSA progression was not reached in the enzalutamide group versus 11.1 months in the bicalutamide group (Table 25).

[redacted] (*** [redacted] 17).

Table 25 Time to PSA progression (nmHRPC ITT population)

Outcome	Enzalutamide (n=70)	Bicalutamide (n=69)
Status of PSA follow-up		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Time to PSA progression (months)[b]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Median (95% CI)	NR (NR, NR)	11.1 (8.4, 13.9)
[redacted]	[redacted]	[redacted]
Treatment comparison[c]		

Outcome	Enzalutamide (n=70)	Bicalutamide (n=69)
P-value	<0.0001	
Hazard ratio (95% CI)	0.182 (0.098, 0.341)	
[redacted]	[redacted]	[redacted]

Source: STRIVE Clinical Study Report[41]
a. Patients who were not known to have had PSA progression were censored at the date of last PSA assessment.
b. Based on Kaplan-Meier estimates.
c. P-value is based on an unstratified log-rank test. Hazard ratio is based on an unstratified Cox regression model (with treatment as the only covariate) and is relative to bicalutamide with <1 favouring enzalutamide.
Abbreviations: ITT: intent-to-treat; NR: not reached; PSA: prostate-specific antigen.

[redacted] 17

Source: STRIVE Clinical Study Report[41]
P-value is based on an unstratified log-rank test. Hazard ratio is based on an unstratified Cox regression model (with treatment as the only covariate) and is relative to bicalutamide with <1 favouring enzalutamide.
Cum, cumulative;
Abbreviations: ITT: intent-to-treat; NR: not reached; PSA: prostate-specific antigen.

B.2.6.2.2.2 PSA response ≥50%

A higher proportion of patients in the enzalutamide group had confirmed ≥50% reduction in PSA from baseline (90.9% enzalutamide and 42.0% bicalutamide).

[redacted]

Table 26 PSA response rate (≥50% decrease from baseline; nmHRPC ITT population)

Outcome	Enzalutamide (n=70)	Bicalutamide (n=69)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Number of evaluable patients[a]	66	69
Confirmed ≥50% PSA responders[b]	60 (90.9%)	29 (42.0%)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
P-value vs bicalutamide[e]	<0.0001	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	

Source: STRIVE Clinical Study Report[41]
a. Patients with at least 1 post-baseline PSA assessment.
b. Number of responders divided by number of evaluable patients.
c. Clopper-Pearson exact binomial CI.
d. Enzalutamide rate minus bicalutamide rate.
e. Comparison of the 2 treatment groups using an unstratified Cochran-Mantel-Haenszel mean score test.
Abbreviations: ITT: intent-to-treat; PSA: prostate-specific antigen.

B.2.6.2.3 Exploratory outcomes: PSA response ≥90%

Enzalutamide also led to a statistically significantly greater proportion of patients with a confirmed (enzalutamide: 75.8%; bicalutamide: 11.6%) and unconfirmed (enzalutamide: 83.3%; bicalutamide: 14.5%) ≥90% reduction in PSA from baseline.

Table 27 PSA response rate (≥90% decrease from baseline) (nmHRPC ITT population)

Outcome	Enzalutamide (n=70)	Bicalutamide (n=69)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Number of evaluable patients[a]	66	69
Confirmed ≥50% PSA responders[b]	50 (75.8%)	8 (11.6%)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
P-value vs bicalutamide[e]	<0.0001	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	

Source: STRIVE Clinical Study Report[41]
a. Patients with at least 1 post-baseline PSA assessment.
b. Number of responders divided by number of evaluable patients.
c. Clopper-Pearson exact binomial CI.
d. Enzalutamide rate minus bicalutamide rate.
e. Comparison of the 2 treatment groups using an unstratified Cochran-Mantel-Haenszel mean score test.
Abbreviations: ITT: intent-to-treat; PSA: prostate-specific antigen.

B.2.6.2.4 Key conclusions

- The findings in STRIVE further support the treatment benefit observed with enzalutamide in PROSPER. STRIVE was a randomised, double-blind, placebo-controlled phase II head-to-head trial comparing enzalutamide to bicalutamide both with ADT in adult men with mHRPC (n=257) or nmHRPC (n=139). The protocol pre-specified analysis of the subgroup of patients with nmHRPC.
- Both treatment arms were well balanced for demographics and baseline characteristics. Overall, 35.1% of patients had nmHRPC (enzalutamide: 70/198, 35.4%; bicalutamide: 69/198, 34.8%).
- In the nmHRPC patient cohort, enzalutamide:
    - Significantly reduced the risk of disease progression or death by 76% compared with bicalutamide (HR: 0.24, 95% CI [0.14; 0.42]). Enzalutamide significantly delayed disease progression or death by more than 1-year (median PFS: 19.4 months vs 5.7 months with bicalutamide)
    - Significantly reduced the risk of radiographic disease progression vs bicalutamide (HR: 0.24, 95% CI [0.10; 0.56], p<0.001
    - Significantly reduced the risk of PSA progression vs bicalutamide (HR: 0.18, 95% CI [0.10; 0.34]; p<0.001.
- In conclusion, the treatment benefit observed with enzalutamide in the nmHRPC cohort in STRIVE further supports the superiority of enzalutamide plus ADT over ADT alone observed in PROSPER.

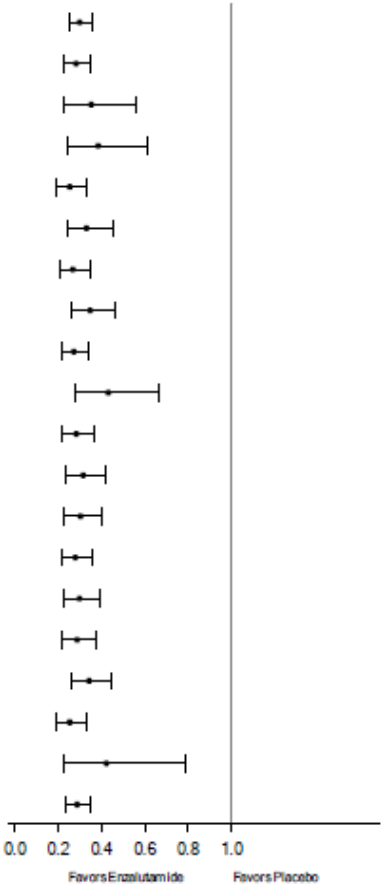
B.2.7 Subgroup analysis

The primary endpoint was examined in several patient subgroups that had been pre-specified in the study protocol on the basis of being accepted prognostic factors for prostate cancer, demographic features of interest, or represent different regional practice patterns. A statistically significant delay for metastasis was observed for enzalutamide consistently in all patient subgroups (Figure 18).

The treatment benefit of enzalutamide over placebo on MFS observed for the overall PROSPER population was maintained in the European cohort (49.3% of all patients).

Figure 18 MFS in the PROSPER protocol predefined patient subgroups (ITT population)

Subgroup	Number of Patients Enzalutamide / Placebo	Number of Events Enzalutamide / Placebo	Hazard Ratio for MFS (95% CI)
All Patients	933 / 468	219 / 228	0.30 (0.25-0.36)
PSA doubling time < 6 months	719 / 361	181 / 190	0.28 (0.23-0.35)
PSA doubling time >= 6 months	214 / 107	38 / 38	0.35 (0.22-0.56)
Geographic Region - North America	141 / 63	37 / 34	0.38 (0.24-0.62)
Geographic Region - European Union	458 / 232	95 / 113	0.25 (0.19-0.34)
Geographic Region - Rest of the World	334 / 173	87 / 81	0.33 (0.24-0.45)
Age at Baseline <= Median (74 Years)	489 / 267	114 / 140	0.27 (0.21-0.35)
Age at Baseline > Median (74 Years)	444 / 201	105 / 88	0.35 (0.26-0.46)
ECOG Performance Status at Baseline=0	747 / 382	163 / 192	0.27 (0.22-0.34)
ECOG Performance Status at Baseline=1	185 / 85	56 / 36	0.43 (0.28-0.66)
Total Gleason Score at Diagnosis <= 7	512 / 242	116 / 120	0.28 (0.22-0.37)
Total Gleason Score at Diagnosis >= 8	381 / 207	92 / 101	0.32 (0.24-0.42)
Baseline PSA Value (ng/mL) <= Median (10.73)	457 / 243	86 / 105	0.30 (0.23-0.40)
Baseline PSA Value (ng/mL) > Median (10.73)	476 / 224	133 / 123	0.28 (0.22-0.36)
Baseline LDH Value (U/L) <= Median (178)	459 / 228	109 / 108	0.30 (0.23-0.39)
Baseline LDH Value (U/L) > Median (178)	451 / 233	103 / 119	0.29 (0.22-0.38)
Baseline Hemoglobin Value (g/L) <= Median (134)	475 / 238	126 / 102	0.34 (0.26-0.45)
Baseline Hemoglobin Value (g/L) > Median (134)	458 / 229	93 / 126	0.25 (0.19-0.33)
Baseline Use of Bone Targeting Agent - Yes	96 / 49	23 / 19	0.42 (0.23-0.79)
Baseline Use of Bone Targeting Agent - No	837 / 419	196 / 209	0.29 (0.24-0.35)



Source: PROSPER Clinical Study Report[2]. Abbreviations: CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; ITT: intent-to-treat; LDH: Lactate dehydrogenase; MFS: metastasis-free survival; PSA=prostate-specific antigen.

B.2.8 Meta-analysis

The systematic literature review identified two RCTs assessing enzalutamide in addition to ADT in the treatment of patients with nmHRPC (see Sections B.2.1 and B.2.2) but no meta-analysis was performed because of differences in the comparator arms between studies (placebo plus ADT in PROSPER vs bicalutamide plus placebo and ADT in STRIVE). Although bicalutamide does not have any significant impact on disease progression, it has a positive impact on PSA progression and therefore, the two arms cannot be considered the same. However, a network meta-analysis was conducted (see Section B.2.9).

B.2.9 Indirect and mixed treatment comparisons

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

B.2.9.1 Trial selection and inclusion

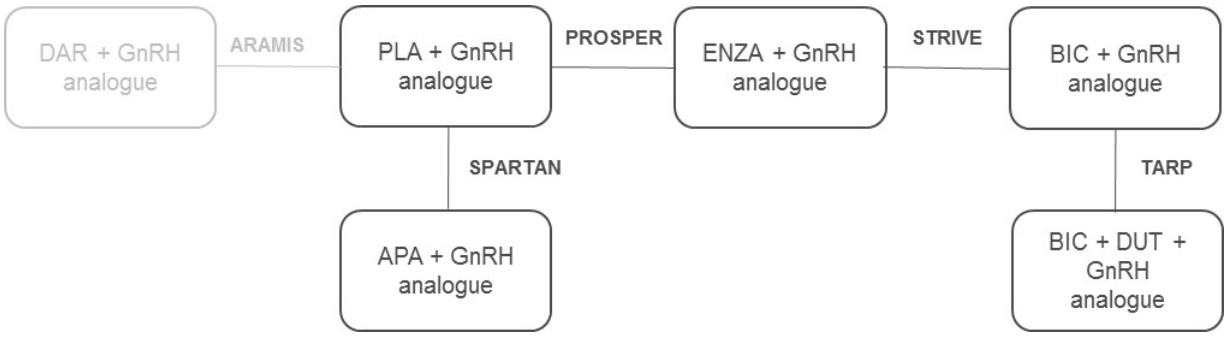
Details of the inclusion and exclusion criteria employed for the SLR and ITC are presented in Table 3. However, for this submission only ADT was considered a relevant comparator.

Of the eleven studies identified in the SLR, five met the NMA inclusion/exclusion criteria listed in Table 3 but data were only available for four of these studies: SPARTAN[47], PROSPER[2], STRIVE[41] and TARP[48]. The fifth study (ARAMIS) is still ongoing[49] and no results had yet been made public at the time of the NMA.

SPARTAN is a randomised, double-blind, placebo-controlled study comparing the efficacy and safety of apalutamide plus ADT to placebo plus ADT in patients with high risk nmHRPC[47]. Apalutamide was not considered a relevant comparator for enzalutamide in the final scope and thus, the indirect comparison between enzalutamide and apalutamide is not detailed here-in.

The evidence network, representing the possible comparisons between these studies is shown in Figure 19. Each “edge” in the network indicates that the treatments at either end was compared in an RCT. TARP compared bicalutamide plus dutasteride and ADT to bicalutamide plus ADT on nmHRPC[48]. Dutasteride is a type I and type II 5-alpha reductase enzyme inhibitor approved for treatment of symptomatic benign prostatic hyperplasia. Addition of dutasteride to bicalutamide did not have any significant impact on nmHRPC patients[48]. The authors do not specify the proportion of patients with PSADT ≤10 months. The uncertainty associated with this and the differences in the definition of endpoints across TARP, PROSPER and STRIVE precluded the inclusion of this study in the NMA. Thus, the final network includes only PROSPER and STRIVE (Figure 20).

Figure 19 Full identified evidence network in the nmHRPC setting



Source: NMA Report[50]
In grey, the ongoing study for which no results are available
Abbreviations: APA: Apalutamide; BIC: Bicalutamide; DAR: Darolutamide; DUT: Dutasteride; ENZA: Enzalutamide; GnRH: Gonadotropin-releasing hormone; PLA: Placebo.

Figure 20 Evidence network used for this submission

Source: edited from NMA Report[50]
Abbreviations: BIC: Bicalutamide; ENZA: Enzalutamide; GnRH: Gonadotropin-releasing hormone; PLA: Placebo.

B.2.9.2 Comparability of PROSPER and STRIVE and heterogeneity

[redacted] [2, 41].

Table 28 Patient characteristics of the studies with available data for the NMA

Characteristic	PROSPER[2]	STRIVE[41]
Mean age (years)	ENZA:73.8 PLA:72.9	[redacted]
BTA	ENZA: 11.3% PLA: 10.3%	[redacted]
PSADT	<6mo: ENZA: 76.6% / PLA: 77.1%	[redacted]
N0/N1	NA	[redacted]
ECOG	ENZA: 0: 80.15% / 1: 19.85% PLA: 0: 81.8% / 1: 18.2%	[redacted]
Total Gleason score	ENZA: ≤7: 54.88% / >7: 40.84% PLA: ≤7: 51.71% / >7: 44.23%	[redacted]

Characteristic	PROSPER[2]	STRIVE[41]
Prior treatment	[redacted]	[redacted]
Concomitant hormonal ADT medication	ENZA: 86.6% / PLA: 87.1%*	[redacted]
Baseline FACT-P Total score	ENZA: 119.5 / PLA: 120.8	[redacted]

Source: NMA Report[50]

*Not all patients received concomitant ADT during the study. Overall, 13% of all patients had undergone orchiectomy, i.e., surgical castration. Abbreviations: ADT: Androgen deprivation therapy; BIC: bicalutamide; BTA: bone-targeting agent; ECOG: Eastern Cooperative Oncology Group; ENZA: enzalutamide; EQ-5D=European Quality of Life 5-Domain Scale; FACT-P=Functional Assessment of Cancer Therapy-Prostate; NA: not available; PLA: placebo; PSADT: prostate-specific antigen doubling time; VAS: visual analogue scale.

The primary endpoints differed between PROSPER (MFS) and STRIVE (PFS). The differences in the definition of these two endpoints were too marked to attempt a comparison. STRIVE included PSA progression as an event in the definition of PFS, which prevented it from being comparable to the definitions for PROSPER. However, STRIVE did include an rPFS outcome which excluded PSA progression from the definition. Given the similarities between MFS and rPFS (Table 29), these two outcomes were considered identical in the NMA.

B.2.9.3 Methods

The complete evidence network for the time to PSA progression outcome is presented in Figure 20. The network included two trials comparing four treatments. However, as discussed in Section B.2.9.1, the SPARTAN trial with apalutamide falls outside the remit of this application, therefore only the results concerning enzalutamide and bicalutamide will be discussed. These results are included for completion but were not used in the economic model.

The NMA was performed using Bayesian methods principles, using fixed-effect (FE) models as supported by the analysis of study heterogeneity. Each outcome was analysed on the logarithm of the hazard ratio (log HR) scale using the normal likelihood and identity link as described in the National Institute for Health and Care Excellence technical support decision unit document (NICE TSD2)[51]. It was assumed that the log HR followed a normal distribution. Only FE models were developed.

For each study, it was necessary to define a baseline (treatment *b*) to which all other treatments were compared. For ease of interpretation this would usually be placebo (unless the study did not include placebo), however, the choice of baseline treatment would not affect the results.

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

For each treatment, other than the baseline treatment:

L_{jkb}~Normal$\left(\theta_{kb}, \sigma_{jkb}^2\right)$ [Equation 1]

where:

$\theta_{kb} = \delta_k - \delta_b$ [Equation 2]

The parameters δ_k and δ_b were the true log HRs for treatment k relative to placebo, and treatment b relative to placebo. The parameters δ_k and δ_b were given vague prior distributions: Normal $\left(0,100^2\right)$.

B.2.9.4 NMA input parameters

The data included in the NMA are provided in Table 29. These data included time to PSA progression and MFS/rPFS. The definition of time to PSA progression was comparable between both trials but the definition of disease progression differed. In PROSPER, disease progression was assessed with MFS while in STRIVE it was assessed with PFS which included PSA progression and rPFS. Although MFS (in PROSPER) and rPFS (in STRIVE) definitions differed slightly, they were considered comparable enough to assess the relative effectiveness of bicalutamide (plus ADT) vs placebo (plus ADT).

Table 29 PROSPER and STRIVE input parameters in the NMA

Outcome		**PROSPER[2]**	**STRIVE (nmHRPC)[41]**
MFS/rPFS	*Definition*	*MFS: time from randomisation to the 1st date of radiographic progression (assessed by BICR) at any time or death within 112 days of treatment discontinuation without evidence of radiographic progression*	[redacted]
	Input parameter (HR [95% CI]	0.292 [0.241; 0.352]	0.238 [0.102; 0.558]
Time to PSA progression	Definition	The time from random assignment to the earliest evidence of PSA progression per PCWG2 guidelines	The time from random assignment to the earliest evidence of PSA progression per PCWG2 guidelines
	Input parameter (HR [95% CI]	0.066 [0.054; 0.081]	0.182 [0.098; 0.341]

Source: PROSPER NMA Report[50]

Abbreviations: BICR: blinded independent central radiology review; HR: hazard ratio; MFS: metastasis-free survival; PCWG2: Prostate Cancer Clinical Trials Working Group 2; PSA: prostate specific antigen; rPFS: radiographic progression-free survival.

B.2.9.5 Results

The NMA results for the FE model are provided in Table 30. Results of the FE model indicated that bicalutamide (+ADT)

[redacted]

Table 30 NMA results for MFS/rPFS and time to PSA progression (FE model)

Outcome Comparison	NMA results Median HR (95% CrI)
MFS/rPFS	
Enzalutamide vs bicalutamide*	[redacted]
Enzalutamide vs placebo*	[redacted]
Bicalutamide vs placebo	[redacted]
Time to PSA progression	
Enzalutamide vs bicalutamide*	[redacted]
Enzalutamide vs placebo*	[redacted]
Bicalutamide vs placebo	[redacted]

Source: PROSPER NMA Report[50]
Abbreviations: CrI: credible interval; HR: hazard ratio; MFS: metastasis-free survival; NMA: network meta-analysis; PSA: prostate specific antigen; rPFS: radiographic progression-free survival. In bold, statistically significant differences.

B.2.9.6 Conclusions and uncertainties

A traditional NMA using Bayesian methods principles as described in the NICE TSD2[51] was performed. The NMA was informed by an SLR, conducted according to a pre-specified protocol with extensive searches in a range of databases. Based on the remit of this application, only the two head-to-head enzalutamide trials (PROSPER and STRIVE) were included in the NMA. For STRIVE, only data for the nmHRPC cohort was considered. Although not all nmHRPC patients in STRIVE were at high risk, the proportion (83%) was sufficiently high to be deemed comparable to that in PROSPER.

Of all outcomes assessed in both trials, only MFS/rPFS and time to PSA progression were included in the NMA.

The relative effectiveness of enzalutamide vs bicalutamide and vs placebo for MFS/rPFS and time to PSA progression originate from the head-to-head studies (PROSPER and STRIVE). The NMA however allowed to assess the relative effectiveness of bicalutamide vs placebo (i.e., bicalutamide plus ADT vs ADT alone).

[redacted]

For the NMA, it was assumed that the enzalutamide arm in PROSPER and STRIVE were comparable. However, in PROSPER, the enzalutamide arm included enzalutamide and ADT, while in STRIVE it also included the bicalutamide placebo. For the NMA, both arms were considered identical.

B.2.10 Adverse reactions

This section provides safety data from PROSPER. Unless stated otherwise, all data in this section originates from the PROSPER CSR[2]. No analysis was conducted for safety data for the nmHRPC cohort in STRIVE. However, the safety profile observed for enzalutamide in STRIVE (mHRPC and nmHRPC) is similar to that observed in PROSPER (nmHRPC). This is in line with the safety profile of enzalutamide in PROSPER being consistent with that observed in previous mHRPC studies (PREVAIL[52] and AFFIRM[53]) and in clinical practice.

B.2.10.1 General adverse reactions

All adverse event-related data reported here-in relate to PROSPER and the cut-off date of 28 June 2017.

An overall summary of TEAEs is presented in Table 31. The incidence of patients with any TEAE was higher in the enzalutamide group compared with the placebo group (86.9% vs 77.4%). Similarly, the incidence rates of Grade 3 or higher TEAEs, serious TEAEs, TEAEs leading to death, and all other subcategories of adverse events were higher in the enzalutamide group compared with the placebo group.

Table 31 Overall summary of TEAEs (safety population)

Outcome	Enzalutamide (n=930)	Placebo (n=465)
Patients with any TEAE	808 (86.9%)	360 (77.4%)
Any TEAE Grade 3 or higher	292 (31.4%)	109 (23.4%)
Any TEAE leading to death	32 (3.4%)	3 (0.6%)
Any serious TEAE	226 (24.3%)	85 (18.3%)
Any TEAE leading to study drug discontinuation[a]	96 (10.3%)	35 (7.5%)
Any TEAE leading to dose reduction of study drug	[redacted]	[redacted]
Any TEAE leading to dose interruption of study drug	[redacted]	[redacted]
Patients with any TEAE related to study drug	[redacted]	[redacted]
Any TEAE Grade 3 or higher related to study drug	[redacted]	[redacted]
Any serious TEAE related to study drug	[redacted]	[redacted]

Source: PROSPER Clinical Study Report[2]
MedDRA Version: 16.1.
a. TEAE with action taken of permanent discontinuation was from Adverse Event case report form.
Abbreviations: MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients; TEAE: treatment-emergent adverse event.

TEAEs of any grade or relationship reported in at least 5% of patients in either treatment group during the study are presented by preferred term in decreasing order of frequency in Table 32. Due to the differences in MFS, the enzalutamide group was exposed to the drug for much longer than the placebo group (median of 18.8±10.67 vs 13.2±9.01 months). To account for differential exposure and safety reporting periods, TEAEs were also evaluated using event rate calculations (events per 100 patient-years).

[redacted]

[redacted]

Table 32 TEAEs occurring in at least 5% of patients in either treatment group and adjusting for length of treatment-emergent period: events per 100 patient-year of reporting (safety population)

	Overall Incidence, n (%)		Events per 100 patient-years of reporting, n (event rate)	
Preferred term	**Enzalutamide (n=930)**	**Placebo (n=465)**	**Enzalutamide (n=930)**	**Placebo (n=465)**
Fatigue	**303 (32.6%)**	**64 (13.8%)**	[redacted]	[redacted]
Hot flush	**121 (13.0%)**	**36 (7.7%)**	[redacted]	[redacted]
Nausea	**106 (11.4%)**	**40 (8.6%)**	[redacted]	[redacted]
Diarrhoea	91 (9.8%)	45 (9.7%)	[redacted]	[redacted]
Hypertension	**111 (11.9%)**	**24 (5.2%)**	[redacted]	[redacted]
Fall	**106 (11.4%)**	**19 (4.1%)**	[redacted]	[redacted]
Constipation	**85 (9.1%)**	**32 (6.9%)**	[redacted]	[redacted]
Dizziness	**91 (9.8%)**	**20 (4.3%)**	[redacted]	[redacted]
Arthralgia	78 (8.4%)	32 (6.9%)	[redacted]	[redacted]
Asthenia	**82 (8.8%)**	**28 (6.0%)**	[redacted]	[redacted]
Decreased appetite	**89 (9.6%)**	**18 (3.9%)**	[redacted]	[redacted]
Back pain	73 (7.8%)	33 (7.1%)	[redacted]	[redacted]
Headache	**85 (9.1%)**	**21 (4.5%)**	[redacted]	[redacted]
Haematuria	62 (6.7%)	36 (7.7%)	[redacted]	[redacted]
Urinary tract infection	38 (4.1%)	30 (6.5%)	[redacted]	[redacted]
Weight decreased	**55 (5.9%)**	**7 (1.5%)**	[redacted]	[redacted]
Urinary retention	20 (2.2%)	28 (6.0%)	[redacted]	[redacted]

Source: PROSPER Clinical Study Report[2]

Note: Time-adjusted rate per 100 patient-year calculated as number of occurrences of event divided by the number of patient-years of treatment-emergent surveillance for each treatment group and then times 100. Patient could have more than 1 occurrence of each event. Events were sorted by system organ class alphabetically and then by decreasing event rate. TEAEs reported with at least a 2% higher incidence overall in the enzalutamide group compared with the placebo group are shown in bold font and TEAEs with at least 2 more events per 100 patient-years in the enzalutamide group compared with the placebo group are shown in bold font. MedDRA Version 16.1.

Abbreviations: MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients; TEAE: treatment-emergent adverse event.

Grade 3 or higher TEAEs reported in at least 1% of patients in either treatment group are displayed by system organ class and preferred term in Table 33. Patients treated with enzalutamide had a higher incidence of Grade 3 or higher TEAEs overall than patients

treated with placebo (31.4% vs 23.4% in the placebo group). Grade 3 or higher TEAEs with at least a 1% higher incidence in the enzalutamide group compared with the placebo group include fatigue (2.9% enzalutamide vs 0.6% placebo), asthenia (1.2% vs 0.2%), and hypertension (4.6% vs 2.2%). Grade 3 or higher TEAEs with at least a 1% higher incidence in the placebo group compared with the enzalutamide group include haematuria (1.7% vs 2.8%) and renal failure acute (0.4% vs 1.5%).

Table 33 Grade 3 or higher TEAEs by system organ class and preferred term - with preferred term reported for at least 1% of patients in either treatment group (safety population)

System organ class Preferred term	**Enzalutamide (n=930)**	**Placebo (n=465)**
Number of patients reporting at least 1 Grade ≥3 TEAE	292 (31.4%)	109 (23.4%)
Blood and lymphatic system disorders	[redacted]	[redacted]
Anaemia	9 (1.0%)	6 (1.3%)
General disorders and administration site conditions	[redacted]	[redacted]
Fatigue	27 (2.9%)	3 (0.6%)
Asthenia	11 (1.2%)	1 (0.2%)
Injury, poisoning and procedural complications	[redacted]	[redacted]
Fall	12 (1.3%)	3 (0.6%)
Infections and infestations	[redacted]	[redacted]
Pneumonia	10 (1.1%)	2 (0.4%)
Nervous system disorders	[redacted]	[redacted]
Syncope	10 (1.1%)	2 (0.4%)
Renal and urinary disorders	[redacted]	[redacted]
Haematuria	16 (1.7%)	13 (2.8%)
Renal failure acute	4 (0.4%)	7 (1.5%)
Urinary retention	4 (0.4%)	5 (1.1%)
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Pulmonary embolism	3 (0.3%)	5 (1.1%)
Vascular disorders	[redacted]	[redacted]
Hypertension	43 (4.6%)	10 (2.2%)

Source: PROSPER Clinical Study Report[2]
Note: TEAE grades were evaluated based on NCI-CTCAE (version 4.03).
Patients with multiple events for a given preferred term, system organ class, or overall were counted once only for each preferred term, system organ class, and overall, respectively.
Events were sorted by system organ class alphabetically and then by decreasing frequency of preferred term.
MedDRA Version: 16.1.
Abbreviations: CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients; NCI: National Cancer Institute; TEAE: treatment-emergent adverse event.

Study drug-related TEAEs occurring in at least 2% of patients in either treatment group were similar to the TEAEs identified in Table 32.

The AEs reported for enzalutamide in PROSPER are in line with the adverse reactions listed in the SmPC (Table 34).

Table 34 Adverse reactions related to enzalutamide as reported in its SmPC

MedDRA system organ class	Very common	Common	Uncommon	Unknown[b]
Blood and lymphatic system disorders			Leucopoenia Neutropenia	Thrombocytopenia
Cardiac disorders		Ischemic heart disease		QT prolongation
Gastrointestinal disorders				Nausea Vomiting Diarrhoea
General disorders	Asthenia Fatigue			
Immune system disorders				Face oedema, Tongue oedema Lip oedema Pharyngeal oedema
Injury, poisoning and procedural complications		Falls		
Musculoskeletal and connective tissue disorders	Fractures[a]			Myalgia Muscle spasms Muscular weakness Back pain
Nervous system disorders		Headache Memory impairment Amnesia Disturbance in attention Restless legs syndrome	Cognitive disorder Seizure	Posterior reversible encephalopathy syndrome
Psychiatric disorders		Anxiety	Visual hallucinations	
Reproductive system and breast disorder		Gynaecomastia		
Skin and subcutaneous tissue disorders		Dry skin Pruritus		Rash
Vascular disorders	Hot flush Hypertension			

Source: Enzalutamide Summary of Product Characteristics[1]

a. Includes all fractures with the exception of pathological fractures

b. Spontaneous reports from post-marketing experience

B.2.10.2 Adverse events of special interest

The TEAEs of special interest for enzalutamide included known identified risks (adverse drug reactions) for enzalutamide, such as convulsion, hypertension, neutropenia, memory impairment, and posterior reversible encephalopathy syndrome (PRES), as well as other pre-specified events of clinical interest defined in the SAP, including major adverse cardiovascular events (MACE) and hepatic impairment. An overall summary of TEAEs of special interest is presented in Table 35. Each of these events is discussed further in the subsections that follow, including an analysis of the events per 100 patient-years of reporting.

Table 35 Overall summary of TEAEs of special interest (safety population)

TEAE of special interest	Enzalutamide (n=930)	Placebo (n=465)
Convulsion	3 (0.3%)	0 (0.0%)
Hypertension	114 (12.3%)	25 (5.4%)
Neutropenia	9 (1.0%)	1 (0.2%)
Memory impairment	48 (5.2%)	9 (1.9%)
Hepatic impairment	11 (1.2%)	9 (1.9%)
Major adverse cardiovascular event (MACE)	48 (5.2%)	13 (2.8%)
Posterior reversible encephalopathy syndrome (PRES)[a]	0 (0.0%)	0 (0.0%)

Source: PROSPER Clinical Study Report[2].
a. The preferred term posterior reversible encephalopathy syndrome (PRES) was not reported for any patient.
Abbreviations: n: number of patients; SMQ: standardised MedDRA query.

B.2.10.2.1 Convulsion

TEAEs of convulsion (seizure) were reported in 3 patients (0.3%) in the enzalutamide group and no patient in the placebo group (Table 35).

[redacted]. All 3 convulsions in the enzalutamide group were considered serious and drug-related, and occurred within 180 days of initiating study drug. One convulsion led to study drug discontinuation.

B.2.10.2.2 Hypertension

The overall incidence of TEAEs within the narrow standardised MedDRA query (SMQ) of 'hypertension' in the enzalutamide group (12.3%) was approximately 2-fold higher than the placebo group (5.4%).

[redacted] Grade 3 or higher hypertension events occurred in 43 patients (4.6%) in the enzalutamide group versus 11 patients (2.4%) in the placebo group; all of these events were Grade 3, except for 1 patient who experienced a Grade 4 hypertension event. Baseline hypertension was reported in more than half of all

patients (561 patients [60.3%] in the enzalutamide group and 303 patients [65.2%] in the placebo group). Hypertension led to study drug discontinuation in only 1 patient (0.1%) in the enzalutamide group and no patient in the placebo group.

B.2.10.2.2 Neutropenia

TEAEs consisting of the preferred terms defined in Table 35 were reported in 9 patients (1.0%) in the enzalutamide group and 1 patient (0.2%) in the placebo group. Of these, 6 patients in the enzalutamide group and 1 patient in the placebo group had events that were considered related per the investigator to study drug. In addition, 5 of 9 patients in the enzalutamide group (4 patients [0.4%] with neutropenia and 1 patient [0.1%] with neutrophil count decreased) and 1 patient (0.2%; neutropenia) in the placebo group experienced a Grade 3 or higher TEAE. No neutropenia event led to study drug discontinuation or led to death.

B.2.10.2.3 Memory impairment

TEAEs involving impaired cognition and memory (terms within the MedDRA high level group term ‘mental impairment disorders’) were reported in 48 patients (5.2%) in the enzalutamide group and 9 patients (1.9%) in the placebo group (Table 35). A total of 28 patients (3.0%) in the enzalutamide group and 5 patients (1.1%) in the placebo group were considered to have a TEAE that was related to study drug.

[redacted] Only 1 patient in the enzalutamide group and no patient in the placebo group experienced a Grade 3 or higher TEAEs of ‘mental impairment’; the event was a Grade 3 cognitive disorder that led to study drug discontinuation. TEAEs of ‘mental impairment’ led to study drug discontinuation in a total of 5 patients (0.5%) in the enzalutamide group and 1 patient (0.2%).

B.2.10.2.4 Hepatic impairment

Hepatic impairment was evaluated by SMQs defined in Table 35. TEAEs within these SMQs were reported in 11 patients (1.2%) in the enzalutamide group and 9 patients (1.9%) in the placebo group (Table 35). 7 patients (0.8%) in the enzalutamide group and 1 patient (0.2%) in the placebo group were considered to have a TEAE that was related to study drug.

[redacted] Grade 3 or higher TEAEs of hepatic impairment occurred in 5 patients (0.5%) in the enzalutamide group and 2 patients (0.4%) in the placebo group. Hepatic impairment led to study drug discontinuation in 1 patient (0.1%) with ALT increased and AST increased in the enzalutamide group and no patient in the placebo group.

B.2.10.2.5 Major adverse cardiovascular events

Major adverse cardiovascular events (MACE) included a composite of cardiovascular and cerebrovascular TEAEs based on narrow SMQs defined in Table 35. As summarised in Table 35, a total of 48 patients (5.2%) in the enzalutamide group and 13 patients (2.8%) in the placebo group experienced a MACE.

[redacted]

[redacted]. Grade 3 or higher MACE occurred in 34 of 48 patients (70.8%) in the enzalutamide group and 8 of 13 patients (61.5%) in the placebo. The majority of Grade 3 or higher MACE occurred after 365 days MACE led to study drug discontinuation in approximately 1% of patients in each arm (12 patients [1.3%] enzalutamide vs 4 patients [0.9%]).
[redacted] had a MACE leading to death, making it the organ class with the highest percentage of TEAEs leading to death, as is discussed later.

In addition, patients with history of cardiovascular disease had higher MACE event rates than patients with no history of cardiovascular disease. In patients with history of cardiovascular disease,
[redacted], and in patients with no history of cardiovascular disease,
[redacted].

B.2.10.2.6 Posterior reversible encephalopathy syndrome

Potential TEAEs of posterior reversible encephalopathy syndrome (PRES) were evaluated by searching preferred terms included in the narrow SMQ of 'non-infectious encephalopathy/delirium'. No events with the preferred term of PRES were reported.
[redacted]

B.2.10.3 Other serious adverse events

Patients treated with enzalutamide had an overall higher incidence of serious TEAEs than patients treated with placebo (226 patients [24.3%] in the enzalutamide group vs 85 [18.3%] in the placebo group). The majority of serious TEAEs were Grade 3 or higher (21.3% vs 15.1%).
[redacted]

[redacted] 36 [redacted]

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

Source: PROSPER Clinical Study Report[2].
Note: Adverse event grades were evaluated based on NCI-CTCAE (version 4.03).
Patients with multiple events for a given preferred term and overall, were counted once only for the preferred term and overall, respectively.
Events were sorted by decreasing frequency of preferred term.
MedDRA Version 16.1.
Abbreviations: CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients; NCI: National Cancer Institute; TEAE: treatment-emergent adverse event.

B.2.10.4 Permanent discontinuations due to adverse events

A total of 96 patients (10.3%) in the enzalutamide group and 35 patients (7.5%) in the placebo group experienced any grade TEAEs leading to discontinuation of study drug. [redacted]

B.2.10.5 Adverse events leading to death

Rates for mortality due to any cause or to disease progression were lower for enzalutamide (Figure 10, Table 37). However, TEAEs leading to death were more common with enzalutamide (32 patients; 3.4%) than placebo (3 patients; 0.6%). The system organ classes with the highest percentage of reported TEAEs leading to deaths were cardiac disorders (1.0% enzalutamide vs 0.4% placebo), neoplasms benign, malignant and unspecified (0.6% enzalutamide vs 0.2% placebo), and general disorders and administration site conditions (0.5% enzalutamide vs 0.0% placebo).

Table 37 Summary of all deaths (ITT population)

Outcome	Enzalutamide (n=933)	Placebo (n=468)
Total number of deaths	103 (11.0%)	62 (13.2%)
Cause of death		
Disease progression	51 (5.5%)	45 (9.6%)
Adverse event	32 (3.4%)	3 (0.6%)
Other	17 (1.9%)	13 (2.8%)
Unknown	3 (0.3%)	1 (0.2%)
Deaths within 30 days of initiation of study drug	1 (0.1%)	0 (0.0%)
Deaths within 30 days of discontinuation of study drug	28 (3.0%)	2 (0.4%)

Source: PROSPER Clinical Study Report[2].
MedDRA Version: 16.1.
Abbreviations: ITT: intent-to-treat; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients.

B.2.11 Ongoing studies

The PROSPER phase III trial, comparing enzalutamide to placebo in high risk nmHRPC patients, is still ongoing for survival follow-up. As of the IA2 data cut-off date, a total of 288 deaths occurred which corresponds to 48% of the 596 deaths specified for the final OS analysis.

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

B.2.12 Innovation

Enzalutamide is expected to be the first treatment to obtain marketing authorisation for high risk nmHRPC patients in Europe. Prior to enzalutamide, no therapy was licenced for these patients other than maintaining ADT until the disease progresses to the metastatic stage. Based on PROSPER data and supported by the findings in STRIVE, enzalutamide delays development of metastases by 21.9 months (i.e., almost two years). In prostate cancer, as in almost all cancer types, diagnosis of the metastatic disease stage has a marked negative impact to the patient. Patients tend to associate the development of metastases as a trigger for HRQoL deterioration, an increase in the symptom burden and inevitably, as an increased risk of mortality. This is supported by clinical evidence. While nmHRPC patients have a good HRQoL and are almost asymptomatic (as shown in PROSPER), their HRQoL decreases when the disease becomes metastatic[20, 54, 55]. Patients with bone metastases are at high risk of skeletal-related events (SREs), including spontaneous fracture and spinal cord compression, that are a source of significant pain and decreased HRQoL[20]. In line with this, in a 1-year observational, cross-sectional, prospective study conducted in Germany in 101 patients with mHRPC showed that these patients experienced impairments in HRQoL with 67.3% of patients exhibiting pain or discomfort, 58.1% problems to perform usual activities, 53.1% mobility problems, 37.7% anxiety/depression troubles and 32.7% self-care problems[21].

In addition to bone, metastases can also occur to other sites including lymph nodes and visceral metastases. Visceral disease, commonly including liver and lung metastases, is a negative prognostic factor[22, 56]. Not only it is associated with an increase in the symptom burden but visceral disease is also associated with poor survival[23].

Thus, delaying the development of metastases by 21.9 months can be considered clinically relevant. This delay was accompanied by a statistically significant and clinically meaningful delay in HRQoL deterioration and symptom worsening of enzalutamide over placebo in PROSPER. This suggests that enzalutamide delays metastases while maintaining good HRQoL and low symptom burden despite being an add-on therapy to ADT. PROSPER also showed a statistically significant delay in time to chemotherapy initiation. This may be perceived positively by patients who often are reluctant to start chemotherapy due to its toxicity and need to attend hospital for infusions. However, with the changing landscape and docetaxel being offered to some patients when they are still at HSPC state, these findings may be less relevant than the treatment benefit observed in MFS and PROs.

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Overall conclusions

Enzalutamide is expected to be the first therapy to be approved for the treatment of high risk nmHRPC patients in Europe. Prior to enzalutamide, the only treatment option for these patients was maintenance of ADT although no robust evidence of its benefit on survival exists. In the UK, current management of high risk nmHRPC patients relies largely on the continuation of ADT. Although neither ADT nor bicalutamide has shown any clear improvement, the modest potential benefits of continuing medical castration are generally considered to outweigh the risks of treatment with ADT and bicalutamide[30].

Eventually approximately 85% of men with nmHRPC will develop metastases, predominantly in the bone. About one-third of patients will develop metastatic disease within 2 years of developing HRPC[15]. In PROSPER, the proportion of patients developing metastases within 2 years in the placebo arm was higher (65%) in line with patients with a PSADT ≤10 months having a higher risk of metastases than patients at low or intermediate risk. As already mentioned in Section B.1.3, development of metastases has devastating consequences to patients. HRQoL deteriorates quickly with bone and visceral metastases, the symptom burden increases and survival decreases[21]. Patients with bone metastases are at high risk of skeletal-related events (SREs), including spontaneous fracture and spinal cord compression, that are a source of significant pain and decreased HRQoL[20]. In line with this, in a 1-year observational, cross-sectional, prospective study conducted in Germany in 101 patients with mHRPC showed that these patients experienced impairments in HRQoL with 67.3% of patients exhibiting pain or discomfort, 58.1% problems to perform usual activities, 53.1% mobility problems, 37.7% anxiety/depression troubles and 32.7% self-care problems[21].

In addition to bone, metastases can also occur to other sites including lymph nodes and visceral metastases. Visceral disease, commonly including liver and lung metastases, is a negative prognostic factor[22, 56]. Not only it is associated with an increase in the symptom burden but visceral disease is also associated with poor survival[23].

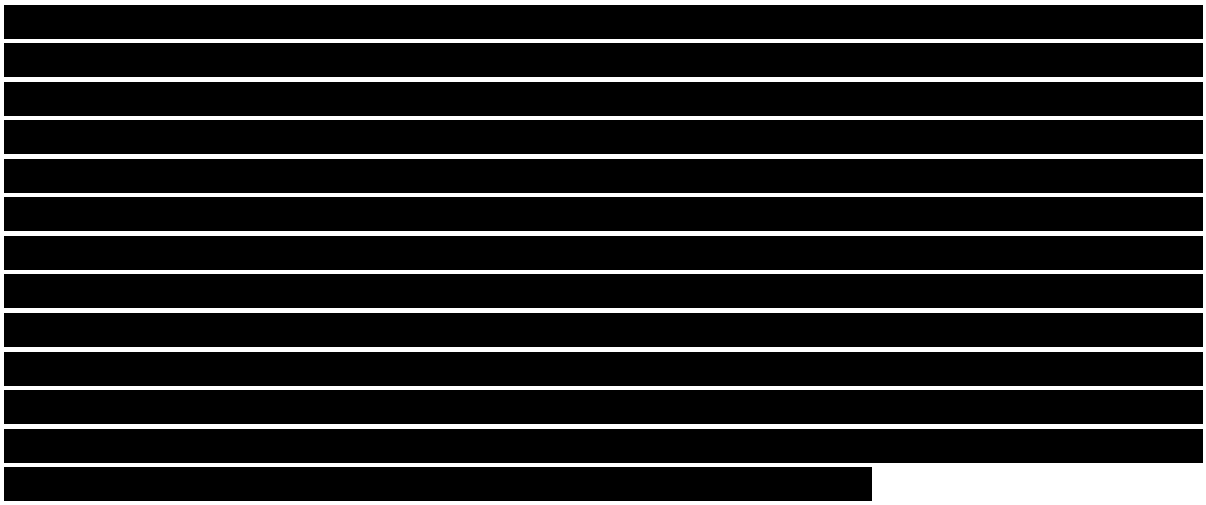
The negative effect of metastases was confirmed in the enzalutamide trials in the mHRPC setting[57, 58]. Therefore, there is a pressing need for a treatment option for men with nmHRPC to delay the onset of metastases and delay disease progression[24].

The evidence of the efficacy and safety of enzalutamide plus ADT in high risk nmHRPC patients originate primarily from the PROSPER study comparing enzalutamide plus ADT vs placebo plus ADT in 1,401 high risk nmHRPC patients. This evidence is supported by the findings for the nmHRPC cohort of STRIVE.

PROSPER demonstrated a statistically significant delay in BICR-assessed MFS in the enzalutamide group compared with the placebo group. The primary analysis of MFS demonstrated a statistically significant and clinically meaningful benefit of enzalutamide, with a 70.8% decrease in the risk of developing metastases or death (HR: 0.292, 95% CI: [0.241; 0.352], p <0.0001) and a delay of metastases by 21.9 months with enzalutamide vs placebo. The improvement in MFS was robust and favoured enzalutamide across all pre-specified subgroups including the European cohort (49.3% of patients), with estimated HRs ranging from 0.25 to 0.43. Furthermore, the results of the MFS analysis were also robust for 5 pre-specified sensitivity analyses, demonstrating statistically significant HRs ranging from 0.275 to 0.330.

The favourable outcomes in the MFS analyses were further supported by statistical superiority for enzalutamide in the key secondary endpoints:

- Statistically significant delay by 33.3 months (37.2 months vs 3.9 months; HR: 0.066, 95% CI: [0.054, 0.081]; p <0.0001) in PSA progression vs placebo.



However, based on MFS a benefit on OS is also to be expected. Using MFS data from 21,140 patients with localised prostate cancer, the ICECaP Working Group has shown that MFS is a strong surrogate for OS in localised prostate cancer[59, 60]. This is in line with the findings of Smith et al who using data from the phase 3 SPARTAN trial in men with high risk nmHRPC showed that MFS has a significant association with OS and is predictive of OS in high risk nmHRPC[61]. The authors observed that patients who developed metastases at 6, 9, and 12 months had significantly shorter median OS compared with those patients without metastasis. After adjusting for baseline covariates, the development of metastases remained associated with OS. A significant positive correlation was observed between MFS and OS (Spearman's correlation coefficient: 0.62; p < 0.0001; parametric Fleischer's correlation coefficient: 0.69).

PROSPER also demonstrated that enzalutamide, although being an active drug, maintains good HRQoL and a low symptom burden. In the nmHRPC setting, the assessment of HRQoL is of paramount importance because patients have not yet been burdened by significant disease-related symptoms. At baseline patients in PROSPER were either asymptomatic or had a low symptom burden, and had good HRQoL as well as good functioning[40]. HRQoL data were collected with the BPI-SF, FACT-P, EORTC QLQ-25, and EQ-5D tools. Enzalutamide did not increase symptom burden in PROSPER and enabled patients to maintain their HRQoL over 97 weeks, despite receiving active treatment. In addition, enzalutamide statistically significantly delayed time to symptom progression and HRQoL deterioration vs placebo.

These findings were further supported by the results for the nmHRPC cohort in the phase II STRIVE trial. Addition of bicalutamide to ADT did not have any significant impact on the results. This is in line with the NMA results that show that although bicalutamide plus ADT does delay time to PSA progression vs ADT alone it does not have any significant impact on disease progression (radiographic or death) vs ADT alone.

Importantly, the treatment benefit of enzalutamide over placebo or bicalutamide in PROSPER and STRIVE was also associated with an acceptable and manageable safety profile. In STRIVE, safety data are available only for the overall cohort. No additional analyses for the nmHRPC cohort alone have been conducted because based on the safety profile for enzalutamide in PROSPER (i.e., for high risk nmHRPC) being comparable to that observed in the mHRPC studies (PREVAIL[52] and AFFIRM[53]), no differences are expected for the safety profile between nmHRPC and mHRPC patients in STRIVE. Although TEAEs were higher in the enzalutamide group (PROSPER: 86.9% vs. 77.4%), enzalutamide was generally well-tolerated and the reported TEAEs were consistent with those reported in previous clinical trials of enzalutamide. In PROSPER, enzalutamide showed low rates of study drug discontinuation (10.3%), [redacted], with toxicities (e.g., hypertension) that could be monitored and generally managed. TEAE of special interest were convulsion, hypertension, neutropenia, memory impairment, PRES and hepatic impairment. When TEAEs of special interest were adjusted for treatment duration, [redacted].

The evidence of the efficacy and safety of enzalutamide in the high risk nmHRPC setting vs current standard of care (i.e., ADT with or without bicalutamide) originate primarily from head-to-head trials. The conducted SLR identified only an additional study (TARP) relevant for this submission. This study compared the efficacy and safety of bicalutamide plus dutasteride and ADT to bicalutamide plus ADT in nmHRPC. However, the uncertainty associated with TARP (study design and proportion of patients with high risk nmHRPC not specified) and the differences in the definition of endpoints across TARP, PROSPER and STRIVE precluded the inclusion of this study in the NMA.

In conclusion, the overall efficacy and safety results support a positive benefit/risk assessment of the use of enzalutamide at a daily dose of 160 mg in adult men with high risk nmHRPC.

B.2.13.2 Strengths and limitations

A key strength of PROSPER is that the use of enzalutamide in this trial reflects its intended use in clinical practice. The efficacy, safety and tolerability profile expected for enzalutamide practice, derived from extensive post-marketing experience in mHRPC in many countries) are generally the same as those observed in the PROSPER trial.

The evidence of the efficacy and safety of enzalutamide plus ADT in high risk nmHRPC originates primarily from the PROSPER trial which included 1,401 adult men with high risk nmHRPC. The PROSPER trial is a robust and clinically relevant study comparing enzalutamide to the UK standard of care in (ADT). This study demonstrated the treatment benefit of enzalutamide plus ADT on several endpoints that are relevant to patients. These findings were further supported by the results for the nmHRPC patient subgroup in STRIVE. In both trials, enzalutamide was superior to the comparator in endpoints that are relevant to patients and clinicians.

The study population in PROSPER comprised high risk nmHRPC patients. These patients were identified based on testosterone levels (≤50 ng/dL), PSADT (≤10 months) and absence of metastases on CT/MRI and whole body radionuclide bone scan. These tests are regularly monitored in UK clinical practice to assess disease progression and thus, enzalutamide eligible patients should be easily identified in this setting. Nevertheless, it cannot be ruled out that patients may have micro-metastases or small metastases that are not easily identified by CT/MRI or radionuclide bone scan. In these cases, patients may be considered non-metastatic erroneously. In line with this, in PROSPER 2.5% and 3.0% of randomised patients to enzalutamide and placebo respectively were considered non-metastatic at baseline but they were determined to be metastatic after blinded independent central review. However, enzalutamide[62] or abiraterone[63] is the standard of care for mHRPC patients for whom chemotherapy is not yet clinically indicated in the UK and thus, this issue of potential issue of misdiagnosis of nmHRPC would not have any negative impact to the patient or the health system.

The comparator in PROSPER was ADT which is the standard of care for nmHRPC patients in the UK. In the UK, bicalutamide tends to be administered prior to the HRPC setting. [redacted]. As demonstrated in STRIVE and the NMA, bicalutamide plus ADT does not have any meaningful impact on radiographic progression or death vs ADT alone.

The primary endpoint in PROSPER was MFS. Baseline characteristics in PROSPER show that patients with high risk nmHRPC are asymptomatic or have very little symptom burden and overall, have a relatively good HRQoL[2, 40]. Progression to metastatic disease is associated with a rapid and significant deterioration in HRQoL, which continues to decline as disease worsens. Preventing the progression from nmHRPC to metastatic HRPC represents a logical treatment goal that will reduce patient morbidity and possibly mortality. The FDA has highlighted the importance of MFS as a clinically relevant endpoint for nmHRPC patients[65] and as a strong surrogate for OS in these patients[47, 59, 60].

An additional strength of enzalutamide is that its safety profile is well stablished. The safety profile of enzalutamide was comparable in PROSPER[2] and STRIVE[41]. The side-effect profile of enzalutamide in these two trials is consistent with that observed in previous enzalutamide

studies with no new or unexpected safety signals. Data are available from over 3100 patients treated as part of clinical trial programmes to evaluate enzalutamide in mHRPC, both before[34, 52, 66] and after chemotherapy[67]. In addition, enzalutamide has been on the market as a treatment for mHRPC since 2012. Up until June 2017, approx. 258,000 patients had been treated worldwide.

Importantly for this submission, almost half (49.3%) of the patients were recruited in Europe. Of these,
[redacted] (MFS HR: 0.25, 95% CI [0.19, 0.34]) [redacted] (MFS HR: 0.29, 95% CI [0.24, 0.35]).

The most important limitation of the PROSPER trial is the length of the follow-up required to have sufficient OS events to perform a statistically powerful analysis. In the latest OS interim analysis (i.e., IA2) after approximately 48% of the 596 deaths specified for the final OS analysis,
[redacted] similarly to the findings in PREVAIL which recruited adult men with asymptomatic or mildly symptomatic mHRPC[52].

Another limitation in PROSPER was the use of post-baseline drugs that differ from the treatment these patients would have received in current UK clinical practice. This is of particular relevance in the placebo arm where 27.7% of patients received abiraterone post-baseline. In the enzalutamide arm 7.0% of patients also received abiraterone post-baseline. The sequencing of abiraterone after enzalutamide or vice versa is not currently implemented in UK clinical practice because of current NICE guidance.

Despite the limitations, the overall efficacy and safety results support a positive benefit/risk assessment of the use of enzalutamide at a daily dose of 160 mg in adult men with high risk nmHRPC. In PROSPER, enzalutamide was associated with a significantly longer time to metastasis while maintaining a low symptom burden, good HRQOL and good functioning and an acceptable safety profile.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

No previous cost-effectiveness studies were identified in the SLR that matched the search criteria or were relevant to this submission. For the full details of the SLR methods and outcomes, see Appendix G.

B.3.2 Economic analysis

B.3.2.1 Patient population

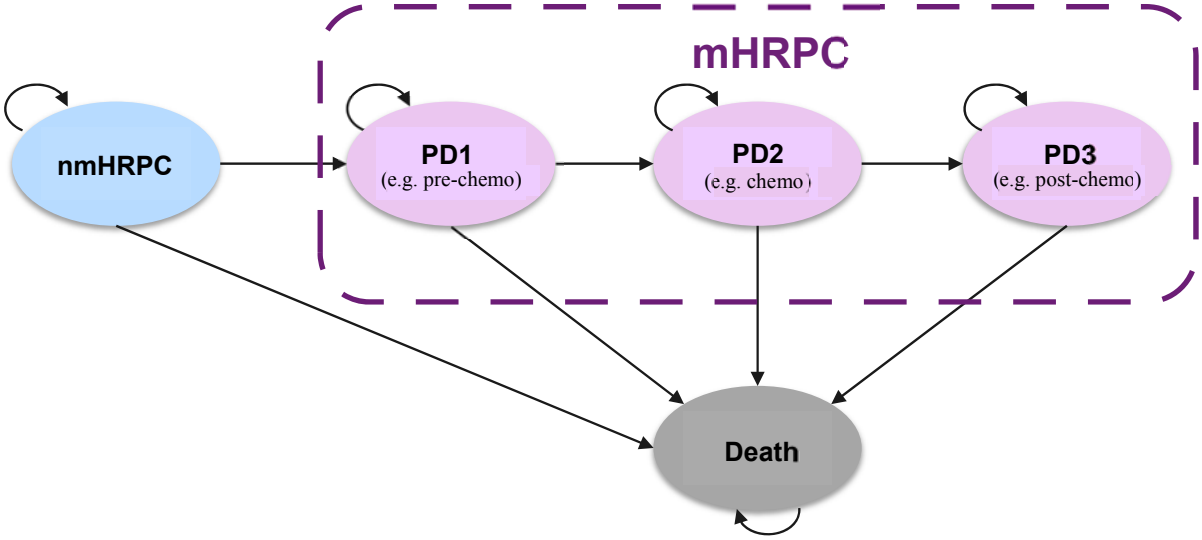
The patient population entering the model is based on baseline characteristics of PROSPER participants (section B.2.3.2). In essence, this population consists of men with high risk nmHRPC who are progressing despite being treated with ADT and having testosterone levels ≤50 ng/dL, rising PSA levels and a PSADT ≤10 months, an ECOG score of 0 or 1, and an expected life expectancy ≥12 months[2]. The mean age of the cohort at baseline was set at 73.5 years based on PROSPER patient baseline characteristics (Table 7).

B.3.2.2 Model structure

In line with previous enzalutamide technology appraisals in mHRPC[62, 68] and most other recent oncology NICE appraisals[69], a semi-Markov model combined with a partitioned survival modelling approach was chosen for the current analysis. Here the 'semi-Markov model with partitioned survival approach' means that for most transitions the partition survival modelling approach is followed, whereas for other transitions a Markov approach was taken. Specifically, we used the area under the curves (AUC) for MFS and OS from PROSPER to inform transitions from nmHRPC to mHRPC and to death, but elements of the Markov model to calculate subsequent disease progressions (transitions from PD1-PD3) and PPS. Therefore, technically speaking the here described analysis presents a Markov model; however, within this framework the portioned survival modelling approach is followed.

The overall model structure (Figure 21) builds upon the economic model in NICE TA377 which related to enzalutamide in the chemotherapy-naïve mHRPC setting[62]. In a Markov model, each disease state is represented by a mutually exclusive Markov state (i.e. a patient can only be in one particular health state at each point in time). All patients enter the model in the nmHRPC health state and remain there until they progress to mHRPC (PD1 health state) or die. Patients move between health states between each Markov cycle and transitions are considered irreversible. This is in line with the current disease pathway where further disease progression of mHRPC patients can be slowed down by available active treatments, but not reverted back to nmHRPC.

Figure 21 Structure of the de novo Markov model



Abbreviations: nmHRPC: non-metastatic hormone-relapsed prostate cancer; mHRPC: metastatic hormone-relapsed prostate cancer; PD: progressed disease.

Upon radiographic progression to bone or soft tissue disease (MFS), patients move to the first mHRPC health state, PD1. MFS was considered to be the most relevant parameter to model the transition between the two first health states, as MFS was the primary efficacy endpoint in PROSPER and the first occurrence of metastases marks an important point in the treatment of HRPC impacting HRQoL[21] and leading to a change in treatment. Moreover, ICECaP has shown MFS to be strongly correlated with OS in localised prostate cancer, further emphasising the clinical importance of delaying metastases[59]. Similar findings have been shown for high risk nmHRPC[61].

All health states are subject to mortality with death being the absorbing final health state of the model. In the earlier NICE submission for enzalutamide in chemo-naïve mHRPC patients (TA377[62]), OS as measured in the pivotal trial PREVAIL was applied to all the health states of the economic model in a time-depended manner[52]. While this allows for a conservative OS extrapolation that accurately reproduces the OS trial results for the entire cohort, the ERG and NICE committee criticised this approach[70]. This critique may apply even more to a model in nmHRPC; the assumption that a stable, asymptomatic or mildly symptomatic nmHRPC patient would have the same probability of dying at a given point in time as a mHRPC patient who progressed on chemotherapy may indeed lack face validity. The lack of face validity of a single survival function for both nmHRPC and mHRPC was confirmed by UK clinical and health economic experts[71,16,72]. Therefore, OS was modelled separately of survival in the nmHRPC health state (PrePS) and in the mHRPC health states (PPS).

Current clinical guidelines and clinical practice in the UK indicate that once the disease has progressed to the metastatic setting, patients are likely to receive different treatment lines[29, 68, 73, 74]. The duration of each subsequent treatment line and related costs and impact on QoL may influence cost-effectiveness of enzalutamide and thus, they have been modelled. The metastatic disease health state was divided into three treatment states (PD1, PD2, and PD3), representing first-, second-, and third-line treatment options for mHRPC, respectively.

Mean treatment durations are used in the model to inform the rate of subsequent progressions from PD1 to PD2 and from PD2 to PD3. Data from PROSPER regarding the use and timing of chemotherapy or other post-baseline neoplastic treatments is compromised by a low number of events (n=187; 13.4%), and to some degree by subsequent use of other therapies that are likely not permitted in the UK (e.g. use of abiraterone after enzalutamide). As such, it is not possible to derive transition probabilities to the subsequent PD2 and PD3 health states (i.e. second-, and third-line mHRPC treatments) directly from the results of the PROSPER trial. Instead, these transition probabilities are based on assumptions about treatment durations informed by data from the published literature (i.e., PREVAIL[52] and COU-AA-302[75] trials for chemo-naïve mHRPC patients, TAX-327[76] and TROPIC[77] for patients on chemotherapy, AFFIRM[53] and COU-AA-301[78] for post-chemotherapy patients), as well as expert UK opinion[71] .

In the first health state (i.e., nmHRPC) patients receive either enzalutamide plus ADT or ADT alone (Table 38). ADT is the current SoC for these patients in the UK. Although the benefits of ADT these patients is uncertain, current guidelines recommend its use because the modest potential benefits of continuing castration outweigh the risk of treatment[30].

Upon progression, patients move to PD1. In the UK, the use of abiraterone after enzalutamide (or vice versa) in clinical practice is not allowed in the NHS[29]. Based on this, in the model patients that develop metastases while on enzalutamide in the nmHRPC health state are assumed to discontinue enzalutamide and continue on ADT alone if chemotherapy is not yet indicated. These patients do not receive abiraterone after enzalutamide. In contrast, patients on ADT alone in the first health state receive enzalutamide or abiraterone plus ADT in PD1. In line with the treatment algorithm in clinical practice, in the PD2 mHRPC health state patients in both arms of the model are treated with either docetaxel or ADT alone. Docetaxel is given only to those patients who are sufficiently fit[16]. However, UK clinical experts have commented that some patients may prefer not to receive chemotherapy despite being eligible[16]. Based on this, it is assumed that in the PD2 health state approximately 40% of patients would receive chemotherapy. An overview of the base case treatment sequence is provided in Table 38.

Table 38 Overview of treatment sequence used for the base-case in the model

Health states	Enzalutamide arm (A)	ADT arm (B)
nmHRPC	Enzalutamide	ADT
PD1	ADT alone	Enzalutamide*
PD2	ADT alone (60%) Docetaxel (40%)	ADT alone (60%) Docetaxel (40%)
PD3	Best supportive care	Best supportive care

Note: ADT is included in all treatment lines, except for best supportive care
*A scenario was included where patients received abiraterone plus ADT in PD1
Abbreviations: ADT: androgen deprivation therapy; nmHRPC: non-metastatic hormone-resistant prostate cancer; PD: progressed disease.

The use of cabazitaxel, radium-223, mitoxantrone, denosumab and sipuleucel-T is disregarded as these products are not used by a majority of patients in the UK[64]. Treatment re-challenges are also not part of the standard treatment pathway and therefore not included in the model.

B3.2.3 Intervention technology and comparators

The initial treatment when patients enter the model is enzalutamide in combination with ADT in the enzalutamide arm of the model and ADT alone in the ADT arm of the model. As discussed in section B.1.3, ADT was considered the most relevant comparator as there currently are no nmHRPC-specific treatments recommended in the UK[16]. This is in line with the NICE scope and the PROSPER study design, where patients in either treatment arm remained on ADT throughout the duration of the trial. A list of endocrine therapy at baseline in PROSPER is provided in Table 39[2].

Table 39 Most common endocrine baseline treatments given in PROSPER

ATC level description generic name	Enzalutamide (n=930)	Placebo (n=465)	Total (n=1,395)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Source: PROSPER Clinical Study Report[2]
*Patients not on endocrine therapy had been surgically castrated. Abbreviations: ATC: anatomical therapeutic chemical.

Other features of the economic analysis along with the justification are listed in Table 40.

Table 40 Features of the economic analysis

Factor	Previous appraisals	Current appraisal	
	N/A	Chosen values	Justification
Time horizon	-	Lifetime horizon implemented as 20 years	Based on published data for nmHRPC patients[44, 79], a maximum time horizon of 20 years was considered sufficiently long even when applying the most optimistic scenario
Cycle length	-	1 month	This allows for sufficient detail in the model calculations taking into account that PSA measurements and digital rectal examination are carried out every 3, 6, or 12 months and it is in line with most other economic models for early or localised prostate cancer, identified from the literature[80-82]
Were health effects measured in QALYs; if not, what was used?	-	Yes	In line with NICE reference case[83]
Discount for utilities and costs	-	3.5%	In line with NICE reference case[83]

Factor	Previous appraisals	Current appraisal	
	N/A	Chosen values	Justification
Perspective (NHS/PSS)	-	The NHS and PSS in England	In line with NICE reference case[83]
Half-cycle correction	-	Yes	In line with NICE reference case[83]
Treatment waning effect?	-	NA	NA
Source of utilities	-	PROSPER[2], PREVAIL[84], AFFIRM[53], and literature[85-89]	Most utilities were derived from PROSPER, as this is the main trial performed in the high risk nmHRPC population. Other trials were used for later stages of the disease and literature for AEs and SRE-related utilities
Source of costs	-	NHS reference costs	In line with NICE reference case[83]

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

B.3.3 Clinical parameters and variables

As far as possible, all clinical parameters included in the model (MFS, TTD, OS, PrePS, PPS) are derived from PROSPER. Where available, external data were used to validate, and if needed augment the PROSPER data. A detailed description of how these data were extrapolated and incorporated into the model is available in the sections below. The Extrapolation report[46] is included as a reference in this submission.

Given the duration and follow-up of the study (the median follow-up at time of the first interim analysis was 18.5 months in the enzalutamide group and 15.1 months in the placebo group), the PROSPER data needed to be extrapolated to be applicable to the 20-year time horizon of the model. In line with NICE decision support unit (DSU) technical support document 14[90], treatment effects were modelled extrapolating patient-level data per arm and the simplest model was chosen, if it showed an adequate fit to the data (i.e. testing standard parametric models first, followed by flexible and piecewise models second). For each outcome of the above-mentioned outcomes (MFS, TTD, OS, PrePS, and PPS), six standard parametric models (i.e. exponential, Weibull, log-logistic, log-normal, generalised gamma and Gompertz), spline-based models and if applicable piecewise models were fitted for each treatment group separately[46]. Spline-based and piecewise models were only considered when none of the six standard parametric models provided an adequate fit. To determine the best model fit in line with the recommendations in the NICE DSU technical support document 14[90], the following steps were undertaken[46]:

- **Akaike information criterion (AiC) / Bayesian information criterion (BiC)** - Model fits were evaluated using AiC and BiC statistics. Lower AiC/BiC figures are indicative of a better statistical fit of the survival function of the Kaplan-Meier data.

- **Visual Inspection** - Visual inspection was carried out by plotting the projected survival curves overlaid with the Kaplan-Meier survival functions.
- **Clinical Validity** - The clinical plausibility of the proportion of patients estimated to be surviving at the tails of the curve was examined.

Extrapolation of each clinical outcome is detailed in the following sections. At the time of submission, two interim analyses had been conducted for OS. The first interim analysis was at approximately 165 (27.7%) of the 596 deaths specified for the final OS analysis events and the second at 288 (48.3%) deaths. MFS and OS from the first interim analysis have been used in the base-case.

B.3.3.1 MFS

As described in section B.3.2.2, MFS was the primary efficacy endpoint of PROSPER. MFS is used in the model to inform the first health state transition as a progression from nmHRPC to the first mHRPC health state (PD1). It is assumed that patients progressing from nmHRPC to mHRPC do transition to the next treatment line. However, in line with clinical practice, ADT is maintained throughout the course of the disease. To this end, patient-level PROSPER MFS KM data (Figure 6) has been used to fit parametric curves to extrapolate the MFS KM data. Among the six evaluated individual parametric distributions, generalised gamma provided the best statistical and visual fit, but none of the standard models (including generalised gamma) seemed to provide an optimal fit. As shown in ***[redacted]22, the best fitting standard parametric curve (generalised gamma) showed large deviations from the Kaplan Meier medians. The generalised gamma curves seem to underestimate median MFS in the ADT arm of the model with an estimated 13.1 months median MFS compared to 14.7 months observed in the placebo arm of PROSPER. At the same time, the generalised gamma curve for the enzalutamide arm of the model estimates median survival at 39.2 months compared to 36.6 months observed in PROSPER. Clinical experts confirmed that the generalised gamma extrapolations were not representing the clinical trial data well and the plausibility of their extrapolations was questionable[16, 91]. Therefore, none of the standard parametric models, including generalised gamma, was deemed a good fit to the PROSPER KM data and flexible (spline) and piecewise models were considered.

[redacted]22[redacted]

Source: PROSPER extrapolation report[46]
Abbreviations: KM: Kaplan Meier; MFS: metastasis-free survival.

More advanced flexible spline and piecewise models were fitted. Of the spline models, spline model 3 (2 knots, hazard scale) offered the most clinically valid extrapolation, with 3-year MFS estimates closest to the actual PROSPER data (16.23% vs 14.85% for placebo and 50.87% vs 50.37% for enzalutamide (*** 23). Of the piecewise models, the fit with log-logistic tail provided the most plausible extrapolations[16, 91]. The consulted health economic experts[72] confirmed that none of the six standard parametric models provided a reasonable fit and/or extrapolation of the data and that the spline model 3 and piecewise fit with log-logistic tail provided much more plausible extrapolations[46]. The HE model uses the spline model 3 because it involves fewer assumptions than the piecewise models (i.e. manual selection of the landmark point) and to avoid the 'tail' commonly seen with log-logistic curves. However, to test the impact of this assumption, a scenario using the piecewise (log-logistic) model has also been considered.

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Source: PROSPER extrapolation report[46]
Abbreviations: KM: Kaplan Meier; MFS: metastasis-free survival.

B.3.3.2 Survival modelling

Survival in the base-case was based on the IA1 data-cut in PROSPER. Although IA2 data were more mature, MFS was not analysed in this data cut. The IA2 analysis included TTD, but that is only a proxy for disease progression that relies on the prespecified protocol for discontinuation. Since progression to mHRPC marks such an important turning point, both in the impact it has on a patient's life and in the HE model, it was felt more important to have a reliable input for MFS than to have more mature OS data. Therefore, the IA1 data was deemed more suitable to inform the survival in the model. Nevertheless, a scenario based on the IA2 data was performed to explore the consequence of this decision.

OS was one of the key secondary outcomes of PROSPER (Figure 10) and it was used to inform the PrePS and PPS used in the model. As mentioned in Section B.3.2.2, splitting up OS into PrePS and PPS was considered to have more face validity, given the low symptom burden and relatively good prognosis of patients pre-progression compared with patients after progression. In order to derive the PrePS from the PROSPER patient-level data, a time-to-event analysis was performed on the entire ITT trial population using the PROSPER OS data where death was accounted as an event, and patients experiencing progression or still alive at the cut-off date were censored.

At the first data cut of data, [redacted] PrePS events had occurred for enzalutamide and placebo respectively (Table 41). The greater number of events in the enzalutamide arm is due to the longer time spent by these patients in the pre-progression stage. The mean time to a PrePS event was [redacted] months for enzalutamide and [redacted] months for placebo, resulting in an HR of a PrePS event of [redacted]. However, given the low number of events in both groups, these results should be interpreted cautiously. Overall, it can be stated that PrePS was high in both groups.

PPS was longer in the placebo group, with a mean time to event of [redacted] months versus [redacted] months (Table 41). However, as shown in Table 13, the shorter PPS was compensated by a much longer MFS in the enzalutamide arm, resulting in a numerically longer OS in favour of enzalutamide.

Table 41 Pre- and post-progression survival (IA1, ITT population)

Outcome	Enzalutamide (n=933)	Placebo (n=468)
PrePS		
Total number of patients	933	468
Number of patients with events	[redacted]	[redacted]
Number of censored cases	[redacted]	[redacted]
Mean time to events, months (SE)	[redacted]	[redacted]
Q1 [95% CI]	NR	NR
Median [95% CI]	NR	NR
Q3 [95% CI]	NR	NR
p-value[a]	[redacted]	
HR [95% CI][b]	[redacted]	
PPS		
Total number of patients	[redacted]	[redacted]
Number of patients with events	[redacted]	[redacted]
Number of censored cases	[redacted]	[redacted]
Mean time to events, months (SE)	[redacted]	[redacted]
Q1 [95% CI]	[redacted]	[redacted]
Median [95% CI]	[redacted]	[redacted]
Q3 [95% CI]	[redacted]	[redacted]
p-value[a]	[redacted]	
HR [95% CI][b]	[redacted]	

Source: PROSPER extrapolation report[46]
a. p-value is based on a stratified log-rank test.

b. Hazard ratio is based on a stratified Cox regression model (with treatment as the only covariate) and is relative to placebo with <1 favouring enzalutamide. The 2 randomisation factors are PSA doubling time (<6 months vs. ≥6 months) and prior or current use of a bone-targeting agent.
Abbreviations: CI: Confidence interval; HR: Hazard ratio; IA1: interim analysis 1; NR: Not reached; PPS: post-progression survival; PrePS: pre-progression survival; SE: standard error; TTD: time to treatment discontinuation.

The models with the best fit for PrePS were log-normal for placebo and Gompertz for enzalutamide, although Weibull was the only model that fitted both arms well[46]. The general population survival (calculated based on a starting age of 73.5 years) at 3 and 5 years (90.7% and 83.5%) was consulted as external reference data[92]. However, this may be an overestimation for this outcome. Therefore, among the individual parametric distributions, the Weibull (3 and 5 year survival: [redacted][46]) seems to be the most plausible fit for PrePS based on visual and statistical criteria (***[redacted]24).

A clinical expert confirmed that the fit seems reasonable, but long-term extrapolation would be hard to validate because in reality there would not be patients that remain progression free for such expanded periods of time (see MFS and TTD extrapolations above)[91].

[redacted]24

Source: PROSPER extrapolation report[46]
Abbreviations: KM: Kaplan Meier; PrePS: pre-progression survival.

The models with the best fit for PPS were log-logistic and Weibull for both arms[46]. Two trials were considered valid external references: PREVAIL[52], a double-blind, phase 3 study, comparing enzalutamide to placebo in asymptomatic or mildly symptomatic mHRPC patients not yet eligible for chemotherapy, and COU-AA-302[75], comparing abiraterone plus prednisone versus placebo plus prednisone in a similar patient population. Overall, the Weibull curve gave the most clinically plausible PPS estimates based on the PREVAIL[52] enzalutamide arm as external OS reference data and log-logistic PPS data showed the closest match to the COU-AA-302[75] abiraterone OS arm data. However, the log-logistic curve had a relatively long tail, suggesting that some patients would survive over extended periods, which may not be clinically plausible given the advanced age of these patients, as

well as their advanced stage of the disease. Therefore, the Weibull curve was selected as the best fit (***[redacted]25).

[redacted]25

Source: PROSPER extrapolation report[46]
Abbreviations: KM: Kaplan Meier; PPS: post-progression survival.

The survival curves used in the base-case of the model are summarised in Table 42.

Table 42 Models and external validation data used for each outcome

Outcome	Model	Validation
MFS	Spline model (2 knots, hazard)	Input from UK clinical and health economic experts[16, 72]
PrePS	Weibull parametric fitting	Expert input[16, 72], UK life tables[92]
PPS	Weibull parametric fitting	Input from UK clinical and health economic experts[16, 72], PREVAIL[52], COU-AA-302[75],

Abbreviations: MFS: metastasis-free survival; OS: overall survival; PrePS: pre-progression survival; PPS: post-progression survival; TTD: time to treatment discontinuation.

B.3.3.3 Transition probabilities

Transition probabilities were calculated from the extrapolated survival curves (Table 42). For each of the fits, the cumulative hazard $H(t)$ was defined according each model's specific cumulative hazard formula. The survival function $S(t)$ was derived from the cumulative hazard as $S(t) = Exp(-H(t))$.The transition probability for a given value of t can then be calculated using the formulas shown below, assuming a cycle length *u*:

$$tp(t) = 1 - \{H(t-u) - H(t)\}$$

In addition, mean treatment durations were used to model the transition from PD1 to PD2 and PD3, as discussed in section B.3.2.2. The durations used are summarised in Table 43.

Table 43 Mean treatment durations used in model for mHRPC health states (PD1-PD3)

	Median Tx duration (months [95% CI])	Prob. per cycle to discontinue	Source
Probabilities for progression in PD1			
Probability to progress on 2nd line enzalutamide	23.7 [17.78; 29.63]	0.033	PREVAIL[84] (pre-chemo model: Gamma June 2014 cut-off)
Probability to progress on 2nd line ADT	7.3 [5.48; 9.13]	0.092	PREVAIL[84] (pre-chemo model: Weibull June 2014 cut-off)
Probability to progress on 2nd line radium-223	7.3 [5.48; 9.13]	0.092	Assumed equal to ADT
Probabilities for progression in PD2			
Probability to progress on 3rd line enzalutamide	8.30 [7.95; 9.13]	0.080	AFFIRM[67]
Probability to progress on 3rd line docetaxel in PD2 (40%)*	6.58 [4.93; 8.22]	0.100	TAX 327[76]
Probability to progress on 3rd line ADT in PD2 (60%)*	6.58 [4.93; 8.22]	0.100	Assumed equal to docetaxel

*Percentages are estimates of patients continuing to that treatment, based on UK clinical expert opinion
Abbreviations: ADT: androgen deprivation therapy; PD: progressed disease; Prob: probability; Tx: treatment.

B.3.4 Measurement and valuation of health effects

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

Patients with high risk nmHRPC are either asymptomatic or mildly symptomatic and generally have good HRQoL and functioning[40]. However, when the disease progresses and metastases develop, patients' HRQoL starts to decline[53, 78]. Bone metastases can cause substantial morbidity and HRQoL is worst in the last phase of life[93]. HRQoL in HRPC patients can be further worsened by the treatments they receive, particularly chemotherapy and their respective toxicities. Notably, in Wolff et al, a German study in mHRPC patients, patients on chemotherapy had worse HRQoL than chemo-naïve patients and patients who were no longer on chemotherapy[21]. In line with this, patient groups, clinical experts and payers have highlighted the positive impact of delaying time to chemotherapy[71].

The EQ‑5D is the preferred instrument to measure health states. In PROSPER the EQ-5D-5L health questionnaire was conducted at baseline (week 1) and every 16 weeks thereafter including during the follow-up period. The EQ-5D was collected at weeks 1, 5, 17 and every 16 weeks thereafter during the study treatment period and every 16 weeks after progression to mHRPC and/or treatment discontinuation. Consequently, EQ-5D-related PROSPER data have been used to derive utility weights for the nmHRPC health state and PD1, i.e., the first line mHRPC health state.

The health state utility value for nmHRPC has been derived from the PROSPER baseline utility based on mapping the observed EQ-5D-5L to the UK tariff EQ-5D-3L utility values using the 'cross-walk' method[94]. The mapped baseline utility value from PROSPER has been estimated at [redacted]. This value reflects a conservative estimate, as the EQ-5D-5L 'England value set', using the Office of Health Economics algorithm[95], results in a utility value of [redacted], which might better reflect the overall low symptom burden of patients in nmHRPC. An age-matched general UK population utility value would be expected within a similar range at 0.92 for men at the age of 65-74[96].

The utility value for the first mHRPC health state (PD1) is also based directly on the observed PROSPER utility value at the first assessment post-progression. As would be expected, this value is lower than the PROSPER baseline utility value at [redacted] using the mapped value, indicating that occurrence of first metastases does indeed have an impact on patients' HRQoL. Using the 'England value set' results in a PD1 utility value of [redacted]. Similarly, the PD2 health state utility value has been estimated based on the first HRQoL assessment post-progression in PREVAIL ([redacted]). The PD3 health state utility is in line with the post-chemotherapy health state of the pre-chemo model, in line with the NICE submission for enzalutamide in chemo-naïve mHRPC patients (TA377[62]), which is derived from AFFIRM[53] (see Table 44 for an overview of utility values).

One of the most distinct and severe consequences of bone metastases experienced by mHRPC patients are skeletal related events (SREs), and therefore SREs were also included in the model. However, the PROSPER trial was performed at an early stage of the disease when the occurrence of SREs is low. Therefore, the frequency and disutility of SREs in the model were based upon PREVAIL[84] and COU-AA-301[78] data.

Disutilities applied for AEs are derived from the NICE submission for enzalutamide in chemo-naïve mHRPC patients (TA377[62]). Similarly, the disutility for undergoing chemotherapy might already be sufficiently covered by applying AE disutilities and thus, this value is set to zero as well in the base-case analysis. The main utility values used for the economic model are shown in Table 44.

Table 44 Utility values for the early health economic model

Health state		Mean	95%CI		Source
nmHRPC	**Mapped value**	[redacted]	[redacted]	[redacted]	PROSPER[2, 40]a first HRQoL assessment post-progression (individual patient-level data analysis using 'mapping' algorithm; data on file)
	EQ-5D-5L tariff	[redacted]	[redacted]	[redacted]	PROSPE[2, 40] first HRQoL assessment post-progression (individual patient-level data analysis using 'England value set'[95]; data on file)
mHRPC	**PD1, mapped value**	[redacted]	[redacted]	[redacted]	PROSPER[2, 40] first HRQoL assessment post-progression (individual patient-level data analysis using 'mapping' algorithm; data on file)
	PD1, EQ-5D-5L tariff	[redacted]	[redacted]	[redacted]	PROSPER[2, 40]as first HRQoL assessment post-progression (individual patient-level data analysis using 'England value set'[95]; data on file)

Health state		Mean	95%CI		Source
	PD2	[redacted]	[redacted]	[redacted]	PREVAIL[84] first HRQoL assessment post-progression (individual patient-level data analysis; data on file)
	PD3	0.688	0.640	0.735	AFFIRM[53]
End-of-life utility		[redacted]	[redacted]	[redacted]	PREVAIL[84] utility value based on final HRQoL assessment before death (within 90 day period before death; data on file)
Death		0	-	-	Definition

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

B.3.4.2 Mapping

As mentioned in the previous section, EQ-5D-5L was administered in PROSPER. The EQ-5D-5L utility index value was derived using the value set for England, available on the EUROQOL website. In August 2017, NICE published a position statement advising companies, academic groups and others preparing evidence submissions to NICE not to use the EQ-5D-5L validation set to derive utility values for their evidence submissions[97]. In their position statement, NICE recommended the mapping function developed by Van Hout et al to be used[94]. In accordance with NICE's statement, the observed EQ-5D-5L values were mapped to the UK tariff EQ-5D-3L utility values. However, to test the consequence of which values were used, a scenario using the EQ-5D-5L value set was also performed.

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

A SLR to identify relevant HRQoL studies was conducted. The SLR identified 3 studies that looked at health utilities in nmHRPC; two cross-sectional surveys[98, 99] and one RCT[40]. For full details on the methods of the SLR and the identified studies, see Appendix H.

An overview of the utilities reported for nmHRPC patients along with the utilities in the model is provided in Table 85. In both Hechmati et al[99] and Dawnson et al[98] the utility weights for mHRPC were significantly lower than for nmHRPC patients. In addition, the utility weights from PROSPER for nmHRPC as well as the utilities for mHRPC included in the model, were higher than the weights from the other two studies. Different factors may account for these differences including:

- Method to derive utility weights: trade-off in Dawson et al vs EQ-5D in Hechmati et al and PROSPER
- Nationality of patients: US in Dawson et al vs the five key European Union countries (EU5; France, Germany, Italy, Spain and the UK) in Hechmati et al and different geographic regions in PROSPER.

It is unclear whether there are also differences in the study population across studies. While all nmHRPC patients in Hechmati et al and PROSPER were at high risk of developing

metastases as defined by PSADT ≤10 months, Dawson et al do not mention whether nmHRPC patients were at high risk of metastases or not.

Table 45 Utility weights reported in the SLR identified studies

Reference	Condition	Utility weight
Dawson 2018[98]	nmHRPC	0.80 ± 0.36
	Chemo-naïve mHRPC	0.74 ± 0.43
	During or post-chemo mHRPC	0.64 ± 0.47 (p<0.01 vs nmHRPC)
Hechmati 2012[99]	nmHRPC at high risk of metastases (n=36)	0.77 ± 0.22
	mHRPC (n=165)	0.59 ± 0.30 (p=0.0001 vs nmHRPC)
PROSPER PRO report 2017[40]	High risk nmHRPC (baseline in PLA arm)	[redacted]
	High risk nmHRPC (baseline in ENZA arm)	[redacted]
HE model base-case	nmHRPC	[redacted]
	PD1	[redacted]
	PD2	[redacted]
	PD3	0.688 ± 0.048

Source: PROSPER SLR report[31]
Abbreviations: ENZA: enzalutamide; HE: health economic; HEOR: health economics and outcomes research; mHRPC: metastatic hormone-relapsed prostate cancer; nmHRPC: non-metastatic hormone-relapsed prostate cancer; PLA: placebo.

B.3.4.4 Adverse reactions

As discussed in Section B.2.6.1, AEs in PROSPER were infrequent and generally well tolerated. AE rates for enzalutamide and ADT are integrated based on PROSPER safety results for the enzalutamide and placebo arm respectively. These rates were calculated based on the number of patients with each AE in PROSPER and the treatment emergent period (total patient-years: 1,435.6 for enzalutamide and 512.7 for placebo)[2].

AEs for enzalutamide in PD1 have been incorporated into the model on the basis of PREVAIL[52] results, in line with the enzalutamide pre-chemo NICE submission[62] and ERG report[70]. Rates have been calculated from the number of patients with each AE in the treatment emergent period (707.5 patient-years). For docetaxel, incidence of the selected AEs has been taken from the publication by Tannock et al[76].

Other active treatments for HRPC patients include cabazitaxel, radium-223, mitoxantrone, sipuleucel-T and denosumab[64]. However, these treatments are currently not considered part of standard care and their AEs are not considered in this economic evaluation. The model only takes into account AEs of grade 3-4, those reported in ≥2% of patients, and AEs of special interest (i.e. AEs with high impact on costs and outcomes), as summarised in Table 46.

Table 46 AE frequency trials relevant to the model

	PROSPER (nmHRPC)[2]		PREVAIL (PD1)[52]		TAX 327 (PD2)[76]	
AEs	**ENZA**	**PLA**	**ENZA**	**PLA**	**DOC**	**MIT**
Patient years	1,435.6	512.7	1,180.1	541.6	182.6	97.7
Anaemia	9	6	29	25	17	7
Asthenia	11	1	-	-	-	-
Back pain	-	-	22	25	-	-
Bone pain	-	-	12	20	-	-
Deterioration in general physical health	-	-	18	10	-	-
Fall	12	3	-	-	-	-
Fatigue	27	3	-	-	17	17
Febrile neutropenia	-	-	-	-	10	0
Haematuria	16	13	-	-	-	-
Hypertension	43	10	59	19	-	-
MACE	34	8	-	-	-	-
Neutropenia	-	-	-	-	106	74
Pneumonia	10	2				
Pulmonary embolism	3	5				
Urinary retention	4	5				
SREs						
Spinal cord compression	-	-	38	21	-	-
Pathological bone fracture	-	-	41	15	-	-
Radiation to the bone	-	-	130	83	-	-
Surgery to the bone	-	-	15	9	-	-

Abbreviations: AE: adverse event; DOC: docetaxel; ENZA: enzalutamide; MIT: mitoxantrone; nmHRPC: non-metastatic hormone-relapsed prostate cancer; SRE: Skeletal-related event.

In general, AEs have a negative impact on the HRQoL of patients. Due to the nature of the adverse events reported in PROSPER, it is assumed that most AEs will be resolved within two weeks[2]. In PROSPER, PROs were collected every 16 weeks with tools that have a recall period of 7 or fewer days. Therefore, it is unlikely that the impact of AEs on HRQoL was captured in the on-treatment benefit. To better model the impact of AEs on patient's HRQoL, disutility values were applied for the most relevant AEs (i.e., grade 3 or higher). In the absence of disutility data from PROSPER, the disutilities of experiencing an AE were sourced from the published literature. When disutility estimates were identified in different sources, an average was taken and this value used to inform the model. The disutilities and durations used in the model are reported in Table 47. The duration of the disutilities correspond to the average duration of the acute phase of the corresponding AE.

Table 47 Duration and disutilities of AEs

AE	Disutility	Duration of disutility (days)	Utility Source	Duration Source
Anaemia	-0.119	10.5	Swinburn et al[89]	NICE ERG report on pre-chemo enzalutamide TA377[70], also reported in NICE ERG report on post-chemo abiraterone TA259[73].
Asthenia	-0.131	91.25	Assumed equal to fatigue: Lloyd et al[88], Nafees et al[87], Swinburn et al[89]	NICE ERG report on pre-chemo enzalutamide TA377[70]; also reported in NICE ERG report on post-chemo abiraterone TA259[73].
Back pain	-0.069	10.5	Doyle et al[86]	
Bone pain	-0.069	10.5	Doyle et al[86]	
Deterioration in general physical health	-0.131	91.25	Assumed equal to fatigue	assumed equal to fatigue
Fall	-0.069	10.5	Assumed equal to pain	
Fatigue	-0.131	91.25	Lloyd et al[88], Nafees et al[87], Swinburn et al[89]	
Febrile neutropenia	-0.120	10.5	Lloyd et al[88] and Nafees et al[87]	
Haematuria		10.5	No (dis-)utilities available	Assumption, requires clinical input
Hypertension	-0.153	10.5	Swinburn et al[89]	NICE ERG report on pre-chemo enzalutamide TA377[70]; also reported in NICE ERG report on post-chemo abiraterone TA259[73].
Major cardiovascular adverse event (MACE)	-0.153	10.5	Assumed equal to hypertension	
Neutropenia	-0.090	10.5	Nafees et al[87]	
Pulmonary embolism	-0.145	10.5	NICE cabazitaxel MS	
Urinary retention	-0.110	10.5	Armstrong (Table 2)[100]	
SREs				
Spinal cord compression	-0.237	30.42	PREVAIL CSR (Tables_12MAR2014 Table 3.6.2.) Botteman et al[101]	NICE ERG report on pre-chemo enzalutamide TA377[70]; also reported in NICE ERG report on post-chemo abiraterone TA259[73].
Pathological bone fracture	-0.201	30.42		
Radiation to the bone	-0.056	30.42		
Surgery to the bone	-0.056	30.42		

Abbreviations: AE: adverse event; ERG: evidence review group; TA: technology appraisal.

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

A summary of the utility values included in the model is provided in Table 48.

Table 48 Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
nmHRPC (3L value set, base case)[2]	[redacted]	[redacted]	Table 44, pages 111-112	PROSPER is the main source of utility weight values for high risk nmHRPC patients (see section B.3.4.3)
nmHRPC (5L value set)[40]	[redacted]	[redacted]	Table 44 pages 111-112	
PD1 (3L value set, base case)[40]	[redacted]	[redacted]	Table 44 pages 111-112	
PD1 (5L value set)[40]	[redacted]	[redacted]	Table 44 pages 111-112	
PD2[84]	[redacted]	[redacted]	Table 44 pages 111-112	PREVAIL is the main source of utility weight values for pre-chemo mHRPC patients (see section B.3.4.3)
PD3[53, 62]	0.688	0.640-0.735	Table 44 pages 111-112	AFFIRM is the main source of utility weight values for pre-chemo mHRPC patients. Its results were in line with several other publications (see section B.3.4.3)
End-of-life utility[84]	[redacted]	[redacted]	Table 44 pages 111-112	PREVAIL utility value based on final HRQoL assessment before death
AE disutilities	See Table 47, pages 115			Literature values were used as impact of individual AEs could not be measured in PROSPER due to frequency of HRQoL measurements
Spinal cord compression[62]	-0.237	SE = 0.079		Disutilities reported for different types of SREs in patients with bone metastases
Pathological bone fracture[62]	-0.201	SE = 0.080		
Radiation to the bone[62]	-0.056	SE = 0.021		
Surgery to the bone[62]	-0.056	SE = 0.021		

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

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

The perspective applied to the model is the NHS England perspective (i.e. a national health care payer's perspective)[83]. Therefore, only direct medical costs (e.g. drug acquisition costs, inpatient bed days, ER visits, diagnostics, AEs, etc.) and indirect medical costs (e.g. future costs relevant to HRPC) have been taken into consideration.

The SLR did not identify health resource utilisation (HRU) specific for high risk nmHRPC patents in the UK. The only HRU-related study identified was Morote et al[102] which compares the annual management costs in Spain of patients with high risk nmHRPC versus the annual management costs during the first, second and subsequent years after development of bone metastases. The authors provide only limited HRU data but conclude that the main differences between nmHRPC and mHRPC relate to the use of additional therapies in the mHRPC setting, management of AEs associated with these therapies and management of metastases and related pain[102].

HRU for patients on enzalutamide in general is well known based on previous related NICE technology enzalutamide appraisals[62, 68] and extensive experience from its use in UK clinical practice. HRU for the high risk nmHRPC model is derived primarily from the PROSPER clinical trial, and monitoring requirements stated on the product label[1, 2].

B.3.5.1 Health-state unit costs and resource use

The following direct medical costs have been considered in the model: cost of outpatient treatment (e.g., visits to urologist and/or oncologist, laboratory examinations, and emergency treatment), cost of drug therapies and concomitant medications if applicable, administration costs, monitoring costs, hospitalisation costs, all follow-up treatment costs and costs for nursing care. HRU values used in the model (Table 49) were validated with UK clinical[16] and are largely in line with the ERG report of the NICE appraisal of enzalutamide in pre-chemo mHRPC (TA377)[70].

The concomitant medication given to patients at each health state is based on the concomitant medication reported in PROSPER for high risk nmHRPC patients and in the TA377 for mHRPC patients (Table 51).

Table 49 Visits and testing included as HRU

Service	nmHRPC state		PD1 – PD3		
	Patients on ENZ	Patients on ADT	Patients on ENZA (PD1)	Patients on ADT (PD1 – PD2)	Patients on DOC (PD2 – PD3)
Outpatient visit consultant	1 every 8 weeks for 50% of patients	1 every 6 weeks for 50% of patients	1 every 8 weeks for 50% of patients	1 every 6 weeks for 50% of patients	1 every 3 weeks for 100% of patients
Outpatient visit nurse	1 every 8 weeks for 50% of patients	1 every 6 weeks for 50% of patients	1 every 8 weeks for 50% of patients	1 every 6 weeks for 50% of patients	None
Community nurse visit	None	1 every 6 weeks for 100% of patients	None	1 every 6 weeks for 100% of patients	None
CT scan	3 every 80.6 weeks for all patients	3 every 22.1 weeks for all patients	3 every 80.6 weeks for all patients	3 every 22.1 weeks for all patients	1 every 6 weeks for 5% of patients
Radiographic/MRI scan	None	None	None	None	1 every 6 weeks for 5% of patients
ECG	None	None	None	None	1 every 6 weeks for 5% of patients
Ultrasound	None	None	None	None	1 every 6 weeks for 5% of patients
Bone scan	1 every 20 weeks for 20% of patients	1 every 12 weeks for 20% of patients	1 every 20 weeks for 20% of patients	1 every 12 weeks for 20% of patients	1 every 6 weeks for 5% of patients
Full blood count	1 every 8 weeks for 100% of patients	1 every 6 weeks for 100% of patients	1 every 8 weeks for 100% of patients	1 every 6 weeks for 100% of patients	1 every 3 weeks for 100% of patients
Liver function test	1 every 8 weeks for 50% of patients	1 every 6 weeks for 100% of patients	1 every 8 weeks for 50% of patients	1 every 6 weeks for 100% of patients	1 every 3 weeks for 100% of patients
Kidney function test	1 every 8 weeks for 100% of patients	1 every 6 weeks for 100% of patients	1 every 8 weeks for 100% of patients	1 every 6 weeks for 100% of patients	1 every 3 weeks for 100% of patients
PSA	1 every 8 weeks for 100% of patients	1 every 6 weeks for 100% of patients	1 every 8 weeks for 100% of patients	1 every 6 weeks for 100% of patients	1 every 3 weeks for 100% of patients

Abbreviations: ADT: androgen deprivation therapy; BSC: basic standard of care; CT: Computer tomography ECG: electrocardiogram; ENZA: enzalutamide; ERG: evidence review group; nmHRPC: non-metastatic hormone-relapsed prostate cancer; PD: progressed disease; PSA: prostate-specific antigen; pts: patients.

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Source: PROSPER Clinical Study Report[2]
*It is assumed that the other patients received surgical castration.

Table 51 PREVAIL concomitant medications reported for at least 5% of patients in either treatment group

Concomitant medication	Enzalutamide	Placebo	Most used drug
Agents acting on the renin-angiotensin system	50.4%	45.0%	Ramipril
Analgesics	64.3%	59.8%	Paracetamol
Antibacterials for systemic use	35.9%	28.9%	Amoxicillin
Corticosteroids for systemic use	26.5%	30.2%	Dexamethasone
Drugs for treatment of bone diseases	34.8%	35.1%	Zolendronic acid
Drugs for acid related disorders	41.7%	37.9%	Omeprazole
Antiemetics and antinauseants	8.3%	7.7%	Ondansetron

Source: ERG report TA377[62]

B.3.5.2 Intervention and comparators' costs and resource use

Cost information has been obtained from UK-specific sources such as the British National Formulary (BNF)[9], eMIT, NHS reference costs tables and the Personal Social Services Research Unit (PSSRU)[103]. If available, lower and upper quartiles have been used for SA. Since the base-case analysis applies a NHS England perspective any taxes applicable to the services used (e.g. value added tax on technology acquisition costs) have been excluded from the base-case analysis.

Table 52 and Table 53 provide an overview of drug acquisition and administration costs, and costs for visits and testing, respectively.

Table 52 Drug unit costs

Drug	Brand	NHS Price / pack (£)	Price per day	Reference
Active treatments				
Enzalutamide	Xtandi	£2,734.67	£97.67	BNF online[9]
Androgen deprivation therapies (ADT)				
Luteinizing hormone releasing hormone (LHRH) (goserelin)	Non-proprietary	£235.00	£2.80	BNF online[9]
Next line treatments				
Abiraterone	Zytiga	£2,735.00	£97.67	BNF online[9]
Docetaxel	Non-proprietary	£46.75	£2.10	eMit database[104], NPC code DHC046:
Concomitant treatments				
Bisphosphonates (zoledronic acid)	Non-proprietary	£11.31	£0.21	eMit database[104], NPC code DFF025:
Antihistamine (chlorphenamine)	Non-proprietary	£0.22	£0.01	eMit database[104], NPC code DCD050:
H2-antagonist (ranitidine)	Non-proprietary	£0.50	£0.01	eMit database[104], NPC code DAE018:
Anti-emetic (ondansetron)	Non-proprietary	£0.73	£0.02	eMit database[104], NPC code DDF028:
GCSF: filgrastim	Neupogen	£52.70	£35.13	BNF online[9]
Prednisone	Non-proprietary	£4.00	£0.08	eMit database[104], NPC code DFN040:

Abbreviations: BNF: British national formulary; GCSF: Granulocyte colony-stimulating factor; NHS: National Health Service.

Table 53 Visits and testing unit costs

Variable	Code	Unit Cost	Reference
Outpatient visit consultant - follow-up	section 15.5	£106.00	PSSRU 2017[103]
Outpatient visit nurse	section 10.4	£42.00	PSSRU 2017[103]
Community nurse visit	section 10.6	£36.00	PSSRU 2017[103]
CT scan	DIAGIMOP RA10Z medical oncology	£120.07	NHS reference costs 2016-2017[105]
Radiographic/MRI scan	DIAGIMOP RA03Z medical oncology	£161.51	NHS reference costs 2016-2017[105]
ECG	OPROC EA47Z Clinical Oncology (Previously Radiotherapy)	£156.52	NHS reference costs 2016-2017[105]
Ultrasound less than 20 min	DIAGIMOP RA23Z medical oncology	£51.78	NHS reference costs 2016-2017[105]
Ultrasound more than 20 min	DIAGIMOP RA24Z medical oncology	£64.95	NHS reference costs 2016-2017[105]
Bone scan	DIAGIMOP RA36Z medical oncology	£223.30	NHS reference costs 2016-2017[105]
Full blood count	DAPS DAPS05	£3.06	NHS reference costs 2016-2017[105]
Liver function test (5 tests required: 5 times DAPS04)	DAPS DAPS04	£5.64	NHS reference costs 2016-2017[105]. 5 tests required as reported in abiraterone manufacturer submission (TA259[73])
Kidney function test	DAPS DAPS04	£11.27	NHS reference costs 2016-2017[105]. Assumed 10 tests, similar to abiraterone manufacturer submission (TA259[73])
PSA	DAPS DAPS04	£1.13	NHS reference costs 2016-2017[105]
Echocardiogram	DIAGIMOP RA60A medical oncology	£73.70	NHS reference costs 2016-2017[105]
Home care visit (cost 1hour visit)	section 11.6	£22.00	PSSRU 2017[103] ; Average of daytime and evening
Hospice centre (cost per day)	SPAL IP SD03A	£115.82	NHS reference costs 2016-2017[105]
Palliative care centre (cost per day)	SPAL IP SD03A	£115.82	NHS reference costs 2016-2017[105]
Administration			
Chemotherapy (IV; per cycle); first attendance	CHEM SB12Z	£253.32	NHS reference costs 2016-2017[105]
Chemotherapy (IV; per cycle); subsequent elements	CHEM SB15Z	£361.04	NHS reference costs 2016-2017[105]

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

B.3.5.3 Adverse reaction unit costs and resource use

AE- and SRE-related costs are shown in Table 54 and Table 55, respectively. Cost information has been obtained from NHS reference costs 2016-2017[105] and NICE ERG report of post-chemo abiraterone[106].

Table 54 AE-related costs

AE	Cost	Source
Anaemia	£1,981.12	NHS reference costs 2016-2017[105]; NEL: weighted average of SA04G, SA04H, SA04J, SA04K, SA04L
Asthenia	£12.00	NICE ERG report abiraterone (post-chemo)[106], table 24, p. 64. IQR assumed ±25%
Back pain	£434.85	NHS reference costs 2016-2017[105]; NES: weighted average of HC32H, HC32J, HC32K
Bone pain	£661.09	NHS reference costs 2016-2017[105]; NES: weighted average of HD40D, HD40E, HD40F, HD40G, HD40H
Deterioration in general physical health	£12.00	Costs are not available in NHS reference costs 2016-2017[105]; assumed to be equal to fatigue: NICE ERG report abiraterone (post-chemo)[106], table 24, p. 64. IQR assumed ±25%
Fall	£209.00	NHS reference costs 2016-2017[105]; NCL: WF02B; service code: 191 (Pain management, Multiprofessional Non-Admitted Non Face to Face Attendance, First)
Fatigue	£12.00	NICE ERG report abiraterone (post-chemo)[106], table 24, p. 64. IQR assumed ±25%
Febrile neutropenia	£4,518.83	Costs are not available in NHS reference costs 2016-2017[105]; assumed equal to NHS reference costs 2012-2013 ; NEI_L: PA45Z
Haematuria	£1,933.12	NHS reference costs 2016-2017[105]; NEL: weighted average of LB38C, LB38D, LB38E, LB38F, LB38G, LB38H
Hypertension	£388.81	NHS reference costs 2016-2017[105]; NES: EB04Z
MACE	£759.30	NHS reference costs 2016-2017[105]; NES: weighted average of AA35A-F (Stroke with CC0-16+)
Neutropenia	£169.36	NHS reference costs 2016-2017[105]; HCD: XD25Z (admitted patient care)
Pneumonia	£2,494.89	NHS reference costs 2016-2017[105]; NEL: weighted average of DZ11K-DZ11V
Pulmonary embolism	£2,246.77	NHS reference costs 2016-2017[105]; NEL: weighted average of DZ09J-DZ09Q
Urinary retention	£521.82	NHS reference costs 2016-2017[105]; NEL: weighted average of LB16D, LB16E, LB16F, LB16G, LB16H, LB16J, LB16K

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

Table 55 SRE-related costs

SREs	Cost	Source
Spinal Cord Compression	£5,692.77	NHS reference costs 2016-2017[105]; NEL: weighted average of HC28H-HC28M
Pathological Bone Fracture	£3,617.43	NHS reference costs 2016-2017[105]; NEL: HD39D-H
Radiation to the Bone	£130.58	NHS reference costs 2016-2017[105]; weighted average of HRG codes SC21Z, SC22Z, SC23Z, SC24Z, SC25Z, SC26Z, SC27Z, SC28Z, radiotherapy (RAD): outpatient.
Surgery to the Bone	£3,617.43	NHS reference costs 2016-2017[105]; NEL: HD39D-H
NEL Vertebral fractures	£3,617.43	NHS reference costs 2016-2017[105]; weighted average of HRG codes HD39D, HD39E, HD39F, HD39G, HD39H.

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

B.3.5.4 Miscellaneous unit costs and resource use

Indirect medical costs can generally be divided into costs accrued in life years gained that are related to the indication under review (i.e. all future costs relevant to HRPC) and costs in life years gained that are unrelated to the indication under review (i.e. future costs due to additional unrelated diseases). In the model, only end of life or terminal treatment costs have been included. Data was adopted from the abiraterone pre-chemo NICE submission[107], which have also been used in the enzalutamide pre-chemo NICE submission. However, there is no separate palliative care health state in this model and an average one-off cost of £3,598 for end-of-life treatment has been incurred for all HRPC-related deaths[63].

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

Table 56 gives a summary of the main variables applied in the economic model.

Table 56 Summary of variables applied in the economic model

Variable description	Base-case [95% CI if applicable]	Source/Comment	Distribution
General Inputs			
Cycle length in years	0.0833	1-month cycle was chosen as a clinically meaningful time interval	None
Time horizon in years	20	20 years time horizon was assumed to be sufficient to capture the remaining life time of a mHRPC patient	None
Discount rate effects and costs	3.5%	NICE guidelines[83]	None
Average age at model entry	73.5 [58.3; 88.7]	PROSPER CSR[2]	Normal

Variable description	Base-case [95% CI if applicable]	Source/Comment	Distribution
Percentage of patients receiving chemotherapy in PD2	40%	Clinical expert opinion[16]	None
Costs (in £)			
Daily drug costs for enzalutamide [redacted]	[redacted]	BNF online[9] [July 2018]	None
Daily drug costs for docetaxel	2.10 [1.57; 2.62]	eMit database[104] Jun2017 (last updated 5 January 2018)	Gamma
Daily drug costs for ADT	2.80 [2.10; 3.50]	BNF online[9] [July 2018]	Gamma
Costs of chemotherapy administration per model cycle	332.88 [249.66; 416.10]	Assuming an average body area of 2.01m^2 for patients on chemotherapy[106]; NHS reference costs 2012-2013	Gamma
Monitoring costs per cycle (based on input from Table 52 and Table 53, in £)			
Health state costs per model cycle for patients on enzalutamide in nmHRPC	85.47 [71.21; 105.49]	For probabilistic SA, standard error is assumed 10%	Gamma
Health state costs per model cycle for patients on enzalutamide in PD1	85.47 [71.21; 105.49]	For probabilistic SA, standard error is assumed 10%	Gamma
Health state costs per model cycle for patients on enzalutamide in PD2-PD3	88.16 [74.22; 109.95]	For probabilistic SA, standard error is assumed 10%	Gamma
Health state costs per model cycle for patients on docetaxel	609.35 [528.67; 783.15]	For probabilistic SA, standard error is assumed 10%	Gamma
Health state costs per model cycle for patients on BSC	463.76 [377.34; 558.97]	For probabilistic SA, standard error is assumed 10%	Gamma
Health state costs per model cycle for patients on ADT	155.43[135.34; 200.49]	For probabilistic SA, standard error is assumed 10%	Gamma
Terminal care costs	3,598.00 [2,698.50; 4,497.50]	Healthcare resource utilisation for the last 3 months of a patient's life. Source: Abiraterone NICE pre-chemo submission[63]. Applied as transition cost to patients moving to the death health state	Gamma
Concomitant medication (costs per cycle; in £)			
Costs of concomitant medications for patients on	2.95 [2.26; 3.74]	Based on PREVAIL[84] data (September 16, 2013 cut-off)	Gamma

Variable description	Base-case [95% CI if applicable]	Source/Comment	Distribution
enzalutamide (per cycle)			
Costs of concomitant medications for patients on docetaxel (per cycle)	273.89 [209.73; 346.48]	Same as in NICE TA377[62]	Gamma
Costs of concomitant medications for patients on ADT	3.05 [2.33; 3.86]	Based on PREVAIL[84] data (September 16, 2013 cut-off)	Gamma
Costs of concomitant medications for patients on palliative therapy (per cycle)	0	Concomitant medication for BSC/palliative care is already included in the health state costs	None
Treatment durations	As described in section B.3.2.2		
Utilities			
Utility value in nmHRPC	[redacted]	PROSPER CSR[2]; mean baseline utility (pooled arms) - 'mapped' values	Beta
Utility value in PD1	[redacted]	PROSPER[2] post-progression/MFS utility value (first assessment) - 'mapped' values	Beta
Utility value in PD2	[redacted]	PREVAIL[84] post-progression utility value (pooled arms) - EQ-5D-3L values	Beta
Utility value in PD3	0.688 [0.640; 0.735]	AFFIRM baseline utility values (pooled arms) - EQ-5D-3L[53]	Beta
Utility value for end-of-life period	[redacted]	PREVAIL[84] utility value based on final HRQoL assessment before death (within 90 day period before death)	Beta
Duration for end-of-life utility value in months	3	Assumption	Beta
Data input			
PrePS ADT	[redacted]	PROSPER CSR[2]; PROSPER Extrapolation Report[46]	Multivariate normal
PrePS enzalutamide	[redacted]	PROSPER CSR[2]; PROSPER Extrapolation Report[46]	Multivariate normal
PPS ADT	[redacted]	PROSPER CSR[2]; PROSPER Extrapolation Report[46]	Multivariate normal
PPS enzalutamide	[redacted]	PROSPER CSR[2]; PROSPER Extrapolation Report[46]	Multivariate normal
MFS ADT	[redacted]	PROSPER CSR[2]; PROSPER Extrapolation Report[46]	Normal
MFS enzalutamide	[redacted]	PROSPER CSR[2]; PROSPER Extrapolation Report[46]	Normal
Monthly probabilities for AEs and SREs (based on inputs from Table 46)			
Probability of AE with enzalutamide in nm	0.00981	Aggregate value, individual AEs varied in OWSA and PSA	None

Variable description	Base-case [95% CI if applicable]	Source/Comment	Distribution
Probability of AE with enzalutamide in PD1	0.00989	Aggregate value, individual AEs varied in OWSA and PSA	None
Probability of AE on ADT	0.00910	Aggregate value, individual AEs varied in OWSA and PSA	None
Probability of AE on BSC	0	Aggregate value, individual AEs varied in OWSA and PSA	None
Probability of AE on docetaxel	0.0685	Aggregate value, individual AEs varied in OWSA and PSA	None
Probability of SRE with enzalutamide in PD1	0.01624	Aggregate value; identical to NICE TA377[62]	None
Probability of SRE on ADT in PD1	0.02155	Aggregate value; identical to NICE TA377[62]	None
Probability of SRE on docetaxel in PD1	0.01624	Aggregate value; identical to NICE TA377[62]	None
Probability of SRE in PD2-3	0.04776	Aggregate value; identical to NICE TA377[62]	None
AE and SRE costs (based on input from Table 43 and Table 47; in £)			
Average cost to treat an AE on enzalutamide in nm	789.57	Aggregate value, individual AEs varied in OWSA and PSA	None
Average cost to treat an AE on enzalutamide in PD1	700.77	Aggregate value, individual AEs varied in OWSA and PSA	None
Average cost to treat an AE on ADT	1,307.85	Aggregate value, individual AEs varied in OWSA and PSA	None
Average cost to treat an AE on BSC	0.00	Aggregate value, individual AEs varied in OWSA and PSA	None
Average cost to treat an AE on docetaxel	646.82	Aggregate value, individual AEs varied in OWSA and PSA	None
Average cost to treat a SRE on enzalutamide in PD1 health state	1,945.88	Aggregate value, individual SREs varied in OWSA and probabilistic SA	None
Average cost to treat a SRE on ADT in PD1 health state	1,696.91	Aggregate value, individual SREs varied in OWSA and probabilistic SA	None
Average cost to treat a SRE on docetaxel in PD1 health state	1,945.88	Assumed equal to enzalutamide	None
Average cost to treat a SRE in PD2-PD3 health state	1,755.02	Aggregate value, individual SREs varied in OWSA and probabilistic SA	None
AE and SRE disutilities (based on input from Table 47 and Table 48)			
Average disutility due to AE while on enzalutamide treatment in nm	-0.01017	Aggregate value, individual AEs varied in OWSA and PSA	None

Variable description	Base-case [95% CI if applicable]	Source/Comment	Distribution
Average disutility due to AE while on enzalutamide treatment in PD1	-0.00725	Aggregate value, individual AEs varied in OWSA and PSA	None
Average disutility due to AE while on ADT	-0.00508	Aggregate value, individual AEs varied in OWSA and PSA	None
Average disutility due to AE while on BSC	0	Aggregate value, individual AEs varied in OWSA and PSA	None
Average disutility due to AE while on docetaxel treatment	-0.00615	Aggregate value, individual AEs varied in OWSA and PSA	None
Average disutility due to SRE while on enzalutamide	-0.00944	Aggregate value, individual SREs varied in OWSA and probabilistic SA	None
Average disutility due to SRE while on ADT treatment	-0.00856	Aggregate value, individual SREs varied in OWSA and probabilistic SA	None
Average disutility due to SRE while on BSC treatment	-0.00856	Aggregate value, individual SREs varied in OWSA and probabilistic SA	None
Average disutility due to SRE while on docetaxel treatment	-0.00944	Aggregate value, individual SREs varied in OWSA and probabilistic SA	None
Duration of AEs and SREs	**See Table 47**		

Abbreviations: AE: adverse event; ADT: androgen deprivation therapy; BNF: British national formulary; BSC: best supportive care; CI: confidence interval; CSR: clinical study report; EQ-5D-3L: European Quality of Life-5 Dimensions-3 Levels; MFS: metastasis-free survival; NHS: national health services OS: overall survival; OWSA: one-way sensitivity analysis; PAS: patient access scheme; PD: progressed disease; PPS: post-progression survival; PrePS: pre-progression survival; SRE: skeletal-related event; SA: sensitivity analysis; TTD: time to treatment discontinuation.

B.3.6.2 Assumptions

The taken assumptions were based on PROSPER, UK clinical practice, published literature and expert opinion. All assumptions (Table 57) were tested with external UK clinical and health economic experts at multiple stages[71, 91] and subsequently refined following the read-out of the PROSPER trial data[16, 72].

Table 57 Summary of key assumptions in the economic model

Assumption	Justification	Reference / Source
The PROSPER trial population adequately reflects the patient population in the UK	PROSPER is an international phase III study recruiting patients with high risk nmHRPC progressing on ADT with no prior or present evidence of metastatic disease. The PROSPER population reflects UK population[16]	PROSPER CSR[2] NICE pathways and CG175 on the management of prostate cancer[29]
The control arm of PROSPER, in combination with literature data, can	Although the benefit of ADT in high risk nmHRPC patients is unclear, guidelines recommend HRPC	NICE pathways and CG 175 on the

Assumption	Justification	Reference / Source
inform modelling for UK patients receiving ADT	patients (metastatic or not) to be maintained on ADT[30]. In line with the above, in PROSPER all patients had to remain on ADT for the duration of the study. Patients in the control arm received placebo plus ADT; this arm can be considered as the equivalent to ADT alone.	management of prostate cancer[29] Liede et al[108]
It is assumed that ADT is continued indefinitely regardless of the treatment arm	European guidelines recommend ADT to be continued indefinitely in HRPC patients[30]. In addition, UK clinical expert confirmed that ADT is frequently being used for men with locally advanced, non-metastatic disease in clinical practice[16].	Clinical expert opinion[16] Treatment guidelines[30]
The main comparator of the economic analysis is ADT, which may include first generation anti-androgens such as bicalutamide	Efficacy of ADT in the model is primarily informed by the placebo arm of PROSPER. Bicalutamide (and other first generation anti-androgens) are not licensed for nmHRPC and as shown in STRIVE and confirmed in the NMA, bicalutamide does not have any significant impact on disease progression. To the best of our knowledge, there currently is no convincing data suggesting that bicalutamide, as add-on to ADT or enzalutamide/ADT in high risk nmHRPC patients, would provide incremental gains in terms of OS or MFS.	BNF online (November 2017)[9]
Various treatment options exist for patients with mHRPC. The model reflects the expected treatment algorithm to be applied in the UK once enzalutamide is available for the high risk nmHRPC setting. In this case, patients on enzalutamide in the nmHRPC state will move to ADT alone in PD1 while patients on ADT will receive enzalutamide when they progress. After progression in PD1, patients are then eligible to docetaxel. Costs for treatment/drug acquisition, administration, monitoring, and AEs, as well as treatment durations and AE disutilities are taken into account for these treatments. However, OS (PPS) outcomes of the model are not adjusted based on post-baseline (i.e. PD1-PD3) treatments.	In UK clinical practice, patients who have received enzalutamide are not likely to receive it again later in the disease course. Current SoC for patients progressing on ADT in nmHRPC would be to receive enzalutamide (or abiraterone). Once these patients progress on these therapies, they would potentially be eligible for chemotherapy. Based on the PROSPER data, it is assumed that patients who progress while being on enzalutamide in the nmHRPC state do not move straightaway to chemotherapy but remain on ADT for some months. Efficacy data for the model (MFS, OS, PrePS, and PPS) are taken from PROSPER. As post-baseline treatments in PROSPER were largely in line with UK clinical practice, no adjustments to the efficacy data were deemed necessary.	Discussion with HTA experts[71] ERG comments TA404[109]
In the model, no assumptions about dosing intensities/compliance and capped treatment durations have been taken into account.	The model assumed that patients remain on the full label dosage for all treatments as per reported times to progression. However, in reality patients and their physicians might choose to (temporarily) reduce the dosage or (temporarily) interrupt treatment altogether, which might reduce actual treatment costs. This was also confirmed by a UK clinical expert[16]. The effect of treatment interruption is further explored in a scenario analysis.	N/A
The PROSPER clinical trial provides the most reliable data source to	PROSPER demonstrated a statistically significant and clinically meaningful MFS benefit for	Nelson 2008[44]; Discussion with HTA

Assumption	Justification	Reference / Source
inform progression and survival in the model. Limitations to the data maturity (i.e. finite follow-up period) can be addressed using publicly available external reference data.	enzalutamide in nmHRPC. As expected based on the results from ICECaP[59] , Smith et al[61], and the SPARTAN trial[47], enzalutamide provided a numerically better OS, however not statistically significant. Therefore, extrapolation is still required for both outcomes due to a limited follow-up period. While there is no alternative data source that would provide a more reliable reference curve for either of the two outcomes, there are data that can be used for external validation of the extrapolations. Data from the atrasentran study[44], UK general population mortality and OS from PREVAIL were used as a reference for OS (i.e. PrePS and PPS) and for MFS (atrasentran study). Additionally, post-progression survival (PPS) after an MFS-event can be modelled separately as described below using OS data from PREVAIL to validate the extrapolations based on the PROSPER data.	experts[71]; PROSPER CSR[2]; Clinical validation with medical expert[91]
OS separate curves - Two separate functions are used in the model to calculate mortality rates in nmHRPC (i.e. the nmHRPC health state) and mHRPC (PD1-PD3) health states based on PROSPER data	It can be argued that it is implausible to assume that a stable, asymptomatic nmHRPC patient would have the same probability of dying as a mHRPC patient who progressed on chemotherapy (i.e. inherent assumption of the single OS curve). Therefore, the base-case setting of the model is to use two separate curves for calculating mortality in nmHRPC and mHRPC patients, respectively. The nmHRPC PrePS reference curve (and HR) only applies until patients progress to mHRPC (i.e. the health states PD1-PD3). Generally, it is assumed that patients in nmHRPC have a relatively lower risk of dying as observed in PROSPER (i.e. PROSPER PrePS results). Following disease progression to mHRPC, the mortality risk increases, which is reflected by the separate PPS reference curve based on PROSPER outcomes. It is important to note that the second mHRPC survival curve is applied equally to all mHRPC health states per model arm in a time-dependent manner.	Discussion with HTA experts[16, 71]; ERG report TA396[110]
Transition rates between the first two health states are informed by the MFS results obtained in PROSPER	MFS is the primary efficacy outcome of the pivotal trials informing the model. The occurrence of metastasis is considered to be an event that is clinically relevant, as it informs treatment decisions, affects prognosis, and is a prelude to symptomatic disease (e.g. SREs, pain) and subsequent lines of treatment.	Discussion with HTA experts[71]
Transition rates between the mHRPC health states (PD1, PD2, and PD3) are informed by the median TTD for each respective treatment.	Due to the uncertainty around (future) mHRPC treatment sequences and the lack of alternative data that could inform transition rates in this stage of the disease, TTD drives the transition between mHRPC health states. This assumption was previously accepted in mHRPC models.	Discussion with HTA experts[71]

ADT: androgen deprivation therapy; BSC: basic standard of care; CT: Computer tomography ECG: electrocardiogram; ERG: evidence review group; HTA: health technology assessment; mHRPC: metastatic

hormone-relapsed prostate cancer; MFS: metastasis-free survival; nmHRPC: non-metastatic hormone-relapsed prostate cancer; OS: overall survival; PD: progressed disease; PPS: post-progression survival; PrePS: pre-progression survival PSA: prostate-specific antigen; pts: patients; TA: technology appraisal; TTD: time to treatment discontinuation.

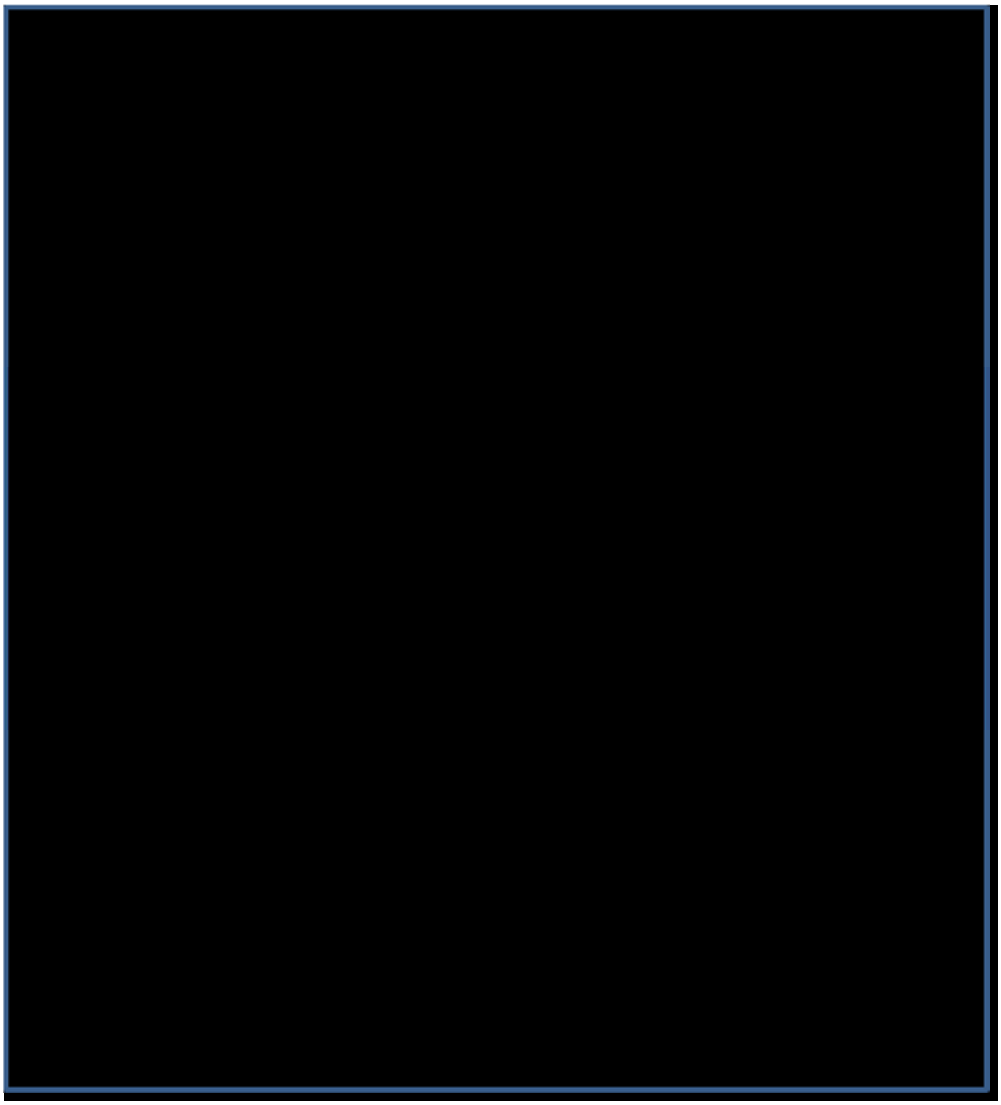
B.3.7 Base-case results

B.3.7.1 Efficacy outcomes

***[redacted]26 shows the Markov traces (i.e. the proportion of patients in each health state) of the enzalutamide and ADT arm of the model over time, using a lifetime horizon of 20 years. Enzalutamide (in light-blue) has a higher OS compared to ADT (in green) throughout the model's time horizon. Similarly, patients on enzalutamide stay longer in the high risk nmHRPC (stable disease) health state. However, as patients on ADT progress faster to PD1 and also stay longer in in this health state, a higher proportion of ADT patients resides in the PD1 health state compared to enzalutamide. There does not seem to be a meaningful difference between the enzalutamide and ADT arm of the model for the time patients reside in PD2 and PD3.

In both arms of the model, approximately [redacted] of patients have died after 2 years when the OS curve starts to separate. In addition, [redacted] of the patients have died at approximately [redacted] and [redacted] months in the enzalutamide and ADT arm of the model, respectively. At ten years (120 months), approximately [redacted] of patients are still alive on enzalutamide and [redacted] on ADT. At 20 years (mean age 94), less than [redacted] are still alive in either of the two arms of the model.

[redacted] 26



Abbreviations: ADT: androgen deprivation therapy; nmHRPC: non-metastatic hormone-relapsed prostate cancer; OS: overall survival; PD: progressed disease.

The mean and median OS for enzalutamide were [redacted] and [redacted] months, respectively, compared to [redacted] months and [redacted] months for ADT, respectively. The difference in mean and median OS for the two arms was [redacted] and [redacted] months, respectively both favouring enzalutamide.

Table 58 shows the discounted accumulated quality-adjusted life years (QALYs) per health state for the two arms of the model. The total number of QALYs in the enzalutamide arm being higher than in the ADT arm ([redacted]) was driven by the higher number of QALYs gained in the enzalutamide arm during the nmHRPC health state ([redacted]).

Table 58 Base-case effectiveness outcomes (discounted QALYs)

Health state	Enzalutamide	ADT
nmHRPC	[redacted]	[redacted]
PD1	[redacted]	[redacted]
PD2	[redacted]	[redacted]
PD3	[redacted]	[redacted]
End-of-life disutility	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]

Abbreviations: ADT: androgen deprivation therapy; nmHRPC: non-metastatic hormone-relapsed prostate cancer; PD: progressed disease; QALY: quality-adjusted life years.

B.3.7.2 Cost outcomes

The breakdown of average costs per patient are shown in Table 59.

For both arms of the model, active treatment (i.e. direct drug costs) was the largest contributor to the total treatment costs. In the enzalutamide arm active treatment costs were £[redacted] in nmHRPC, which compared to [redacted] for ADT. In PD1, patients in the enzalutamide arm of the model are assumed to only receive ADT and therefore, direct treatment costs were [redacted]. In the ADT arm of the model, direct treatment costs were highest in PD1, totalling at [redacted]. Overall, treatment costs over the lifetime horizon of the model (20 years) with enzalutamide were higher than ADT at [redacted] and [redacted], respectively.

Table 59 Base-case cost outcomes (discounted)

Outcome	Enzalutamide	ADT
nmHRPC treatment costs	[redacted]	[redacted]
PD1 treatment costs	[redacted]	[redacted]
PD2 treatment costs	[redacted]	[redacted]
PD3 treatment costs	[redacted]	[redacted]
nmHRPC Health state cost	[redacted]	[redacted]
PD1 Health state cost	[redacted]	[redacted]
PD2 Health state cost	[redacted]	[redacted]
PD3 Health state cost	[redacted]	[redacted]
nmHRPC Conmed costs	[redacted]	[redacted]
PD1 Conmed costs	[redacted]	[redacted]
PD2 Conmed costs	[redacted]	[redacted]
PD3 Conmed costs	[redacted]	[redacted]
nmHRPC AEs	[redacted]	[redacted]
PD1 AEs	[redacted]	[redacted]
PD2 AEs	[redacted]	[redacted]
PD3 AEs	[redacted]	[redacted]
PD1 SREs	[redacted]	[redacted]
PD2 SREs	[redacted]	[redacted]

Outcome	Enzalutamide	ADT
PD3 SREs	[redacted]	[redacted]
Terminal care costs	[redacted]	[redacted]
Subtotal nmHRPC	[redacted]	[redacted]
Subtotal PD1	[redacted]	[redacted]
Subtotal PD2	[redacted]	[redacted]
Subtotal PD3	[redacted]	[redacted]
Terminal care	[redacted]	[redacted]
Total	[redacted]	[redacted]

Abbreviations: ADT: androgen deprivation therapy; nmHRPC: non-metastatic hormone-relapsed prostate cancer; PD: progressed disease; Tx: treatment.

B.3.7.3 Base-case incremental cost-effectiveness analysis results

The base-case cost-effectiveness results are presented in Table 60. On average, a patient starting on enzalutamide accumulated [redacted] additional QALYs (discounted) compared to a patient starting on ADT. Total treatment costs were [redacted] for enzalutamide and [redacted] in the ADT arm of the model with an incremental difference of [redacted]. Enzalutamide treatment for high risk nmHRPC patients was more effective, but also more costly than ADT with an incremental cost-effectiveness ratio (ICER) of £28,853.

Table 60 Base-case cost-effectiveness results

Outcome	Enzalutamide	ADT
Technology acquisition cost (first line)*	[redacted]	[redacted]
Subsequent lines treatment costs	[redacted]	[redacted]
Other costs	[redacted]	[redacted]
Total costs	[redacted]	[redacted]
Incremental costs	[redacted]	
LYG	[redacted]	[redacted]
Incremental LYG	[redacted]	
QALYs	[redacted]	[redacted]
QALYs gained	[redacted]	
ICER (incremental cost/QALY gained)	**£28,853**	

*Note: enzalutamide technology acquisition cost are based on the UK list price and no PAS has been taken into account.
Abbreviations: ADT: androgen deprivation therapy; LYG: life-years gained; nmHRPC: non-metastatic hormone-relapsed prostate cancer; PD: progressed disease; QALY: quality-adjusted life years.

Additional clinical outcomes and disaggregated costs are summarised in Appendix J.

B.3.8 Sensitivity analyses

B.3.8.1 Deterministic sensitivity analysis

One-way SA has been performed for input parameters of the model within their 95% confidence interval or their most plausible ranges (***[redacted]27). Table 61 gives an overview of the fifteen most important drivers of the model with their respective base-case values and lower/upper limits used in this deterministic SA. Most of the parameters with the largest impact on the model results were in relation to the parametric curves informing MFS, PrePS and PPS. Other parameters that had an impact on the model outcomes were the age at baseline, the discount rate applied to effects and costs, health state costs in nmHRPC for enzalutamide and ADT patients, and the utility value in PD1.

[redacted]27

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

Table 61 One-way SA results for enzalutamide vs. ADT

Parameter	Model Input (BC)	Low	High	ICER Low	ICER High
Base-case	NA	NA	NA	£28,853	
Parametric uncertainty (Gamma parameter) of fitted Spline curve to PROSPER MFS placebo data	[redacted]	[redacted]	[redacted]	£99,582	£13,523
Average age at baseline	[redacted]	[redacted]	[redacted]	£29,206	£52,160
Parametric uncertainty (intercept parameter) of fitted Weibull curve to PROSPER PPS placebo data	[redacted]	[redacted]	[redacted]	£24,448	£44,180

Parameter	Model Input (BC)	Low	High	ICER Low	ICER High
Parametric uncertainty (Gamma0 parameter) of fitted Spline curve to PROSPER MFS enzalutamide data	[redacted]	[redacted]	[redacted]	£22,965	£3,282
Parametric uncertainty (intercept parameter) of fitted Weibull curve to PROSPER PrePS enzalutamide data	[redacted]	[redacted]	[redacted]	£39,957	£25,922
Parametric uncertainty (intercept parameter) of fitted Weibull curve to PROSPER PPS enzalutamide data	[redacted]	[redacted]	[redacted]	£36,033	£24,236
Parametric uncertainty (intercept parameter) of fitted Weibull curve to PROSPER PrePS placebo data	[redacted]	[redacted]	[redacted]	£24,789	£32,247
Discount rate for effects	[redacted]	[redacted]	[redacted]	£24,557	£30,836
Parametric uncertainty (scale parameter) of fitted Weibull curve to PROSPER PrePS enzalutamide data	[redacted]	[redacted]	[redacted]	£27,346	£31,201
Median treatment duration of ADT in PD1	[redacted]	[redacted]	[redacted]	£30,217	£27,397
Median treatment duration of enzalutamide in PD1	[redacted]	[redacted]	[redacted]	£29,749	£27,130
Discount rate for costs	[redacted]	[redacted]	[redacted]	£30,654	£28,205
Health state costs for patients on enzalutamide in nmHRPC	[redacted]	[redacted]	[redacted]	£28,029	£29,760
Health state costs for patients on ADT in nmHRPC	[redacted]	[redacted]	[redacted]	£29,606	£28,023
Health state utility value in PD1	[redacted]	[redacted]	[redacted]	£28,120	£29,595

Abbreviations: ADT: androgen deprivation therapy; BC: base-case; ICER: incremental cost-effectiveness ratio; nmHRPC: non-metastatic hormone-relapsed prostate cancer; PD: progressed disease; PPS: post-progression survival; PrePS: pre-progression survival; QALY: quality-adjusted life years; SA: sensitivity analysis.

B.3.8.2 Probabilistic sensitivity analysis

For the probabilistic SA, all parameters (i.e., ratios, probabilities, utilities, costs) were varied simultaneously in order to explore the universe of possible model outcomes. Each of the input parameters was considered as a random variable and drawn from a range of values within a known distribution. This exercise, was repeated 10,000 times.

An overview of the probabilistic SA results is shown in Table 62. Overall, the probabilistic cost-effectiveness outcomes are slightly higher compared to the deterministic model outcomes with an average ICER of £30,175 /QALY.

Table 62 Probabilistic SA statistical results (probabilistic cost-effectiveness outcomes)

	Enzalutamide		ADT		Incremental		
	Costs	QALYs	Costs	QALYs	Costs	QALYs	CE ratio
Deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,853
Probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,175
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,994
# values	10,000	10,000	10,000	10,000	10,000	10,000	10,000
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£19,064
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,970
95% LCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,919
95% UCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£106,757

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

The individual results of the probabilistic SA were plotted in cost-effectiveness planes to visualise the distribution of possible ICERs relative to the selected comparator (***[redacted]28). Each dot resembles one Monte Carlo simulation where the effectiveness input parameters are sampled from the distributions in a total of 10,000 loops. The black line represents a willingness to pay (WTP) threshold of £30,000 per QALY gained.

[redacted]28

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

***[redacted]29 shows the cost-effectiveness acceptability curves that estimates the probability of a treatment strategy to be (more) cost-effective over an existing or alternative treatment

strategy. The curve below shows a probability of [redacted] of enzalutamide being cost-effective compared to ADT at a WTP threshold of £30,000/QALY.

[redacted]29

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

B.3.8.3 Scenario analyses

As mentioned before, there are some uncertainties around structural assumptions and parameter uncertainties in the model which have been tested through scenario analysis:

- The appropriate input parameter to determine progression in the model (i.e. based on radiographic progression as defined in PROSPER or based on treatment discontinuation)
- The impact of different survival model structures, extrapolations and input data (i.e. single OS curve vs. separate curves, different extrapolations based on various external reference data, and using a newer PROSPER OS IA)
- The methodology applied for the extrapolation of the PROSPER time to event data, in particular parametric extrapolation of MFS
- Treatment sequences following progression on enzalutamide or ADT in nmHRPC

The scenario analyses conducted to investigate these uncertainties as well as the methods to perform each analysis are described in below. Of these, scenario 1 and 2 will be discussed in more detail in this section. For the others, a brief description is provided in section B.3.8.3.3 and details are discussed in appendix L.

B.3.8.3.1 Scenario 1: PROSPER IA2 data

As discussed in Section B.2.6.1, the PROSPER IA2 data-cut occurred on May 31, 2018. These data were not used in the base-case, primarily because MFS was not analysed in the IA2 data cut-off. Nevertheless, given that the IA2 OS data are more mature than those is

IA1, a scenario analysis was performed using the IA2 data, to explore the effects of incorporating the more mature survival data into the model.

In this scenario, TTD was used as an input for the nmHRPC PD1 progression because MFS was not analysed in IA2. This data again had to be extrapolated to fit the 20-year time frame of the model. Similar to MFS, none of the standard parametric models showed adequate fit, so a more advance spline based model (2 knots, hazard) was used to extrapolate the data (*** [redacted] 30)[46]. A clinical expert confirmed that the extrapolated TTD estimates could realistically reflect the proportion of high risk nmHRPC patients that are metastasis free after an extended period of time[16].

[redacted] 30

Source: PROSPER extrapolation report[46]
Abbreviations: KM: Kaplan Meier; TTD: time to treatment discontinuation .

The IA2 OS data was also split into survival in nmHRPC and survival in the progressed health states, to be able to model survival in a more clinically valid manner. However, since progression was not specifically defined in the IA2 data, pre-treatment discontinuation survival (PreTD) and post-treatment discontinuation survival (PostTD) were modelled instead.

At the IA2 cut-off date only [redacted] patients in the enzalutamide and [redacted] in the placebo group had a PreTD event. This indicated a [redacted] increase in the risk of a PreTD event for the enzalutamide group ([redacted]). However, given the low numbers of patients in both groups, these results should be interpreted with caution, as shown by the wide 95% CI. The only conclusion that can confidently be drawn from these data was that the chance of a PreTD event was low in both groups. PostTD was more favourable for the placebo arm, as was the case for IA1 PPS (Table 63). This is again most likely explained by the fact that patients in the placebo arm of PROSPER were eligible for enzalutamide post-progression.

Table 63 PROSPER IA2 PreTD and PostTD (ITT population)

Outcome	Enzalutamide (n=933)	Placebo (n=468)
Outcome: PreTD		
Number of patients with events	[redacted]	[redacted]
Number of censored cases	[redacted]	[redacted]
Time to event (months)		
Mean (SE)	[redacted]	[redacted]
Q1 [95% CI]	[redacted]	[redacted]
Median [95% CI]	[redacted]	[redacted]
Q3 [95% CI]	[redacted]	[redacted]
Treatment comparison: enzalutamide versus placebo		
HR [95% CI] (b)	[redacted]	
p-value (a)	[redacted]	
Outcome: PostTD		
Number of patients	[redacted]	[redacted]
Number of patients with events	[redacted]	[redacted]
Number of censored cases	[redacted]	[redacted]
Time to event (months)		
Mean (SE)	[redacted]	[redacted]
Q1 [95% CI]	[redacted]	[redacted]
Median [95% CI]	[redacted]	[redacted]
Q3 [95% CI]	[redacted]	[redacted]
Treatment comparison: enzalutamide versus placebo		
HR [95% CI] (b)	[redacted]	
p-value (a)	[redacted]	

Source: PROSPER extrapolation report[46]
(a) P-value is based on a stratified log-rank test. (b) Hazard ratio is based on a stratified Cox regression model (with treatment as the only covariate) and is relative to placebo with < 1 favouring enzalutamide. The 2 randomisation factors are PSA doubling time (< 6 months vs. >= 6 months) and prior or current use of a bone targeting agent.
Abbreviations: CI: Confidence interval; HR: Hazard ratio; NR: Not reached.

PreTD and PostTD were also extrapolated, as explained in the extrapolation report[46]. The best fitting curves were Weibull for PreTD and gamma for PostTD (***[redacted]31 and ***[redacted]32)

[redacted]31

Source: PROSPER extrapolation report[46]
Abbreviations: KM: Kaplan Meier; PreTD: pre-treatment discontinuation survival.

[redacted]32

Source: PROSPER extrapolation report[46]
Abbreviations: KM: Kaplan Meier; PostTD: post-treatment discontinuation survival.

Both the modelled MFS and OS results changed when the IA2 data was used as input for the model. Due to the relatively long tail in the extrapolated enzalutamide TTD data (***[redacted]30), the modelled mean MFS increased from [redacted] months for enzalutamide, while it decreased from [redacted] months for ADT. Nevertheless, mean OS increased in both the enzalutamide and ADT arm to [redacted] and [redacted] months respectively. In addition, the longer survival also resulted in increased costs in both arms (Table 64). Due to these

changes, the ICER has dropped from £28,853/QALY in the base case to £24,874/QALY in this scenario (Table 64).

Table 64 Cost-effectiveness results scenario 1: PROSPER IA2 data

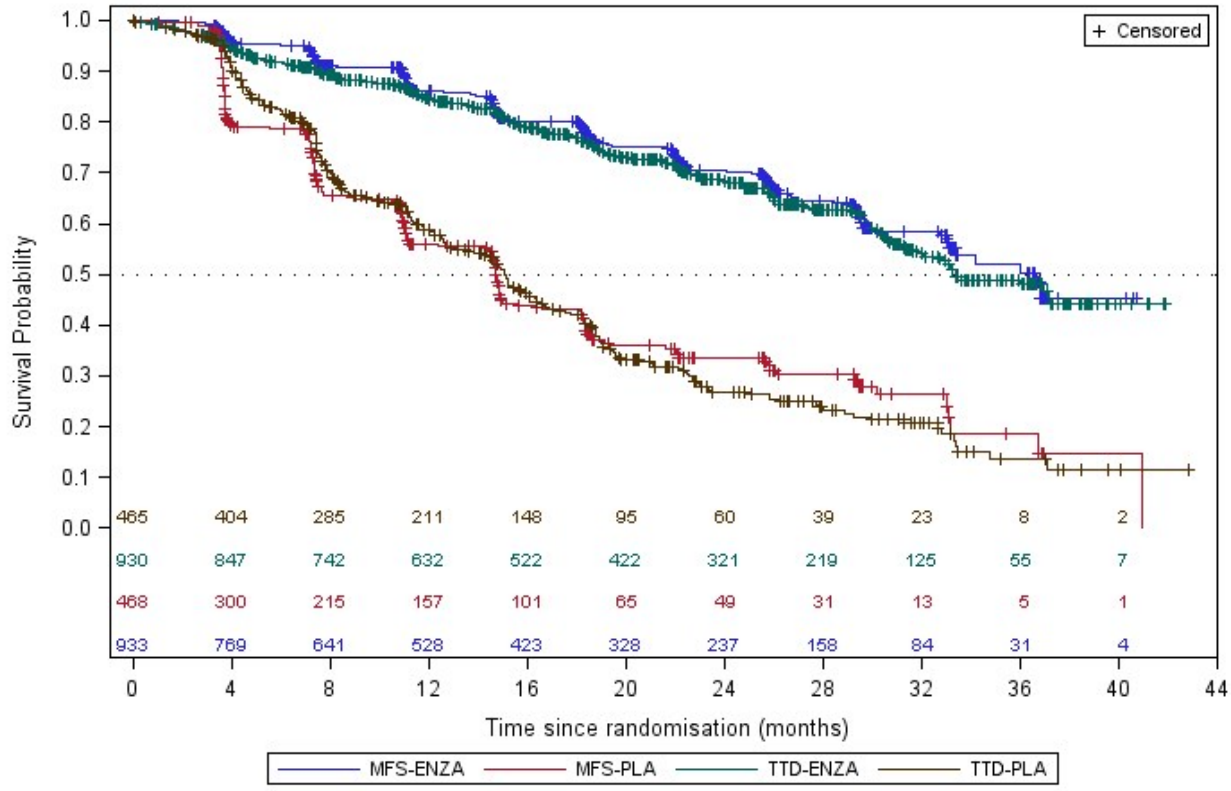
Outcome	Enzalutamide	ADT
Technology acquisition cost (first line)*	[redacted]	[redacted]
Subsequent lines treatment costs	[redacted]	[redacted]
Other costs	[redacted]	[redacted]
Total costs	[redacted]	[redacted]
Incremental costs	[redacted]	
LYG	[redacted]	[redacted]
Incremental LYG	[redacted]	
QALYs	[redacted]	[redacted]
QALYs gained	[redacted]	
ICER (change from base case)	£24,874 (-£3,979)	

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

B.3.8.3.2 Scenario 2: TTD for nmHRPC PD1 transition

As discussed in Section B.3.2.2, the base-case was based upon MFS to inform the first transition, meaning that the model assumes treatment is discontinued and a new treatment is started when a patient progresses from nmHRPC to mHRPC. However, theoretically and per PROSPER study protocol[2] there could be deviations between the time to an MFS event (i.e. progression) and the duration patients remain on treatment. Patients may for example discontinue treatment prior to progression or remain on treatment after first metastasis has occurred until a decision has been made with regard to the next subsequent treatment. TTD results from PROSPER are very similar to MFS (Figure 33). In fact, the area under the curve (AUC) of the TTD curve is approximately 3% smaller than MFS. Nevertheless, TTD can be considered as an alternative input parameter for the first health state transition from nmHRPC to PD1 (mHRPC). This was explored in the second scenario analysis.

Figure 33 Comparison of PROSPER MFS with TTD KM curves



Abbreviations: ENZA: enzalutamide; MFS: metastasis-free survival; PLA: placebo; TTD: time to treatment discontinuation.

[redacted]

[redacted]

Source: PROSPER extrapolation report[46]
Abbreviations: KM: Kaplan Meier; TTD: time to treatment discontinuation.

The PROSPER TTD data was extrapolated and generalised gamma provided the best fit (***[redacted]34). As discussed in section B.2.6.1.3.4, PROSPER median TTD was lower than MFS for enzalutamide ([redacted] vs [redacted] months) while being almost equal to MFS for the placebo arm (15.1 vs 14.7 months, Table 22). Consequently, the modelled mean MFS and OS decreased for enzalutamide from 40.4 to 35.0 months for the modelled MFS and [redacted] to [redacted] months for OS, while costs only decreased marginally from [redacted] to [redacted]. Outcomes for placebo remained largely unchanged. The ICER therefore increased from £28,853 to £30,456 when TTD was used.

Table 65 Cost-effectiveness results scenario 2: TTD for nmHRPC PD1 transition

Outcome	Enzalutamide	ADT
Technology acquisition cost (first line)*	[redacted]	[redacted]
Subsequent lines treatment costs	[redacted]	[redacted]
Other costs	[redacted]	[redacted]
Total costs	[redacted]	[redacted]
Incremental costs	[redacted]	
LYG	[redacted]	[redacted]
Incremental LYG	[redacted]	
QALYs	[redacted]	[redacted]
QALYs gained	[redacted]	
ICER (change from base case)	£30,456 (+£1,603)	

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

B.3.8.3.3 Other scenarios

To further investigate the uncertainties in the model, 10 additional scenario analyses were performed. A description of these scenarios is provided Table 66. The results of all the scenario analyses are shown in Table 67.

Table 66 Scenario analyses

Model scenario	Description
Scenario 1: Second PROSPER OS interim analysis	Described in section B.3.8.3.1
Scenario 2: TTD for nmHRPC PD1 transition	Described in section B.3.8.3.2
Scenario 3: MFS piecewise survival model	The NICE DSU support document 14 suggests to explore more advanced survival models when 'standard' models do not provide a good fit to the observed trial data. The two most commonly applied advanced survival models in the context of HTA seem to be spline and piecewise models. However, there does not seem to be a consensus on which of the two models to use. Therefore, we explore the structural

Model scenario	Description
	uncertainty around the MFS survival modelling by using the best fitting piecewise model instead of the spline model.
Scenario 4: No prostate cancer mortality in nmHRPC	In the base-case, PROSPER PrePS is used to inform mortality in nmHRPC (before metastases have occurred). However, PROSPER OS and PrePS data is very immature, leading to uncertainty in the longer-term extrapolations. This scenario assumes no prostate cancer-related mortality in nmHRPC, using age-matched general (UK) population mortality only in both arms of the model instead of PROSPER PrePS.
Scenario 5: PREVAIL PPS reference curve	This scenario explores the structural uncertainty around PPS due to the immaturity of the PROSPER OS (i.e. PPS) data. Instead of using the extrapolated PROSPER PPS data directly, PPS in this scenario is informed by the more mature PREVAIL OS as a reference curve with the PROSPER PPS HR applied to derive the enzalutamide PPS curve.
Scenario 6: PROSPER PPS log-logistic guided by COU-AA-302 abiraterone OS	Similar to scenario 3 above, this scenario explores an alternative input for PPS using the log-logistic curve for the PROSPER PPS KM data. The choice for the log-logistic curve has been informed by the COU-AA-302 abiraterone arm OS data.
Scenario 7: Single OS curve	In this report it was established that applying a single survival curve over all four health states of the model lacks face validity. However, it is the most common approach in oncology models. Therefore, this scenario explores the structural uncertainty of the separate survival curve assumption by applying a single survival curve across all health states of the model based on the extrapolated PROSPER OS data (Weibull).
Scenario 8: 'England value set' utilities	HRQoL in PROSPER was captured using EQ-5D-5L. However, the utility values for the model were derived using a mapping algorithm to EQ-5D-3L, instead of using the 'England value set', which marks a conservative assumption. This scenario explores the impact of using the 'England value set' instead of 'mapped' utility values.
Scenario 9: Earlier chemotherapy after enzalutamide in nmHRPC	This scenario analyses the impact of moving chemotherapy (docetaxel) treatment earlier in the treatment pathway for patients who received enzalutamide in nmHRPC.
Scenario 10: No patients opt-out of chemo	This scenario analyses the impact of assuming all patients will receive chemo in the PD2 health state
Scenario 11: Treatment interruptions	The model assumes that all patients remain on their initial treatment until they progress. Additionally, it is assumed that all patients receive the full daily dose for the entire treatment period. In reality, some patients and their physicians may choose to temporarily interrupt treatments e.g. to manage AEs. This scenario explores the impact of incorporating treatment modifications as observed in PROSPER.
Scenario 12: Abiraterone in PD1 (ADT/AS arm)	The model assumes that all patients in the ADT arm receive enzalutamide in PD1. In reality, patients progressing to mHRPC in the UK might be eligible for abiraterone as well. This scenario explores the structural uncertainty around the choice of PD1 treatment in the ADT arm, assuming all patients receive abiraterone instead of enzalutamide.

Abbreviations: ADT: androgen deprivation therapy; AE: adverse event; DSU: decision support unit; ICER: incremental cost-effectiveness ratio; HRPC: hormone relapsed prostate cancer; m: metastatic; nm: non-

metastatic; OS: overall survival; PD: progressed disease; PrePS: pre-progression survival; PPS: post-progression survival; WTP: willingness to pay.

Table 67 Results of scenario analyses

Model scenario		Cost ENZA	Cost ADT	QALY ENZA	QALY ADT	ICER
	Base-case	[redacted]	[redacted]	[redacted]	[redacted]	£28,853
1	TTD for nmHRPC PD1 transition	[redacted]	[redacted]	[redacted]	[redacted]	£30,456
2	PROSPER IA2 data	[redacted]	[redacted]	[redacted]	[redacted]	£24,874
3	MFS piecewise survival model	[redacted]	[redacted]	[redacted]	[redacted]	£27,852
4	No PCa mortality in nmHRPC	[redacted]	[redacted]	[redacted]	[redacted]	£28,859
5	PREVAIL PPS reference curve	[redacted]	[redacted]	[redacted]	[redacted]	£26,237
6	PROSPER PPS log-logistic guided by COU-AA-302 abiraterone OS	[redacted]	[redacted]	[redacted]	[redacted]	£30,394
7	Single OS curve	[redacted]	[redacted]	[redacted]	[redacted]	£26,829
8	'England value set' utilities	[redacted]	[redacted]	[redacted]	[redacted]	£28,138
9	Earlier chemotherapy after enzalutamide in nmHRPC	[redacted]	[redacted]	[redacted]	[redacted]	£30,937
10	No patients opt-out of chemo	[redacted]	[redacted]	[redacted]	[redacted]	£29,794
11	Treatment interruptions	[redacted]	[redacted]	[redacted]	[redacted]	£24,712
12	Abiraterone in PD1 (ADT/AS arm)	[redacted]	[redacted]	[redacted]	[redacted]	£24,303

Abbreviations: ADT: androgen deprivation therapy; AS: active surveillance; ENZA: enzalutamide; ICER: incremental cost-effectiveness ratio; MFS: metastasis-free survival; OS: overall survival; PCa: prostate cancer; PPS: post-progression survival; TTD: time to treatment discontinuation; WTP: willingness to pay.

B.3.8.4 Summary of sensitivity analyses results

Although there is uncertainty around the cost-effectiveness calculations, these areas of uncertainty were extensively explored and quantified in a series of SAs, as described in this chapter. An important source of uncertainty in the model was the immature OS data. Due to the low number of OS events, there is still a lot of uncertainty in the OS data used. Consequently, several of the input parameters that had the most effect on the ICER estimate related to the PPS and PrePS extrapolations, due to the large spread in the PPS and PrePS data. To account for this uncertainty, survival modelling was extensively analysed in with four separate scenario analyses. Three out of four scenarios related to survival modelling resulted in a similar (+£6) or lower ICER estimate. Only the scenario using the abiraterone OS as guidance resulted in a slightly higher ICER (£30,394), however, from the four scenarios, this one was the least relevant, as it was guided by data from a trial that investigated abiraterone instead of enzalutamide. It can therefore be stated with a reasonable degree of confidence

that, despite the uncertainty in the OS data, the ICER will remain cost effective for all plausible PrePS, PPS and OS values.

In addition, the one-way SA indicated that the most influential drivers of the model were related to MFS, followed by PPS. The probability of enzalutamide being cost effective against ADT was quantified with a probabilistic SA. From the 10,000 randomly generated probabilistic SA analyses run, [redacted] resulted in an ICER below £30,000/QALY.

Along with the four scenarios that explored the OS data, a series of additional scenarios were tested, to explore the effect of some more structural uncertainties on the ICER estimates. The majority of the scenarios resulted in a lower ICER estimate, although in most scenarios the change was only marginal. The scenarios that resulted in higher ICERs compared to the base-case were:

- Using TTD for nmHRPC PD1 transition: £30,456/QALY (+£1,603)
- Assuming no PCa-related mortality in nmHRPC: £28,859/QALY (+£6)
- Using a log-logistic PPS extrapolation: £30,394/QALY (+£1,541)
- Assuming earlier chemotherapy: £30,937/QALY (+£2,084)
- No patients opt-out of chemotherapy £29,794/QALY (+£941)

All other scenarios resulted in lower ICERs compared to the base-case scenario, confirming the conservative approach taken in the base-case. Overall, these SAs demonstrated that the ICER generally remained within cost-effective ranges.

B.3.9 Subgroup analysis

No subgroup analysis has been conducted.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

The de novo model structure described in this report closely follows the current nmHRPC disease pathway. Notably, the model allows to differentiate mortality in non-metastatic and metastatic disease to reflect the much lower risk of death in this early stage of the disease. The model has been populated with robust clinical data from the well-conducted, randomised, placebo-controlled, double-blinded phase III trial PROSPER.

For internal validity, the assumptions employed in the model were made in a manner consistent with the published literature and previous NICE appraisals. In particular, the model structure closely follows the structure of the thoroughly reviewed model used for the NICE submission of enzalutamide in mHRPC[62]. Additionally, a series of face-to-face advisory boards were held to validate the HE model and its inputs, including an extrapolation validation meeting[91], one advisory board meeting[71], and individual one-on-one interviews with clinical[16] and economic experts[72]. For the advisory board clinical experts and health economic experts were invited to participate. Clinical experts were selected based on their experience with nmHRPC and consisted of clinical oncologists, and urologists. Experts from the UK participated in all advisory boards.

Some uncertainty remains regarding the extrapolation of the PROSPER data. However, as described in section B.3.3, for most extrapolations, reliable external reference data were available to ensure the extrapolations gave clinically plausible outcomes. These included the phase III study by Nelson et al to validate the OS and MFS extrapolations, the overall UK population life tables to validate the PrePS extrapolation, and the PREVAIL phase III trial to validate the PPS extrapolations[44, 52, 92]. Furthermore, the model fits and the plausibility of clinical outcomes for all extrapolations were validated by UK clinical and health economic experts[16, 91].

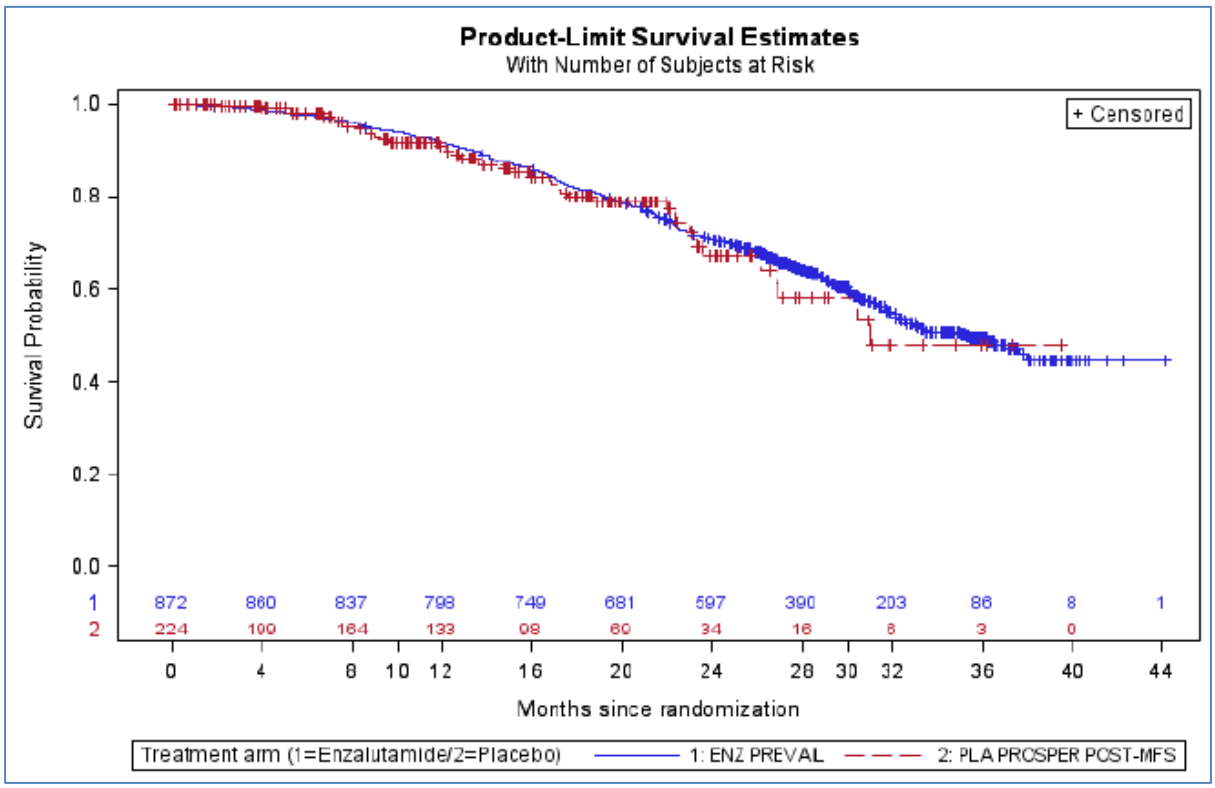
B.3.11 Interpretation and conclusions of economic evidence

The model base-case results reflect the clinical superiority of enzalutamide over ADT alone in high risk nmHRPC patients demonstrated in the phase III trial, PROSPER. The model estimates median MFS for enzalutamide to be [redacted] vs. [redacted] for ADT. These estimates are close to those observed in PROSPER (36.6 months and 14.7 months, respectively). Median OS in the model base-case was estimated at [redacted] months for enzalutamide and ADT, respectively. While there is some uncertainty with regard to the survival of patients in both model arms due to the immaturity of the PROSPER OS data, these outcomes are consistent with historic median OS data from the placebo control arms of Nelson et al (46.1 months)[44] and Smith et al (44.8 months)[111]. The total QALYs and costs in the base-case analysis were estimated at [redacted] for enzalutamide and [redacted] for ADT, respectively, resulting in an ICER of £28,853 per QALY-gained. The model results were sensitive to the parameters of the MFS extrapolation in both arms of the model, as well as to the parametric uncertainty in the OS data. Additionally, scenario analysis demonstrated that OS becomes a driver of the model indirectly as well through its dependency of MFS.

The major limitation of the presented analysis is the immaturity of the PROSPER OS data, as discussed in Section B2. Any long-term extrapolation of these data to inform a lifetime model horizon without any external reference, becomes a mere statistical exercise without face validity. However, the available long-term survival data of high risk nmHRPC is limited; all available trials were either performed in a slightly different patient population, or did not report more mature OS data[34, 44, 111].

In order to present a robust and clinically valid economic analysis, the OS data in the model differentiates mortality in nmHRPC and mHRPC (PrePS and PPS). This offers the possibility to use a wider range of external reference data. For instance, the PrePS in the enzalutamide arm of PROSPER shows comparable mortality risks as observed in the general (UK) population[92]. Similarly, there have been multiple trials conducted fairly recently in mHRPC that could be used as an external reference to the observed PROSPER PPS. Most notably, a very similar patient cohort compared to those patients who developed metastatic disease in PROSPER had been enrolled into the enzalutamide trial in chemo-naïve mHRPC, PREVAIL[52]. When overlaying the PROSPER PPS KM results of the placebo group with the much more mature final OS analysis from PREVAIL using the OS KM data of the enzalutamide arm, the data seems to be a near perfect match, indicating that despite the immaturity of the PROSPER OS (and PPS) data, the observed PPS mortality does indeed follow the expected, clinically plausible trajectory (Figure 35).

Figure 35 Comparison of PROSPER placebo PPS and PREVAIL enzalutamide OS



Abbreviations: ENZ: enzalutamide; OS: overall survival; PPS: post-progression survival.

Given the immaturity of the PROSPER data, it should be noted that this PPS KM curve is mainly informed by 'rapid progressors', i.e. patients that quickly progressed from nmHRPC to mHRPC. These patients might be associated with a higher mortality compared to patients that have a longer time to an MFS event (which would be in line with ICECaP[59] and Smith et al[61] results). Therefore, the current shape of the PROSPER PPS KM curve might still change when the data becomes more mature and PREVAIL OS might turn out to be an underestimation of the mortality post-MFS.

Per May 31, 2018 the IA2 PROSPER data have become available. In the IA2 OS data in a total of 288 (20.6%) patients had an OS event, making the data 48% mature (relative to the 596 deaths predetermined for the final OS analysis). The OS data were comparable to the IA1 data-cut, with a slightly [redacted] HR of [redacted] compared to 0.795 [95% CI: 0.580; 1.089] in IA1. The model input was based on IA1 OS and MFS data, as MFS was not analysed for IA2. However, a scenario analysis using IA2 data has been performed which resulted in a lower ICER of £24.874/QALY. So, the ICER is not negatively affected by using IA1 data. If anything, the model based on IA1 data gives a more conservative ICER estimation.

PROSPER patients at baseline appear to have a low symptom burden, which is reflected in an overall high utility score of [redacted], using the 'mapped' utility value from EQ-5D-5L to EQ-5D-3L, and [redacted] with the EQ-5D-5L 'England value set', which is only slightly below the age-matched general UK population utility value of [redacted][96]. As mentioned in section B.2, no statistically significant difference in QoL was observed between the enzalutamide and placebo group in PROSPER. However, the model does assume a deterioration of QoL

based on the health state utility values that drop from [redacted] in nmHRPC to [redacted] in PD1 to [redacted] in PD2 to [redacted] PD3 and lastly, to [redacted] in the final 3 months of life (i.e. end-of-life utility value). In other words, according to the model, patients on enzalutamide maintain their HRQoL for an extended period of time. This is in accordance with the PROSPER data presented in section B.2.

In the base-case, patients in the enzalutamide arm of the model are assumed to receive several months of ADT alone following progression (MFS event). However, it cannot be ruled out that those patients sufficiently fit would receive chemotherapy straight after disease progression. Assuming earlier use of chemotherapy directly after progression has been shown to impact the model outcomes (assuming chemotherapy costs, but without additional treatment effects), raising the ICER from £28.853 to £30.937 per QALY-gained. Nevertheless, a treatment break before chemotherapy does seem to be in line with PROSPER, where a median TTD for enzalutamide of [redacted] was reported, whereas the 25% percentile time to first chemo was [redacted] (median not reached). Given that patients who progressed on enzalutamide were only mildly symptomatic, it seems reasonable to assume that chemotherapy would not necessarily be initiated immediately after disease progression.

In summary, the presented health economic analysis provides a robust framework to inform the cost-effectiveness of enzalutamide in high risk nmHRPC. The ICER of the base-case is £28,853. Despite the parametric uncertainties around the extrapolated data, enzalutamide was cost effective in the majority of the probabilistic SA, as well as most of the explored scenarios. Furthermore, the performed extrapolations were extensively validated with UK clinical and health economic experts[16, 72, 91], and the extrapolated data matched several robust external data sources[44, 46, 52, 92]. Therefore, it can be concluded with a reasonable level of confidence that enzalutamide presents a cost-effective treatment option for patients with high risk nmHRPC in the UK.

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B.5 Appendices

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

C1.1 SmPC

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

C1.2 EPAR

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

Appendix D: Identification, selection and synthesis of clinical evidence

D1.1 Identification and selection of relevant studies

A SLR was conducted in July 2018 to identify the clinical evidence (efficacy and safety) of enzalutamide and standard of care in the management of nmHRPC. The SLR was conducted in two separate phases. The initial one, in November 2016, included searches in PubMed, Cochrane, and key congresses. An update was conducted in July 2018 to identify any new evidence. For the SLR update, the databases searched were expanded to include:

- Medline and Medline in Process
- Embase.

D1.1.1 Search strategy

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

The databases searched and provider used to identify clinical evidence are provided in Table 68. No timeframe, country or language limit was applied to the clinical effectiveness searches.

Table 68 Databases searched and provider used for the clinical SLR

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

Source: PROSPER SLR report[31]
*PubMed was searched only up to November 2016. In the updated SLR, PubMed was searched through Medline.

Abbreviations: CDRS: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects.

The complete search strategies used for PubMed, Cochrane, and Medline, including all the search terms: textwords (free text), subject index headings (for example, MeSH), the relationship between the search terms (for example, Boolean) when applicable, and the number of hits for each search are given in Table 69, Table 70, and Table 71.

Table 69 Search strategy in PubMed for the clinical review

ID	Search string	# of hits
#1	"prostatic neoplasms"[MeSH Terms]	105,036
#2	prostat*[Title/Abstract]	17,785
#3	"cancer"[Title/Abstract] OR carcinoma[Title/Abstract] OR malignant*[Title/Abstract] OR tumor[Title/Abstract] OR tumoral[Title/Abstract] OR tumour[Title/Abstract] OR adenocarcinoma[Title/Abstract]	2,369,022
#4	#2 AND #3	125,266
#5	#4 OR #1	142,907
#6	"hormone-refractory"[Title/Abstract] OR "hormone-resistant"[Title/Abstract] OR "hormone-independent"[Title/Abstract] OR "androgen-independent"[Title/Abstract] OR "androgen-resistant"[Title/Abstract] OR "castration-resistant"[Title/Abstract] OR HRPC[Title/Abstract] OR AIPC[Title/Abstract] OR CRPC[Title/Abstract]	11,650
#7	#5 AND #6	9,998
#8	"prostatic neoplasms, castration resistant"[MeSH Terms]	1,434
#9	#7 OR #8	10,267
#10	"non-metastatic"[Title/Abstract] OR nmCRPC[Title/Abstract] OR "nonmetastatic"[Title/Abstract] or "non-metastasized"[Title/Abstract] OR "non-metastasised"[Title/Abstract] OR "nonmetastasized"[Title/Abstract] OR M0[Title/Abstract] OR "not metastasized"[Title/Abstract] OR “early stage”[Title/Abstract] OR “early disease”[Title/Abstract] OR “early phase”[Title/Abstract] OR “localized”[Title/Abstract] OR “localised”[Title/Abstract] OR “locally advanced”[Title/Abstract]	364,231
#11	#9 AND #10	803
#12	"randomized controlled trials as topic"[MeSH Terms]	106,976
#13	"double-blind method"[MeSH Terms]	136,754
#14	"cohort studies"[MeSH Terms]	1,565,205
#15	"randomized controlled trial"[Publication Type]	422,727
#16	(“double blind”[Title/Abstract] OR “double blinded"[Title/Abstract] OR RCT[Title/Abstract] OR Randomi*[Title/Abstract] OR controlled[Title/Abstract] OR controled[Title/Abstract] OR control[Title/Abstract] OR Placebo[Title/Abstract] OR Trial[Title/Abstract])	2,977,859
#17	(Study[Title/Abstract] OR studies[Title/Abstract]) AND (open[Title/Abstract] OR open-label[Title/Abstract] OR non-randomised[Title/Abstract] OR non-randomized[Title/Abstract] OR "cohort"[Title/Abstract])	456,654
#18	#12 OR #13 OR #14 OR #15 OR #16 OR #17	4,524,954
#19	#11 AND #18	299

Source: PROSPER SLR report[31]
This search was conducted on the 24th of November 2016 and no time restriction was applied. This search was not updated in July 2018. PubMed was searched through Medline in the SLR update.

Table 70 Search strategy in Cochrane for the clinical review

ID	Search string	# of hits (15 MAY 2018*[2])
#1	MeSH descriptor: [Prostatic Neoplasms]	5,391
#2	prostat*:ti,ab,kw	16,891
#3	"cancer":ti,ab,kw or carcinoma:ti,ab,kw or malignant*:ti,ab,kw or tumor:ti,ab,kw or tumoral:ti,ab,kw or tumour:ti,ab,kw or adenocarcinoma:ti,ab,kw	151,384
#4	#2 and #3	10,914
#5	#4 or #1	11,328
#6	"hormone-refractory":ti,ab,kw or "hormone-resistant":ti,ab,kw or "hormone-independent":ti,ab,kw or "androgen-independent":ti,ab,kw or "androgen-resistant":ti,ab,kw or "castration-resistant":ti,ab,kw or HRPC:ti,ab,kw OR AIPC:ti,ab,kw or CRPC:ti,ab,kw	1,717
#7	#5 and #6	1,663
#8	MeSH descriptor: [Prostatic Neoplasms, Castration-Resistant] explode all trees	177
#9	#7 or #8	1,663
#10	"non-metastatic":ti,ab,kw or nmCRPC:ti,ab,kw or "nonmetastatic":ti,ab,kw or "non-metastasized":ti,ab,kw or "non-metastasised":ti,ab,kw or "nonmetastasized":ti,ab,kw or M0:ti,ab,kw or "not metastasized":ti,ab,kw or “early stage”:ti,ab,kw or “early disease”:ti,ab,kw or “early phase”:ti,ab,kw or “localized”:ti,ab,kw or “localised”:ti,ab,kw or “locally advanced”:ti,ab,kw	18,629
#11	#9 and #10	123
#12	MeSH descriptor: [Randomized Controlled Trials as Topic] explode all trees	23,123
#13	MeSH descriptor: [Double-Blind Method] explode all trees	141,448
#14	MeSH descriptor: [Cohort Studies] explode all trees	143,171
#15	"randomized controlled trial":pt	453,018
#16	(“double blind”:ti,ab,kw or “double blinded":ti,ab,kw or RCT:ti,ab,kw or Randomi*:ti,ab,kw or controlled:ti,ab,kw or controled:ti,ab,kw or control:ti,ab,kw or Placebo:ti,ab,kw or Trial:ti,ab,kw)	925,939
#17	(Study:ti,ab,kw or studies:ti,ab,kw) and (open:ti,ab,kw or open-label:ti,ab,kw or non-randomised:ti,ab,kw or non-randomized:ti,ab,kw or "cohort":ti,ab,kw)	107,132
#18	#12 or #13 or #14 or #15 or #16 or #17	1,017,279
#19	#11 and #18	117

Source: PROSPER SLR report[31]

*[1] The search was conducted on the 24th of November 2016 with no timeframe restriction and updated on the 15th of May 2018. Only the final numbers from the SLR update are shown here.

Table 71 Search strategy in Medline, Medline in Process and Embase for the clinical review

ID	Search string	# of hits
1.	exp Prostatic Neoplasms/	304,652
2.	exp prostate tumor/	190,005
3.	(prostat* and (cancer or carcinoma or malignant* or tumor or tumoral or tumour or adenocarcinoma)).ab,ti.	318,343
4.	1 or 2 or 3	377,017

ID	Search string	# of hits
5.	("hormone-refractory" or "hormone-resistant" or "hormone-independent" or "androgen-independent" or "androgen-resistant" or "castration-resistant" or HRPC or AIPC or CRPC).ab,ti.	32,421
6.	4 and 5	29,161
7.	exp castration resistant prostate cancer/	9,685
8.	exp Prostatic Neoplasms, Castration-Resistant/	12,070
9.	6 or 7 or 8	31,661
10.	(non-metastatic or nmCRPC or nonmetastatic or non-metastasized or non-metastasised or nonmetastasized or M0 or early stage or early disease or early phase or localized or localised or locally advanced).ab,ti.	810,945
11.	9 and 10	2,632
12.	exp Randomized Controlled Trials as Topic/	267,202
13.	exp "randomized controlled trial (topic)"/	148,096
14.	exp randomized controlled trial/	924,671
15.	exp randomized controlled trial/	924,671
16.	(double blind or double blinded or RCT or Randomi* or controlled or controled or control or Placebo or Trial).ab,ti.	6,771,120
17.	(Study OR studies) AND (open OR open-label OR non-randomised OR non-randomized OR cohort) {Including Related Terms}	11,704
18.	or 13 or 14 or 15 or 16 or 17	7,051,580
19.	11 and 18	830
20.	remove duplicates from 19	600

Source: PROSPER SLR report[31]
The search in Medline, Medline in Process and Embase for the clinical component was conducted on 10th of July 2018. The timeframe covered was: Embase: 1996 to 2018 Week 28, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R): 1946 to Present

The details for the search strategies for congress presentations are given below. All related searches in the initial SLR were conducted on December 16, 2016 while the searches in the SLR update were conducted between the first and tenth of July 2018.

- American Society of Clinical Oncology (ASCO) and American Society of Clinical Oncology Genitourinary Cancers symposium (ASCO-GU): In the initial SLR, a total of 423 abstracts were identified using the search string of: “castration resistant prostate cancer”. In the SLR update, a total of 473 abstracts were identified using the same search string.
- American Urological Association (AUA): Seven abstracts related to nmHRPC were identified in the AUA website for 2015 and 2017. Twenty-three abstract related to HRPC were identified for 2017 and 2018.
- European Association of Urology (EAU): Seven nmHRPC related abstracts were identified in the EAU website for 2015 and 2016. Forty-six abstracts related to HRPC were identified for 2017 and 2018.
- European Society for Medical Oncology (ESMO): A total of 130 abstracts related to HRPC were identified for 2015 and 2016 and 61 for 2017 and 2018.

- International Society for Pharmacoeconomics and Outcomes Research (ISPOR): The number of abstracts identified at the ISPOR website for each search string is provided in Table 72. The searches were conducted on the 24th of November 2016 for the initial SLR and on the 1st of July 2018 for the SLR update.

Table 72 Search string for the ISPOR website

Search string	2015 - 2016	2017 - 2018
“Castration resistant prostate cancer” in title	8	6
“Castration-resistant prostate cancer” in title	29	19
“Castration resistant prostate cancer” in abstract	11	4
“Castration-resistant prostate cancer” in abstract	19	21

Source: PROSPER SLR report[31]

- ClinicalTrials.gov portal: A total of 724 unique trials were identified using the following terms as condition: “Castration-resistant prostate cancer”, “Hormone-relapsed prostate cancer”, “Hormone relapsed prostate cancer”, “Hormone-resistant prostate cancer”, “Hormone resistant prostate cancer”, “Hormone-refractory prostate cancer”, "Failed primary androgen deprivation therapy" OR "failed androgen deprivation therapy" (as condition) AND prostate cancer (as condition).
  Of the 724 unique trials, 39 included nmHRPC patients and included at least two treatment arms. However, only nine of these studies were deemed relevant and are discussed here-in. The remaining of the trials were excluded because they were withdrawn or early terminated (n=11) with no results or assessed new interventions still at clinical phase II development for nmHRPC (n=19).
- ClinicalTrialsRegister portal: Four studies were identified with the following terms: “non-metastatic castration-resistant prostate cancer”. All four studies had already been identified in the clinicaltrials.gov portal.

D1.1.2 Study selection

The inclusion and exclusion criteria of the systematic literature review, including the comparators of interest are presented in Section B.2.1; Table 3. The PRISMA flow diagram is shown in Section B.2.1, Figure 3.

Of the 11 studies identified in the clinical SLR, only two (PROSPER and STRIVE) are relevant for this submission. However, an overview of all 11 studies were identified in the SLR is provided in Table 73.

Table 73 Summary of studies identified by clinical SLR

Study acronym - NCTC ID	Country	Duration	Study design	Aim of the study	Study population	Intervention (n randomised)	Comparator (n randomised)
ARAMIS - NCT02200614[49]	>30 countries	Not reported	RCT, DB, placebo - controlled, phase III, multicentre	To evaluate the efficacy and safety of ODM-201 compared to placebo, in prolonging MFS in high-risk nmHRPC patients	High-risk nmHRPC	DAR 2 x 300mg (oral) BID (n=1000)*	PLA (n=550)*
ENTHUSE 0 - NCT00626548 [112]	Not reported	Between January 2008 and May 2011	RCT, DB, placebo - controlled, phase III, multicentre	To assess the efficacy and safety of zibotentan vs placebo in nmHRPC	nmHRPC	ZIB 10mg (oral) OD (n=592)	PLA (n=589)
NCT00020254[113]	Not reported	Not reported Median FU >4 years	RCT, OL, phase II	To evaluate primarily the efficacy, and secondarily the immunological effects, of a vaccination regimen relative to the efficacy of anti-androgen therapy with NIL in patients with HRPC and increasing PSA levels but with no radiographic evidence of metastatic disease	nmHRPC	Poxviral vaccine: Priming on Day 1 Boost 1 month after priming GM-CSF: 100 □g/d (SC) on days 1 to 4 + IL2: 6 million IU/m2 (SC) on days 8 to 12 (n=21)	NIL 300 mg/d for the 1st month and 150 mg/d thereafter (n=21)
NCT00286091[111]	30 countries	Between Feb 3, 2006, and July 23, 2008	RCT, DB, placebo - controlled, phase III, multicentre international	To assess denosumab, a fully human anti-RANKL monoclonal antibody, for prevention of bone metastasis or death in nmHRPC	High-risk nmHRPC	DEN 120 mg (SC) every 4 weeks (n=718)	PLA (n=717)
NCT00036556[44]	US (75 centres) and other countries (108 centres)	Not reported	RCT, DB, placebo - controlled, phase III, multicentre	Not reported	nmHRPC	ATR (oral) 10 mg OD (n=467)	PLA (n=474)

Study acronym - NCTC ID	Country	Duration	Study design	Aim of the study	Study population	Intervention (n randomised)	Comparator (n randomised)
NCT00450463[114]	Not reported	Not reported	RCT, OL, phase II	Not reported	nmHRPC	PSA-TRICOM, SC monthly	FLU 400 mg TID
PROSPER - NCT02003924[2]	International (254 centres)	26 Nov 2013 to 28 Jun 2017 (date for primary completion)	RCT, DB, placebo - controlled, phase III, multicentre	To evaluate the efficacy and safety of enzalutamide in patients with nmHRPC	High risk nmHRPC	ENZA 160mg (oral) OD (n=933)	PLA (n=468)
Retrospective[115]	Japan (1 centre)	July 2007 to March 2016	Retrospective	To retrospectively investigate potential roles and toxicity of docetaxel in nmHRPC compared with mHRPC	nmHRPC and mHRPC	Docetaxel (nmHRPC: n=46; mHRPC: n=52)	NA
SPARTAN - NCT01946204[47]	Not reported	Not reported	RCT, DB, placebo - controlled, phase III, multicentre	To evaluate the efficacy and safety of apalutamide in adult men with high-risk nmHRPC	High risk nmHRPC	APA 240 mg (oral) OD (n=806)	PLA (n=401)
STRIVE - NCT01664923[41]	US	Between August 2012	RCT, DB, placebo -	To compare the safety and efficacy of enzalutamide	HRPC patients	ENZA 160mg (oral) OD	BIC 50 mg (oral) OD

Study acronym - NCTC ID	Country	Duration	Study design	Aim of the study	Study population	Intervention (n randomised)	Comparator (n randomised)
		and March 2014	controlled, phase II, multicentre	and bicalutamide in HRPC patients	(High risk M0 and M1)	BIC PLA (n=198 [M0=70])	ENZA PLA (n=198 [M0=69])
TARP - NCT00470834[48]	Canada and USA	18 months followed by 2 year extension on same tx if no disease progression	RCT, DB, placebo - controlled, phase IV, multicentre international	To prospectively evaluate dutasteride plus bicalutamide in men with asymptomatic, nmHRPC with rising PSA	nmHRPC	BIC 50 mg + DUT 3.5 mg, OD (n=62)	BIC 50 mg + PLAPLA OD (n=65)

Source: PROSPER SLR report[31]

*Expected sample size. **Key study publication.

Abbreviations: APA: apalutamide; ATR: atrasentan; BIC PLA: matching placebo for bicalutamide; BIC: bicalutamide; BID: twice daily; DAR: darolutamide; DB: double-blinded; DEN: denosumab; DUT: dutasteride; ENZA PLA: matching placebo for enzalutamide; ENZA: enzalutamide; EST: Estramustine; FLU: flutamide; GMC-SF: granulocyte-macrophage colony-stimulating factor; IL2: interleukin 2; IV: intravenous; MFS: metastasis-free survival; NA: not applicable; NIL: nilutamide; OD: once daily; OL: open-label; PLA: placebo; RCT: randomised controlled trial; SC: subcutaneous; TID: three times daily; tx: treatment; ZIB: zibotentan.

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

As discussed in Section B.2.9.1, from the 11 studies identified by the SLR, only two were included in the NMA: PROSPER and STRIVE. The other studies were either not yet completed, or not relevant for the scope of this submission. Methods and outcomes for PROSPER and STRIVE are elaborately discussed in Section B.2.6.

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

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

Programming language for the indirect or mixed treatment comparison

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

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

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

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

# ranking on relative scale
for (k in 1:nt) {
     Rk_g[k] <- nt+1-rank(d[],k)                # assumes events are "good"
```



```
    Rk_b[k] <- rank(d[],k)                  # assumes events are "bad"
    best_g[k] <- equals(Rk_g[k],1)    #calculate probability that treat k is best
    best_b[k] <- equals(Rk_b[k],1)    #calculate probability that treat k is best
   for (i in 1:nt){
    prk_g[k,i] <- equals(Rk_g[k],i)   #calculate probability of treat k being each rank i
    prk_b[k,i] <- equals(Rk_b[k],i)   #calculate probability of treat k being each rank i
    }
}

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

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

}
}                          # *** PROGRAM ENDS
```

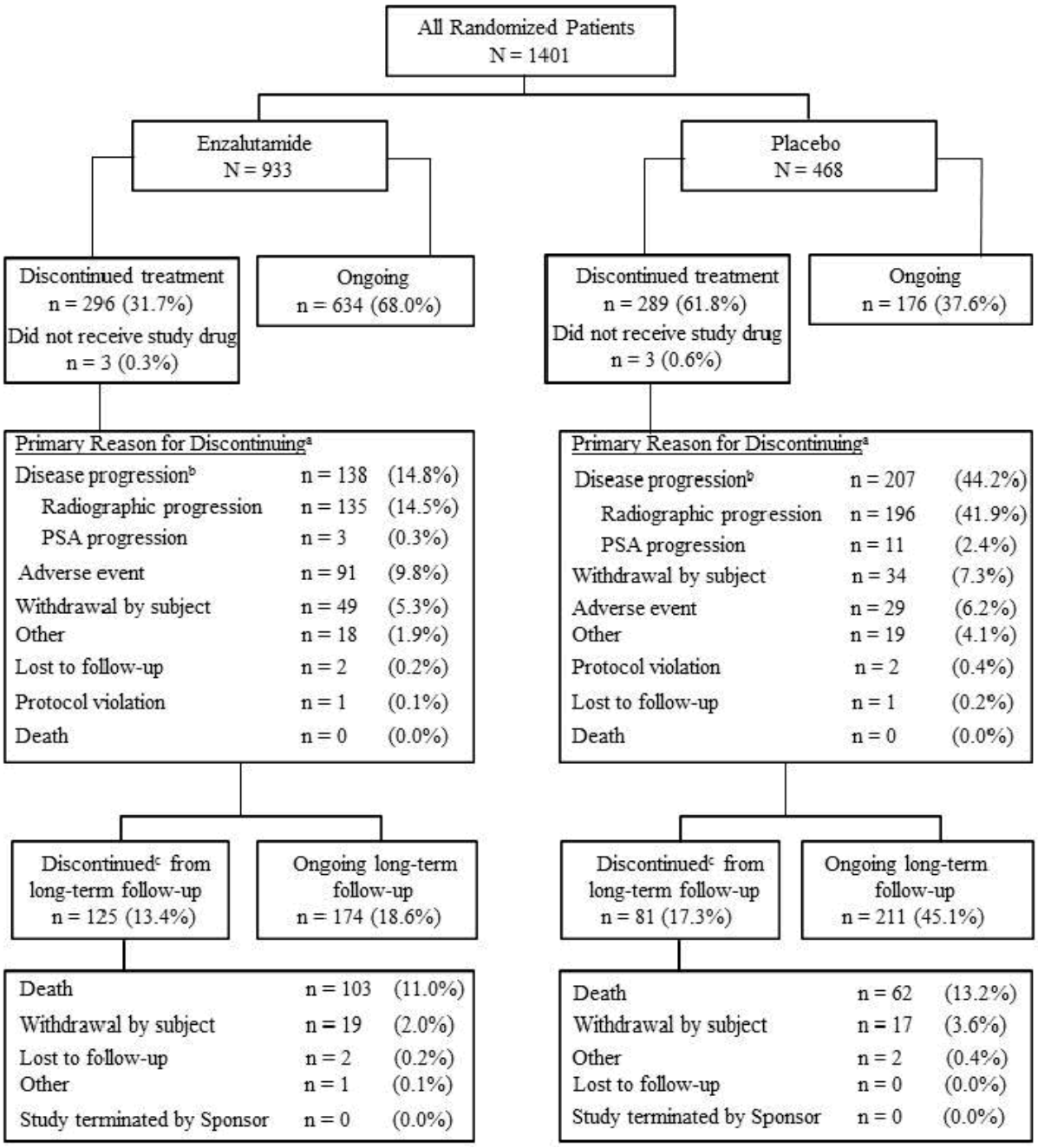
Risk of bias of studies included in indirect or mixed treatment comparisons

Summary of qualitative assessment is provided in Appendix D1.3. None of the studies were identified as being at a high risk of bias, so the validity of the results was not affected in each individual study.

D1.2 Participant flow in the relevant randomised control trials

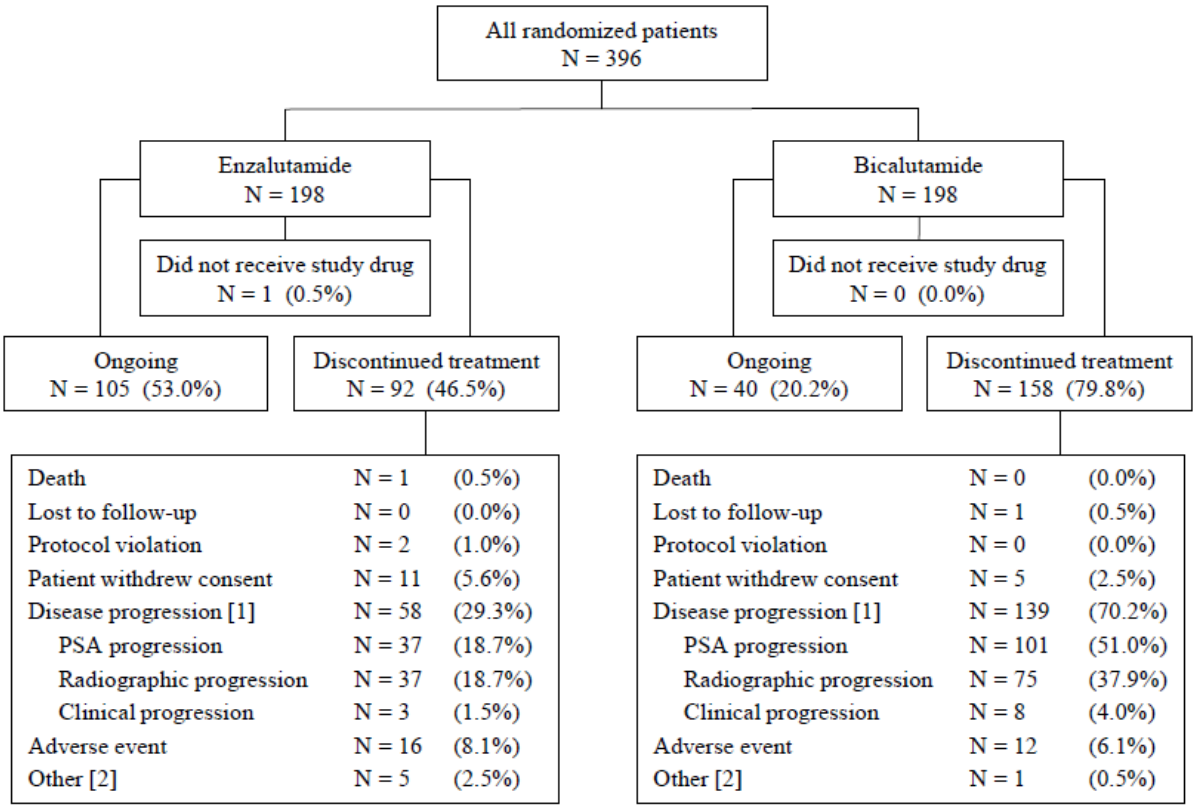
The participant flow of the relevant randomized trials (PROSPER and STRIVE) is given in Figure 36 and Figure 37.

Figure 36 PROSPER participant flow as of 28 June 2017 (ITT Population)



Source: PROSPER Clinical study report[2]
Percentages are based on total number of randomized patients in each treatment group and overall.
[1] Patients discontinued due to disease progression could be counted in more than 1 subcategory.
[2] Reasons included physician decision, not tolerating therapy, patient requested hospice care, unable to swallow study drug, patient's insurance changed, laboratory abnormalities.
Abbreviations: n: number of patients; PSA: prostate-specific antigen

Figure 37 STRIVE participant flow



Source: STRIVE Clinical study report[41]
Percentages are based on total number of randomized patients in each treatment group and overall.
[1]Patients discontinued due to disease progression could be counted in more than 1 subcategory.
[2] Reasons included physician decision, not tolerating therapy, patient requested hospice care, unable to swallow study drug, patient's insurance changed, laboratory abnormalities.
Abbreviations: N: number of patients; PSA, prostate-specific antigen.

D1.3 Quality assessment for each trial

The quality appraisals of PROSPER and STRIVE to assess the risk of bias and generalisability in parallel group RCTs are shown in Table 74. The quality appraisal was based on the key publication. Both trials met most criteria, indicating that the trials were of high quality with little risk of bias.

Table 74 Quality assessment results for PROSPER and STRIVE

Quality assessment criteria	PROSPER	STRIVE
Was randomisation carried out appropriately?	Y	Y
Was the concealment of treatment allocation adequate?	Y	Y
Was the blinding of participants and personnel sufficient?	Y	Y
Was the blinding of the outcome assessment sufficient?	Y	Y
Was the outcome data complete?	N*	N*
Was reporting performed appropriately?	Y	Y

Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	N	N
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Y	Y
Did the analysis include an intention-to-treat analysis?	Y	Y
If there was an ITT, was this appropriate and were appropriate methods used to account for missing data?	Y	Y

Source: PROSPER SLR report[31]; Hussain et al[35]; Penson et al[34]
*Not all PROSPER and STRIVE-related results were published in the key publications.

Appendix E: Subgroup analysis

A pre-specified subgroup analysis on MFS was performed as discussed in Section B.2.7. The results are shown in Figure 18. No further subgroup analyses were performed for this submission.

Appendix F: Adverse reactions

No studies providing additional safety information for enzalutamide in high risk nmHRPC were identified other than the PROSPER and STRIVE-related publications.

Appendix G: Published cost-effectiveness studies

A SLR was conducted in July 2018 to identify the economic evidence of enzalutamide and standard of care in the management of nmHRPC. The SLR was conducted in two separate phases. The initial one, in November 2016, included searches in PubMed, Cochrane, and key congresses. An update was conducted in July 2018 to identify any new evidence. For the SLR update, the databases searched were expanded to include:

- Medline and Medline in Process
- Embase
- EconLit.

G1.1 Search strategy

The research questions for the cost-effectiveness SLR were:

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

The databases searched and provider used to identify cost-effectiveness evidence are provided in Table 75. The timeframe was restricted to the last 10 years in the initial SLR (i.e., between 01 January 2006 and 24 November 2016) but no timeframe was applied to the SLR update. No additional limitations were applied.

Table 75 Databases searched and provider used to for cost-effectiveness SLR

Database / information source	Interface / URL
PubMed	http://www.ncbi.nlm.nih.gov/pubmed
Medline and Medline in Process	OvidSP
EMBASE	OvidSP
EconLit	OvidSP
CDSR in the Cochrane Library	Cochrane Library/Wiley Interscience
HTA in the Cochrane Library	Cochrane Library/Wiley Interscience
NHS EED in the Cochrane Library	Cochrane Library/Wiley Interscience
HTA Accelerator	https://hta.quintiles.com/

Source: PROSPER SLR report[31]
*PubMed was searched only up to November 2016. PubMed was searched through Medline in the SLR update.

Abbreviations: CDRS: Cochrane Database of Systematic Reviews; HTA: Health Technology Assessment; NHS EED: NHS Economic Evaluation Database.

The complete search strategies used for PubMed, Cochrane, Medline, Medline in Process, and Embase, including all the search terms: textwords (free text), subject index headings (for example, MeSH), the relationship between the search terms (for example, Boolean) when applicable, and the number of hits for each search are given in Table 76, Table 77, and Table 78.

Table 76 Search strategy in PubMed for the cost-effectiveness review

ID	Search string	# of hits
#1	"prostatic neoplasms"[MeSH Terms]	49,543
#2	prostat*[Title/Abstract]	85,868
#3	"cancer"[Title/Abstract] OR carcinoma[Title/Abstract] OR malignant*[Title/Abstract] OR tumor[Title/Abstract] OR tumoral[Title/Abstract] OR tumour[Title/Abstract] OR adenocarcinoma[Title/Abstract]	1,105,115
#4	#2 AND #3	68,293
#5	#4 OR #1	75,060
#6	"hormone-refractory"[Title/Abstract] OR "hormone-resistant"[Title/Abstract] OR "hormone-independent"[Title/Abstract] OR "androgen-independent"[Title/Abstract] OR "androgen-resistant"[Title/Abstract] OR "castration-resistant"[Title/Abstract] OR HRPC[Title/Abstract] OR AIPC[Title/Abstract] OR CRPC[Title/Abstract]	7,093
#7	#5 AND #6	6,586
#8	"prostatic neoplasms, castration resistant"[MeSH Terms]	1,434
#9	#7 OR #8	6,855
#10	"non-metastatic"[Title/Abstract] OR nmCRPC[Title/Abstract] OR "nonmetastatic"[Title/Abstract] or "non-metastasized"[Title/Abstract] OR "non-metastasised"[Title/Abstract] OR "nonmetastasized"[Title/Abstract] OR M0[Title/Abstract] OR "not metastasized"[Title/Abstract] OR “early stage”[Title/Abstract] OR “early disease”[Title/Abstract] OR “early phase”[Title/Abstract] OR “localized”[Title/Abstract] OR “localised”[Title/Abstract] OR “locally advanced”[Title/Abstract]	161,592
#11	#9 AND #10	526
#12	"costs and cost analysis"[MeSH Terms]	72,258
#13	"models, economic"[MeSH Terms]	6,835
#14	productivity[MeSH Terms]	3,029
#15	hospitalization[MeSH Terms]	82,746
#16	budget[MeSH Terms]	3,386
#17	expenditure[MeSH Terms]	6,393
#18	"costs"[Title/Abstract] OR "cost"[Title/Abstract] OR "costing"[Title/Abstract] OR "costly"[Title/Abstract] OR "economic burden"[Title/Abstract] OR economic*[Title/Abstract] OR pharmacoeconomic*[Title/Abstract] OR "budget"[Title/Abstract] OR "healthcare cost"[Title/Abstract] OR "healthcare costs"[Title/Abstract] OR "expenditure"[Title/Abstract] OR "hospital finance"[Title/Abstract]	338,818
#19	"model"[Title/Abstract] AND ("economic"[Title/Abstract] OR "cost-effectiveness"[Title/Abstract] OR "cost-benefit"[Title/Abstract] OR "cost-utility"[Title/Abstract] OR "discrete event"[Title/Abstract])	18,778

ID	Search string	# of hits
#20	"healthcare utilisation"[Title/Abstract] OR "health care utilisation"[Title/Abstract] OR “resource utilization”[Title/Abstract] OR “resource use”[Title/Abstract] OR "health care resource"[Title/Abstract] OR "health care resources"[Title/Abstract]	10,157
#21	"productivity"[Title/Abstract] OR "absenteeism"[Title/Abstract] OR ("work"[Title/Abstract] AND "loss"[Title/Abstract]) OR ("work"[Title/Abstract] AND "disability"[Title/Abstract])	47,567
#22	"hospitalisation"[Title/Abstract] OR "hospitalization"[Title/Abstract] OR "ICU"[Title/Abstract] OR "intensive care"[Title/Abstract] OR "urologist"[Title/Abstract] OR "physician"[Title/Abstract] OR "oncologist"[Title/Abstract] OR "outpatient visit"[Title/Abstract] OR "outpatient visits"[Title/Abstract] OR "admission"[Title/Abstract] OR "inpatient visit"[Title/Abstract] OR "inpatient visits"[Title/Abstract]	234,991
#23	"QALY"[Title/Abstract] OR "quality adjusted life year"[Title/Abstract] OR "ICER"[Title/Abstract] OR "incremental cost effectiveness ratio"[Title/Abstract]	7,083
#24	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #`9 OR #20 OR #21 OR #22 OR #23	657,209
#25	#11 AND #24	15

Source: PROSPER SLR report[31]
The search was conducted on the 24th of November 2016 with a timeframe restriction of 10 years.

Table 77 Search strategy in Cochrane for the cost-effectiveness review

ID	Search string	# of hits (15 MAY 2018*[2])
#1	MeSH descriptor: [Prostatic Neoplasms]	5,391
#2	prostat*:ti,ab,kw	16,891
#3	"cancer":ti,ab,kw or carcinoma:ti,ab,kw or malignant*:ti,ab,kw or tumor:ti,ab,kw or tumoral:ti,ab,kw or tumour:ti,ab,kw or adenocarcinoma:ti,ab,kw	151,384
#4	#2 and #3	10,914
#5	#4 or #1	11,328
#6	"hormone-refractory":ti,ab,kw or "hormone-resistant":ti,ab,kw or "hormone-independent":ti,ab,kw or "androgen-independent":ti,ab,kw or "androgen-resistant":ti,ab,kw or "castration-resistant":ti,ab,kw or HRPC:ti,ab,kw OR AIPC:ti,ab,kw or CRPC:ti,ab,kw	1,717
#7	#5 and #6	1,663
#8	MeSH descriptor: [Prostatic Neoplasms, Castration-Resistant] explode all trees	177
#9	#7 or #8	1,663
#10	"non-metastatic":ti,ab,kw or nmCRPC:ti,ab,kw or "nonmetastatic":ti,ab,kw or "non-metastasized":ti,ab,kw or "non-metastasised":ti,ab,kw or "nonmetastasized":ti,ab,kw or M0:ti,ab,kw or "not metastasized":ti,ab,kw or “early stage”:ti,ab,kw or “early disease”:ti,ab,kw or “early phase”:ti,ab,kw or “localized”:ti,ab,kw or “localised”:ti,ab,kw or “locally advanced”:ti,ab,kw	18,629
#11	#9 and #10	123
#12	MeSH descriptor: [Costs and Cost Analysis] explode all trees	26,144
#13	MeSH descriptor: [Models, Economic] explode all trees	2,060
#14	MeSH descriptor: [Efficiency] explode all trees	452
#15	MeSH descriptor: [Hospitalization] explode all trees	15,614

ID	Search string	# of hits (15 MAY 2018*[2])
#16	MeSH descriptor: [Budgets] explode all trees	78
#17	MeSH descriptor: [Health Expenditures] explode all trees	354
#18	"costs":ti,ab,kw or "cost":ti,ab,kw or "costing":ti,ab,kw or "costly":ti,ab,kw or "economic burden":ti,ab,kw or economic*:ti,ab,kw or pharmacoeconomic*:ti,ab,kw or "budget":ti,ab,kw or "healthcare cost":ti,ab,kw or "healthcare costs":ti,ab,kw or "expenditure":ti,ab,kw or "hospital finance":ti,ab,kw	75,129
#19	"model":ti,ab,kw and ("economic":ti,ab,kw or "cost-effectiveness":ti,ab,kw or "cost-benefit":ti,ab,kw or "cost-utility":ti,ab,kw or "discrete event":ti,ab,kw)	4,156
#20	"healthcare utilisation":ti,ab,kw or "health care utilisation":ti,ab,kw or “resource utilization”:ti,ab,kw or “resource use”:ti,ab,kw or "health care resource":ti,ab,kw or "health care resources":ti,ab,kw	2,996
#21	"productivity":ti,ab,kw or "absenteeism":ti,ab,kw or ("work":ti,ab,kw and "loss":ti,ab,kw) or ("work":ti,ab,kw and "disability":ti,ab,kw)	5,887
#22	"hospitalisation":ti,ab,kw or "hospitalization":ti,ab,kw or "ICU":ti,ab,kw or "intensive care":ti,ab,kw or "urologist":ti,ab,kw or "physician":ti,ab,kw or "oncologist":ti,ab,kw or "outpatient visit":ti,ab,kw or "outpatient visits":ti,ab,kw or "admission":ti,ab,kw or "inpatient visit":ti,ab,kw or "inpatient visits":ti,ab,kw	74,879
#23	"QALY":ti,ab,kw or "quality adjusted life year":ti,ab,kw or "ICER":ti,ab,kw OR "incremental cost effectiveness ratio":ti,ab,kw	3,223
#24	#20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31	148143
#25	#11 and #32	10
#26	#25 - between 2016 and 2018	2

Source: PROSPER SLR report[31]

*[1]. The search was conducted on the 24th of November 2016 with no timeframe restriction and on the 15th of May 2018. Only results for the SLR update are provided here.

Table 78 Search strategy in Medline, Medline in Process and Embase for the cost-effectiveness review

ID	Search string	# of hits
1	exp Prostatic Neoplasms/	304,664
2	exp prostate tumor/	190,005
3	(prostat* and (cancer or carcinoma or malignant* or tumor or tumoral or tumour or adenocarcinoma)).ab,ti.	318,382
4	1 or 2 or 3	377,057
5	("hormone-refractory" or "hormone-resistant" or "hormone-independent" or "androgen-independent" or "androgen-resistant" or "castration-resistant" or HRPC or AIPC or CRPC).ab,ti.	32,425
6	4 and 5	29,164
7	exp castration resistant prostate cancer/	9,685
8	exp Prostatic Neoplasms, Castration-Resistant/	12,071
9	6 or 7 or 8	31,664

ID	Search string	# of hits
10	(non-metastatic or nmCRPC or nonmetastatic or non-metastasized or non-metastasised or nonmetastasized or M0 or early stage or early disease or early phase or localized or localised or locally advanced).ab,ti.	811,126
11	9 and 10	2,633
12	exp economic aspect/	1,175,003
13	exp economic model/ or exp economics/	721,178
14	exp models, economic/	14,246
15	exp economics/ or exp "costs and cost analysis"/	956,964
16	exp Health Expenditures/	254,159
17	exp financial statement/	177
18	exp budget/	35,377
19	exp Budgets/	35,377
20	exp Hospitalization/	494,262
21	exp hospitalization/	494,262
22	exp productivity/	61,198
23	exp Efficiency/	61,198
24	(costs or cost or costing or costly or economic burden or economic* or pharmacoeconomic* or budget or healthcare cost or healthcare costs or expenditure or financ*).ab,ti.	1,587,904
25	(model and (economic or cost-effectiveness or cost-benefit or cost-utility or discrete event)).ab,ti.	77,809
26	(utilization or utilization or resource).ab,ti.	547,941
27	(productivity or absenteeism or ((work and loss) or (work and disability))).ab,ti.	198,785
28	(hospitalisation or hospitalization or ICU or intensive care or urologist or physician or oncologist or outpatient visit or outpatient visits or admission or inpatient visit or inpatient visits).ab,ti.	1,227,647
29	(QALY or quality adjusted life year or ICER or incremental cost effectiveness ratio).ab,ti.	30,115
30	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29	4,513,229
31	11 and 30	157
32	remove duplicates from 31	117

Source: PROSPER SLR report[31]
The search in Medline, Medline in Process and Embase for the clinical component was conducted on 10th of July 2017. The timeframe covered was: Embase: 1996 to 2018 Week 28; Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R): 1946 to Present

Searches were also conducted in:

- ISPOR website: see Appendix D for details.
- EconLit: The search was conducted on the 10th of July 2018. The search strategy was:

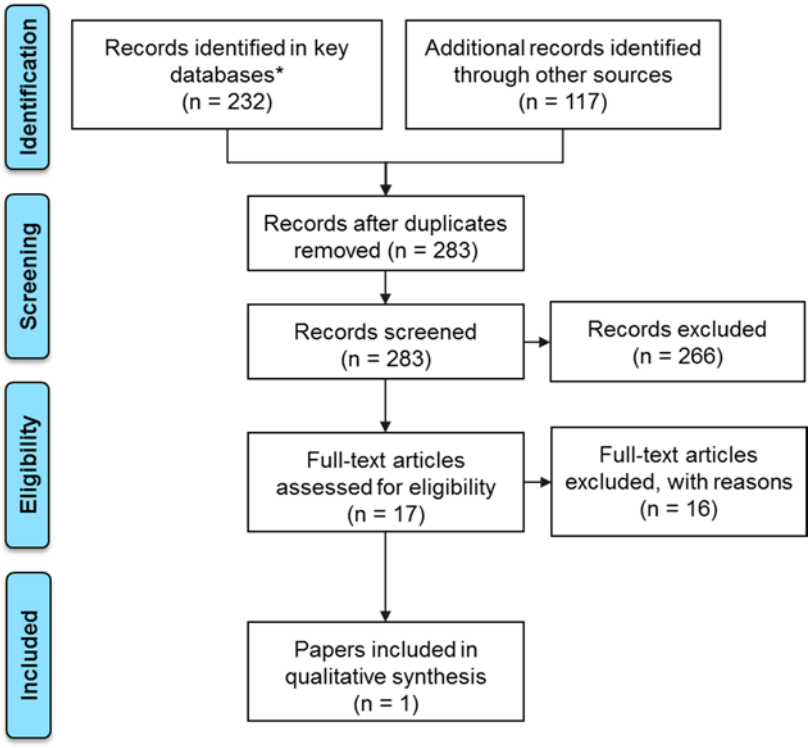
- S1: TX castration 87
- S2: TX CRPC 5
- S1 OR S2: 91

- HTA Accelerator (IQVIA proprietary database): No relevant study was identified for nmHRPC patients.

G1.2 Results

The literature search for the economic burden identified 349 references of which 283 were unique (Figure 38). After the initial screening of titles and abstracts, 17 references were considered as potentially relevant. Following detailed examination of the full article, only one was included for abstraction. This study is available only as a poster[102].

Figure 38 PRISMA flow diagram with the identified studies from cost-effectiveness SLR



Source: PROSPER SLR report[31]

*Key databases included Pubmed (n=385; search included until 24 NOV 2016 only), Cochrane (n=118), and Medline, Medline in Process and Embase (n=600).

Morote 2013 is a costing study that compares the annual management costs of patients with HRPC at high risk of developing bone metastases versus the annual management costs during the first, second and subsequent years after bone metastases development, in Spain[102]. The costs were derived from an expert panel of five urologists and three oncologists from Spanish health centres. The experts were asked to estimate the average annual resource use in the management of nmHRPC patients and in the first, second and subsequent years after developing bone metastases. Following the Delphi technique,

participants completed a self-administered questionnaire. Individual answers were merged in an anonymous manner and the derived results discussed during a live meeting where consensus was reached. Costs were estimated from the Spanish national health system (NHS) perspective.

The identified costing study was not considered relevant to this submission as it describes the costs specific for Spain. In addition, the study has several important limitations. The authors do not report the HRU used by patients at any of the disease stages. The authors only provide average annual costs per patient without explaining how these costs were calculated. No sensitivity analyses were conducted either. The costs exclude costs associated with prevention or treatment of SREs. This may have underestimated the total costs particularly after two or more years of the development of metastases. However, the authors included costs of analgesia which increased with the development of metastases (nmHRPC: €14.69; 1st year: €632.87; 2nd year: €960.12; 2+ year: €1,174.82) due to an increase in the drug costs (from €11 for nmHRPC patients to €1,031 from the third year onwards) and pre-medication costs (from €3.59 for nmHRPC to €143.62 from third year onwards).

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

A SLR was conducted in July 2018 to identify the HRQoL evidence of enzalutamide and standard of care in the management of nmHRPC. The SLR was conducted in two separate phases. The initial one, in November 2016, included searches in PubMed, Cochrane, CEA Registry and key congresses. An update was conducted in July 2018 to identify any new evidence. For the SLR update, the databases searched were expanded to include:

- Medline and Medline in Process
- Embase.

H1.1 Search strategy

The research questions for the HRQoL SLR were:

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

The databases searched and provider used to identify HRQoL evidence are provided in Table 79. No timeframe, country or language limit was applied to the clinical effectiveness searches

Table 79 Databases searched and provider used to for cost-effectiveness SLR

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

Source: PROSPER SLR report[31]
*PubMed was searched only up to November 2016. In the SLR update, Pubmed was searched through Medline.
Abbreviations: CDRS: Cochrane Database of Systematic Reviews; CEA: cost-effectiveness analysis; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; HTA: Health Technology Assessment.

The complete search strategies used for PubMed, Cochrane, and Medline, Medline in Process and Embase including all the search terms: textwords (free text), subject index headings (for example, MeSH), the relationship between the search terms (for example, Boolean) when applicable, and the number of hits for each search are given in Table 80-Table 83.

Table 80 Search strategy in PubMed for humanistic review – utility weights

ID	Search string	# of hits
#1	"prostatic neoplasms"[MeSH Terms]	105,036
#2	prostat*[Title/Abstract]	17,785
#3	"cancer"[Title/Abstract] OR carcinoma[Title/Abstract] OR malignant*[Title/Abstract] OR tumor[Title/Abstract] OR tumoral[Title/Abstract] OR tumour[Title/Abstract] OR adenocarcinoma[Title/Abstract]	2,369,022
#4	#2 AND #3	125,266
#5	#4 OR #1	142,907
#6	"hormone-refractory"[Title/Abstract] OR "hormone-resistant"[Title/Abstract] OR "hormone-independent"[Title/Abstract] OR "androgen-independent"[Title/Abstract] OR "androgen-resistant"[Title/Abstract] OR "castration-resistant"[Title/Abstract] OR HRPC[Title/Abstract] OR AIPC[Title/Abstract] OR CRPC[Title/Abstract]	11,650
#7	#5 AND #6	9,998
#8	"prostatic neoplasms, castration resistant"[MeSH Terms]	1,434
#9	#7 OR #8	10,267
#10	"non-metastatic"[Title/Abstract] OR nmCRPC[Title/Abstract] OR "nonmetastatic"[Title/Abstract] or "non-metastasized"[Title/Abstract] OR "non-metastasised"[Title/Abstract] OR "nonmetastasized"[Title/Abstract] OR M0[Title/Abstract] OR "not metastasized"[Title/Abstract] OR “early stage”[Title/Abstract] OR “early disease”[Title/Abstract] OR “early phase”[Title/Abstract] OR “localized”[Title/Abstract] OR “localised”[Title/Abstract] OR “locally advanced”[Title/Abstract]	364,231
#11	#9 AND #10	803
#12	"health status"[MeSH]	129,359
#13	"health utility"[Title/Abstract] OR "health utilities"[Title/Abstract] OR disutility[Title/Abstract] OR disutilities[Title/Abstract] or "EQ-5D"[Title/Abstract] OR EuroQoL[Title/Abstract] OR "SF6"[Title/Abstract] OR "SF12"[Title/Abstract] OR "SF36"[Title/Abstract] OR "short form 6"[Title/Abstract] OR "short form 12"[Title/Abstract] OR "short form 36"[Title/Abstract] OR “HUI”[Title/Abstract] OR “Health utilities index”[Title/Abstract]	19,098
#14	#12 OR #13	145,044
#15	#11 AND #14	2

Source: PROSPER SLR report[31]
The search was conducted on the 24th of November 2016.

Table 81 Search strategy in Cochrane for humanistic review – utility weights

ID	Search string	# of hits (15 MAY 2018*2)
#1	MeSH descriptor: [Prostatic Neoplasms]	5,391
#2	prostat*:ti,ab,kw	16,891
#3	"cancer":ti,ab,kw or carcinoma:ti,ab,kw or malignant*:ti,ab,kw or tumor:ti,ab,kw or tumoral:ti,ab,kw or tumour:ti,ab,kw or adenocarcinoma:ti,ab,kw	151,384
#4	#2 and #3	10,914
#5	#4 or #1	11,328

#6	"hormone-refractory":ti,ab,kw or "hormone-resistant":ti,ab,kw or "hormone-independent":ti,ab,kw or "androgen-independent":ti,ab,kw or "androgen-resistant":ti,ab,kw or "castration-resistant":ti,ab,kw or HRPC:ti,ab,kw OR AIPC:ti,ab,kw or CRPC:ti,ab,kw	1,717
#7	#5 and #6	1,663
#8	MeSH descriptor: [Prostatic Neoplasms, Castration-Resistant] explode all trees	177
#9	#7 or #8	1,663
#10	"non-metastatic":ti,ab,kw or nmCRPC:ti,ab,kw or "nonmetastatic":ti,ab,kw or "non-metastasized":ti,ab,kw or "non-metastasised":ti,ab,kw or "nonmetastasized":ti,ab,kw or M0:ti,ab,kw or "not metastasized":ti,ab,kw or “early stage”:ti,ab,kw or “early disease”:ti,ab,kw or “early phase”:ti,ab,kw or “localized”:ti,ab,kw or “localised”:ti,ab,kw or “locally advanced”:ti,ab,kw	18,629
#11	#9 and #10	123
#12	MeSH descriptor: [Health Status] explode all trees	25,361
#13	"health utility":ti,ab,kw or "health utilities":ti,ab,kw or disutility:ti,ab,kw or disutilities:ti,ab,kw or "EQ-5D":ti,ab,kw or EuroQoL:ti,ab,kw or "SF6":ti,ab,kw or "SF12":ti,ab,kw or "SF36":ti,ab,kw or "short form 6":ti,ab,kw or "short form 12":ti,ab,kw OR "short form 36":ti,ab,kw	8,826
#14	#40 or #41	31,921
#15	#11 and #42	7
#16	#15 – between 2016 and 2018	6

Source: PROSPER SLR report[31]

*1. The search was conducted on the 24th of November 2016 with no timeframe restriction and on the 15th of May 2018. Only the results for the SLR update are provided here.

Table 82 Search strategy in Medline for the HRQoL review – utility weights

ID	Search string	# of hits
1	exp Prostatic Neoplasms/	304,664
2	exp prostate tumor/	190,005
3	(prostat* and (cancer or carcinoma or malignant* or tumor or tumoral or tumour or adenocarcinoma)).ab,ti.	318,382
4	1 or 2 or 3	377,057
5	("hormone-refractory" or "hormone-resistant" or "hormone-independent" or "androgen-independent" or "androgen-resistant" or "castration-resistant" or HRPC or AIPC or CRPC).ab,ti.	32,425
6	4 and 5	29,164
7	exp castration resistant prostate cancer/	9,685
8	exp Prostatic Neoplasms, Castration-Resistant/	12,071
9	6 or 7 or 8	31,664
10	(non-metastatic or nmCRPC or nonmetastatic or non-metastasized or non-metastasised or nonmetastasized or M0 or early stage or early disease or early phase or localized or localised or locally advanced).ab,ti.	811,126
11	9 and 10	2,633

12	exp health status/	477,196
13	exp Health Status/	477,196
14	(health utility or health utilities or disutility or disutilities or EQ-5D or EuroQoL or SF6 or SF12 or SF36 or short form 6 or short form 12 or short form 36 or HUI or Health utilities index).ab,ti.	57,730
15	12 or 13 or 14	515,281
16	11 and 15	49
17	remove duplicates from 16	

Source: PROSPER SLR report[31]
The search in Medline, Medline in Process and Embase for the clinical component was conducted on 10th of July 2017. The timeframe covered was: Embase: 1996 to 2018 Week 28, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R): 1946 to Present

Table 83 Search strategy used in the CEA registry database for HRQoL review

Search terms	Number of utility weights	Number of articles
Castration-resistant prostate cancer	48	7
Castration resistant prostate cancer	0	0
CRPC	28	4
Androgen-independent prostate cancer	8	1
Androgen independent prostate cancer	0	0
Hormone-refractory prostate cancer	4	2
Hormone-resistant prostate cancer	0	1
Hormone resistant prostate cancer	0	0
Hormone refractory prostate cancer	0	0
Hormone-relapsed prostate cancer	0	0
Hormone relapsed prostate cancer	0	0

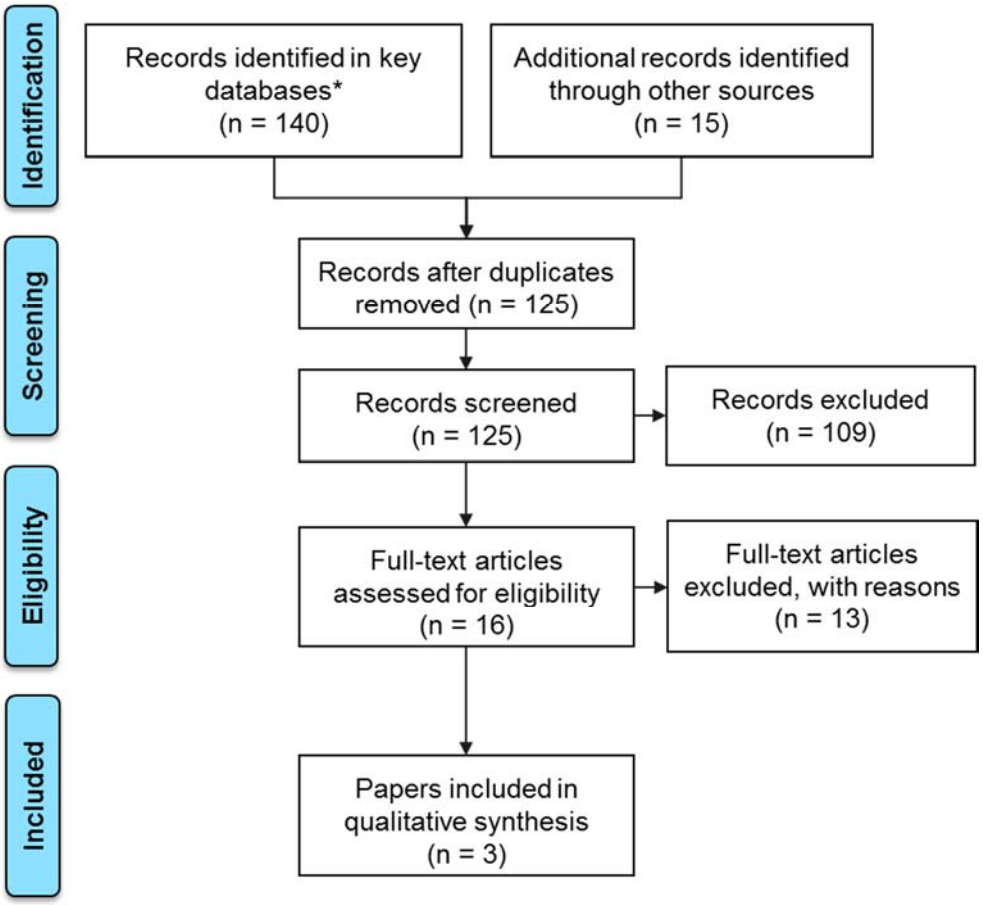
Source: PROSPER SLR report[31]
The search was conducted on the 10th of July 2018.

H1.2 Results utility weights

The SLR identified 155 references of which 125 were unique (Figure 39). Overall, 114 corresponded to unique full articles or abstracts retrieved from searches in the key databases (PubMed, Cochrane, Medline and Medline in Process, and Embase) and 11 from searches in other sources (CEA and manual searches).

After the initial screening of titles and abstracts, 16 references were considered as potentially relevant. Following detailed examination of the full article, only three publications were included for abstraction. Two of these publications were available only as congresses presentations[98, 99]. The third one (PROSPER HEOR 2018) corresponds to Astellas data on file[40].

Figure 39 PRISMA flow diagram with the utility studies identified through the predefined search strategy



Source: PROSPER SLR report[31]
*Key databases included Pubmed (n=87), Cochrane (n=7), Medline, Medline in Process and Embase (n=46).

An overview of the three studies identified by the SLR is provided in Table 84. Two of these studies were cross-sectional surveys[98, 99] while the third one was a RCT[40]. The study population and methods to derive health utilities clearly differed across studies.

Dawson et al included US nmHRPC patients as well as mHRPC patients that had not yet initiated chemotherapy, were on chemotherapy or had already completed chemotherapy[98]. The authors do not provided details regarding PSADT of these patients. Hechmati et al included high risk nmHRPC patients and mHRPC patients from the EU5[99]. The authors defined high risk as patients with the most recent PSA being ≥8 ng/mL, PSADT ≤10 months, Gleason score ≥ 8 and having received local therapy in addition to systemic medication. Finally, the third study is PROSPER which included high risk nmHRPC patients from different geographic regions including Europe and North America[40].

Regarding the method to derive utility weights, both Hechmati et al and PROSPER used EQ-5D[40, 99]. Hechmati et al do not specify which version was used while in PROSPER, the 5L was administered[99]. In Dawson et al, the authors used a trade-off method to derive utility weights[98].

Table 84 Overview of selected studies providing health utilities

	Study type	Patient population	Nationality	Utility derivation method
Dawson et al (2018)[98]	Cross-sectional, vignette-based, online time trade-off web-based survey study	nmHRPC Chemo-naïve mHRPC During and post-chemo mHRPC	USA	Trade-off
Hechmati et al (2012)[99]	Cross-sectional survey	High risk nmHRPC mHRPC	EU5	EQ-5D (no further specified)
PROSPER HEOR 2018[40]	RCT (PROSPER)	High risk nmHRPC	North America (14.6%) Europe (49.3%), RoW (36.2%)	EQ-5D-5L

Source: PROSPER SLR report[31]
Abbreviations: HEOR: health economics and outcomes research; mHRPC: metastatic hormone-relapsed prostate cancer; nmHRPC: non-metastatic hormone-relapsed prostate cancer; RoW: rest of world

An overview of the utilities reported for nmHRPC patients is provided in Table 85.

The utility weights reported for nmHRPC patients ranged from 0.77 in Hechmati et al and [redacted] in PROSPER[40, 99]. Hechmati et al and Dawson et al also provided health utilities for mHRPC patients. In both studies these utility weights were significantly lower than for nmHRPC patients. Differences are also observed for the utility weights reported for mHRPC patients. Dawson et al provide utility weights for chemo-naïve (0.74 ± 0.43) and post-chemo (0.64 ± 0.47) mHRPC patients separately[98] while Hechmati et al provides utilities for a population of HRPC patients with bone metastases (0.59 ± 0.30) and do not specify the treatment history for mHRPC.

Table 85 Utility weights reported in nmHRPC studies

Reference	Condition	Utility weight
Dawson 2018[98]	nmHRPC	0.80 ± 0.36
	Chemo-naïve mHRPC	0.74 ± 0.43
	During or post-chemo mHRPC	0.64 ± 0.47 (p<0.01 vs nmHRPC)
Hechmati 2012[99]	nmHRPC at high risk of metastases (n=36)	0.77 ± 0.22
	mHRPC (n=165)	0.59 ± 0.30 (p=0.0001 vs nmHRPC)
PROSPER HEOR 2018[40]	High risk nmHRPC (baseline in PLA arm)	[redacted]
	High risk nmHRPC (baseline in ENZA arm)	[redacted]

Source: PROSPER SLR report[31]
Abbreviations: ENZA: enzalutamide; HEOR: health economics and outcomes research; mHRPC: metastatic hormone-relapsed prostate cancer; nmHRPC: non-metastatic hormone-relapsed prostate cancer; PLA: placebo.

Although both Hechmati et al and PROSPER included high risk nmHRPC patients, the utility weights were higher (i.e., better health state)[40, 99] in PROSPER. Health utilities in PROSPER were also higher than in Dawson et al. Different factors may account for these differences including:

- Method to derive utility weights: trade-off in Dawson et al vs EQ-5D in Hechmati et al and PROSPER
- Nationality of patients: US in Dawson et al vs EU5 in Hechmati et al and different geographic regions in PROSPER.

It is unclear whether there are also differences in the study population across studies. While all nmHRPC patients in Hechmati et al and PROSPER were at high risk of developing metastases as defined by PSADT ≤10 months, Dawson et al do not mention whether nmHRPC patients were at high risk of metastases or not.

Both Hechmati et al and Dawson et al also provide utility weights for mHRPC patients[98]. The health utility values reported for these patients are statistically significantly lower than for nmHRPC patients in both studies. The utility weights reported in Dawson et al and Hechmati et al for mHRPC patients are also lower than those reported for these patients in previous enzalutamide trials[40, 98, 99]. In PREVAIL, a RCT phase III trial comparing the efficacy and safety of enzalutamide to placebo in chemotherapy-naive asymptomatic or mildly symptomatic mHRPC patients, the baseline utility wright was 0.844 [95% CI: 0.836-0.852] vs 0.74±0.43 reported in Dawson et al[84].

The baseline utility value in AFFIRM, a RCT phase III trial comparing the efficacy and safety of enzalutamide to placebo in mHRPC patients that had progressed during or after chemotherapy was 0.688 using the actual EQ-5D (N = 209, SE = 0.028), and 0.702 using the mapped values (N = 1,008, SE = 0.0065)[53]. Dawson et al report a utility value of 0.64±0.47 for a similar population.

The findings reported here suggest that patients report better health states in clinical trials than in clinical practice.

Appendix I: Cost and healthcare resource identification, measurement and valuation

Cost and healthcare resource identification was also included in the cost-effectiveness SLR and is discussed in appendix G.

Appendix J: Clinical outcomes and disaggregated results from the model

J1.1 Clinical outcomes from the model

The clinical outcomes from the model are shown in Table 86. Where comparison was possible, the outcomes in the model closely resembled the clinical outcomes from PROSPER. For survival, the model even seems to slightly underestimate the OS for patients on enzalutamide.

Table 86 Clinical outcomes from PROSPER including the corresponding model results

Outcome	Clinical trial result	Model result
Median metastasis-free survival	ENZA: 36.6 months ADT 14.7 months	ENZA: [redacted] months ADT: [redacted] months
OS probability of being event free at 1, 2, 3 years	ENZA: 1 year: 98% 2 years: 91% 3 years: 77% ADT: 1 year: 97% 2 years: 87% 3 years: 71%	ENZA: 1 year: 97% 2 years: 89% 3 years: 77% ADT: 1 year: 97% 2 years: 87% 3 years: 69%
Time to prostate-specific antigen progression	See section B.2.6.1.2.1	Not used in model
Adverse effects of treatment	See section B.2.10	PROSPER data directly used in model
Health-related quality of life	See section B.2.6.1.3.4	PROSPER data directly used in model

Abbreviations: ADT: androgen deprivation therapy; ENZA: enzalutamide; OS: overall survival;

J1.2 Disaggregated results of the base-case incremental cost-effectiveness analysis

The QALY gain and costs disaggregated by health state is shown in Table 87 and Table 88. The predicted resource use by category of cost is shown in Table 89. The 'health state' category included all monitoring and administration costs and other direct medical costs not included by any of the other categories.

Table 87 Summary of QALY gain by health state

Health state	QALY ENZA	QALY ADT	Increment	Absolute increment	% absolute increment
nmHRPC	[redacted]	[redacted]	[redacted]	[redacted]	54%
PD1	[redacted]	[redacted]	[redacted]	[redacted]	35%

PD2	[redacted]	[redacted]	[redacted]	[redacted]	6%
PD3	[redacted]	[redacted]	[redacted]	[redacted]	5%
End of life disutility	[redacted]	[redacted]	[redacted]	[redacted]	0%
Total	[redacted]	[redacted]	[redacted]	[redacted]	100%

Abbreviations: ADT: androgen deprivation therapy; ENZA: enzalutamide; nmHRPC: non-metastatic hormone-relapsed prostate cancer; PD: progressed disease; QALY, quality-adjusted life year.

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 88 Summary of costs by health state

Health state	Cost ENZA	Cost ADT	Increment	Absolute increment	% absolute increment
nmHRPC	[redacted]	[redacted]	[redacted]	[redacted]	61%
PD1	[redacted]	[redacted]	[redacted]	[redacted]	34%
PD2	[redacted]	[redacted]	[redacted]	[redacted]	3%
PD3	[redacted]	[redacted]	[redacted]	[redacted]	2%
Terminal care	[redacted]	[redacted]	[redacted]	[redacted]	0%
Total	[redacted]	[redacted]	[redacted]	[redacted]	100%

Abbreviations: ADT: androgen deprivation therapy; ENZA: enzalutamide; nmHRPC: non-metastatic hormone-relapsed prostate cancer; PD: progressed disease.

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 89 Summary of predicted resource use by category of cost

Category of costs	Cost ENZA	Cost ADT	Increment	Absolute increment	% absolute increment
Active tx costs	[redacted]	[redacted]	[redacted]	[redacted]	90%
Health state costs	[redacted]	[redacted]	[redacted]	[redacted]	8%
Conmed costs	[redacted]	[redacted]	[redacted]	[redacted]	1%
AE and SRE costs	[redacted]	[redacted]	[redacted]	[redacted]	0%
Terminal care costs	[redacted]	[redacted]	[redacted]	[redacted]	0%
Total	[redacted]	[redacted]	[redacted]	[redacted]	100%

Abbreviations: ADT: androgen deprivation therapy; conmed: concomitant medication; ENZA: enzalutamide; tx: treatment

Appendix K: Checklist of confidential information

Appendix L: Additional scenario analyses

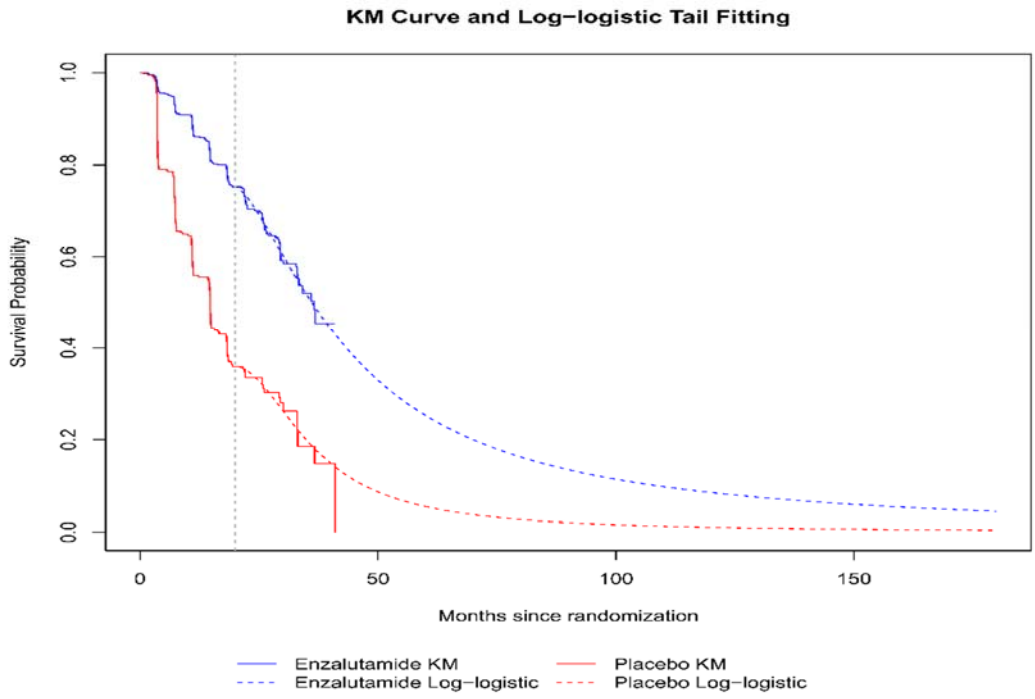
In addition to the base case analysis, one-way and probabilistic sensitivity analyses, scenario analyses have been conducted to test some of the main structural uncertainty and key assumptions of the model. In this appendix, the rationale, key input parameters, and results are presented for each scenario presented in section B.3.8.3. Scenarios 1 and 2 have been included in section B.3.8.3.

L1.1 Rationale and input

Scenario 3: MFS piecewise survival model (instead of 'spline' model)

As discussed in section B.3.3.1, more advanced survival models were applied for the MFS extrapolations, because the standard parametric models did not provide a good fit. The two most commonly applied advanced survival models in the context of HTA are spline and piecewise models[51]. However, there currently does not seem to be a consensus on which of the two models would be the preferred alternative. Therefore, the structural uncertainty around the MFS survival modelling by using the best fitting piecewise model instead of the spline model was explored. Of all the piecewise models, the log-logistic model showed the best fit to the PROSPER MFS data (Figure 40). In this scenario the model uses the first piece directly from the PROSPER MFS KM data, then the parametric model from 20 months onwards (log-logistic; individually fitted curves).

Figure 40 PROSPER MFS extrapolation with log-logistic piecewise fitting



Source: PROSPER extrapolation report[46]
Abbreviations: KM: Kaplan Meier; MFS: metastasis-free survival.

Scenario 4: No PCa mortality in nmHRPC

In the base case, extrapolated PROSPER PrePS (Weibull) was used to inform mortality in nmHRPC (before metastases have occurred). However, PROSPER OS and PrePS data is very immature. However, one might argue that there is no compelling reason to assume that patients would die from prostate cancer-related causes as long as the cancer is confined to the prostate. Indeed, the PROSPER PrePS closely resembles the expected survival based on age-matched general population mortality (*** [redacted] 41). However in the extrapolated PrePS data the trajectories of the PrePS extrapolations and age-matched general UK population mortality do diverge (*** [redacted] 42). In this scenario, it is assumed that patients would not die from PCa-related causes in the nmHRPC health state (i.e. assuming 'background mortality' only for both arms of the model), testing the structural uncertainty of relying on PROSPER PrePS extrapolations. In contrast to the base-case, PrePS will therefore be the same for ADT and enzalutamide in this scenario.

[redacted] 41

[redacted]

Source: PROSPER extrapolation report[46]
Abbreviations: ADT: androgen-deprivation therapy KM: Kaplan Meier; nmHRPC: non-metastatic hormone-relapsed prostate cancer PrePS: pre-progression survival

[redacted] 42 [redacted]

Source: edited from PROSPER extrapolation report[46]
Abbreviations: ADT: androgen-deprivation therapy KM: Kaplan Meier; nmHRPC: non-metastatic hormone-relapsed prostate cancer PrePS: pre-progression survival

Scenario 5: PREVAIL OS as PPS reference curve

This scenario explores the structural uncertainty around PPS. Due to the immaturity of the PROSPER OS (i.e. PPS) data, this scenario looks to leverages PREVAIL as a much more mature external data source to inform PPS in the model. Patients in PREVAIL at baseline are in many ways very similar to patients who have just progressed in the PROSPER placebo arm. In fact, looking at the PROSPER placebo arm PPS in comparison to the PREVAIL enzalutamide arm OS does confirm the similarity in terms on life expectancy (*** [redacted] 43). This scenario explores the impact of using the more mature, extrapolated PREVAIL (enzalutamide arm) OS data (Weibull) as a reference curve for PPS in the model[62]. The enzalutamide effects are applied using the PPS HR observed in PROSPER (HR= [redacted]).

[redacted]43

Source: PROSPER extrapolation report[46]
Abbreviations: ENZ: enzalutamide; OS: overall survival; PPS: post-progression survival.

Scenario 6: PROSPER PPS log-logistic

Similar to scenario 3 above, this scenario explores an alternative input for PPS. As discussed in Sections B.3.2.2, PREVAIL was used to guide the extrapolation of PROSPER PPS KM data. An alternative external reference data source is COU-AA-302, a phase III clinical trial of abiraterone in chemotherapy naïve patients with mHRPC. The patient population in COU-AA-302 was very similar to patients in PREVAIL and thus, very similar to patients in the PROSPER placebo arm who just progressed to mHRPC (notably, abiraterone was the most frequent post-baseline antineoplastic treatment observed in 27,7% of PROSPER patients in the placebo arm)[2]. Therefore, this separate PPS scenario analysis is included using the PROSPER PPS data extrapolated with the log-logistic curve (instead of Weibull, ***[redacted]44), which provides a near perfect fit to the COU-AA-302 abiraterone arm OS data (***[redacted]45).

[redacted] 44

Source: PROSPER extrapolation report[46]
Abbreviations: KM: Kaplan Meier; PPS: post-progression survival.

[redacted] 45

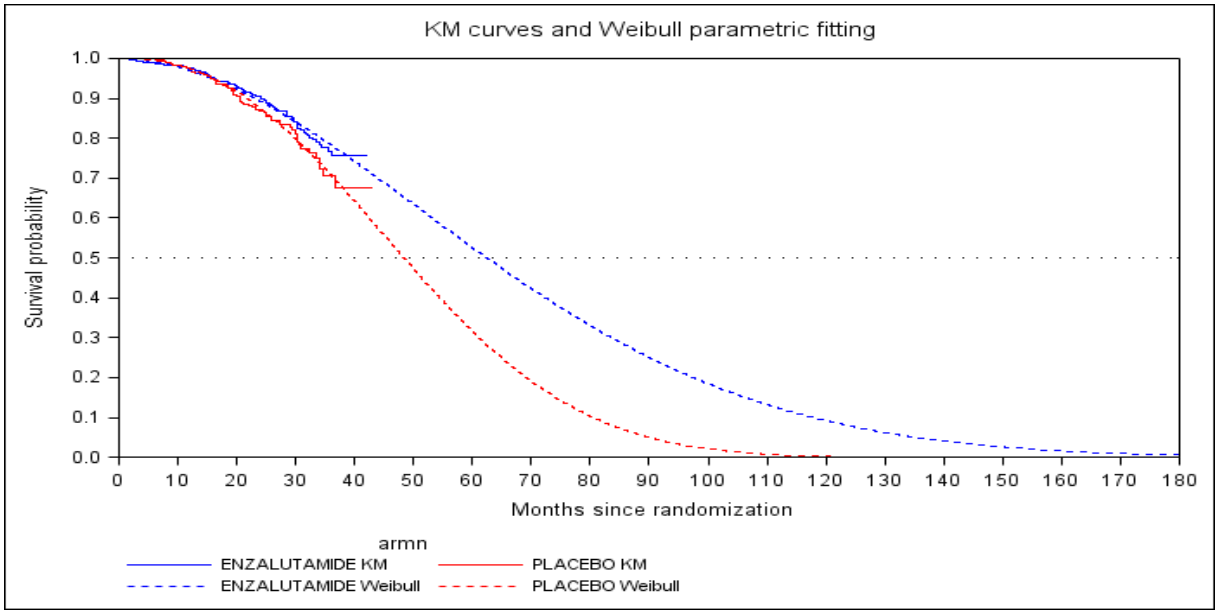
Source: PROSPER extrapolation report[46]
Abbreviations: ABI: abiraterone; ENZ: enzalutamide; KM: Kaplan Meier; OS: overall survival; PPS: post-progression survival; PLA: placebo.

Scenario 7: Single OS curve

In this report it was established that applying a single survival curve over all four health states of the model lacks face validity. However, using a single OS curve is a common approach in oncology models. To test the structural uncertainty related to assuming two

separate survival curves, this scenario explores the impact of modelling survival based on a single survival curve applied to all health states (i.e. from nmHRPC to PD3), using extrapolated PROSPER OS data. As outlined in the extrapolation report, Weibull was selected as the best fit for the OS data (Figure 46).

Figure 46 PROSPER OS extrapolation with Weibull parametric fitting



Source: PROSPER extrapolation report[46]
Abbreviations: KM: Kaplan Meier; OS: overall survival.

Scenario 8: PROSPER EQ-5D-5L 'England value set'

HRQoL in PROSPER was captured using EQ-5D-5L. However, the utility values for the model were derived using a mapping algorithm to approximate EQ-5D-3L utility values, using the 'cross-walk' method[94]. As described in section B.3.4.1, using the England value set would potentially better reflect the low symptom burden and overall good HRQoL of high-risk nmHRPC patients. This scenario explores the impact of using the 'England value set' instead of 'mapped' utility values. This scenario will assume a utility value of [redacted] for nmHRPC and [redacted] for PD1, based on the English tariff for the EQ-5D-5L (Table 44)

Scenario 9: Earlier chemotherapy after enzalutamide in nmHRPC

In the current base-case, it is assumed that patients in the enzalutamide arm have a treatment gap in which they only receive ADT after progressing to PD1. This is supported by the PROSPER data, where a median TTD ([redacted] months) was shorter than median time to first antineoplastic therapy ([redacted] months) or the 25% percentile for time to first chemo ([redacted] months, median not reached). This scenario analyses the impact of moving chemotherapy (docetaxel) treatment earlier in the treatment pathway for patients who received enzalutamide in nmHRPC. In this scenario patients in the enzalutamide arm are assumed to receive chemotherapy directly after progression, assuming no treatment break as observed in PROSPER (Table 90). The treatment sequencing in the ADT arm of the model remains unchanged (i.e. enzalutamide in PD1, 40% docetaxel 60% BSC in PD2, and BSC in PD3).

Table 90 Overview of treatment sequence used for scenario 9

Health states	Enzalutamide arm (A)	ADT arm (B)
nmHRPC	Enzalutamide	ADT
PD1	ADT alone (60%) Docetaxel (40%)	Enzalutamide
PD2	ADT alone	ADT alone (60%) Docetaxel (40%)
PD3	Best supportive care	Best supportive care

Abbreviations: ADT: androgen deprivation therapy; nmHRPC: non-metastatic hormone-resistant prostate cancer; PD: progressed disease.

Scenario 10: No patients opt-out of chemo

Similar to scenario 8, this scenario explores the uncertainty around how chemotherapy is included in the model. It is currently assumed 60% of patients opt-out of chemo, based on the fact that some patients may prefer not to receive chemotherapy despite being eligible[16]. This scenario analyses the impact of assuming all patients would receive chemotherapy in PD2 (Table 91). The treatment sequencing in the ADT arm of the model remains unchanged (i.e. enzalutamide or ADT alone in PD1, and BSC in PD3).

Table 91 Overview of treatment sequence used for scenario 10

Health states	Enzalutamide arm (A)	ADT arm (B)
nmHRPC	Enzalutamide	ADT
PD1	ADT alone	Enzalutamide
PD2	Docetaxel (100%)	Docetaxel (100%)
PD3	Best supportive care	Best supportive care

Abbreviations: ADT: androgen deprivation therapy; nmHRPC: non-metastatic hormone-resistant prostate cancer; PD: progressed disease.

Scenario 11: PROSPER enzalutamide treatment modifications

The model assumes that all patients remain on their initial treatment until progression (i.e. patients in the enzalutamide and ADT arm of the model receive enzalutamide and ADT, respectively, until they progress to PD1). Additionally, it is assumed that all patients receive the full daily dose for the entire treatment period. However, some patients and their physicians may choose to temporarily interrupt treatments e.g. to manage AEs. This scenario explores the impact of incorporating enzalutamide treatment modifications as observed in PROSPER. Based on the mean cumulative exposure dose and mean treatment duration, it was estimated that, based on the calculated daily dose, these treatment modifications account for an average [redacted]% less enzalutamide use than what would be expected (Table 92)[2]. As there would not be any wastage of the capsules not taken, this scenario accounts for the [redacted]% less enzalutamide use in the calculations of the treatment acquisition costs, while all other assumptions remain unchanged.

Table 92 Mean treatment duration and total cumulative dose in PROSPER

	Enzalutamide (n=930)	Placebo (n=465)
Mean treatment duration (months)[a]	18.8	13.2
Mean total cumulative dose (mg)[b]	[redacted]	[redacted]

Source: PROSPER Clinical study report[2]
a. Treatment duration was calculated as (last dose date of study drug minus first dose date of study drug + 1)/30.4375.
b. Total cumulative dose was calculated as number of capsules taken × 40 mg
abbreviations: n: number of patients

Scenario 12: Abiraterone in PD1 (ADT arm)

The model assumes that all patients in the ADT arm receive enzalutamide in PD1. In reality, patients progressing to mHRPC in the UK might be eligible for abiraterone as well. This scenario explores the structural uncertainty around the choice of PD1 treatment in the ADT arm, assuming all patients receive abiraterone instead of enzalutamide.

The input for the model was primarily based on COU-AA-302[75] data. Duration in the health states was again based on TTD from the enzalutamide pre-chemo model[62]. Daily treatment costs were based on the list price of £2,735.00 per pack[9], on which the same PAS as enzalutamide was applied. AE frequencies were also based on COU-AA-302[75], as shown in Table 93. The average costs and probability of an AE with abiraterone per model cycle (1 month) were calculated at £294.27 and 0.00931 respectively. Health resource utilisation was the same as enzalutamide (Table 49) with a couple of exceptions; outpatient visit urologist and oncologist, liver function test, and kidney function test were performed once every 4 weeks instead of 8.

Table 93 AE rates and costs for abiraterone

AEs	ABI	PLA	Costs	Source
Patient years	707.5	495	-	-
Arthralgia	11	11	£181.08	Costs assumed to be equal to pain: NHS reference costs 2015-2016; NCL: WF02B; service code: 191 (pain management, multi-professional non-admitted non-face to face attendance, first)
Dyspnoea	13	5	£0.00	NICE ERG report abiraterone (post-chemo)[106], table 24, p. 64. IQR assumed ±25%
Fatigue	13	10	£12.00	NICE ERG report abiraterone (post-chemo)[106], table 24, p. 64. IQR assumed ±25%
Hypertension	23	17	£401.79	NHS reference costs 2015-2016[105]; NES: EB04Z
Hypokalaemia	14	10	£520.61	NHS reference costs 2015-2016[105]; HCD: XD26Z (outpatients; intravenous nutrition, band 1)
Oedema Peripheral/Fluid retention	5	9	£914.00	NICE ERG report abiraterone (post-chemo)[106], table 24, p. 64

Abbreviations: ABI: abiraterone; AE: adverse events; ERG: evidence review group; NEL: non-elective long stay; NES: non-elective short stay; NHS: National Health Service; PLA: placebo.

L1.2 Outcomes

Scenario 3: MFS piecewise survival model (instead of 'spline')

Median MFS outcomes closely resembled the PROSPER results. However, due to the 'tail' commonly seen with log-logistic curves, mean MFS outcomes were higher with the piecewise model compared to spline at [redacted] vs. [redacted] months for enzalutamide and [redacted] vs. [redacted] for ADT. Mean OS had increased by [redacted] months in the enzalutamide arm of the model and decreased by [redacted] months in the ADT arm. Due to these changes, the ICER has dropped slightly from £28,853/QALY in the base case to £27.768/QALY in this scenario (Table 94).

Table 94 Scenario 3 outcomes: MFS piecewise survival model (instead of 'spline')

Outcome	Enzalutamide	ADT
Technology acquisition cost (first line)*	[redacted]	[redacted]
Subsequent lines treatment costs	[redacted]	[redacted]
Other costs	[redacted]	[redacted]
Total costs	[redacted]	[redacted]
Incremental costs	[redacted]	
LYG	[redacted]	[redacted]
Incremental LYG	[redacted]	
QALYs	[redacted]	[redacted]
QALYs gained	[redacted]	
ICER (change from base case)	£27,852 (-£1,001)	

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

Scenario 4: No PCa mortality in nmHRPC

In comparison with the base case, mean OS was [redacted] and [redacted] months longer for enzalutamide and ADT, respectively. However, the ICER only changed minimally from £28,853/QALY in the base case to £28,859/QALY in this scenario (Table 95).

Table 95 Scenario 4 outcomes: No PCa mortality in nmHRPC

Outcome	Enzalutamide	ADT
Technology acquisition cost (first line)*	[redacted]	[redacted]
Subsequent lines treatment costs	[redacted]	[redacted]
Other costs	[redacted]	[redacted]
Total costs	[redacted]	[redacted]
Incremental costs	[redacted]	
LYG	[redacted]	[redacted]
Incremental LYG	[redacted]	
QALYs	[redacted]	[redacted]
QALYs gained	[redacted]	

Outcome	Enzalutamide	ADT
ICER (change from base case)	£28,859 (+£6)	

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

Scenario 5: PREVAIL OS as PPS reference curve

In this scenario, the median and mean MFS outcomes remained unchanged compared to the base case. However, mean OS increased by [redacted] months for enzalutamide and by [redacted] months for ADT. This was combined with a comparable increase in costs in both the enzalutamide and the ADT arm, which resulted in an ICER decrease from £28,853/QALY in the base case to £26.237/QALY in this scenario (Table 96).

Table 96 Scenario 5 outcomes: PREVAIL OS as PPS reference curve

Outcome	Enzalutamide	ADT
Technology acquisition cost (first line)*	[redacted]	[redacted]
Subsequent lines treatment costs	[redacted]	[redacted]
Other costs	[redacted]	[redacted]
Total costs	[redacted]	[redacted]
Incremental costs	[redacted]	
LYG	[redacted]	[redacted]
Incremental LYG	[redacted]	
QALYs	[redacted]	[redacted]
QALYs gained	[redacted]	
ICER (change from base case)	£26,237 (-£2,616)	

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

Scenario 6: PROSPER PPS log-logistic

Using the PROSPER PPS log-logistic extrapolations instead of the Weibull distribution results in [redacted] and [redacted] months longer mean OS for the enzalutamide arm and ADT arm of the model, respectively. Although, the costs also raised more in the ADT arm from £[redacted] to £[redacted] compared to [redacted] and £[redacted] in the enzalutamide arm, this still led to a higher ICER of £30,394 (Table 97).

Table 97 Scenario 6 outcomes: PROSPER PPS log-logistic

Outcome	Enzalutamide	ADT
Technology acquisition cost (first line)*	[redacted]	[redacted]
Subsequent lines treatment costs	[redacted]	[redacted]
Other costs	[redacted]	[redacted]
Total costs	[redacted]	[redacted]
Incremental costs	[redacted]	
LYG	[redacted]	[redacted]

Outcome	Enzalutamide	ADT
Incremental LYG	[redacted]	
QALYs	[redacted]	[redacted]
QALYs gained	[redacted]	
ICER (change from base case)	£30,394 (+£1,541)	

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

Scenario 7: Single OS curve

In comparison with the base case, mean OS increases by [redacted] and drops by [redacted] months for enzalutamide and ADT, respectively. Again, MFS is not affected by this scenario and remains near identical to the base case and costs only change slightly. As a consequence, the ICER drops from £28,853/QALY in the base case to £26,829/QALY in this scenario (Table 98).

Table 98 Scenario 7 outcomes: Single OS curve

Outcome	Enzalutamide	ADT
Technology acquisition cost (first line)*	[redacted]	[redacted]
Subsequent lines treatment costs	[redacted]	[redacted]
Other costs	[redacted]	[redacted]
Total costs	[redacted]	[redacted]
Incremental costs	[redacted]	
LYG	[redacted]	[redacted]
Incremental LYG	[redacted]	
QALYs	[redacted]	[redacted]
QALYs gained	[redacted]	
ICER (change from base case)	£26,829 (-£2,024)	

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

Scenario 8: PROSPER EQ-5D-5L 'England value set'

In this scenario, neither MFS, nor OS, nor costs change. However, due to the higher health state utility values in this scenario, the overall (discounted) QALY increase from [redacted] to [redacted] in the enzalutamide arm of the model and from [redacted] to [redacted] in the ADT arm of the model. Therefore, the ICER has drops marginally from £28,853/QALY in the base case to £28.045/QALY in this scenario.

Table 99 Scenario 8 outcomes: PROSPER EQ-5D-5L 'England value set'

Outcome	Enzalutamide	ADT
Technology acquisition cost (first line)*	[redacted]	[redacted]
Subsequent lines treatment costs	[redacted]	[redacted]
Other costs	[redacted]	[redacted]

Outcome	Enzalutamide	ADT
Total costs	[redacted]	[redacted]
Incremental costs	[redacted]	
LYG	[redacted]	[redacted]
Incremental LYG	[redacted]	
QALYs	[redacted]	[redacted]
QALYs gained	[redacted]	
ICER (change from base case)	£28,138 (-£715)	

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

Scenario 9: Earlier chemotherapy after enzalutamide in nmHRPC

In this scenario, the clinical outcomes remain identical compared to the base case. However, total treatment costs for enzalutamide change from [redacted] in the base case to [redacted] in this scenario, while ADT treatment cost remain unchanged at [redacted]. As a consequence, the ICER increases from £28,853/QALY in the base case to £30.861/QALY in this scenario (Table 100).

Table 100 Scenario 9 outcomes: Earlier chemotherapy after enzalutamide in nmHRPC

Outcome	Enzalutamide	ADT
Technology acquisition cost (first line)*	[redacted]	[redacted]
Subsequent lines treatment costs	[redacted]	[redacted]
Other costs	[redacted]	[redacted]
Total costs	[redacted]	[redacted]
Incremental costs	[redacted]	[redacted]
LYG	[redacted]	[redacted]
Incremental LYG	[redacted]	
QALYs	[redacted]	[redacted]
QALYs gained	[redacted]	
ICER (change from base case)	£30,937 (+£2084)	

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

Scenario 10: No patient opts out-of chemotherapy

In this scenario, the clinical outcomes again remain identical compared to the base case. However, total treatment costs for enzalutamide change more than those in the ADT group due to patients spending a longer time in PD2 (from [redacted] to [redacted] compared to [redacted] to [redacted]). Consequently, the ICER increases from £28,853/QALY in the base case to £29,794/QALY in this scenario (Table 101).

Table 101 Scenario 10 outcomes: no patient opt out of chemo

Outcome	Enzalutamide	ADT
Technology acquisition cost (first line)*	[redacted]	[redacted]

Outcome	Enzalutamide	ADT
Subsequent lines treatment costs	[redacted]	[redacted]
Other costs	[redacted]	[redacted]
Total costs	[redacted]	[redacted]
Incremental costs	[redacted]	
LYG	[redacted]	[redacted]
Incremental LYG	[redacted]	
QALYs	[redacted]	[redacted]
QALYs gained	[redacted]	
ICER (change from base case)	£29,794 (-£941)	

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

Scenario 11: PROSPER treatment modifications

The clinical outcomes, as well as QALY, remain identical compared to the base case in both arms of the model. However, the overall drug acquisition costs for enzalutamide drop from [redacted] in the base case to [redacted] in this scenario. The ICER drops markedly from £28,853/QALY in the base case to £24.616/QALY in this scenario (Table 102).

Table 102 Scenario 11 outcomes: PROSPER treatment modifications

Outcome	Enzalutamide	ADT
Technology acquisition cost (first line)*	[redacted]	[redacted]
Subsequent lines treatment costs	[redacted]	[redacted]
Other costs	[redacted]	[redacted]
Total costs	[redacted]	[redacted]
Incremental costs	[redacted]	
LYG	[redacted]	[redacted]
Incremental LYG	[redacted]	
QALYs	[redacted]	[redacted]
QALYs gained	[redacted]	
ICER (change from base case)	£24,712 (-£4,141)	

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

Scenario 12: Abiraterone in PD1 (ADT arm)

MFS and OS remain unchanged in this scenario. The total treatment discounted costs for ADT increase from [redacted] to [redacted], while the total discounted, accumulated QALY for ADT increase from [redacted] to [redacted]. The outcomes for the enzalutamide arm of the model remain unchanged. Therefore, the ICER drops from £28,853/QALY in the base case to £24,303/QALY in this scenario (Table 103).

Table 103 Scenario 12: Abiraterone in PD1 (ADT arm)

Outcome	Enzalutamide	ADT
Technology acquisition cost (first line)*	[redacted]	[redacted]
Subsequent lines treatment costs	[redacted]	[redacted]
Other costs	[redacted]	[redacted]
Total costs	[redacted]	[redacted]
Incremental costs	[redacted]	
LYG	[redacted]	[redacted]
Incremental LYG	[redacted]	
QALYs	[redacted]	[redacted]
QALYs gained	[redacted]	
ICER (change from base case)	£24,303 (-£4,550)	

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

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Single technology appraisal

Enzalutamide for treating non-metastatic hormone-relapsed prostate cancer [ID1359]

Dear Company,

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The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **11 October**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

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If you have any queries on the technical issues raised in this letter, please contact Adam Brooke, Technical Lead (Adam.Brooke@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (Jeremy.Powell@nice.org.uk).

Yours sincerely

Melinda Goodall
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Section A: Clarification on effectiveness data

A1. **PRIORITY QUESTION** Please state the reason for exclusion for each excluded study in the systematic literature review.

A2. **PRIORITY QUESTION**

i) Please reproduce Table 7 (baseline characteristic) for the [redacted] UK PROSPER study participants only.

ii) Please state the proportion of the [redacted] UK participants that were exposed to bicalutamide prior to study entry.

A3. **PRIORITY QUESTION** (Table 15). Please clarify if the drugs in table 15 are 2nd line only or all post progression lines of treatment. If the latter, could Table 15 be reproduced for each line of treatment, including the number treated with enzalutamide.

A4. **PRIORITY QUESTION:** Please supply the Kaplan–Meier metastasis-free survival data of Figure 22, and provide for each timepoint, the number of patients at risk, the number of events, and the number of censoring events sufficient to reconstruct the Kaplan–Meier curves for the enzalutamide and placebo arms (2 tables).

Timepoint	N at risk	N events	N Censoring events
T=0	N=???	0	0
T=???	N=???	N=???	N=???
Etc.	Etc.	Etc.	Etc.

A5. **PRIORITY QUESTION:** Please supply the Kaplan–Meier pre-progression survival data of Figure 24, and provide for each timepoint, the number of patients at risk, the number of events, and the number of censoring events sufficient to reconstruct the Kaplan–Meier curves for the enzalutamide and placebo arms (2 tables).

Timepoint	N at risk	N events	N Censoring events
T=0	N=???	0	0
T=???	N=???	N=???	N=???
Etc.	Etc.	Etc.	Etc.

A6. **PRIORITY QUESTION:** Please supply the Kaplan–Meier post progression survival data of Figure 25, and provide for each timepoint, the number of patients at risk, the number of events, and the number of censoring events sufficient to reconstruct the Kaplan–Meier curves for the enzalutamide and placebo arms (2 tables).

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Timepoint	N at risk	N events	N Censoring events
T=0	N=???	0	0
T=???	N=???	N=???	N=???
Etc.	Etc.	Etc.	Etc.

A7. Please explain the inclusion criteria violations in Table 7, e.g. baseline PSADT median range values >10 and serum PSA median range values <2.

Section B: Clarification on cost-effectiveness data

B1. (section B3.2.2) PRIORITY QUESTION The company describes its economic model as a semi-Markov model combined with a partitioned survival modelling approach. However, the company's use of pre and post-progression transition probabilities for death is not typical of partitioned survival models, which utilise a set of non-mutually exclusive survival curves to directly estimate the proportion of people alive and in various states of progression at any point in time. Please provide further detail on how your approach compares with a standard partitioned survival model.

B2. **PRIORITY QUESTION** The company's economic model assumes that following progression to metastasis on enzalutamide, all patients move to treatment on androgen deprivation therapy alone for a median duration of 7.3 months in "PD1" based on data from the PREVAIL trial (Table 43). However, the comparability of the progressed PROSPER population and the baseline PREVAIL population is not clear; the PROSPER population was considered high risk at baseline based on a PSA doubling time <10 months. Given the above, please:

i) Report the difference in time from radiographic progression (PD1), to initiation of further antineoplastic therapy in the PROSPER enzalutamide arm.
ii) Provide a scenario that utilises the above analysis to determine time in PD1 following progression on enzalutamide.
iii) Provide the distribution of first antineoplastic treatments following progression to metastasis on enzalutamide.

B3. PRIORITY QUESTION The company's model assumes that all patients in the placebo arm receive enzalutamide upon progression to "PD1". However, Table 15 of the company submission (Document B) does not report the number of patients that receive enzalutamide. Presumably, these patients are part of the [redacted] Given the above, please:

(i) Provide the actual distribution of first antineoplastic treatments received following progression to metastasis in the placebo arm of PROSPER.

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(ii) Comment on any difference in cost and overall survival that might be expected with the company's base case assumption (i.e. all patients move to enzalutamide) compared with the actual distribution of PD1 treatments received in PROSPER.

(iii) Explore a scenario where the actual distribution of first antineoplastic treatments received is used to estimate the treatment costs incurred in health state PD1 in the placebo arm of the model.

B4. **PRIORITY QUESTION** Please provide full details of how the utility value for the PD1 health state was derived, and comment on its applicability to the modelled PD1 treatments; was the PD1 health state utility estimate adjusted for baseline utility? And how would the range of treatments that patients received upon progression to PD1 in the PROSPER trial impact on health state utility compared with those treatments that are assumed for PD1 in the model (ADT or enzalutamide)?

B5. **PRIORITY QUESTION** Given that there was no significant difference in pre-progression survival in PROSPER, and patients would be expected to progress to metastasis before dying of prostate cancer related causes, please provide justification for applying a pre-progression survival benefit for enzalutamide over androgen deprivation therapy.

B6. **PRIORITY QUESTION** Table 11 in the company submission suggests that more of the events in the metastasis-free survival analysis were soft tissue progression rather than bone progression. Please comment further on the compatibility of this observation with the skeletal-related event rates that are applied to the progressed states in the model based on data from PREVAIL and COU-AA-301? Also, please provide further details on how these rates of skeletal-related events were derived.

B7. PRIORITY QUESTION Section B.3.8.3.1 provides a scenario analysis using overall survival data from the second interim analysis. However, time to treatment discontinuation is used as the point of progression instead of metastasis-free survival. Please provide a scenario analysis that uses metastasis-free survival data from interim analysis 1 as in the base case, with updated pre-progression survival/ post-progression survival extrapolations from interim analysis 2.

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Yours sincerely

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Section A: Clarification on effectiveness data

A1. **PRIORITY QUESTION** Please state the reason for exclusion for each excluded study in the systematic literature review.

The list of articles excluded and the reason for exclusion is provided in Appendix A. An overview of the reasons for exclusion is provided in Table 1.

Table 1 List of reasons for exclusion or each systematic literature review

Reason for exclusion	Number of publications
Non-relevant indication	96
No-relevant intervention and comparator	27
Non-relevant outcome	52
No results (only study design already described in other selected studies)	15
Data already included in a more recent publication	7

A2. **PRIORITY QUESTION**

i) Please reproduce Table 7 (baseline characteristic) for the 70 UK PROSPER study participants only.

The baseline characteristics of the UK PROSPER study participants are provided in Table 2. The baseline characteristics of the UK cohort are comparable to those of the overall PROSPER population with some differences observed in, for example:

- A higher proportion of subjects with white race
- A higher proportion of subjects between the ages of 65 and 75
- A higher proportion of subjects with a pain score 2 or higher in the enzalutamide arm
- A lower proportion of subjects with a pain score of 0-1 in the placebo arm.

Table 2 Demographic and baseline disease characteristics in PROSPER for the ITT population and the UK cohort

	ITT cohort		UK Cohort	
	Enzalutamide (n=933)	Placebo (n=468)	Enzalutamide (n=47)	Placebo (n=23)
Age (years)				
<65	121 (13.0%)	69 (14.7%)	[redacted]	[redacted]
65 to <75	368 (39.4%)	198 (42.3%)	[redacted]	[redacted]
≥75	444 (47.6%)	201 (42.9%)	[redacted]	[redacted]
Median (range)	74.0 (50.0, 95.0)	73.0 (53.0, 92.0)	[redacted]	[redacted]
Race				

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	ITT cohort		UK Cohort	
	Enzalutamide (n=933)	Placebo (n=468)	Enzalutamide (n=47)	Placebo (n=23)
American Indian or Alaskan Native	0 (0.0%)	0 (0.0%)	[redacted]	[redacted]
Asian	142 (15.2%)	88 (18.8%)	[redacted]	[redacted]
Black or African American	21 (2.3%)	10 (2.1%)	[redacted]	[redacted]
Native Hawaiian or Other Pacific Islander	3 (0.3%)	2 (0.4%)	[redacted]	[redacted]
White	671 (71.9%)	320 (68.4%)	[redacted]	[redacted]
Multiple	4 (0.4%)	4 (0.9%)	[redacted]	[redacted]
Other	15 (1.6%)	5 (1.1%)	[redacted]	[redacted]
Missing	77 (8.3%)	39 (8.3%)	[redacted]	[redacted]
Weight (kg)				
Mean (SD)	84.0 (15.87)	83.6 (16.21)	[redacted]	[redacted]
Median (min, max)	82.0 (43.1, 149.8)	82.0 (38.0, 167.0)	[redacted]	[redacted]
Missing	0	1	[redacted]	[redacted]
Baseline ECOG performance status				
0	747 (80.1%)	382 (81.6%)	[redacted]	[redacted]
1	185 (19.8%)	85 (18.2%)	[redacted]	[redacted]
>1	0 (0.0%)	0 (0.0%)	[redacted]	[redacted]
Missing	1 (0.1%)	1 (0.2%)	[redacted]	[redacted]
Disease status (by blinded independent central review)				
Non-metastatic	910 (97.5%)	454 (97.0%)	[redacted]	[redacted]
Metastatic	23 (2.5%)	14 (3.0%)	[redacted]	[redacted]
Baseline prior or concurrent use of BTA				
No (0)	828 (88.7%)	420 (89.7%)	[redacted]	[redacted]
Yes	105 (11.3%)	48 (10.3%)	[redacted]	[redacted]
1	103 (11.0%)	47 (10.0%)	[redacted]	[redacted]
2	2 (0.2%)	1 (0.2%)	[redacted]	[redacted]
PSADT category				
<6 months	715 (76.6%)	361 (77.1%)	[redacted]	[redacted]
≥6 months	217 (23.3%)	107 (22.9%)	[redacted]	[redacted]
Missing	1 (0.1%)	0 (0.0%)	[redacted]	[redacted]
Stratification				
PSADT <6 months and no baseline BTA	642 (68.8%)	327 (69.9%)	[redacted]	[redacted]
PSADT <6 months and baseline BTA	73 (7.8%)	34 (7.3%)	[redacted]	[redacted]
PSADT ≥6 months and no baseline BTA	185 (19.8%)	93 (19.9%)	[redacted]	[redacted]
PSADT ≥6 months and baseline BTA	32 (3.4%)	14 (3.0%)	[redacted]	[redacted]
Missing	1 (0.1%)	0 (0.0%)	[redacted]	[redacted]

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	ITT cohort		UK Cohort	
	Enzalutamide (n=933)	Placebo (n=468)	Enzalutamide (n=47)	Placebo (n=23)
PSADT (months)				
Mean (SD)	4.3 (2.8)	4.3 (3.9)	[redacted]	[redacted]
Median (range)	3.8 (0.4, 37.4)	3.6 (0.5, 71.8)	[redacted]	[redacted]
Missing	1 (0.1%)	0 (0.0%)	[redacted]	[redacted]
Serum PSA (ng/mL)				
Mean (SD)	22.2 (46.1)	22.1 (41.1)	[redacted]	[redacted]
Median (range)	11.1 (0.8, 1071.1)	10.2 (0.2, 467.5)	[redacted]	[redacted]
Missing	0 (0.0%)	1 (0.2%)	[redacted]	[redacted]
Pain score as assessed by BPI-SF Question 3				
0-1	639 (68.5%)	336 (71.8%)	[redacted]	[redacted]
2-3	106 (11.4%)	52 (11.1%)	[redacted]	[redacted]
>3	142 (15.2%)	51 (10.9%)	[redacted]	[redacted]
Missing	46 (4.9%)	29 (6.2%)	[redacted]	[redacted]

Abbreviations: BPI-SF: Brief Pain Inventory Short form; BTA: bone-targeting agent; ECOG: Eastern Cooperative Oncology Group; PSA: prostate specific antigen; PSADT: prostate specific antigen doubling time.

ii) Please state the proportion of the 70 UK participants that were exposed to bicalutamide prior to study entry.

The percentage of participants with prior exposure to bicalutamide in the UK PROSPER cohort was [redacted] and [redacted] for enzalutamide and placebo, respectively. In the overall population these percentages were [redacted] and [redacted], respectively.

A3. **PRIORITY QUESTION** (Table 15). Please clarify if the drugs in table 15 are 2nd line only or all post progression lines of treatment. If the latter, could Table 15 be reproduced for each line of treatment, including the number treated with enzalutamide.

Table 15 of Document B of the manufacturer submission lists all therapies PROSPER subjects received after study treatment discontinuation. This table includes all post-progression lines of treatment for which data are available.

An overview of the first therapy subjects received after disease progression is provided in Table 3. The study Case Report Form (CRF) captured all therapies subjects received but only the first antineoplastic therapy subjects received after study treatment discontinuation have been analysed. Subjects in the enzalutamide arm remained on study treatment longer than placebo, so it is not possible to make a direct comparison for the new therapies received after study treatment discontinuation in both arms. Overall, a limited number of

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subjects started new antineoplastic therapies. Median follow-up at first interim analysis (IA1) was 18.5 and 15.1 months for enzalutamide and placebo subjects, respectively. Not all subjects with disease progression who had received first antineoplastic therapy after progression had time to move to the next therapy line. The CRF was not designed to collect data on subsequent therapies, by line, in a systematic way. Data for subsequent lines are therefore incomplete and thus are not presented.

Regarding the first antineoplastic therapy after study treatment discontinuation, given the large number of regimens that subjects could have received as next therapy after progression, regimens have been pooled based on the key active drug. Overall, the regimens that were used as therapy after study treatment discontinuation included:

- Abiraterone with or without supportive therapy (e.g., ADT, corticosteroids, etc)
- Abiraterone plus enzalutamide with or without supportive therapy (e.g., ADT)
- Docetaxel with or without supportive therapy (e.g., ADT, corticosteroids, etc)
- Enzalutamide with or without supportive therapy (e.g., ADT, corticosteroids, etc)
- Chemotherapy (other than docetaxel) or any targeted therapy with or without supportive therapy (e.g., ADT, corticosteroids, etc)
- Other (Sipuleucel-T) with or without supportive therapy (e.g., ADT, corticosteroids, etc)
- None of the therapies listed above (i.e., only supportive therapy which included ADT).

In Table 3, data are provided for subjects receiving the different regimens regardless of which supportive therapy they received as part of the next therapy after study treatment discontinuation. Overall, 139 subjects in the PROSPER enzalutamide arm and 222 subjects in the PROSPER placebo arm received an antineoplastic therapy after treatment discontinuation.

Table 3 First therapy regimen subjects received after study treatment discontinuation (IA1; ITT)

	Enzalutamide	Placebo
	N (%)	N (%)
Subjects who discontinued treatment	296/933 (31.7%)	289/468 (61.8%)
Subjects who started any new anti-neoplastic treatment after treatment discontinuation	139/933 (14.9%)	222/468 (47.7%)
First regimen after study treatment discontinuation		
ABI ± BSC	[redacted]	[redacted]
ABI + DOC ± BSC	[redacted]	[redacted]
ABI + ENZA ± BSC	[redacted]	[redacted]
DOC ± BSC	[redacted]	[redacted]
ENZA ± BSC	[redacted]	[redacted]
Other chemotherapy* ± BSC	[redacted]	[redacted]
Other agents# ± BSC	[redacted]	[redacted]
Investigational drug ± BSC	[redacted]	[redacted]
None of the above (i.e., BSC)	[redacted]	[redacted]

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Abbreviations: ABI: abiraterone; BSC: best supportive care; DOC: docetaxel; ENZA: enzalutamide. *Includes any chemotherapy other than docetaxel as well as any targeted therapy. #It includes Sipuleucel-T and ubenimex.

A4. **PRIORITY QUESTION:** Please supply the Kaplan–Meier metastasis-free survival data of Figure 22, and provide for each timepoint, the number of patients at risk, the number of events, and the number of censoring events sufficient to reconstruct the Kaplan–Meier curves for the enzalutamide and placebo arms (2 tables).

The data for the timepoints shown in Figure 22 in Document B of the manufacturer submission is provided in Table 4.

Table 4 Full data for Figure 22 of Document B (Kaplan Meier metastasis-free survival)

Enzalutamide				Placebo			
Timepoint (month)	N at risk	N events	N Censoring events	Timepoint (month)	N at risk	N events	N Censoring events
0	***	*	*	0	***	*	*
4	***	**	***	4	***	**	**
8	***	**	***	8	***	***	***
12	***	***	***	12	***	***	***
16	***	***	***	16	***	***	***
20	***	***	***	20	**	***	***
24	***	***	***	24	**	***	***
28	***	***	***	28	**	***	***
32	**	***	***	32	**	***	***
36	**	***	***	36	*	***	***
40	*	***	***	40	*	***	***
44	*	***	***	44	*	***	***

A5. **PRIORITY QUESTION:** Please supply the Kaplan–Meier pre-progression survival data of Figure 24, and provide for each timepoint, the number of patients at risk, the number of events, and the number of censoring events sufficient to reconstruct the Kaplan–Meier curves for the enzalutamide and placebo arms (2 tables).

The data for the timepoints shown in Figure 24 in Document B of the manufacturer submission is provided in Table 5.

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Table 5 Full data for Figure 24 of Document B (Kaplan Meier pre-progression survival)

Enzalutamide				Placebo			
Timepoint (month)	N at risk	N events	N Censoring events	Timepoint (month)	N at risk	N events	N Censoring events
0	[redacted]	[redacted]	[redacted]	0	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	4	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	8	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	12	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	16	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	20	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	24	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	28	[redacted]	[redacted]	[redacted]
32	[redacted]	[redacted]	[redacted]	32	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	36	[redacted]	[redacted]	[redacted]
40	[redacted]	[redacted]	[redacted]	40	[redacted]	[redacted]	[redacted]
44	[redacted]	[redacted]	[redacted]	44	[redacted]	[redacted]	[redacted]

A6. **PRIORITY QUESTION:** Please supply the Kaplan–Meier post progression survival data of Figure 25, and provide for each timepoint, the number of subjects at risk, the number of events, and the number of censoring events sufficient to reconstruct the Kaplan–Meier curves for the enzalutamide and placebo arms (2 tables).

The data for the timepoints shown in Figure 25 in Document B of the manufacturer submission is provided in Table 6.

Table 6 Full data for Figure 25 of Document B (Kaplan Meier post-progression survival)

Enzalutamide				Placebo			
Timepoint (month)	N at risk	N events	N Censoring events	Timepoint (month)	N at risk	N events	N Censoring events
0	[redacted]	[redacted]	[redacted]	0	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	4	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	8	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	12	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	16	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	20	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	24	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	28	[redacted]	[redacted]	[redacted]

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Enzalutamide				Placebo			
Timepoint (month)	**N at risk**	**N events**	**N Censoring events**	**Timepoint (month)**	**N at risk**	**N events**	**N Censoring events**
32	[redacted]	[redacted]	[redacted]	32	[redacted]	[redacted]	[redacted]
-	[redacted]	[redacted]	[redacted]	36	[redacted]	[redacted]	[redacted]
-	[redacted]	[redacted]	[redacted]	40	[redacted]	[redacted]	[redacted]

A7. Please explain the inclusion criteria violations in Table 7, e.g. baseline PSADT median range values >10 and serum PSA median range values <2.

The list of all inclusion and exclusion criteria violations in PROSPER is provided in Table 7. Overall, [redacted] and [redacted] of subjects in the enzalutamide and placebo arms, respectively did not meet, or violated, at least one of the inclusion or exclusion criteria. The criteria violated by the highest proportion of subjects included [redacted]. Although all these criteria have an impact on the outcomes in terms of efficacy and/or safety, the overall proportion of subjects with any of these deviations was low and thus, no bias in the overall efficacy or safety was expected. None of these violations were considered major violations and therefore, these patients were not excluded from the intent to treat analysis. No *per protocol* analyses had been pre-specified in the study protocol.

Regarding the UK PROSPER cohort, no patient violated any of the key selection criteria. As observed in Table 2, all subjects had a baseline PSA level ≥2 ng/mL, a PSADT ≤10 months and no metastatic disease at baseline.

Table 7 Inclusion and exclusion criteria violations

Number of patients reporting at least 1	Enzalutamide (N = 933)	Placebo (N = 468)	Total (N = 1401)
Any Inclusion/Exclusion Criteria Deviations	[redacted]	[redacted]	[redacted]
Inclusion criteria			
Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation, signet cell, or small cell features	[redacted]	[redacted]	[redacted]
Testosterone ≤50 ng/dL (≤1.73 nmol/L) at screening	[redacted]	[redacted]	[redacted]
Progressive disease on androgen deprivation therapy at enrolment defined as a minimum of 3 rising PSA values (PSA1 <PSA2 <PSA3) assessed ≥1 week between each determination	[redacted]	[redacted]	[redacted]
The most recent local PSA and the screening PSA assessed by the central laboratory (central PSA)	[redacted]	[redacted]	[redacted]

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Number of patients reporting at least 1	Enzalutamide (N = 933)	Placebo (N = 468)	Total (N = 1401)
should be ≥2 mg/L (2 ng/mL). In the event of prior androgen receptor inhibitor use, the most recent local PSA and the central PSA assessed at screening must be obtained at least 4 weeks after the last dose of the androgen receptor inhibitor			
PSA doubling time ≤10 months calculated by the sponsor	[redacted]	[redacted]	[redacted]
No prior or present evidence of metastatic disease as assessed by CT/MRI for soft tissue disease and whole-body radionuclide bone scan for bone disease. If the screening one scan shows a lesion suggestive of metastatic disease, the patient will be eligible only if a second imaging modality (plain film, CT, or MRI) does not show bone metastasis. If the imaging results are equivocal or consistent with metastasis, the patient is not eligible for enrolment. Patients with soft tissue pelvic disease may be eligible if lesions do not qualify as target lesions (e.g., lymph nodes below aortic bifurcation are permissible if the short axis of the largest lymph node is <15 mm)	[redacted]	[redacted]	[redacted]
Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1	[redacted]	[redacted]	[redacted]
Exclusion criteria			
Prior cytotoxic chemotherapy, aminoglutethimide, ketoconazole, abiraterone acetate, or enzalutamide for the treatment of prostate cancer or participation in a clinical trial of an investigational agent that inhibits the androgen receptor or androgen synthesis (unless treatment was placebo)	[redacted]	[redacted]	[redacted]
Treatment with hormonal therapy (e.g., androgen receptor inhibitors, oestrogens, 5-alpha reductase inhibitors) or biologic therapy for prostate cancer (other than approved bone-targeting agents and GnRH agonist/antagonist therapy) within 4 weeks of randomization	[redacted]	[redacted]	[redacted]
History of seizure or any condition that may predispose to seizure (e.g., prior cortical stroke or significant brain trauma). History of loss of consciousness or transient ischemic attack within 12 months of randomization	[redacted]	[redacted]	[redacted]
Clinically significant cardiovascular disease	[redacted]	[redacted]	[redacted]

Source: PROSPER Clinical Study Report[2]

Section B: Clarification on cost-effectiveness data

B1 **(section B3.2.2) PRIORITY QUESTION** The company describes its economic model as a semi-Markov model combined with a partitioned survival modelling approach.

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However, the company's use of pre and post-progression transition probabilities for death is not typical of partitioned survival models, which utilise a set of non-mutually exclusive survival curves to directly estimate the proportion of people alive and in various states of progression at any point in time. Please provide further detail on how your approach compares with a standard partitioned survival model.

Partitioned survival analysis (PartSA) is generally considered the gold standard for an oncology cost-effectiveness model, but there are instances where state-transition (semi-)Markov models may be preferred over PartSA[1]. As described in section B3.2.2 of the manufacturer submission, the submitted model is in essence a Markov model. This allows for the incorporation of several lines of post-progression treatments and to differentiate mortality before and after progression to better reflect clinical practice and the nature of the disease, respectively.

In line with the PartSA approach, the PROSPER metastasis-free survival (MFS) curve was used to model the number of subjects in the nmHRPC and mHRPC health states at any given point in time. However instead of calculating the area under the curve, transition probabilities are derived from the fitted curves to calculate the transition per individual cycle (Markov approach). In addition, in the single overall survival (OS) curve scenario, a PartSA approach is followed to model all health state transitions, except for disease progression from PD1 to PD2 and PD2 to PD3, which depends on the duration of the specific treatments. In the base case, however, pre-progression survival (Pre-PS) and post-progression survival (PPS) is used.

Authors of the NICE DSU PartSA guidelines (in Table 2 of PartSA guidelines[1]) commented that Xtandi (enzalutamide) models in earlier NICE submissions (TA316, TA377), constructed in a similar manner, have been incorrectly described as Markov models. Therefore, the submitted model has now been described as a semi-Markov model with elements of a PartSA.

B2 **PRIORITY QUESTION** The company's economic model assumes that following progression to metastasis on enzalutamide, all patients move to treatment on androgen deprivation therapy alone for a median duration of 7.3 months in "PD1" based on data from the PREVAIL trial (Table 43). However, the comparability of the progressed PROSPER population and the baseline PREVAIL population is not clear; the PROSPER population was considered high risk at baseline based on a PSA doubling time <10 months. Given the above, please:

i) Report the difference in time from radiographic progression (PD1), to initiation of further antineoplastic therapy in the PROSPER enzalutamide arm.

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The median time from radiographic progression to initiation of next antineoplastic therapy was 113 days for subjects who progressed on enzalutamide. The median time from radiographic progression to initiation of each regimen is provided in Table 8.

Table 8 First treatment after disease progression in the enzalutamide arm and time from disease progression to initiation of first antineoplastic (IA1; ITT)

	Enzalutamide	
	N (%)	Median days (min; max) §
Subjects who started any new anti-neoplastic treatment after disease progression	107/933 (11.5%)	[redacted]
First regimen after study treatment discontinuation		
ABI ± BSC	[redacted]	[redacted]
ABI + ENZA ± BSC	[redacted]	[redacted]
DOC ± BSC	[redacted]	[redacted]
ENZA ± BSC	[redacted]	[redacted]
Other chemotherapy* ± BSC	[redacted]	[redacted]
Other agents# ± BSC	[redacted]	[redacted]
Investigational drug ± BSC	[redacted]	[redacted]
None of the above (i.e., BSC)	[redacted]	[redacted]

Abbreviations: ABI: abiraterone; BSC: best supportive care; DOC: docetaxel; ENZA: enzalutamide. §Median days between disease progression and initiation of first antineoplastic therapy. *Includes any chemotherapy other than docetaxel as well as any targeted therapy. #It includes Sipuleucel-T and ubenimex.

The manufacturer agrees with the ERG that there is uncertainty regarding how similar subjects who progressed in PROSPER are to subjects at study entry in PREVAIL. However, the manufacturer is not aware of data for any other cohort that would be closer to the progressed study population in PROSPER.

In the cohort of PROSPER subjects who progressed while on enzalutamide, 62.0% (n=116/187) and 41.7% (n=78/187) had soft tissue and bone metastases, respectively. In PREVAIL, these percentages were 59.3% (n=517/872) and 85.0% (n=741/872) at baseline, respectively. The proportion of subjects with bone metastases with or without soft tissue involvement was higher in the PREVAIL trial while the proportion of subjects with soft tissue metastases was comparable between trials.

In PROSPER, the majority of subjects reported no change from baseline for BPI SF question 3 or FACT-P total score at the time of disease progression suggesting that these subjects were still fairly asymptomatic and had good HRQoL at disease progression[2].

Taking all of the above, it seems appropriate to consider the cohort of subjects progressing in PROSPER comparable to subjects at baseline in PREVAIL. Despite the high risk status of PROSPER subjects at study entry, there is no evidence suggesting that subjects with disease progression in PROSPER would be at a more advanced stage or at higher risk for further progression than subjects at baseline in PREVAIL.

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PROSPER did not collect sufficient data to clearly assess all post-disease progression therapies subjects received. However, it should be noted that the therapies subjects received post-disease progression in PROSPER may have been unrepresentative of clinical practice because physicians did not know what treatment subjects were on when they progressed. Not knowing whether subjects had received enzalutamide or placebo, may have prompted physicians to recommend docetaxel earlier than they may do in clinical practice.

ii) Provide a scenario that utilises the above analysis to determine time in PD1 following progression on enzalutamide.

If duration in PD1 is set as 113 days for subjects who progressed on enzalutamide but all other base-case parameters are kept unchanged, the ICER becomes £31,671 (Table 9). For this scenario it is considered that subjects who progressed on enzalutamide receive ADT alone in PD1 for 113 days. The treatment these subjects receive in PD2 and PD3 and the duration of treatment in these two health states is the same as in the base-case.

Table 9 Cost-effectiveness results based on PD1 duration for subjects progressing on enzalutamide in PROSPER

	Scenario results		**Base-case**	
	Enzalutamide	**ADT**	**Enzalutamide**	**ADT**
Technology acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent lines treatment costs	[redacted]	[redacted]	[redacted]	[redacted]
Other costs	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs	[redacted]	[redacted]	[redacted]	
QALYs	[redacted]	[redacted]	[redacted]	[redacted]
QALY difference	[redacted]		[redacted]	
ICER (Cost/QALY gained)	**£31,671**		**£28,853**	

iii) Provide the distribution of first antineoplastic treatments following progression to metastasis on enzalutamide.

The distribution of first antineoplastic treatments PROSPER subjects received after disease progression is provided in Table 8.

B3 **PRIORITY QUESTION** The company's model assumes that all patients in the placebo arm receive enzalutamide upon progression to "PD1". However, Table 15 of the company submission (Document B) does not report the number of patients that receive enzalutamide. Presumably, these patients are part of the [redacted]

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[redacted]. Given the above, please:

(i) Provide the actual distribution of first antineoplastic treatments received following progression to metastasis in the placebo arm of PROSPER.

In Table 15 of Document B of the manufacturer submission, all [redacted]% of subjects receiving antiandrogens in the placebo arm, received enzalutamide. Enzalutamide was captured under the heading "antiandrogens" in Table 15.

The distribution of the first antineoplastic treatment in the placebo arm received after treatment discontinuation is provided in Table 10.

Table 10 First treatment after disease progression in the placebo arm (IA1; ITT)

	Placebo
	N (%)
Subjects who started any new anti-neoplastic treatment after disease progression	169/468 (36.1%)
First regimen after study treatment discontinuation	
ABI ± BSC	[redacted]
ABI + ENZA ± BSC	[redacted]
DOC ± BSC	[redacted]
ENZA ± BSC	[redacted]
Other chemotherapy* ± BSC	[redacted]
Other agents# ± BSC	[redacted]
Investigational drug ± BSC	[redacted]
None of the above (i.e., BSC)	[redacted]

Abbreviations: ABI: abiraterone; BSC: best supportive care; DOC: docetaxel; ENZA: enzalutamide. §Median days between disease progression and initiation of first antineoplastic therapy. *Includes any chemotherapy other than docetaxel as well as any targeted therapy. #It includes Sipuleucel-T and ubenimex.

(ii) Comment on any difference in cost and overall survival that might be expected with the company's base case assumption (i.e. all patients move to enzalutamide) compared with the actual distribution of PD1 treatments received in PROSPER.

Based on the analysis of the first antineoplastic received by placebo subjects after disease progression in PROSPER, the four most prevalent first antineoplastic regimens after disease progression were abiraterone (35.5% of subjects), ADT either alone or with best supportive care (26.0%), docetaxel (21.9%), and enzalutamide (12.4%). Based on a network meta-analysis (NMA) using the PREVAIL trial as a source for enzalutamide data, COU-AA-302 for abiraterone and TAX327 for docetaxel[3],
[redacted]. However, enzalutamide was associated with significantly longer OS than placebo in PREVAIL[3].

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It is difficult to assess the precise effect of these post-progression treatments on overall survival in the model, as overall survival is determined by the PROSPER pre- and post-progression survival rather than the efficacy of the PD1 treatments. However, based on the NMA, that showed similar efficacy for enzalutamide compared to abiraterone and docetaxel, but a higher efficacy of enzalutamide compared to ADT, it can be argued that switching subjects from 100% enzalutamide to 26% ADT will lower the median overall survival. In addition, it results in lower costs because of subjects receiving ADT alone rather than with enzalutamide in PD1 (Table 11). In the case of docetaxel, although the acquisition costs are lower, the overall costs, when administration costs are included, are comparable to those of enzalutamide. Regarding abiraterone, costs would only be marginally higher than with enzalutamide.

(iii) Explore a scenario where the actual distribution of first antineoplastic treatments received is used to estimate the treatment costs incurred in health state PD1 in the placebo arm of the model.

If the first treatment placebo subjects receive after disease progression (i.e., in PD1) is based on the treatment received in PROSPER but all other base-case parameters are kept as in the base-case, the ICER becomes £33,863 (Table 11).

Table 11 Cost-effectiveness results based on PD1 treatments for subjects progressing on placebo in PROSPER

	Scenario results		Base-case	
	Enzalutamide	**ADT**	**Enzalutamide**	**ADT**
Technology acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent lines treatment costs	[redacted]	[redacted]	[redacted]	[redacted]
Other costs	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs	[redacted]	-	[redacted]	
QALYs	[redacted]	[redacted]	[redacted]	[redacted]
QALY difference	[redacted]		[redacted]	
ICER (Cost/QALY gained)	**£33,863**		**£28,853**	

B4 **PRIORITY QUESTION** Please provide full details of how the utility value for the PD1 health state was derived, and comment on its applicability to the modelled PD1 treatments; was the PD1 health state utility estimate adjusted for baseline utility? And how would the range of treatments that patients received upon progression to PD1 in the PROSPER trial impact on health state utility compared with those treatments that are assumed for PD1 in the model (ADT or enzalutamide)?

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The PD1 utility value was directly derived on the EQ-5D-5L data in PROSPER. For each study subject, the first EQ-5D-5L assessment post progression was translated to the corresponding UK tariff EQ-5D-3L utility values using the 'cross-walk' method[4]. The post-progression utilities were pooled for all subjects in both arms to derive one average PD1 utility value for the entire population. In line with previous enzalutamide-related submissions, the utility was not adjusted for the baseline value.

In the model, no on-treatment disutilities were applied for specific post-baseline treatments. Albeit certain treatments (e.g. chemotherapy) may have HRQoL implications, there was insufficient data / evidence to incorporate treatment-specific disutilities in the analysis. In PROSPER, EQ-5D was collected every 16 weeks post-progression. The PD1 utility was derived from the first post-progression assessment which can be considered a conservative approach. At the time of the first post-progression assessment, the impact of post-progression treatment, if any, or even the disease progression itself on HRQoL may still be low.

The average PD1 utility weight derived from PROSPER is [redacted] using the mapped value and [redacted] after using the UK tariff. This value is higher than that for baseline subjects in PREVAIL (0.844 using the UK tariff). This confirms the conservative approach taken in the model.

As shown in Table 8 and Table 10, in PROSPER the key therapies received by subjects after disease progression include abiraterone, enzalutamide, docetaxel and best supportive care. Of these therapies, only chemotherapy is expected to differ in terms of impact to subjects' HRQoL. As already highlighted in the TA377 (enzalutamide submission in the treatment of metastatic hormone-relapsed prostate cancer before chemotherapy is indicated) Final Appraisal Determination[5], no differences are expected between enzalutamide and abiraterone. [redacted]

B5 **PRIORITY QUESTION** Given that there was no significant difference in pre-progression survival in PROSPER, and patients would be expected to progress to metastasis before dying of prostate cancer related causes, please provide justification for applying a pre-progression survival benefit for enzalutamide over androgen deprivation therapy.

The model uses PROSPER data as primary source for all input parameters. To be consistent with this approach, the base-case includes the pre-progression data observed for both groups in PROSPER.

Nevertheless, a scenario analysis (scenario 4) was conducted using age-matched general UK population mortality rates for both groups (i.e. assuming no prostate cancer-mortality) before subjects progress to metastatic hormone relapsed prostate cancer (mHRPC), demonstrating that the model is not sensitive to pre-progression mortality. The ICER for this scenario is £28,859 (vs £28,853 for the base-case).

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B6 **PRIORITY QUESTION** Table 11 in the company submission suggests that more of the events in the metastasis-free survival analysis were soft tissue progression rather than bone progression. Please comment further on the compatibility of this observation with the skeletal-related event rates that are applied to the progressed states in the model based on data from PREVAIL and COU-AA-301? Also, please provide further details on how these rates of skeletal-related events were derived.

Data on skeletal-related events (SREs) that occurred in PROSPER are limited. Only data on SREs that occurred at the time of disease progression were collected. Data on SREs that subjects experienced after disease progression were not collected.

Bone is the predominant site of metastases in subjects with prostate cancer[6]. Although the proportion of subjects with soft tissue progression as MFS events was slightly higher in PROSPER particularly in the placebo arm (enzalutamide: 62.0%, n=116/187; placebo: 64.7%, n=145/224)[7] than in PREVAIL (enzalutamide: 59.3%; n=517/872; placebo: 53.4%, n=451/845)[8], one would expect that bone metastases will nevertheless develop when the disease further progresses on the next line of treatment.

For the submitted model, SRE rates are derived from PREVAIL and only applied to post-progression health states PD1-PD3. The SRE rates applied to the model are the same as those that were applied to the enzalutamide pre-chemotherapy model. SRE rates were calculated separately for the PD1 and PD2. SRE rates for PD1 were estimated based on the PREVAIL trial data. SRE rates were calculated based on the number of events and the treatment emergent period (patient-years, 1,149.7 for enzalutamide and 494.9 for ADT alone prior to disease progression; 1,572.2 for enzalutamide and ADT post-progression).

Nevertheless, in order to explore the impact of SREs on the model results, a scenario analysis has been run excluding all SREs (Table 12). The impact of SREs in the model is minimum.

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Table 12 Cost-effectiveness results for a scenario excluding SREs

	Scenario results		Base-case	
	Enzalutamide	**ADT**	**Enzalutamide**	**ADT**
Technology acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent lines treatment costs	[redacted]	[redacted]	[redacted]	[redacted]
Other costs	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs	[redacted]		[redacted]	
QALYs	[redacted]	[redacted]	[redacted]	[redacted]
QALY difference	[redacted]		[redacted]	
ICER (Cost/QALY gained)	**£28,878**		**£28,853**	

B7 **PRIORITY QUESTION** Section B.3.8.3.1 provides a scenario analysis using overall survival data from the second interim analysis. However, time to treatment discontinuation is used as the point of progression instead of metastasis-free survival. Please provide a scenario analysis that uses metastasis-free survival data from interim analysis 1 as in the base case, with updated pre-progression survival/ post-progression survival extrapolations from interim analysis 2.

The cost-effectiveness results for the scenario with overall survival from the second interim analysis (IA2) and MFS from the first interim analysis (IA1) are provided in Table 13.

Table 13 Cost-effectiveness results for a scenario using IA1 MFS and IA2 OS

	Scenario results		Base-case	
	Enzalutamide	**ADT**	**Enzalutamide**	**ADT**
Technology acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent lines treatment costs	[redacted]	[redacted]	[redacted]	[redacted]
Other costs	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs	[redacted]		[redacted]	
LYG	[redacted]	[redacted]	[redacted]	[redacted]
LYG difference	[redacted]	[redacted]	[redacted]	
QALYs	[redacted]	[redacted]	[redacted]	[redacted]
QALY difference	[redacted]		[redacted]	
ICER (Cost/QALY gained)	**£38,918**		**£28,853**	

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2 Astellas. PROSPER HEOR report. Final version, January 2018. [Available on file].

3 Astellas. Systematic Review and Mixed Treatment Comparison of Enzalutamide for Chemotherapy Naïve Castration-Resistant Prostate Cancer Final Report. January 2015.

4 van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, Lloyd A, Scalone L, Kind P, Pickard AS. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012 Jul-Aug;15(5):708-15.

5 TA377 Final Appraisal Determination. Available at: https://www.nice.org.uk/guidance/ta377/documents/final-appraisal-determination-document

6 Macedo F, Ladeira K, Pinho F, Saraiva N, Bonito N, Pinto L, Goncalves F. Bone Metastases: An Overview. Oncol Rev. 2017 May 9;11(1):321. doi: 10.4081/oncol.2017.321. eCollection 2017 Mar 3.

7 Medivation-Pfizer. Clinical Study Report - PROSPER: a multinational, phase 3, randomized, double-blind, placebo-controlled, efficacy and safety study of enzalutamide in patients with nonmetastatic castration-resistant prostate cancer. 8 December 2017.

8 Medivation. Clinical Study Report - PREVAIL. 2014.

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Appendix A – Studies excluded from the clinical systematic literature review and reason for exclusion

Reference	Reason
Amato RJ, Teh BS, Henary H, Khan M & Saxena S. A retrospective review of combination chemohormonal therapy as initial treatment for locally advanced or metastatic adenocarcinoma of the prostate. Urologic Oncology: Seminars and Original Investigations, 2009;27, 165-169	Non-relevant indication
Antonarakis ES, Kibel AS, Adams GW, et al. Immune responses and clinical outcomes in STAND, a randomized phase 2 study evaluating optimal sequencing of sipuleucel-T (sip-T) and androgen deprivation therapy (ADT) in biochemically-recurrent prostate cancer (BRPC) after local therapy failure. Journal of Clinical Oncology 33, no. 15_suppl (May 20 2015) 5030-5030.	Non-relevant indication
Arlen PM, Gulley JL, Todd N, Lieberman R, Steinberg SM, Morin S, et al . Antiandrogen, vaccine and combination therapy in patients with nonmetastatic hormone refractory prostate cancer. Journal of Urology, 2005;174, 539-546	Non-relevant outcome
Aronson W, Yu E, Hancock M, Babicz T, Tutrone R, Ng C, et al . A phase 2 open-label trial of GTX-758 in men with castration-resistant prostate cancer, final analysis of the primary endpoint. Journal of Urology, 2016;195; 4 SUPPL (1), e761-e762	Non-relevant outcome
Bahl A, Challapalli A, Masson S, et al. A randomized controlled trial to determine the effect of triptorelin on reduction of prostate volume preradiotherapy compared with standard therapy (goserelin). Journal of Clinical Oncology 34, no. 2_suppl (January 10 2016) 30-30.	Non-relevant indication
Banck MS, Chugh R, Natale RB, Algazi A, Carthon BC, Rosen LS, et al . Phase 1 results of emibetuzumab (LY2875358), a bivalent MET antibody, in patients with advanced castration-resistant prostate cancer, and MET positive renal cell carcinoma, non-small cell lung cancer, and hepatocellular carcinoma. Molecular Cancer Therapeutics, 2015;14, no pagination	Non-relevant outcome
Beauval JB, Loriot Y, Hennequin C, Rozet F, Barthelemy P, Borchiellini D, et al . Loco-regional treatment for castration-resistant prostate cancer: Is there any rationale? A critical review from the AFU-GETUG. Critical Reviews in Oncology-Hematology, 2018;122, 144-149	Non-relevant indication
Beekman KW, Colevas AD, Cooney K, DiPaola R, Dunn RL, Gross M, et al . Phase II evaluations of cilengitide in asymptomatic patients with androgen-independent prostate cancer: Scientific rationale and study design. Clinical Genitourinary Cancer, 2006;4, 299-302	Non-relevant interventions
Bolla M, Van Den Bergh ACM, Carrie C, et al. EORTC trial 22991: Results of a phase III study comparing 6 months of androgen suppression and irradiation versus irradiation alone for localized T1b-cT2aN0M0 prostate cancer. Journal of Clinical Oncology 34, no. 2_suppl (January 10 2016) 22-22.	Non-relevant indication
Borgmann V, al-Abadi H & Nagel R . Treatment of locally advanced prostatic carcinoma with LHRH analogues: cytological, DNA-cytophotometrical, and clinical results. American Journal of Clinical Oncology, 1988;11 Suppl 1, S19-28	Non-relevant indication
Bossi A, Dearnaley D, McKenzie M, Baskin-Bey E, Tyler R, Tombal B, et al . ATLAS: A phase 3 trial evaluating the efficacy of apalutamide (ARN-509) in patients with high-risk localized or locally advanced prostate cancer receiving primary radiation therapy. Annals of Oncology, 2016;27, no pagination	Non-relevant indication
Botticella A, Guarneri A, Filippi AR, Levra NG, Munoz F, Ragona R, et al . May non-metastatic clinically localized castration-resistant prostate cancer after primary androgen ablation benefit from salvage prostate radiotherapy?. Journal of Cancer Research and Clinical Oncology, 2013;139, 1955-1960	Non-relevant outcome

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Bruchovsky N, Klotz L, Crook J & Goldenberg SL. Locally advanced prostate cancer - Biochemical results from a prospective phase II study of intermittent androgen suppression for men with evidence of prostate-specific antigen recurrence after radiotherapy. Cancer, 2007;109, 858-867	Non-relevant indication
Brungs D, Chen J, Masson P & Epstein RJ. Intermittent androgen deprivation is a rational standard-of-care treatment for all stages of progressive prostate cancer: results from a systematic review and meta-analysis. Prostate Cancer & Prostatic Diseases, 2014;17, 105-11	Non-relevant indication
Carles J, Gallardo Diaz E, Domenech M, et al. A phase IIb trial of docetaxel concurrent with radiotherapy plus hormotherapy versus radio hormonotherapy in high-risk localized prostate cancer (QRT SOGUG trial): Preliminary report for design, tolerance, and toxicity. ournal of Clinical Oncology 33, no. 7_suppl (March 1 2015) 15-15.	Non-relevant indication
Challapalli A, Masson S, Humphrey P, et al. High dose rate brachytherapy as monotherapy for localized prostate cancer: Our initial experience. Journal of Clinical Oncology 34, no. 2_suppl e626	Non-relevant outcome
Cheng W-S, Dzojic H, Nilsson B, Totterman TH & Essand M. An oncolytic conditionally replicating adenovirus for hormone-dependent and hormone-independent prostate cancer. Cancer Gene Therapy, 2006;13, 13-20	Non-relevant interventions
Chow H, Ghosh P, D'Abronzo LS, et al. Everolimus plus bicalutamide for castration resistant prostate cancer (CRPC): Bench to bedside and back. Journal of Clinical Oncology 33, no. 7_suppl (March 1 2015) 189-189.	No results
Crawford ED, Daneshgari F, Majeski SA. Etoposide in the treatment of hormone-refractory advanced carcinoma of the prostate. Semin Oncol. 1992 Dec;19(6 Suppl 14):53-7.	Non-relevant outcome
Crawley D, van Hemelrijck M, Chowdhury S, et al. Effect of baseline metabolic aberrations in men with locally advanced/metastatic prostate cancer treated with ADT on time to disease progression, prostate cancer specific and all cause death. Ann Oncol 2016 27 (suppl 6): doi:10.1093/annonc/mdw372.46.	Non-relevant outcome
Creak A, Hall E, Horwich A et al. Randomised pilot study of dose escalation using conformal radiotherapy in prostate cancer long-term follow-up. British journal of cancer. 2013;109(3): 651-7	Non-relevant outcome
D'Amico AV, Chen MH, de Castro M, Loffredo M, Lamb DS, Steigler A, Kantoff PW, Denham JW. Surrogate endpoints for prostate cancer-specific mortality after radiotherapy and androgen suppression therapy in men with localised or locally advanced prostate cancer: an analysis of two randomised trials. Lancet Oncol. 2012 Feb;13(2):189-95. doi: 10.1016/S1470-2045(11)70295-9.	Non-relevant indication
D'Amico AV, Chen M-H, Renshaw A, Loffredo M & Kantoff PW. Long-term follow-up of a randomized trial of radiation with or without androgen deprivation therapy for localized prostate cancer. JAMA - Journal of the American Medical Association, 2015;314, 1291-1293	Non-relevant indication
Davda R, Hughes S, Jones R, Crabb SJ, Troup J & Payne H. Chemotherapy at First Diagnosis of Advanced Prostate Cancer - Revolution or Evolution? Findings from a British Uro-oncology Group UK Survey to Evaluate Oncologists' Views on First-line Docetaxel in Combination with Androgen Deprivation Therapy in Castrate-sensitive Metastatic and High-risk/Locally Advanced Prostate Cancer. Clinical Oncology, 2016;28, 376-385	Non-relevant indication
Davis EJ, Yee C, Beebe-Dimmer J, et al. The risk of second malignancies after treatment for localized prostate cancer. Journal of Clinical Oncology 32, no. 15_suppl (May 20 2014) 5034-5034.	Non-relevant indication

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Denham JW, Joseph DJ, Lamb DS, et al. Main oncologic endpoints of the TROG 03.04 (RADAR) Trial for men with locally advanced prostate cancer. Journal of Clinical Oncology 32, no. 15_suppl (May 20 2014) 5004-5004.	Non-relevant indication
DiBlasio CJ, Malcolm JB, Hammett J, Wan JY, Aleman MA, Patterson AL, Wake RW, Derweesh IH. Survival outcomes in men receiving androgen-deprivation therapy as primary or salvage treatment for localized or advanced prostate cancer: 20-year single-centre experience. BJU Int. 2009 Nov;104(9):1208-14. doi: 10.1111/j.1464-410X.2009.08593.x.	Non-relevant indication
Donahue TF, Morris MJ, Hilton WM, et al. Pelvic exenteration in patients with nonmetastatic, locally advanced castration-resistant prostate cancer. Journal of Clinical Oncology 32, no. 4_suppl (February 1 2014) 168-168.	Non-relevant outcome
Drake CG, Fan L-Q, GuhaThakurta D, et al. Antigen spread and survival with sipuleucel-T in patients with advanced prostate cancer. Journal of Clinical Oncology 32, no. 4_suppl (February 1 2014) 88-88.	Non-relevant indication
Dreicer R, Carducci M. E-1899: An Eastern Cooperative Oncology Group Study Comparing Ketoconazole Plus Hydrocortisone with Docetaxel Plus Estramustine for Asymptomatic, Androgen-Independent, Nonmetastatic Prostate Cancer Patients with Rising PSA Levels. Rev Urol. 2003;5 Suppl 3:S52-8.	No results
Dubray BM, Salleron J, Guerif SG, et al. Does short-term androgen depletion add to high dose radiotherapy (80 Gy) in localized intermediate risk prostate cancer? Final analysis of GETUG 14 randomized trial (EU-20503/NCT00104741). Journal of Clinical Oncology 34, no. 15_suppl (May 20 2016) 5021-5021.	Non-relevant indication
Efstathiou E, Davis JW, Titus MA, et al. Neoadjuvant enzalutamide (ENZA) and abiraterone acetate (AA) plus leuprolide acetate (LHRHa) versus AA+ LHRHa in localized high-risk prostate cancer (LHRPC). Journal of Clinical Oncology 34, no. 15_suppl (May 20 2016) 5002-5002.	Non-relevant indication
Fabricius MJ, Pickard R, McColl E. Outcome measures in advanced prostate cancer trials: A systematic review of contemporary trial registrations. Journal of Clinical Oncology 33, no. 15_suppl e16123	Non-relevant outcome
Feibus AH, Guccione JR, Vasudevamurthy A, et al. Early assessment of PSA response in CRPC patients treated with enzalutamide (Enza) or abiraterone (Abi). Journal of Clinical Oncology 35, no. 6_suppl (February 20 2017) e574-e574.	Non-relevant indication
Ferrari AC, Chen YH, Hudes GR, et al E2809. Androgen receptor (AR) modulation by bicalutamide (Bic) and MK-2206 (MK) in prostate cancer (PC) patients (pts) with rising PSA at high risk of progression after local treatment (tx). Ann Oncol (2016) 27 (suppl 6): doi:10.1093/annonc/mdw372.17.	Non-relevant indication
Ferrari AC, Chen YH, Hudes GR, et al. E2809: Androgen receptor (AR) modulation by bicalutamide (Bic) and MK-2206 (MK) in men with rising PSA at high-risk of progression after local prostate cancer (PC) treatment. Journal of Clinical Oncology 2016;34, no. 2_suppl (January 10 2016) 9-9.	Non-relevant indication
Fizazi K, Faivre L, Lesaunier F et al. Androgen deprivation therapy plus docetaxel and estramustine versus androgen deprivation therapy alone for high-risk localised prostate cancer (GETUG 12) a phase 3 randomised controlled trial. The Lancet Oncology. 2015;16(7): 787-94	Non-relevant indication
Fizazi K, Habibian M, Laplanche A, et al. A randomized phase III, factorial design, of cabazitaxel and pelvic radiotherapy in patients with localized prostate cancer and high-risk features of relapse. Journal of Clinical Oncology 32, no. 15_suppl	Non-relevant indication
Fizazi K, Laplanche A, Lesaunier F, et al. Docetaxel-estramustine in localized high-risk prostate cancer: Results of the French Genitourinary Tumor Group	Non-relevant indication

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GETUG 12 phase III trial. Journal of Clinical Oncology 32, no. 15_suppl (May 20 2014) 5005-5005.	
Fossa SD, Widmark A, Klepp OH, et al. Ten- and 15-year prostate cancer-specific survival in patients with nonmetastatic high-risk prostate cancer randomized to lifelong hormone treatment alone or combined with radiotherapy (SPCG VII). Journal of Clinical Oncology 32, no. 4_suppl (February 1 2014) 4-4.	Non-relevant indication
Gandhok N, Sartor O. Unexpected response of hormone-refractory prostate cancer to treatment with an antileukemic chemotherapy regimen. Urology. 2004 Oct;64(4):807-9.	Non-relevant indication
George DJ, Halabi S, Shepard TF, Vogelzang NJ, Hayes DF, Small EJ, et al . Prognostic significance of plasma vascular endothelial growth factor levels in patients with hormone-refractory prostate cancer treated on Cancer and Leukemia Group B 9480. Clinical Cancer Research, 2001;7(7), 1932-1936	Non-relevant outcome
Golabek T, Belsey J, Drewa T, Kolodziej A, Skoneczna I, Milecki P, et al . Evidence-based recommendations on androgen deprivation therapy for localized and advanced prostate cancer. Central European Journal of Urology, 2016;69, 131-138	No results
Gomella LG, Gelpi F, Kelly WK. New treatment options for castrate-resistant prostate cancer: a urology perspective. Can J Urol. 2011 Aug;18(4):5767-77. Review.	Non-relevant outcome
Gomez-Veiga F, Patrick D, Smith M et al. Bone metastases and associated pain progression and analgesic use Evidence from a posthoc analysis of a phase iii study with denosumab in men with non-metastatic castration-resistant prostate cancer (CRPC). Urology. 2013;82(3 SUPPL. 1): S30	No results
Gomez-Veiga F, Ponce-Reixa J, Martinez-Breijo S, Planas J & Morote J. Advances in prevention and treatment of bone metastases in prostate cancer. Role of RANK/RANKL inhibition. Actas Urologicas Espanolas, 2013;37, 292-304	No results
Gravis G, Boher J-M, Joly F, et al. Androgen deprivation therapy (ADT) plus docetaxel (D) versus ADT alone for hormone-naïve metastatic prostate cancer (PCa): Long-term analysis of the GETUG-AFU 15 phase III trial. Journal of Clinical Oncology 33, no. 7_suppl (March 1 2015) 140-140.	Non-relevant indication
Gross ME, Dorff TB, Quinn DI. Safety and efficacy of everolimus (E), bevacizumab (B), and docetaxel (D) for castration resistant prostate cancer (CRPC). Journal of Clinical Oncology 33, no. 15_suppl (May 20 2015) 5066-5066.	Non-relevant interventions
Hanna C & Jones RJ. Emerging treatments for recurrent prostate cancer. Future Oncology, 2015;11, 2873-80	Non-relevant outcome
Hindson B, Turner S, Do V. Palliative radiation therapy for localized prostate symptoms in hormone refractory prostate cancer. Australas Radiol. 2007 Dec;51(6):584-8.	Non-relevant indication
Howard LE, De Hoedt AM, Aronson WJ, Kane CJ, Amling CL, Cooperberg MR, Terris MK, Divers CH, Valderrama A, Freedland SJ. Do skeletal-related events predict overall survival in men with metastatic castration-resistant prostate cancer?. Prostate Cancer Prostatic Dis. 2016 Dec;19(4):380-384. doi: 10.1038/pcan.2016.26.	Non-relevant indication
Hsieh CL, Yang L, Miao L, Yeung F, Kao C, Yang H, Zhau HE, Chung LW. A novel targeting modality to enhance adenoviral replication by vitamin D(3) in androgen-independent human prostate cancer cells and tumors. Cancer Res. 2002 Jun 1;62(11):3084-92.	Non-relevant outcome
Hussain M, Corn PG, Michaelson MD, Hammers HJ, Alumkal JJ, Ryan CJ, Bruce JY, Moran S, Lee SY, Lin HM, George DJ; Prostate Cancer Clinical Trials Consortium, a program of the Department of Defense Prostate Cancer Research	Non comparative

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Program and the Prostate Cancer Foundation. Phase II study of single-agent orteronel (TAK-700) in patients with nonmetastatic castration-resistant prostate cancer and rising prostate-specific antigen. Clin Cancer Res. 2014 Aug 15;20(16):4218-27. doi: 10.1158/1078-0432.CCR-14-0356.	
Izumi K, Lin WJ, Miyamoto H, Huang CK, Maolake A, Kitagawa Y, Kadono Y, Konaka H, Mizokami A, Namiki M. Outcomes and predictive factors of prostate cancer patients with extremely high prostate-specific antigen level. J Cancer Res Clin Oncol. 2014 Aug;140(8):1413-9. doi: 10.1007/s00432-014-1681-8.	Non-relevant indication
Jeong CW, Ahn S, Lee M, et al. Quality-adjusted survival comparison between androgen deprivation with radiation therapy versus radiation therapy alone for locally advanced prostate cancer: Decision analysis from RTOG 85-31 trial. Journal of Clinical Oncology 34, no. 2_suppl (January 10 2016) 265-265.	Non-relevant indication
Jeong JH, Hyun H, Jeong IG, Hong JH, Ahn H & Lee J-L. Randomized phase II trial of docetaxel plus prednisolone with or without androgen deprivation treatment in castration-resistant prostate cancer. Journal of Clinical Oncology, 2016;34(2 SUPPL 1), no pagination	Non-relevant indication
Jeong JY, Koo KC, Bang WJ. Cancer-specific mortality among men with localized prostate cancer treated with radical prostatectomy versus radiotherapy: a multi-center study using propensity score matching and competing risk regression analyses. J Urology 2017;197(4):e1362–e1363	Non-relevant indication
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Kalapurakal JA, Mittal BB & Sathiaseelan V. Re-irradiation and external hyperthermia in locally advanced, radiation recurrent, hormone refractory prostate cancer: A preliminary report. British Journal of Radiology, 2001;74(884), 745-751	Non-relevant indication
Kalbasi A, Li J, Berman AT, et al. Impact of dose-escalated radiation on overall survival in men with nonmetastatic prostate cancer. Journal of Clinical Oncology 33, no. 7_suppl (March 1 2015) 28-28.	Non-relevant interventions
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Klotz L, Nabid A, Higano C, Ryanm C, Kebabdjian M & Chin J. Effect of dutasteride in men receiving intermittent androgen ablation therapy: The AVIAS trial. Canadian Urological Association Journal, 2014;8, E789-94	Non-relevant indication
Klotz L, O'Callaghan CJ, Ding K et al. A phase III randomized trial comparing intermittent versus continuous androgen suppression for patients with PSA	Non-relevant indication

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Klotz L, Sweeney C, Dicker A, Vogelzang N, Morris M, Verholen F, et al . Efficacy and safety of radium-223 by radical local therapy at initial diagnosis: A retrospective subgroup analysis of alsympca trial. Journal of Urology, 2017;197(4 Supplement 1), e454	Non-relevant indication
Koo KC, Lee JS, Kim JW, Han KS, Lee KS, Kim DK, et al. Impact of clinical trial participation on survival in patients with castration-resistant prostate cancer: a multi-center analysis. BMC Cancer, 2018;18, 468	Non-relevant outcome
Kotwal S, Whelan P. Does failure of single hormone therapy delineate hormone refractoriness for prostate cancer?. Scandinavian journal of urology and nephrology. 2008;42(2): 116-20	Non-relevant outcome
Kramer G, Steiner GE, Sokol P, Handisurya A, Klingler HC, Maier U, FÃ¶ldy M, Marberger M. Local intratumoral tumor necrosis factor-alpha and systemic IFN-alpha 2b in patients with locally advanced prostate cancer. J Interferon Cytokine Res. 2001 Jul;21(7):475-84.	Non-relevant indication
Kubo H, Gardner TA, Wada Y, Koeneman KS, Gotoh A, Yang L, et al . Phase I dose escalation clinical trial of adenovirus vector carrying osteocalcin promoter-driven herpes simplex virus thymidine kinase in localized and metastatic hormone-refractory prostate cancer. Human Gene Therapy, 2003;14, 227-241	Non-relevant interventions
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Lankford SP, Pollack A & Zagars GK. Radiotherapy for regionally localized hormone refractory prostate cancer. International Journal of Radiation Oncology, Biology, Physics, 1995;33(4), 907-12	Non-relevant interventions
Latif MF, Tirmazy SH, Hussain SA, et al. Management of non metastatic castrate resistant prostate cancer (NM-CRPC), results of a UK wide national survey. Journal of Clinical Oncology 34, no. 15_suppl	Non-relevant outcome
Leonard GD, Dahut WL, Gulley JL, Arlen PM & Figg WD. Docetaxel and thalidomide as a treatment option for androgen- independent, nonmetastatic prostate cancer. Reviews in Urology, 2003;5 Suppl 3, S65-70	Non-relevant interventions
Lo Re G, Boccalon M, Maruzzi D, Bortolus R, Lenardon O, Marus V, et al. A phase II noncomparative study of neoadjuvant (NA) chemohormone therapy (CHT), radical prostatectomy (RP), and postoperative radiotherapy (RT) in locally advanced (LA) high-risk prostate cancer (HRPC): A monoinstitutional 6-year experience with two NA CHT regimens. Journal of Clinical Oncology, 2009;27(15 SUPPL 1), e16091	Non-relevant indication
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Marshall DT, Golshayan A, Kraft A & Chaudhary U. Final results of a phase I trial of total androgen blockade, Weekly docetaxel, and image-guided intensity modulated radiotherapy for localized high-risk prostate cancer. International Journal of Radiation Oncology Biology Physics, 2011;81 (2 SUPPL 1), S395	Non-relevant indication
Marx GM, Smith MR, Saad F et al. Denosumab prolongs bone-metastasis-free survival in men with non-metastatic castrate-resistant prostate cancer presenting with aggressive prostate-specific antigen kinetics A post hoc subset analysis. Asia-Pacific journal of clinical oncology. 2012;8:45	More recent results available
Matsumura Y. [Multidisciplinary therapy of urogenital cancer]. Gan No Rinsho. 1985 Jul;31(9 Suppl):1165-9. Japanese.	Non-relevant outcome
McKay RR, Gray KP, Hayes JH, et al. Results of a phase II trial of docetaxel (DOC), bevacizumab (BEV), and androgen deprivation therapy (ADT) for biochemical relapse (BCR) after definitive local therapy for prostate cancer (PC). J Clin Oncol 32, 2014 (suppl 4; abstr 54)	Non-relevant indication
McKenzie M, Dearnaley D, Tombal B, Baskin-Bey E, Freedland SJ, Roach M, et al . ATLAS: A randomized, double-blind, phase 3 study of ARN-509 in patients with high-risk localized or locally advanced prostate cancer receiving primary radiation therapy. Canadian Urological Association Journal, 2016;10(5-6 Supplement 1), S73-S74	Non-relevant indication
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Merseburger AS, Alcaraz A & von Klot CA. Androgen deprivation therapy as backbone therapy in the management of prostate cancer. OncoTargets and Therapy, 2016;9, 7263-7274	No results
Miller K, Mulders P, Freedland SJ, et al . EMBARK: A phase 3, randomized, efficacy and safety study of enzalutamide plus leuprolide, enzalutamide monotherapy and placebo plus leuprolide in men with high-risk nonmetastatic prostate cancer progressing after definitive therapyAnn Oncol (2016) 27 (suppl 6): doi:10.1093/annonc/mdw372.53.	Non-relevant indication
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Minami T, Kimura T, Nozawa M, Yoshimura K, Nakagawa T, Yamada A, et al . The clinical role of peptide vaccines for castration-resistant prostate cancer. Annals of Oncology, 2012;23, xi96	Non-relevant outcome
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Moser L, Schubert T, Hinkelbein W. Hormone-refractory and metastatic prostate cancer - Palliative radiotherapy . Front Radiat Ther Oncol, 2008;41, 117-125	Non-relevant interventions
Mostaghel EA, Marck B, Matsumoto AM, et al. Association of serum (SR) and tissue (TX) abiraterone (ABI) levels with intraprostatic steroids and pathologic outcomes in men with high-risk localized prostate cancer (PCa). Journal of Clinical Oncology 32, no. 15_suppl (May 20 2014) 5015-5015.	Non-relevant outcome
Munoz-Velez D. [Management of non metastatic castration resistant prostate cancer]. Archivos Espanoles de Urologia, 2015; 68(2), 125-34	Non-relevant outcome
Nabid A, Carrier N, Martin A, Bahary J, Duclos M, Vincent F, et al . Adherence to long-term androgen blockade in localized high-risk prostate cancer and causes of noncompliance. International Journal of Radiation Oncology Biology Physics, 2012;84, S374-S375	Non-relevant indication
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Nakabayashi M& Oh WK. Neoadjuvant and adjuvant chemotherapy for high-risk localized prostate cancer. Current Treatment Options in Oncology, 5(5), 349-355	Non-relevant indication
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Oh WK, Kantoff PW, Sellers WR & Rosen N. An overview of chemotherapy trials in localized and recurrent nonmetastatic prostate cancer. Journal of Urology, 2004;172, S34-S37	Non-relevant indication
Oh WK. High-risk localized prostate cancer: Integrating chemotherapy. Oncologist, 2005;10, 18-22	Non-relevant indication
Oosterhof GO, Roberts JT, de Reijke TM, Engelholm SA, Horenblas S, von der Maase H, et al. Strontium (89) chloride versus palliative local field radiotherapy in patients with hormonal escaped prostate cancer: a phase III study of the European Organisation for Research and Treatment of Cancer, Genitourinary Group. European Urology, 2003;44(5), 519-26	Non-relevant indication
Oudard S, Smith M, Karsh L et al. Denosumab and bone metastasis-free survival in men with castrate-resistant prostate cancer - Subgroup analyses from an international, double-blind, randomized, phase 3 trial. European journal of cancer. 2011;47:S484-S485	Non-relevant indication
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Parker C, Vogelzang NJ, Sartor AO, et al. 3-year posttreatment follow-up of radium-223 dichloride (Ra-223) safety in patients (pts) with castration-resistant prostate cancer (CRPC) and symptomatic bone metastases from the phase 3 ALSYMPCA study. Journal of Clinical Oncology 33, no. 15_suppl.	Non-relevant indication
Patrick D, Smith MR, Cleeland C et al. The impact of bone metastases on pain Results from a phase III denosumab study in men with nonmetastatic castration-resistant prostate cancer. European Urology, Supplements. 2013;12(1): e99-e100	Non-relevant outcome
Pfister D, Porres D, Epplen R, von Erps T & Heidenreich A. [Palliative radical cysto)prostatectomy in locally advanced castration-resistant prostate cancer]. Urologe Ausg(A), 2011;50, 1101-5	Non-relevant interventions
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Ponholzer A, Steinbacher F, Madersbacher S & Schramek P. [Current treatment of locally advanced and metastatic prostate cancer]. Wiener Medizinische Wochenschrift, 2011; 161, 377-81	Non-relevant outcome
Rajan P, Frew JA, Wilson JM, Azzabi AST, McMenemin RM, Stockley J, et al . Feasibility study of a randomized controlled trial comparing docetaxel chemotherapy and androgen deprivation therapy with sequential prostatic biopsies from patients with advanced non-castration-resistant prostate cancer. Urologic Oncology: Seminars and Original Investigations, 2015;33, 337	Non-relevant indication
Rajpar S, Vielh P, Laplanche A, et al. A study of ERG, PTEN, and ki-67 in a phase III trial assessing docetaxel and estramustine in high-risk localized prostate cancer (GETUG 12). Journal of Clinical Oncology 32, no. 15_suppl (May 20 2014) 5063-5063.	Non-relevant indication
Ramey SJ, Golshayan AR, Keane TE, Kraft AS, Chaudhary UB & Marshall DT. Phase I trial of total androgen blockade, weekly docetaxel, and image-guided intensity-modulated radiotherapy for localized high-risk prostate adenocarcinoma. Journal of Clinical Oncology, 2013;31(6 SUPPL 1), no pagination	Non-relevant indication
Rathkopf DE, Danila DC, Slovin SF, Morris MJ, Steinbrecher JE, Chen Y, et al . A first-in-human, open-label, phase I/II safety, pharmacokinetic, and proof-of-concept study of ARN-509 in patients with progressive advanced castration-resistant prostate cancer (CRPC). Journal of Clinical Oncology, 2011; 29(15 SUPPL 1), no pagination	Non-relevant outcome
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Reza M, Wirth M, Tammela TLJ, et al. Bone Scan Index as an imaging biomarker to predict overall survival in the Zeus/SPCG11 study. Journal of Clinical Oncology 34, no. 15_suppl	Non-relevant indication
Rozet F, Hennequin C, Beauval JB, Beuzeboc P, Cormier L, Fromont G, et al. [CCAFU french national guidelines 2016-2018 on prostate cancer]. Progres en Urologie, 27 Suppl 1, S95-S143	Non-relevant outcome
Ruizeveld de Winter JA, Janssen PJ, Sleddens HM, Verleun-Mooijman MC, Trapman J, Brinkmann AO, et al. Androgen receptor status in localized and locally progressive hormone refractory human prostate cancer. American Journal of Pathology, 1994;144(4), 735-46	Non-relevant interventions
Ryan CJ & Eisenberger M. Chemotherapy for hormone-refractory prostate cancer: Now it's a question of "when?". Journal of Clinical Oncology, 2005;23, 8242-8246	No results
Ryan CJ, Crawford ED, Shore ND, et al. IMAAGEN trial safety and efficacy update: Effect of abiraterone acetate and low-dose prednisone on prostate-specific antigen and radiographic disease progression in patients with nonmetastatic castration-resistant prostate cancer. Journal of Clinical Oncology 34, no. 15_suppl (May 20 2016) 5061-5061.	Non-relevant interventions
Ryan CJ, Crawford ED, Shore NF, et al. Effect of abiraterone acetate and low-dose prednisone on PSA in patients with nonmetastatic castration-resistant prostate cancer: The results from IMAAGEN core study. Journal of Clinical Oncology 32, no. 15_suppl (May 20 2014) 5086-5086.	Non-relevant outcome
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Saad F, Patrick DJ, Smith M et al. The impact of bone metastases on pain Post-hoc analysis of a phase III study of denosumab in men with non-metastatic Castration-Resistant Prostate Cancer (CRPC). BJU international. 2013;111:38	More recent results available
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Saad F, Small E, Hadaschik B, Graff J, Mainwaring P, McQuarrie K, et al . Patient (pt) reported outcomes (PROs) in SPARTAN, a phase 3, double-blind, randomized study of apalutamide (APA) plus androgen deprivation therapy (ADT) vs placebo (PBO) plus ADT in men with nonmetastatic castration-resistant prostate cancer (nmCRPC). European Urology, Supplements, 2018;17(2), e1070-e1071	Non-relevant outcome
Saad F, Smith MR, Shore ND et al. Effect of denosumab on prolonging bone-metastasis free survival (BMFS) in men with nonmetastatic castrate-resistant prostate cancer (CRPC) presenting with aggressive PSA kinetics. Journal of clinical oncology. 2012;30(15 SUPPL. 1)	More recent results available
Sachdeva A, van der Meulen J, Cathcart P. Comparison of radical treatment and mortality in patients with nonmetastatic prostate cancer in England and the United States. Journal of Clinical Oncology 32, no. 4_suppl (February 1 2014) 46-46.	Non-relevant interventions
Saldana C, Salomon L, Rousseau B et al. Weekly paclitaxel versus ADT alone in localized high-risk prostate cancer Results of a single-institution phase II trial. Journal of clinical oncology. 2015;33(7 SUPPL. 1)	Non-relevant indication
Sandler HM, Hu C, Rosenthal SA, et al. A phase III protocol of androgen suppression (AS) and 3DCRT/IMRT versus AS and 3DCRT/IMRT followed by chemotherapy (CT) with docetaxel and prednisone for localized, high-risk prostate cancer (RTOG 0521). Journal of Clinical Oncology 33, no. 18_suppl	Non-relevant indication
Sandler HM, McKenzie MR, Tombal BF, et al. ATLAS: A randomized, double-blind, placebo-controlled, phase 3 trial of apalutamide (ARN-509) in patients with high-risk localized or locally advanced prostate cancer receiving primary radiation therapy. Journal of Clinical Oncology 34, no. 15_suppl .	Non-relevant indication
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Sanyal C, Aprikian AG, Cury FL, Chevalier S, Dragomir A. Management of localized and advanced prostate cancer in Canada: A lifetime cost and quality-adjusted life-year analysis. Cancer. 2016 Apr 1;122(7):1085-96. doi: 10.1002/cncr.29892.	Non-relevant outcome
Sartor O, Gomella LG, Gagnier P. Dutasteride and bicalutamide in patients with hormone-refractory prostate cancer the Therapy Assessed by Rising PSA (TARP) study rationale and design. The Canadian journal of urology. 2009;16(5): 4806-12	No results
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Scher HI, Morris MJ, Basch E & Heller G. End points and outcomes in castration-resistant prostate cancer: From clinical trials to clinical practice. Journal of Clinical Oncology, 2011;29, 3695-3704	Non-relevant outcome
Schulman C. Atrasentan: The first endothelin receptor antagonist for hormone-refractory prostate cancer. European Urology, 2003;Supplement, 2, 20-27	No results
Schweizer MT, Antonarakis ES, Wang H, et al. A pilot study of supraphysiologic testosterone (T) and oral etoposide (E) in men with castrate-resistant prostate cancer (CRPC). ournal of Clinical Oncology 32, no. 4_suppl (February 1 2014) 45-45.	Non-relevant interventions
Shore ND, Vourganti S, Silberstein JL, et al . A randomized study of enzalutamide in patients with localized prostate cancer undergoing active surveillance (ENACT). Journal of Clinical Oncology, 2017;35(15 Supplement 1), no pagination	Non-relevant indication
Slawin KM, Ellis WJ, Tenke P, et al. A phase 2 study of 99m Tc-trofolastat chloride (MIP-1404) SPECT/CT to identify and localize prostate cancer (PCa) in high-risk patients (pts) undergoing radical prostatectomy (RP) and extended pelvic lymph node (ePLN) dissection compared to histopathology: An interim analysis. Journal of Clinical Oncology 32, no. 4_suppl (February 1 2014) 94-94.	Non-relevant indication
Small EJ, Fontana J, Tannir N, DiPaola RS, Wilding G, Rubin M, Iacona RB, Kabbinavar FF. A phase II trial of gefitinib in patients with non-metastatic hormone-refractory prostate cancer. BJU Int. 2007 Oct;100(4):765-9.	Non-relevant interventions
Small EJ, Saad F, Hadaschik BA, Graff JN, Mainwaring PN, McQuarrie K, et al . Patient reported outcomes (PROS) in spartan, a phase 3, double-blind, randomized study of apalutamide (APA) plus androgen deprivation therapy (ADT) vs placebo plus ADT in men with nonmetastatic castration-resistant prostate cancer (NMCRPC). Journal of Urology, 2018;199(4 Supplement 1), e703-e704	Non-relevant outcome
Smith M, Oudard S, Karsh L et al. Subgroup analyses from an international, doubleblind, randomised, phase 3 trial evaluating the effect of denosumab on bone metastasis-free survival in men with castrate-resistant prostate cancer. Asia-Pacific journal of clinical oncology. 2011;7(190):XR EMBASE 70587004	More recent results available
Smith M, Saad F, Shore N et al. Denosumab delays development of multiple bone metastases in men with castrate-resistant prostate cancer. Journal of urology. 2012;187(4 SUPPL. 1): e278	More recent results available
Smith MR, Antonarakis ES, Ryan CJ, Berry WR, Shore ND, Liu G, Alumkal JJ, Higano CS, Chow Maneval E, Bandekar R, de Boer CJ, Yu MK, Rathkopf DE. Phase 2 Study of the Safety and Antitumor Activity of Apalutamide (ARN-509), a Potent Androgen Receptor Antagonist, in the High-risk Nonmetastatic Castration-resistant Prostate Cancer Cohort. Eur Urol. 2016 May 6. pii: S0302-2838(16)30133-6. doi: 10.1016/j.eururo.2016.04.023. [Epub ahead of print]	Non-relevant outcome
Smith MR, Antonarakis ES, Ryan CJ, Berry WR, Shore ND, Liu G, et al . ARN-509 in men with high risk non-metastatic castration-resistant prostate cancer. European Journal of Cancer, 2013;49, S695	No results
Smith MR, Antonarakis ES, Ryan CJ, et al. 761 PD. Novel antiandrogen ARN-509 in high-risk non-metastatic (M0) castration-resistant prostate cancer(CRPC). Ann Oncol 2014;25 (suppl 4): iv258-iv259 doi:10.1093/annonc/mdu336.9	No results
Smith MR, Cook R, Lee K-A & Nelson JB. Disease and host characteristics as predictors of time to first bone metastasis and death in men with progressive castration-resistant nonmetastatic prostate cancer. Cancer, 2011;117, 2077-2085	Non-relevant outcome

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Smith MR, Fizazi K, Miller K et al. Denosumab in men with nonmetastatic castration-resistant prostate cancer (CRPC) at high risk for bone metastases. European journal of cancer. 2013;49:S682	Non-relevant outcome
Smith MR, Saad F, Oudard S, Shore N, Fizazi K, Sieber P, Tombal B, Damiao R, Marx G, Miller K, Van Veldhuizen P, Morote J, Ye Z, Dansey R, Goessl C. Denosumab and bone metastasis-free survival in men with nonmetastatic castration-resistant prostate cancer: exploratory analyses by baseline prostate-specific antigen doubling time. J Clin Oncol. 2013 Oct 20;31(30):3800-6. doi: 10.1200/JCO.2012.44.6716.	Non-relevant outcome
Smith MR, Saad F, Shore ND et al. Effect of denosumab on prolonging bone-metastasis-free survival (BMFS) in men with nonmetastatic castrate-resistant prostate cancer (CRPC) presenting with aggressive PSA kinetics. Journal of clinical oncology. 2012;30(5 SUPPL. 1)	More recent results available
Solaric M, Grgic M, Omrcen T, Petkovic M, Frobe A, Belaj N, et al. [Clinical guidelines for diagnosing, treatment and monitoring patients with prostate cancer--Croatian Oncology Society and Croatian Urology Society, Croatian Medical Association]. Lijecnicki Vjesnik, 2013; 135(11-12), 298-305	Non-relevant outcome
Song DY, Narang A, Robertson RP, et al. Very high-risk localized prostate cancer: Outcomes following definitive radiation. J Clin Oncol 33, 2015 (suppl 7; abstr 36)	Non-relevant indication
Studer UE, Whelan P, Albrecht W et al. Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent European Organisation for Research and Treatment of Cancer (EORTC) Trial 30891. Journal of clinical oncology official journal of the American Society of Clinical Oncology. 2006;24(12): 1868-76	Non-relevant indication
Studer UE, Whelan P, Wimpissinger F et al. Differences in time to disease progression do not predict for cancer-specific survival in patients receiving immediate or deferred androgen-deprivation therapy for prostate cancer final results of EORTC randomized trial 30891 with 12 years of follow-up. European urology. 2014;66(5): 829-38	Non-relevant indication
Suzuki K, Kuss I, Smith MR & Fizazi K. ARAMIS trial: Efficacy and safety of ODM-201 in men with high-risk nonmetastatic castration-resistant prostate cancer. Annals of Oncology, 2016;27(Supplement 7), vii106	No results
Sweeney C, Xie W, Regan MM, et al. Disease-free survival (DFS) as a surrogate for overall survival (OS) in localized prostate cancer (CaP). Journal of Clinical Oncology 34, no. 15_suppl (May 20 2016) 5023-5023.	No results
Talwar S, Cohen SM, Romas NA & Ennis RD. Phase I/II study of sorafenib concurrent with androgen deprivation and radiotherapy in treatment of intermediate- and high-risk localized prostate cancer. Journal of Clinical Oncology, 2010;28(15 SUPPL 1), no pagination	Non-relevant indication
Taplin M-E & Montgomery RB. ARMOR2: Galeterone in progressive CRPC patients who have failed oral therapy. Journal of Clinical Oncology, 2014;32(4 SUPPL 1), no pagination	Non-relevant outcome
Terao S, Shirakawa T, Acharya B, Miyata M, Hinata N, Tanaka K, et al . A pilot study of quality of life of patients with hormone-refractory prostate cancer after gene therapy. Anticancer Research, 2009;29(5), 1533-1537	Non-relevant outcome
Tombal B, Cornel EB, Persad R, Stari A, Gomez Veiga F& Schulman C. Clinical Outcomes and Testosterone Levels Following Continuous Androgen Deprivation in Patients with Relapsing or Locally Advanced Prostate Cancer: A Post Hoc Analysis of the ICELAND Study. J Urology, 2017;198, 1054-1060	Non-relevant indication
Tombal B, Damber J-E, Malmberg A, et al. Degarelix monotherapy versus luteinizing hormone-releasing hormone (LHRH) agonists plus antiandrogen flare	Non-relevant indication

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protection in the treatment of men with advanced prostate cancer. Journal of Clinical Oncology 32, no. 4_suppl (February 1 2014) 86-86.	
Tombal B, Hussain M, Penson D, Attard G, Sternberg CN, Phung D, et al . Patient-reported outcome measures in men with non-metastatic castration-resistant prostate cancer: Baseline data from the PROSPER trial. European Urology, Supplements, 2018;17(2), e870-e871	Non-relevant outcome
Uemura H, Kimura T, Yoshimura K, Minami T, Nozawa M, Nakagawa T, et al . Combination therapy of peptide vaccines and dexamethasone for chemotherapy naive castration resistant prostate cancer-a randomized phase-2 study. European Urology, Supplements, 2013;12(1), e98-e99	Non-relevant indication
Veccia A, Ortega C, di Lorenzo G, et al. Clinical outcomes of patients (pts) age 60 or younger treated with docetaxel (DOC) for castration-resistant prostate cancer (CRPC): Results of an Italian multicenter retrospective study (CYCLOP study). Journal of Clinical Oncology 32, no. 4_suppl (February 1 2014) 214-214.	Non-relevant indication
Veccia A, Ortega C, di Lorenzo G, et al. Clinical outcomes of patients (pts) age 80 or older treated with docetaxel (DOC) as first-line chemotherapy for castration-resistant prostate cancer (CRPC): Results of an Italian multicenter retrospective study (DELPHI study). Journal of Clinical Oncology 32, no. 4_suppl (February 1 2014) 92-92.	Non-relevant indication
Vicier C, Faivre L, Lesaunier F, et al. Modelling relapse in patients with high-risk localised prostate cancer treated randomly in the GETUG 12 phase III trial reveals two populations of relapsing patients. Ann Oncol (2016) 27 (suppl 6): doi:10.1093/annonc/mdw372.07.	Non-relevant indication
Von Moos R & Skacel T. Denosumab: First data and ongoing studies on the prevention of bone metastases. Recent Results Cancer Res, 2012;192, 187-196	More recent results available
Walczak JR & Carducci MA. Phase 3 randomized trial evaluating second-line hormonal therapy versus docetaxel-estramustine combination chemotherapy on progression-free survival in asymptomatic patients with a rising prostate-specific antigen level after hormonal therapy for prostate cancer: An Eastern Cooperative Oncology Group (E1899), intergroup/Clinical Trials Support Unit study. Urology, 2003;62, 141-146	Non-relevant indication
White R, Khor R, Bressel M, Bowden P, Williams S, Duchesne G, et al. High dose palliative radiotherapy for localised, castrate resistant prostate cancer. Journal of Medical Imaging and Radiation Oncology, 2013;57, 44	Non-relevant outcome
White R, Khor R, Bressel M, Duchesne G, Williams S, Bowden P, Tai K, Foroudi F. Efficacy of high-dose palliative radiotherapy for localised, castration-resistant prostate cancer. Clin Oncol (R Coll Radiol). 2015 Jan;27(1):16-21. doi: 10.1016/j.clon.2014.09.013.	Non-relevant outcome
Williams S, Davis ID, Sweeney C, et al. Randomised phase 3 trial of enzalutamide in androgen deprivation therapy (ADT) with radiation therapy for clinically localised high-risk or node-positive prostate cancer: ENZARAD (ANZUP 1303). Journal of Clinical Oncology 35, no. 15_suppl TPS5096	Non-relevant indication
Wilson KL, Foley KA. PSA Monitoring and Results Among Men with Non-Metastatic Prostate Cancer. Value in Health 2014;17(3), A96	Non-relevant indication
Wirth M, Tammela T, Cicalese V, Gomez Veiga F, Delaere K, Miller K, Tubaro A, Schulze M, Debruyne F, Huland H, Patel A, Lecouvet F, Caris C, Witjes W. Prevention of bone metastases in patients with high-risk nonmetastatic prostate cancer treated with zoledronic acid: efficacy and safety results of the Zometa European Study (ZEUS). Eur Urol. 2015 Mar;67(3):482-91. doi: 10.1016/j.eururo.2014.02.014.	Non-relevant indication

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Wirth M. Hormonal therapy for locally advanced prostate. International Journal of Urology, 2012;19, 453	Non-relevant indication
Wong S, Miller K, Smith MR et al. Denosumab in men with nonmetastatic castration-resistant prostate cancer (CRPC) and PSA doubling time (PSADT) < 6 months-a post-hoc analysis of a randomised trial. BJU international. 2013;111(37-8):XR EMBASE 71037585	Non-relevant outcome
Wong S, Smith M, Oudard S et al. Bone metastasis-free survival in men with castrationresistant prostate cancer treated with denosumab Sub-group analyses from a phase III randomised, double-blind trial. Asia-Pacific journal of clinical oncology. 2012;8(41-2)	Non-relevant indication
Wong S, Smith M, Oudard S et al. Denosumab and bone metastasis-free survival in men with castrate-resistant prostate cancer Subgroup analyses from an international, double-blind, randomised, phase 3 trial. Journal of oncology pharmacy practice. 2012;18:21	Non-relevant indication
Wu S. Efficacy of new agents on advanced castration-refractory prostate cancer with RAPID progression. Journal of Clinical Oncology 32, no. 4_suppl (February 1 2014) 257-257.	Non-relevant outcome
Xie W, Sweeney C, Regan M, et al. Metastasis free survival (MFS) is a surrogate for overall survival (OS) in localized prostate cancer (CaP). Ann Oncol 2016;27 (suppl 6): doi:10.1093/annonc/mdw372.01.	No results
Ye F, Hendrix LH, Waddle MR, et al. Population-based evaluation of treatment patterns and survival of localized prostate cancer (CaP) patients with high prostate-specific antigen (PSA). Journal of Clinical Oncology 32, no. 15_suppl e16008	Non-relevant indication
Yong C, Onukwugha E, Mullins CD, Zuckerman IH, Hussain A, Naslund M. Use of Bone-Modifying Agents Following Androgen Deprivation Therapy for Medicare Non-Metastatic Prostate Cancer Patients. Value in Helath 2014;17(3),A99	Non-relevant indication
Yu EY, Hancock ML, Babicz T, Aronson WJ, Papai Z, Geczi L, et al. Effect of the ERalpha agonist, GTx-758 (250 mg daily), on total and free testosterone, and PSA, in men with castration resistant prostate cancer (CRPC) maintained on LHRH therapy. Journal of Clinical Oncology, 2015;33(15 SUPPL 1), no pagination	Non-relevant outcome
Yu EY, Hancock ML, Babicz T, et al. Evaluation of the ERα agonist, GTx-758 (250 mg daily), in men with metastatic (mCRPC) and nonmetastatic castration-resistant prostate cancer (nmCRPC). Journal of Clinical Oncology 33, no. 7_suppl (March 1 2015) 201-201.	Non-relevant outcome
Yu EY, Hancock ML, Babicz T, Tutrone RF, Ng C, Belkoff L, et al . A phase II open-label trial of GTx-758 in men with castration-resistant prostate cancer: Final analysis of the primary endpoint. Journal of Clinical Oncology, 2016; 34(2 SUPPL 1), no pagination	Non-relevant interventions
Yu EY, Miller K, Nelson J, Gleave M, Fizazi K, Moul JW, et al . Detection of previously unidentified metastatic disease as a leading cause of screening failure in a phase III trial of zibotentan versus placebo in patients with nonmetastatic, castration resistant prostate cancer. Journal of Urology, 2012;188, 103-108	Non-relevant indication
Yu EY, Nathan FE & Higano CS. Detection of metastatic disease as a leading cause of screening failure in a phase III trial of zibotentan versus placebo in patients with nonmetastatic castration-resistant prostate cancer (CRPC). Journal of Clinical Oncology, 2011;29(15 SUPPL 1), no pagination	Non-relevant outcome
Yu EY, Nathan FE & Higano CS. Role of detection of metastatic disease as a leading cause of screening failure in an ongoing phase III trial of zibotentan	Non-relevant outcome

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versus placebo in patients with nonmetastatic castration-resistant prostate cancer (CRPC). Journal of Clinical Oncology, 2011;29(7 SUPPL 1), no pagination	

NICE National Institute for Health and Care Excellence

Patient organisation submission

Enzalutamide for treating non-metastatic hormone-relapsed prostate cancer [ID1359]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Name of organisation	Prostate Cancer UK
3. Job title or position	Policy Manager
4a. Brief description of the organisation (including who funds it). How many members does it have?	Prostate Cancer UK is the UK's leading charity for men with prostate cancer and prostate problems. We support men and provide information, find answers through funding research and lead change to raise awareness and improve care. The charity is committed to ensuring the voice of people affected by prostate disease is at the heart of all we do.

	Prostate Cancer UK has a policy that funding from pharmaceutical and medical device companies will not exceed 5% of its total annual income. During the financial year 2014/2015 donations from such organisations, expressed as a percentage of our total annual income, were less than 0.1%.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Desk research and our own knowledge of the experiences of men. We have spoken with our specialist nurses about their experience of speaking with men in this indication. We have also questioned leading clinicians on approaches to treatment in this indication.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Localised and locally-advanced prostate cancer are largely unsymptomatic. Men with this condition may experience lower urinary tract symptoms including poor stream and frequency. Men with localised and locally advanced prostate cancer, whose PSA levels indicate that they are no longer castrate will, if no visible metastases are identified suffer from the anxiety of having no treatment options available. They will have to wait, receiving periodic scans, to determine whether their prostate cancer has metastasised before any further treatment options are open to them. This is because there are no other treatments licensed for this indication. This will cause particular anxiety in those men with 'high risk' disease, who will experience a rapidly rising PSA, understand the likelihood of prostate cancer progression, but have nothing available to them to prevent or delay that progression. Enzalutamide will enable them to delay progression to advanced prostate cancer which is symptomatic and which includes the following evidence-based symptoms for advanced prostate cancer[i]: • Fatigue.

	• Pain, most commonly caused by prostate cancer that has spread to the bones. • Urinary problems, this includes problems emptying the bladder, incontinence, blood in urine and kidney problems. • Bowel problems including constipation, diarrhoea, faecal urgency, faecal incontinence, pain, bowel obstruction and flatulence. • Broken bones, fractures caused by bone thinning. • Sexual problems, including reduced libido and difficult getting or keeping an erection. • Lymphoedema, primarily around the legs. • Anaemia, caused by damage to bone marrow. • Metastatic spinal cord compression, as cancer cells grow in or near the spine, which evidence suggests can occur in 1 to 12% of patients[ii]. • Hypercalcaemia, caused by calcium leaking from the bones into the blood. • Eating problems It is important to note that men are unlikely to experience all the above symptoms, as some will depend on the treatments received, while others will be the result of metastases and therefore dependent on their location. The severity of symptoms will also differ among men, while the likelihood of some of the most severe symptoms, for example Lymphoedema can be rare and vary between 1-20%[iii]. For some men, living with metastatic prostate cancer can be hard to deal with emotionally, especially as there are no current curative treatments for this stage of the disease. Symptoms and treatments can be draining and make men feel unwell.. The pressure of advanced cancer can also put a strain on relationships. Metastatic prostate cancer and its treatments might mean that partners or family need to do more for patients, such as running the home or caring responsibilities. Additionally, the symptoms of metastatic prostate cancer and the side effects of treatments can make it difficult to work. a partner providing care might not be able to work as much either. Everyday tasks may become more difficult and respite care may be required to give carers a break. As the disease progresses, more palliative care and treatments will be offered. This includes palliative radiotherapy to ease bone pain, blood in urine and swollen lymph nodes

	Men and their carers will benefit from the opportunity for an average 22 months delay progression to advanced prostate cancer and its potential to impact negatively on their quality life.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Currently, men who are castrate resistant but with no visible metastases have no treatment options. They must wait for their cancer to metastasise, receiving periodic tests to diagnose metastases, before treatment options become available to them. More advanced imaging modalities give increased diagnostic scanning accuracy. It is possible that the men in this indication already have advanced prostate cancer, but current imaging techniques are unable to identify metastases. These men will have exhausted or ruled out radical treatment options including radical prostatectomy, radiotherapy and brachytherapy. These men and their carers will experience anxiety at the lack of treatment options, particularly if the man's PSA is rising rapidly.
8. Is there an unmet need for patients with this condition?	Yes, once radical treatment options have been exhausted or ruled out and the man has become castrate-resistant, there are no further treatment options for men until the prostate cancer metastasises elsewhere in the body. Patients are left in limbo, periodically receiving bone scans to determine whether the cancer has metastasised. Once the cancer progresses, treatment options for metastatic prostate cancer will be available to these patients.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The PROSPER trial has found that this treatment delays the progression of prostate cancer by an average of 22 months. This is 22 months without progression to the point where the man suffers from the symptoms of advanced protate cancer. . Research has found metastases free survival is a strong surrogate of overall survival in prostate cancer[iv]. This treatment gives patients the ability to actively treat their condition rather than to just wait for their cancer to progress. It can delay the time that the patient can live without the symptoms and side-effects associated with advanced prostate cancer. For men with chronic comorbiditiesThis treatment has the potential to delay prostate cancer progression to the point of non-cancer specific mortality.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The label and license have yet to be granted for enzalutamide in this indication. But, common side effects are tiredness, headache, hot flushes and hypertension. Other important side effects include falls, fractures, cognitive disorder (problems with thinking, learning and memory), and neutropenia. In addition, seizures can occur in around 5 patients in 1,000.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	As the clinical trial for apalutamide (PROSPER) and the licence will likely reflect, this treatment will be more effective in patients the representing companies have classified as 'high risk' non-metastatic castrate-resistant prostate cancer. High risk is defined as a prostate-specific antigen doubling time of 10 months or less during continuous androgen-deprivation therapy. Further analysis of the data from the PROSPER trial may find stratified patient groups are more or less likely to benefit from the treatment. Patients in the PROSPER trial were stratified according to PSA doubling time (>6 months vs. <6 months), and previous or current use of a bone targeting agent at baseline.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None

Other issues	
13. Are there any other issues that you would like the committee to consider?	There is not yet clear evidence on whether it is better to take enzalutamide at this stage, later in the prostate cancer pathway or on the impact of rechallenge with enzalutamide. Enzalutamide gives an average increase in overall survival of 5 months to M1CR patients. Enzalutamide in M0CR gives metastases free survival of 22 months. Research has found metastases free survival is a strong surrogate of overall survival in prostate cancer[v]. Currently, the NHS does not allow abiraterone or enzalutamide to be taken in sequence by patients due to the lack of evidence supporting a second novel treatment. However, the SPARTAN study into apalutamide for non-metastatic castrate-resistant prostate cancer includes data on the use of a second novel treatment in the prostate cancer pathway which could be relevant to the consideration of enzalutamide in this indication and in allowing subsequent novel treatments to be prescribed.

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- There is currently unmet need with no treatment options available to men with M0CR prostate cancer. However, More advanced imaging modalities give increased diagnostic scanning accuracy. It is possible that the men in this indication already have advanced prostate cancer, but current imaging techniques are unable to identify metastases.
- The lack of treatment options can cause great anxiety to men and then carers, who can see evidence of cancer progression with a rising PSA level.
- This treatment improves metastases free survival, delaying the time before the patient becomes symptomatic and so improving their quality of life.
- Evidence is emerging on the efficacy of rechallenge or the use of second novel treatments in the prostate cancer treatment pathway.
- Metastases free survival is the primary end point under consideration in this appraisal. Research has found metastases free survival is a strong surrogate of overall survival in prostate cancer.

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[i] References for each symptom available on request.
[ii] European Urology Volume 44 Issue 5 *Spinal Cord Compression in Metastatic Prostate Cancer* H Tazi et al. November 2003
[iii] Journal of Lymphoedoma Volume 5 Number 2 *Cancer-related lymphoedema in males: a literature review* Cosgriff & Gordon 2010
[iv] http://ascopubs.org/doi/10.1200/JCO.2017.73.9987
[v] http://ascopubs.org/doi/10.1200/JCO.2017.73.9987

NICE National Institute for Health and Care Excellence

Professional organisation submission

Enzalutamide for treating non-metastatic hormone-relapsed prostate cancer [ID1359]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you

NICE National Institute for Health and Care Excellence

1. Your name	[redacted]
2. Name of organisation	**NCRI-ACP-RCP-RCR**
3. Job title or position	**RCP registrar**
4. Are you (please tick all that apply):	an employee or representative of a healthcare professional organisation that represents clinicians? a specialist in the treatment of people with this condition? a specialist in the clinical evidence base for this condition or technology? other (please specify):
5a. Brief description of the organisation (including who funds it).	**NCRI-ACP-RCP-RCR**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim of treatment in non-metastatic castration-resistant prostate cancer is to • Prolong overall survival (OS) (cure is not considered possible). • Delay onset of metastases (prevent progression) • Maintain quality of life (QOL) • Improve progression-free survival (PFS) • Reduce skeletal related events (SREs).
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Treatment success in this setting is monitored by failure to develop metastatic disease whilst on treatment, but this has no clinical or symptomatic effect on the patient per se. In the setting being discussed here, there is no disease to monitor radiologically. If the patient has a very fast PSA doubling time we may accept a stabilisation of PSA as a treatment objective. Patients with non-metastatic CRPC have no symptoms due to cancer, unless they have untreated primary disease in the prostate. The objective of treatment is therefore to delay the onset of metastases (as documented on CT, bone scan, PET or MRI imaging), maintain QOL and to prolong survival.

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Currently this condition may sometimes be treated with sequential use of unproven therapies such as Bicalutamide and Dexamethasone Thereafter, if both of these agents fail, the patient and clinician must wait until metastases develop before Enzalutamide or Abiraterone can be prescribed within the NHS. It is difficult for a clinician not to be able to offer any further therapy until the disease becomes metastatic, but by definition the patients are asymptomatic at this point. This can be a time of anxiety for patients. There is an unmet need for a treatment which improves MFS after Bicalutamide and Dexamethasone have failed to control PSA. However, this group of patients is very small. Most clinicians now do not start ADT in the setting of PSA-only failure, hence few patients will develop castration-resistant disease in the non-metastatic setting. In addition, for many patients with PSA failure, we can find the source of the PSA (ie locate the metastases) as imaging modalities have improved. These patients will proceed down the metastatic prostate cancer treatment pathway.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	As above – Bicalutamide as part of maximal androgen blockade (MAB) or dexamethasone.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	[1]NCCN (US) guidelines mention non-metastatic CRPC, other guidelines do not. 1. National Comprehensive Cancer Network prostate cancer guidelines Version 4.2018. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The early part of the pathway is well defined: MAB followed by dexamethasone and we would consider this to be standard across UK.
• What impact would the technology have on the current pathway of care?	It would bring Enzalutamide from the metastatic to the non-metastatic part of the treatment paradigm for the minority of patients who develop CRPC with a rapid psa doubling time before metastases.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Enzalutamide will be delivered and monitored in the same way as it is in metastatic prostate cancer, just used earlier in the patient pathway.
• How does healthcare resource use differ between the technology and current care?	This drug is already NICE approved, just later in the pathway. This would not significantly increase workload for hospitals or oncologists. In some centres, it is possible that the care of these patients will shift from urology to oncology services.

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist oncology or urology clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None, already a drug we use.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	If the drug delays the onset of metastatic disease, this may be associated with improved QOL but this has not been proven yet. The drug delays time to next therapy which may maintain QOL for longer, but again this is not shown in the current evidence.
• Do you expect the technology to increase length of life more than current care?	Overall survival benefit has not been shown to date in this setting. Conversely, Enzalutamide has already been shown to produce a 3 month survival advantage in the metastatic setting.

• Do you expect the technology to increase health-related quality of life more than current care?	Not demonstrated at this point. However, as these patients have a low symptom burden from their cancer, it is unlikely that HRQOL will improve during treatment, although there may be a delay until the time of deterioration in HRQOL.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
The use of the technology	

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Enzalutamide requires closer monitoring than MAB and dexamethasone (monthly initially vs 3 monthly) hence patients will need more clinic appointments and blood tests in this scenario. However, this will be offset by (we presume) not having access to Enzalutamide again in the metastatic setting.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment will continue until development of radiologically proven metastases, either without associated symptoms.

15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	There is a large DFS benefit but no QOL or OS benefit shown to date and therefore we would not consider this a significant and substantial improvement for patients.
• Is the technology a 'step-change' in the management of the condition?	No. It may represent an incremental improvement but is not a step change.

• Does the use of the technology address any particular unmet need of the patient population?	It would provide another line of therapy for these patients.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Possible side effects include fatigue and cognitive changes. These are usually reversible and not usually serious or life-threatening but these can adversely affect QOL.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	UK practice generally will not start ADT for PSA only failure, unless the PSA is rising very fast, so the scenario of non-metastatic CRPC is rare and should become rarer due to more sensitive imaging in the future. These patients are therefore not common in UK practice.
• If not, how could the results be extrapolated to the UK setting?	The eligible population will be small in the UK.

• What, in your view, are the most important outcomes, and were they measured in the trials?	Overall survival is the most important outcome and there is no evidence of an overall survival benefit for in this setting yet. QOL data is not yet presented – this is an important endpoint in this trial.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Metastasis Free Survival (MFS) has been found to be a surrogate of overall survival in castration resistant prostate cancer, but does not always translate thus.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None that we are aware of.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

20. Are you aware of any new evidence for the comparator treatment(s) since the publication of the relevant NICE technology appraisal guidance?	The PROSPER[2] and SPARTAN[3] trials were published almost simultaneously. The SPARTAN study was conducted in the equivalent patient population but used Apalutamide as the investigational agent. This showed very similar results to PROSPER (MFS benefit but no OS benefit). 2. Enzalutamide in Men With Non-Metastatic, Castration-Resistant Prostate Cancer. Hassan M, Fizzazi K, Saad F, *et al.* N Engl J Med 2018; 378:2465-2474 3. Apalutamide Treatment and Metastasis-Free Survival in Prostate Cancer. Smith MR, Saad F, Chowdury S *et al*. N Engl J Med 2018; 378:1408-1418
21. How do data on real-world experience compare with the trial data?	Not used in the 'real world' in this scenario. The drug is well tolerated in the metastatic setting.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

22b. Consider whether these issues are different from issues with current care and why.	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Enzalutamide improves MFS but not OS in the non-metastatic castration-resistant setting
- Improving MFS may delay symptomatic progression of disease but is not always a surrogate for OS
- This trial would move Enzalutamide from metastatic to non metastatic setting for the small minority of patients who initially have non-metastatic, castration-resistant prostate cancer
- No QOL data has been presented
- There is no clear benefit to moving Enzalutamide from the metastatic setting, where there is evidence of a significant survival advantage, to the non-metastatic setting where there is not.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NHS England submission on the use of enzalutamide in high risk non metastatic castration resistant prostate cancer (nmCRPC)

1. Currently many high risk nmCRPC patients will have (in addition to the anti-androgen therapy they are already on) trials of treatment with 1st generation anti-androgen receptor drugs (such as bicalutamide) as additional therapy and then on withdrawal of therapy. Steroids such as dexamethasone are also used at low doses. Neither bicalutamide or steroids have any randomised trial evidence base to support use as treatment to delay metastatic spread or increase survival in the nmCRPC setting. Enzalutamide is the first agent to demonstrate a clear impact on at least metastasis-free survival. Apalutamide is a second agent to also show this benefit and this will be appraised by NICE and very probably this committee next year.
2. NHS England notes the modest duration of follow-up in the PROSPER trial population of patients who have a life-expectancy measured in a considerable number of years. The current differences between the enzalutamide and placebo arms in terms of times to next treatment and subsequent treatment rates could largely relate to the current modest duration of follow-up. The key outcome of overall survival is awaited in respect of the PROSPER trial design randomising patients to early enzalutamide before metastatic spread vs enzalutamide/abiraterone at the time of metastatic spread. As yet there is no evidence of any benefit in overall survival with use of enzalutamide in the nmCRPC setting.
3. Enzalutamide has significant toxicity, in particular this being fatigue. It also exacerbates osteoporosis, particularly when taken for extended periods of time (as is likely in this nmCRPC setting). NHS England would wish the costs of identifying and treating osteoporosis taken into consideration in the cost effectiveness analyses eg for treatment with zoledronic acid. NHS England notes the higher (but small) number of cardiac deaths in the enzalutamide arm (despite the 2:1 randomisation).
4. The imaging to show an absence of metastasis at entry into the PROSPER trial was with CT or MR scans and isotope bone scans. Imaging is becoming much better (more sensitive and more specific) in prostate cancer with PSMA PET scans and whole body MRI scans. These new types of scan are pushing more patients into the mCRPC category and this trend will increase as these types of imaging become more widespread. The numbers of patients with nmCRPC will therefore reduce.
5. The duration of therapy with enzalutamide in the NHS will be significantly longer than in the PROSPER trial. This is for several reasons. The first is that in routine practice regular imaging will be far less frequent than in the PROSPER trial which was every 16 weeks. Some patients and clinicians will elect to have no imaging until the development of symptoms. Other patients and clinicians will agree to annual scanning, others to scans every 6 months. Thus mCRPC will be detected at a later time. The second reason will be that many patients who start with nmCRPC who

remain well but have seemingly indolent and modest disease progression (and thus have mCRPC) will then continue treatment with enzalutamide until they become symptomatic or develop further disease progression, particularly with visceral disease. A third reason is that for many patients with CRPC who would not tolerate docetaxel chemotherapy, the treatment option of enzalutamide offers them the greatest chance of benefit of any systemic therapy. Unless they are symptomatic or have visceral metastasis or have rapidly progressive disease, patients and clinicians will be reluctant to discontinue enzalutamide. Thus the extra costs of enzalutamide must be taken into account in the cost effectiveness model. The benefit of such continued enzalutamide is unknown but likely to be modest at best.

6. The modelled use of subsequent therapies after either enzalutamide given for nmCRPC or enzalutamide administered for mCRPC is likely to be similar. NHS England estimates that about 40% would have docetaxel and 20% or less cabazitaxel. Since only about 25% or less of patients have bone metastases which would be indicated for treatment with radium 223 and such patients represent part of the population relapsing with mCRPC, the use of radium-223 would be in 10-20% of all patients.
7. NHS England notes some of the subsequent therapies recorded in the PROSPER trial. Denosumab for prostate cancer is not recommended by NICE and nor does it offer a survival benefit. Sipuleucel T's marketing authorisation was withdrawn in 2015 at the request of its manufacturer; it was never appraised by NICE. Carboplatin is not used in England for the treatment of adenocarcinoma of the prostate and no other histologies were allowed entry into the PROSPER trial.
8. NHS England does not commission the sequential use of abiraterone and then on progression a treatment switch to enzalutamide and vice versa. This is because of very much reduced efficacy observed in the second place in the sequence and the absence of any information as to the cost effectiveness of the use of the second drug in the sequence.
9. If NICE recommends the use of enzalutamide for patients with nmCRPC, NHS England will only commission its use when patient care on enzalutamide is supervised by an oncologist. This is because oncologists have the necessary training in systemic anti-cancer therapies, they have the nursing teams in their practises which also have appropriate training in systemic anti-cancer therapies and the oncologists and the nurses have the expertise in assessing what other systemic therapies (eg docetaxel, radium-223) and active local treatments (eg palliative radiotherapy) would be appropriate..
10. If NICE recommends the use of enzalutamide for patients with nmCRPC, NHS England would currently wish (in the absence of knowing any considerations and conclusions by the NICE Technology Appraisal Committee) to consider setting the following treatment criteria which would all have to be satisfied for access to enzalutamide to be funded: i) histologically or cytologically confirmed diagnosis of adenocarcinoma of the prostate, ii) disease progression on androgen deprivation

therapy, iii) asymptomatic prostate cancer, iv) continuing androgen deprivation therapy, v) no prior or present evidence of metastatic disease on at least recent CT/MR and isotope bone scans, vi) a PSA doubling time of ≤10 months, vii) patient fit enough to tolerate a potentially long duration of treatment with enzalutamide, viii) a risk assessment if patient has clinically significant cardiovascular disease.

Prof Peter Clark

NHS England Chemotherapy Lead and National Clinical Lead for the Cancer Drugs Fund

November 2018

Enzalutamide for treating non-metastatic hormone-relapsed prostate cancer

Produced by Aberdeen HTA Group

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Rider on responsibility for report

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

This report should be referenced as follows:

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Graham Scotland acted as the lead health economist for this appraisal and supervised Huey Chong who acted as the health economist. Together they critiqued the cost-effectiveness evidence, checked the economic model, and conducted further sensitivity analyses. Lorna Aucott acted as the lead statistician for this appraisal and supervised David Cooper, who acted as the statistician: critiqued the statistical methods presented in the submission, checked the numerical results, analyses, tables, and figures related to the review of the clinical effectiveness evidence. Clare Robertson acted as systematic reviewer: critiqued the company's definition of the decision problem and the clinical effectiveness evidence and critiqued the methods used for identifying relevant studies and checked the search strategies used in the submission. Gordon Urquhart acted as clinical expert: provided clinical advice and general guidance. Craig Ramsay acted as project lead for this appraisal: contributed to the critique of the clinical effectiveness methods, checked the final report and supervised the work throughout the project.

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ADT	Androgen deprivation therapy
BICR	Blinded independent central review
BPI-SF	Brief pain inventory – Short form
CI	Confidence interval
CS	Company submission
CSR	Clinical study report
HRPC	Hormone-relapsed prostate cancer
HRQOL	Health-related quality of life
IA1	First interim analysis
IA2	Second interim analysis
ICER	Incremental cost-effectiveness ratio
ITT	Intention to treat
MFS	Metastasis-free survival
nmHRPC	Non-metastatic hormone-relapsed prostate cancer
OS	Overall survival
PFS	Progression free survival
PFS	Progression free survival
PPS	Post-progression survival
PrePS	Pre-progression survival
PSA	Prostate-specific antigen
PSADT	PSA doubling time
RCT	Randomised controlled trial
SmPC	Summary of product characteristics
TEAE	Treatment-emergent adverse event
TTD	Time to treatment discontinuation

1 Summary

Prostate cancer is the most common male cancer in the UK and is the second most common cause of cancer deaths in men in the UK. Androgen deprivation therapy (ADT) is one of several treatment options for hormone-sensitive prostate cancer but, as the disease progresses, ADT becomes less effective, at which point the disease stage is known as hormone-relapsed prostate cancer (HRPC). Metastatic disease is associated with a deterioration in health-related quality of life (HRQOL), increased symptom burden and increased risk of death. Treatment options for people with high risk nmHRPC are therefore required to delay the onset of metastases and disease progression.

The company note that incidence and prevalence data for high-risk nmHRPC are rare. Based on the results of a physician survey it is estimated that the incidence of metastatic and non-metastatic HRPC patients in the UK is [redacted], corresponding to [redacted] per 100,000 men, in 2018 and that [redacted]% ([redacted]) of these HRPC patients are non-metastatic. UK clinical experts indicated that 60% of nmHRPC patients could be assumed to match the company's criteria for high risk of developing metastatic disease.

1.1 Critique of the decision problem in the company submission

The company's description of high risk non-metastatic hormone-relapsed prostate cancer (nmHRPC) in terms of prevalence, symptoms and complications appears generally accurate and appropriate to the decision problem. The ERG believe the company's description of current service provision is accurate. Presently, there is no specific UK or European guidance for the management of people with nmHRPC and no current treatment has demonstrated significant survival benefits in this patient group. The European Association of Urology (EAU) guidelines note that the modest potential benefits of continuing ADT treatment outweigh the treatment risks and, therefore, recommend ADT be continued indefinitely in people with HRPC.

The company state that they expect that enzalutamide would be used with ADT as the first line treatment for high risk nmHRPC, with the aim of delaying the development of metastases and the associated deterioration in HRQOL. Current NICE guidance

recommends enzalutamide or abiraterone, in conjunction with ADT, once patients progress to the asymptomatic/mildly symptomatic metastatic disease stage. Symptomatic patients can be offered docetaxel with ADT, or ADT alone, and those who progress during or after docetaxel can be offered cabazitaxel, radium-223 or best supportive care. Abiraterone and enzalutamide can be offered to patients who have not previously received these treatments. NICE do not recommend sequential enzalutamide and abiraterone treatment and, therefore, nmHRPC patients who receive enzalutamide as a first line treatment in the proposed future care pathway will not be able to receive abiraterone or enzalutamide at later stages of the disease under the current guideline restrictions.

1.1.1 Population

The NICE final scope for this appraisal specified the population as adults with nmHRPC. The company submission (CS) addresses adults with high risk nmHRPC. The company define high risk as PSADT being $\leq$10 months and a PSA $\geq$2 ng/mL.

1.1.2 Intervention

The intervention in both the NICE final scope and the CS is enzalutamide with ADT. Enzalutamide is an androgen receptor (AR) signalling inhibitor that targets the AR signalling pathway. Enzalutamide currently has European Medicines Agency (EMA) approval for the treatment of adults with metastatic castrate resistant prostate cancer (mCRPC) who are asymptomatic or mildly symptomatic after ADT failure in the chemotherapy naïve setting and adults with mCRPC whose disease has progressed in the post-chemotherapy (docetaxel) setting. The company note that a type II variation has been submitted to the EMA to include market authorisation for the treatment of adults with high risk nmHRPC (the population indicated in the CS) and final authorisation for this indication is expected by November 2018.

1.1.3 Comparator

The NICE final scope and the CS specify the comparator as ADT. The company state that although no treatments are currently recommended specifically for nmHRPC patients, several European and International guidelines recommend continued use of ADT. The ERG note that apalutamide for treating localised hormone-relapsed prostate cancer is currently under draft scoping with NICE (ID1174). The ERG also note that

bicalutamide is not a proposed comparator for enzalutamide. The ERG view is that, while the benefits of ADT in this setting are unclear, ADT is the only valid comparator for enzalutamide.

1.1.4 Outcomes

The company submission included all the outcomes listed in the NICE final scope and reports additional outcomes: time to next therapy for prostate cancer, time to treatment discontinuation, time to first use of cytotoxic chemotherapy, chemotherapy-free disease specific survival, chemotherapy-free survival, time to pain progression and PSA response rates.

1.2 Summary of clinical effectiveness evidence submitted by the company

The company provide evidence for the effectiveness of enzalutamide plus ADT from the PROSPER RCT, with data from the STRIVE RCT presented as supporting evidence. PROSPER is a manufacturer-sponsored, international, double-blind, phase 3 trial of 1401 participants, comparing enzalutamide (at a dose of 160mg daily) (n=933) versus placebo (n=468) in people with nmHRPC. The primary end point was MFS, which was defined as the time from randomisation to radiographic progression, or as the time to death without radiographic progression. STRIVE was a multicentre, phase 2 trial which was conducted in the US and compared enzalutamide versus bicalutamide in people with both metastatic and, high- and non-high risk, non-metastatic HRPC. Only a subset of the N=396 STRIVE participants were high risk nmHRPC (enzalutamide N=70; bicalutamide N=69). The primary end point in STRIVE was progression free survival (PFS). The company did not include data from STRIVE in their economic model. Main reasons given for this are the smaller sample size of STRIVE compared to PROSPER, the fact that STRIVE was conducted in the US population, STRIVE and PROSPER differed in their assessed endpoints, OS data, in particular, was not collected in STRIVE, and the fact that bicalutamide was not included in the remit of the NICE final scope.

In PROSPER the sample size was determined as a total of 440 MFS events to provide 90% power to detect a target HR of 0.72 based on a two-sided log-rank test and an overall significance level of 0.05. Allowing for 10% loss to follow up, the target sample size was 1,440 (960 enzalutamide and 480 placebo). No interim

analyses/stopping rules were pre-planned for any outcomes apart from overall survival. For overall survival, three interim and one final analysis was pre-specified at 135, 285, 440 and 596 death events respectively. At time of submission, the OS data are immature with only the first two interim analyses available.

In STRIVE a minimum of 231 PFS events provided 90% power to detect a HR of 0.65 based on a two-sided log-rank test with 5% significance level. No interim analyses were planned.

In the opinion of the ERG, both trials are of overall good quality with little risk of bias.

The ERG agrees with the company that the baseline characteristics of the UK participants are similar to the wider PROSPER participants. The ERG believes that the nmHRPC participants in the enzalutamide arm of the STRIVE trial are broadly comparable to the participants in the enzalutamide arm of the PROSPER trial.

The PROSPER trial showed a statistically and clinically significant 70.8% risk reduction of an MFS event (hazard ratio [HR] 0.292, 95% CI [0.241, 0.352], p<0.0001) in favour of enzalutamide. The ERG considers there is strong evidence of a difference in MFS in PROSPER favouring enzalutamide and that the differences are consistent across predefined subgroups.

Treatment with enzalutamide in PROSPER was associated with a 93.4% reduction in risk of PSA progression (HR: 0.066, 95% CI: [0.054; 0.081], p<0.0001). In total, 142 patients in PROSPER (15.2% of the enzalutamide arm and 48.3% of the placebo arm) received post-baseline first use of a new antineoplastic therapy. The median time to first use of a new antineoplastic therapy was 39.6 months in the enzalutamide arm and 17.7 months in the placebo arm, a difference of 21.9 months (HR: 0.208, 95% CI: [0.168; 0.258], p value<0.0001)

At second interim analysis, overall survival HR was [redacted] in favour of enzalutamide.

The ERG notes that enzalutamide is associated with an earlier deterioration in HRQOL due treatment-related symptoms compared to placebo but, overall, enzalutamide is associated with a delay in the worsening of HRQOL.

Patients treated with enzalutamide also had a higher incidence of ≥ Grade 3 TEAEs than the placebo group (31.4% vs 23.4% in the placebo group). ≥ Grade 3 TEAEs with at least a 1% higher incidence in the enzalutamide group included fatigue (2.9% enzalutamide vs 0.6% placebo), asthenia (1.2% vs 0.2%), and hypertension (4.6% vs 2.2%). In the placebo group, > Grade 3 TEAEs with at least a 1% higher incidence than the enzalutamide group include haematuria (1.7% vs 2.8%) and renal failure acute (0.4% vs 1.5%).

The antineoplastic therapy administered to at least 1% of patients in either treatment group after treatment discontinuation is not representative of UK practice. The ERG opinion is that the numbers receiving abiraterone following enzalutamide treatment (37.4%) would unlikely be seen in UK practice, due to the lack of supportive evidence for abiraterone treatment at this stage of the care pathway; participants are more likely to continue with enzalutamide or receive docetaxel. The ERG also notes that the company's economic model assumes that all participants receive either enzalutamide or abiraterone following progression, but the trial data did not follow that assumption making it difficult to translate the clinical findings to a UK setting.

The ERG used the WINBUGS code provided by the Company and were able to reproduce the results of the fixed effects network meta-analysis. As the Company acknowledge, disease progression was assessed with metastases free survival in PROSPER while in STIVE radiographic progression free survival was used, the ERG suggest that a random effects model should therefore have been developed and the results compared as a sensitivity check. The ERG ran a random effects model and obtained NMA results for enzalutamide v placebo of [redacted] for MFS/rPFS and [redacted] for time to PSA progression. The results for Bicalutamide v placebo from the same model are [redacted] for MFS/rPFS and [redacted] for time to PSA progression.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG agree that the evidence on clinical effectiveness provided by the Company shows that there is a beneficial effect from enzalutamide compared to placebo. There is a large effect size on the primary outcome of metastases free survival and the difference between the experimental arm and the control arm are significant. The survival curves and summary statistics show a delay in the development of metastases.

The ERG also agree that the five secondary endpoints highlighted by the Company; time to prostate-specific antigen progression, time to first use of cytotoxic chemotherapy, chemotherapy free survival, chemotherapy-free disease specific survival and time to treatment discontinuation all show hazard ratios and significance levels which indicate a benefit for enzalutamide in comparison to placebo.

The ERG recognise that there is a beneficial effect on MFS from enzalutamide but would question the size of the anticipated overall survival benefit as stated at interim analysis 2. The OS data are immature and not statistically significant by second interim analysis.

The ERG agrees that the safety of enzalutamide in PROSPER is consistent with previous mHRPC studies. There was a higher incidence of TEAEs with enzalutamide primarily driven by hypertension, memory impairment and major adverse cardiac events.

It is the ERG opinion that the biggest weakness with the effectiveness data is that the PROSPER study does not closely match the decision problem because the post progression treatments in PROSPER do not match UK treatment pathways.

1.4 Summary of cost effectiveness submitted evidence by the company

The company's cost-effectiveness evidence is based on a semi-Markov model with three main health states: nmHRPC, mHRPC and death. The mHRPC state incorporates three sub-states (PD1-PD3) to capture progression through subsequent treatment lines for mHRPC, but which are not separately linked with survival in the model. The company model was generally consistent with NICE reference case. The

base case analysis utilised parametric curves for metastases free survival (MFS) and pre and post-progression survival to estimate transitions from nmHRPC to mHRPC by treatment arm, and from nmHRPC and mHRPC to death by treatment arm. Median durations of subsequent treatments for mHRPC, reported in the literature, were used to estimate transition probabilities through the PD sub-states. Health state utility values were applied by health state and were not adjusted by treatment allocation. The model also incorporates common and severe adverse events (AEs) and skeletal related events (SREs) associated with progression to mHRPC. These attract utility decrements for defined durations of time. Costs included in the model are treatment acquisition costs, administration costs where relevant, health care visits and testing costs, hospitalisation costs, costs of concomitant medications, costs of subsequent treatments, costs of AEs and SREs, and costs of palliative care (applied as a one-off cost for end of life treatment). With respect to post-progression treatment sequences, the company assumed a period on ADT alone following progression on enzalutamide (PD1), followed by docetaxel (40%) or ADT alone (60%) at PD2, then BSC at PD3. In the control arm, 100% of the cohort was modelled to receive enzalutamide at PD1, followed by the same sequence at PD2 and PD3 as in the enzalutamide arm.

MFS data from the primary analysis data cut of the PROSPER trial, corresponding to interim analysis one (IA1) for overall survival, was used to model progression from nmHRPC to mHRPC. The ERG are satisfied that this outcome based on radiographic assessment accurately captures the progression event of interest and that the approach to extrapolation is robust. The company also used OS data from the PROSPER IA1 data cut to model pre- and post-progression survival based on the same definition of progression used in the MFS outcome. The company base case ICER comes to £28,853.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG had some concerns about the about the suitability of the PROSPER trial for informing post-progression survival in the model, since the distribution of post-progression treatments in PROSPER differed from the modelled treatment pathway. However, it is reassuring to note that extrapolation of the post progression survival data has been externally validated against OS data from the PREVAIL trial.

PREVAIL compared enzalutamide to placebo in chemotherapy naïve patients with mHRPC. The ERG also had some concerns about:

- The duration that patients would spend on ADT alone following progression to mHRPC on enzalutamide, which in the company base case was based on the median duration that patients spent on placebo in the PREVAIL trial. The ERG requested a scenario based on the observed time from progression to initiation of first antineoplastic treatment in the PROSPER trial to model the transition from PD1 to PD2 in the enzalutamide arm of the model. This reduced the time in state PD1 following progression on enzalutamide and increased the ICER to £31,671
- The assumption that everyone would receive enzalutamide following progression on ADT, when the distribution of first antineoplastic treatments observed in the PROSPER trial suggested a lower cost for PD1 treatments. The ERG requested a scenario analysis where the PD1 treatment cost following progression on ADT was based on the observed distribution. This change increased the ICER to £33,863.
- The fact that the company used the less mature OS data from the IA1 of PROSPER trial in their base case, when more mature IA2 data were available. Whilst the company did provide a scenario that utilised the IA2 OS data, they applied it in conjunction with an extrapolation of time to treatment discontinuation (TTD) from IA2 (to model progression), rather than the more robust measure MFS. This was because the company noted that the MFS analysis was not available for IA2, and so TD was used to split the OS into preTD survival and postTD survival. However, the ERG had concerns about the suitability of TTD as a proxy for progression to mHRPC, and so requested a scenario analysis using the MFS analysis (from the IA1 cut) to model progression in combination with the more mature IA2 OS data from to inform pre and post progression mortality.
- The assumption that people on enzalutamide would visit health care providers and be monitored for progression less frequently on average than people on ADT alone. The ERGs clinical expert was of the opinion that monitoring and testing would be similar between groups.

- The utility value applied to the PD1 mHRPC health state was based on the mean of the first post-progression EQ-5D assessment in PROSPER, without adjustment for baseline. Further, since the EQ-5D measurement schedule was every 16 weeks in PROSPER, the ERG is concerned that the estimated value may account for some people who have already progressed to PD2.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The company have provided a clear explanation and description of their model, which is based on high quality evidence from randomised controlled trials. There is strong evidence for an improvement in MFS based on relatively mature data.

1.6.2 Weaknesses and areas of uncertainty

Key uncertainties relate to:

- The relative immaturity of the OS data in PROSPER, with no significant difference found between the groups at the most recent interim analysis (IA2). Further analyses are planned which would provide more information for modelling.
- The choice of data for modelling progression to mHRPC (MFS or TTD), and the measure of progression that is used to split overall survival by progression status (MFS from the IA1 data cut or TTD from the IA2 data cut).
- The modelled downstream treatment pathways in the enzalutamide and ADT arms of the model, in terms of:
    - Differences between the modelled pathway of subsequent treatments and the subsequent treatments received in the PROSPER trial.
    - Duration of ADT treatment following progression to mHRPC on enzalutamide.
    - The applicability of the modelled treatment pathway to the NHS in England.
- The cost of monitoring and testing patients on enzalutamide and ADT alone.
- The utility value associated with progression to sub-state PD1 in the model.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG conducted several exploratory analyses which included the following:

1. Equalising the testing and monitoring the costs for patients on enzalutamide and ADT in the company model. This increased the ICER to £30,435
2. Increasing the cost of MACE adverse events in the model, which appeared the ERG believed to be undercosted. This increased the ICER only slightly, to £29,058
3. Basing the PD1 mHRPC utility value on the adjusted baseline value that was reported for chemotherapy naïve mHRPC patients in PREVAIL, and was used as the baseline value for the BSC arm in the model for TA377. This increased the ICER to £30,257

Combining these three changes in the model, the ICER increased to £32,132. The ERG then assessed the impact of combining these changes with the scenarios requested from the company; basing the transition from PD1 to PD2 following progression on enzalutamide on the data from PROSPER, and applying the company's MFS curve in combination with pre- and postTD survival extrapolation based on data from IA2. With all these changes incorporated, the ICER for enzalutamide increased to £56,168.

Further uncertainty in the ICER relates to the applicability of the downstream treatment pathway. If shifting enzalutamide further up the treatment pathway results in more time for subsequent lines of therapy compared to the standard care pathway, this could also potentially increase the ICER for enzalutamide. However, it should be noted that changes in mHRPC treatment sequences in the model are not structurally linked to changes in OS, so analyses that explore changes in the downstream distribution of treatments should be treated with caution.

2 Background

2.1 Critique of company's description of underlying health problems

The company's description of high risk non-metastatic hormone-relapsed prostate cancer (nmHRPC) in terms of prevalence, symptoms and complications appears generally accurate and appropriate to the decision problem. Prostate cancer is the most common male cancer in the UK and is the second most common cause of cancer deaths in men in the UK. [1] Androgen deprivation therapy (ADT) is one of several treatment options for hormone-sensitive prostate cancer but, as the disease progresses, ADT becomes less effective, at which point the disease stage is known as hormone-relapsed prostate cancer (HRPC). Although the relationship between hormonal relapse and the development of metastases is unclear, it is estimated that 33% of nmHRPC patients will develop metastases within 2 years. [2] (Astellas. Minutes of the validation interview with a UK clinical expert. 2018. [Unpublished data]) company cites three studies that indicate that absolute prostate specific antigen (PSA) level and PSA doubling time (PSADT), which is the length of time in months for PSA levels to double in an individual patient, are key predictors for the development of metastases. The company defines nmHRPC patients at high risk of developing metastases as "patients with a PSADT of less than or equal to 10 months and a PSA $\geq$2 ng/ml." Metastatic disease is associated with a deterioration in health-related quality of life (HRQOL), increased symptom burden and increased risk of death. Treatment options for people with high risk nmHRPC are therefore required to delay the onset of metastases and disease progression.

The company note that incidence and prevalence data for high-risk nmHRPC are rare, citing a retrospective study [3] of the UK Health Improvement Network primary care database of 8678 patients with prostate cancer, which indicated that 11.2% of patients were at the HRPC stage. The company also cite a survey conducted by Kantar Health to [redacted] physicians in the UK. Based on the results of this survey it is estimated that the incidence of metastatic and non-metastatic HRPC patients in the UK is [redacted], corresponding to [redacted] per 100,000 men, in 2018 and that [redacted]% ([redacted]) of these HRPC patients are non-metastatic. (Kantar-Health. Market Research on CRPC in the UK 2018, [Unpublished data]) There are no specific UK data on the numbers of

nmHRPC classed as high risk, as defined by the company, although the company report in their submission that a UK clinical expert indicated that 60% of nmHRPC patients could be assumed to match the company's criteria for high risk of developing metastatic disease. The ERG clinical advisors agree that 60% is a plausible proportion. The company present data on the expected number of patients eligible for treatment with enzalutamide in the high risk nmHRPC setting from 2019 to 2023, and are reproduced in Table 1 below.

Table 1. Anticipated number of nmHRPC patients eligible for enzalutamide in England between 2019 and 2023 (reproduced from the company submission, budget impact analysis document, page 9)

	2019	2020	2021	2022	2023	Source
Males in England	27,9M	28,1M	28,2M	28,4M	28,6M	ONS projections [4, 5]
New PCa cases (149.2 per 100,000)	41,603	41,879	42,137	42,384	42,620	Cancer Research UK data [1]
HRPC ([redacted] per 100.000 men)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Kantar market data [Unpublished data]
nmHRPC ([redacted]% of all HRPC men)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Kantar market data [Unpublished data]
High-risk nmHRPC (60% of all nmHRPC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Hernandez et al [6] UK clinical expert
Eligible population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

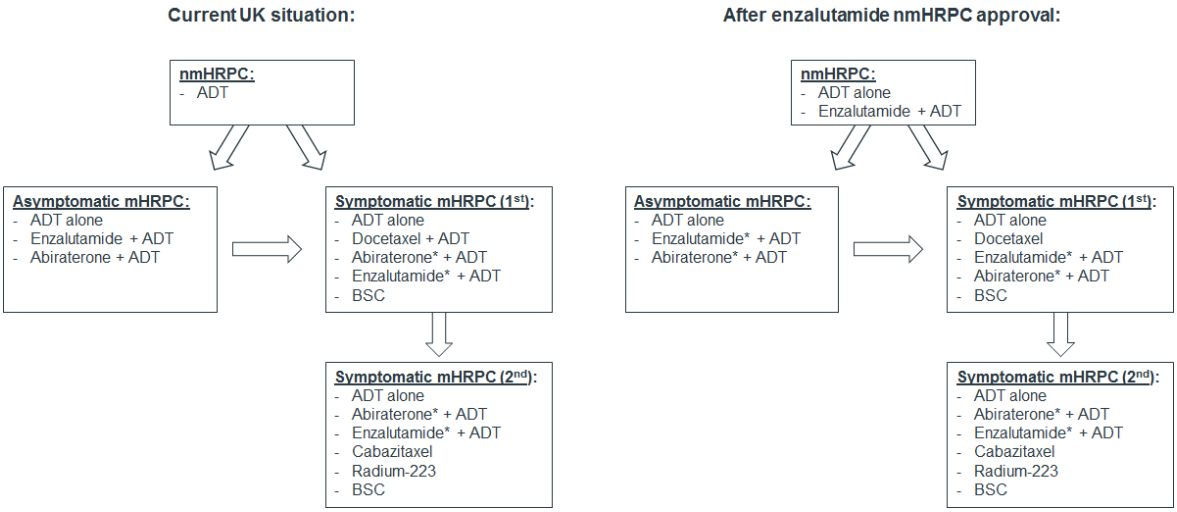
HRPC, hormone-relapsed prostate cancer; M, million; nm, non-metastatic; ONS, office for national statistics; PCa, prostate cancer.

2.2 Critique of company's overview of current service provision

The ERG believe the company's description of current service provision is accurate. Presently, there is no specific UK or European guidance for the management of people with nmHRPC and no current treatment has demonstrated significant survival benefits in this patient group. The European Association of Urology (EAU) guidelines

note that the modest potential benefits of continuing ADT treatment outweigh the treatment risks and, therefore, recommend ADT be continued indefinitely in people with HRPC.[7] The company also state that clinical expert opinion has indicated that ADT is frequently being used for men with locally advanced, non-metastatic disease in UK clinical practice.

The company provide details of the current clinical pathway of care and the proposed future pathway should their submission to introduce enzalutamide as a treatment option for high risk nmHRPC be approved (see Figure 1). The company state that they expect that enzalutamide would be used with ADT as the first line treatment for high risk nmHRPC, with the aim of delaying the development of metastases and the associated deterioration in HRQOL. Current NICE guidance recommends enzalutamide or abiraterone, in conjunction with ADT, once patients progress to the asymptomatic/mildly symptomatic metastatic disease stage. Symptomatic patients can be offered docetaxel with ADT, or ADT alone, and those who progress during or after docetaxel can be offered cabazitaxel, radium-223 or best supportive care. Abiraterone and enzalutamide can be offered to patients who have not previously received these treatments. The company note that, NICE do not recommend sequential enzalutamide and abiraterone treatment and, therefore, nmHRPC patients who receive enzalutamide as a first line treatment in the proposed future care pathway will not be able to receive abiraterone or enzalutamide at later stages of the disease under the current guideline restrictions.



Source: Company UK clinical expert (Astellas. Minutes of the validation interview with a UK clinical expert. 2018. [Unpublished data]) and NICE Prostate Cancer Pathway {, 2018 #16
*If neither enzalutamide nor abiraterone has been given before.
Abbreviations: ADT: androgen deprivation therapy; BSC: best supportive care; mHRPC: metastatic hormone-relapsed prostate cancer; nmHRPC: non-metastatic hormone-relapsed prostate cancer.

Figure 1 Current and future treatment pathway for high risk nmHRPC patients (reproduced from the company submission, document A, page 5)

3 Critique of company's definition of decision problem

3.1 Population

The NICE final scope for this appraisal specified the population as adults with nmHRPC. The company submission (CS) addresses adults with high risk nmHRPC. The company define high risk as PSADT being ≤10 months and a PSA ≥2 ng/mL. The ERG agrees that this is in line with the study population of the PROSPER randomised controlled trial (RCT), which is presented as the main evidence in the CS.

3.2 Intervention

The intervention in both the NICE final scope and the CS is enzalutamide with ADT. Ennzalutamide is an androgen receptor (AR) signalling inhibitor that targets the AR signalling pathway, which is regarded as the main drivers for oncogenic progression in prostate carcinogenesis, by blocking androgen binding, inhibiting nuclear translocation, and impairing DNA binding and inhibiting gene transcription. Enzalutamide currently has European Medicines Agency (EMA) approval for the treatment of adults with metastatic castrate resistant prostate cancer (mCRPC) who are asymptomatic or mildly symptomatic after ADT failure in the chemotherapy naïve setting and adults with mCRPC whose disease has progressed in the post-chemotherapy (docetaxel) setting. The company note that a type II variation has been submitted to the EMA to include market authorisation for the treatment of adults with high risk nmHRPC (the population indicated in the CS) and final authorisation for this indication is expected by November 2018. In the UK, NICE currently recommends enzalutamide, within its marketing authorisation, as an option for treating mHRPC: (i) in people who have no or mild symptoms after androgen deprivation therapy has failed, and before chemotherapy is indicated and (ii) only when the company provides Enzalutamide in line with the commercial access agreement with NHS England. [8]

The company provided details of enzalutamide in Table 2 of the CS (document B, page 16) as is reproduced by the ERG in the report as Table 2 below.

Table 2 Technology being appraised

UK approved name and brand name	Brand name: XTANDI™. Approved name: Enzalutamide (formerly known as MDV3100) Therapeutic class: The World Health Organisation International Working Group for Drug Statistics Methodology has assigned the following therapeutic class to enzalutamide: [9] • L: Antineoplastic and immunomodulating agents • L02: Endocrine therapy • L02B: Hormone antagonists and related agents • L02BB: Anti-androgens • L02BB04: Enzalutamide.
Mechanism of action	Androgens and androgen receptor (AR) signalling pathways are regarded as the main oncogenic drivers in prostate carcinogenesis; as such, they represent a logical target for prostate cancer therapy. [10] Prostate cancer is androgen-sensitive and responds to inhibition of AR signalling. Despite low or even undetectable levels of serum androgen, AR signalling continues to promote disease progression. Stimulation of tumour cell growth via the AR requires nuclear localisation and DNA binding. Enzalutamide is an AR signalling inhibitor that targets the AR signalling pathway [11 12] Enzalutamide binds AR with a 5–8-fold greater relative affinity than bicalutamide (a first-generation anti-androgen). [12] Also, in contrast to bicalutamide, enzalutamide show no evidence of AR agonist activity. [12] Enzalutamide has a novel mechanism of action that directly and potently inhibits three stages of the AR signalling pathway: [11 12] - Blocking androgen binding - Inhibiting nuclear translocation - Impairing DNA binding, inhibiting gene transcription.

Marketing authorisation	In Europe, enzalutamide has been granted market authorisation in: • June 2013 for treatment of adult men with metastatic CRPC (mCRPC) whose disease has progressed on or after docetaxel therapy (i.e., post-chemotherapy setting) • November 2014 for treatment of adult men with mCRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated (i.e., chemotherapy naïve setting). A Type II variation has been submitted to the European Medicines Agency (EMA) to include market authorisation for: the treatment of adult men with high risk nmCRPC. Final authorisation in this indication is expected by November 2018. This is the indication of relevance for this submission. Enzalutamide has regulatory approval throughout Europe, as well as in several other countries including the US, Canada and Australia for the treatment of mCRPC patients in the post-chemotherapy and chemotherapy-naïve settings. In addition, in July 2018, the Food and Drug Administration (FDA) approved enzalutamide for nmCRPC patients. [13]
Indications and any restriction(s) as described in the Summary of product characteristics (SmPC)	At time of submission, in Europe enzalutamide has market authorisation for the following indications: • "*Treatment of adult men with mCRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated*" • "*Treatment of adult men with mCRPC whose disease has progressed on or after docetaxel therapy*" EMA authorisation for the indication of relevance here (i.e., high risk nmCRPC) is expected by November 2018. A risk management plan (RMP) was developed for enzalutamide in the post-chemotherapy setting and extended to include the treatment of chemotherapy-naïve mCRPC patients. This RMP is

	expected to be further extended to include the treatment of high risk nmHRPC patients. Based on this RMP, safety information on enzalutamide has been included in its Summary of product characteristics. In addition, Astellas is undertaking active pharmacovigilance for the following safety concerns: seizures, hypertension, falls, hallucination, neutrophil count decreased, non-pathologic fracture, interactions with strong inhibitors or inducers of CYP2C8 and interactions with medicinal products that are substrates of CYP3A4, CYP2C9 or CYP2C19.
Method of administration and dosage	Enzalutamide is formulated as both 40 mg soft capsules and tablets. The tablet formulation is licensed in Europe and will be made available in coming months. The enzalutamide dose for high risk nmCRPC in the licence applications is a single daily oral dose of 160 mg (as four × 40 mg soft capsules)
Additional tests or investigations	This indication for enzalutamide does not require any additional tests beyond what is currently done for patients with prostate cancer e.g. PSA levels[14]. Identification of patients eligible for enzalutamide does not require any additional tests either. The PSA monitoring test needed for their identification is in line with UK clinical practice.[15]
List price and average cost of a course of treatment	The current UK list price is £2,734.67 per pack (112 units of 40 mg)[16]. With a daily dose of 160 mg, daily UK treatment costs are £97.64, based on the UK list price. Based on the PROSPER median treatment duration, a course of treatment would be [redacted] which would result in a total costs of [redacted] for an entire course of enzalutamide in nmHRPC (without applying patient access scheme and excluding additional costs).
Patient access scheme (if applicable)	[redacted].

3.2.1 Safety

As detailed in the SmPC, enzalutamide treatment should be initiated and supervised by experience specialist physicians. The recommended dose is 160 mg daily (four 40 mg soft capsules) as a single oral administration. In the event of > Grade 3 toxicity or intolerable adverse reaction, treatment should be withheld for one week or until

symptoms improve to < Grade 2, then resumed at the same or reduced dose of 120 mg or 80 mg. The concomitant use of strong CYP2C8 inhibitors should be avoided, or enzalutamide should be reduced to a 80 mg daily dose if the avoidance of co-administration is not possible. Co-administration with warfarin and coumarin-like anticoagulants should be avoided. Patients receiving enzalutamide and anticogaulants metabolised by CYP2C9 should receive additional International Normalised Ration monitoring.

The company state that "interactions with certain medicinal products that are eliminated through metabolism or active transport are expected" and "these products should be avoided or used with caution. The risk for liver injury after paracetamol administration is suspected to be higher in patients concomitantly treated with enzyme inducers". The SmPC lists the following medicinal products that can be affected, but are not limited to:

- Analgesics (e.g. fentanyl, tramadol)
- Antibiotics (e.g. clarithromycin, doxycycline)
- Anticancer agents (e.g. cabazitaxel)
- Antiepileptics (e.g. carbamazepine, clonazepam, phenytoin, primidone, valproic acid)
- Antipsychotics (e.g. haloperidol)
- Antithrombotics (e.g. acenocoumarol, warfarin, clopidogrel)
- Betablockers (e.g. bisoprolol, propranolol)
- Calcium channel blockers (e.g. diltiazem, felodipine, nicardipine, nifedipine, verapamil)
- Cardiac glycosides (e.g. digoxin)
- Corticosteroids (e.g. dexamethasone, prednisolone)
- HIV antivirals (e.g. indinavir, ritonavir)
- Hypnotics (e.g. diazepam, midazolam, zolpidem)
- Immunosuppressant (e.g. tacrolimus)
- Proton pump inhibitor (e.g. omeprazole)
- Statins metabolised by CYP3A4 (e.g. atorvastatin, simvastatin)
- Thyroid agents (e.g. levothyroxine)

The safety and efficacy of concomitant treatment with enzalutamide and cytotoxic chemotherapy has not been established. Enzalutamide has not been studied in patients with severe renal impairment and patients with recent cardiovascular disease were excluded from phase 3 studies. People with rare hereditary problems of fructose intolerance should not take enzalutamide. It is noted in the SmPC that studies in animals have shown reproductive toxicity. Patients engaged in sexual activity with a pregnant woman or woman of childbearing potential should use a condom and another form of contraceptive during, and for 3 months following, enzalutamide treatment. Studies have not evaluated the effects of enzalutamide on the ability to drive or use machinery but patients should be advised that there is a potential risk of experiencing a psychiatric or neurological event, such as seizure, whilst driving or operating machinery.

3.2.2 Adverse reactions

The company present the adverse reactions associated with enzalutamide, as reported in the SmPC, in Table 34 of the CS, document B, on page 87 and is reproduced by the ERG in this report as Table 3. Frequency categories are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). The most common adverse reactions are asthenia/fatigue, hot flush, fractures and hypertension.

Table 3 Adverse reactions related to enzalutamide as reported in its SmPC

MedDRA system organ class	Very common	Common	Uncommon	Unknown[b]
Blood and lymphatic system disorders			Leucopoenia Neutropenia	Thrombocytopenia
Cardiac disorders		Ischemic heart disease		QT prolongation
Gastrointestinal disorders				Nausea Vomiting Diarrhoea
General disorders	Asthenia Fatigue			
Immune system disorders				Face oedema, Tongue oedema Lip oedema Pharyngeal oedema
Injury, poisoning and procedural complications		Falls		
Musculoskeletal and connective tissue disorders	Fractures[a]			Myalgia Muscle spasms Muscular weakness Back pain
Nervous system disorders		Headache Memory impairment Amnesia Disturbance in attention Restless legs syndrome	Cognitive disorder Seizure	Posterior reversible encephalopathy syndrome
Psychiatric disorders		Anxiety	Visual hallucinations	
Reproductive system and breast disorder		Gynaecomastia		
Skin and subcutaneous tissue disorders		Dry skin Pruritus		Rash
Vascular disorders	Hot flush Hypertension			

Source: Enzalutamide Summary of Product Characteristics[14]

a. Includes all fractures with the exception of pathological fractures

b. Spontaneous reports from post-marketing experience

3.3 Comparators

The NICE final scope and the CS specify the comparator as ADT. The company state that although no treatments are currently recommended specifically for nmHRPC patients, several European and International guidelines recommend continued use of ADT [7] and state in the CS that ADT is "the standard of care for nmHRPC patients in the UK". The ERG note that Apalutamide for treating localised hormone-relapsed prostate cancer is currently under draft scoping with NICE (ID1174), The ERG also note that bicalutamide is not a proposed comparator for enzalutamide. Given that the CS evidence includes a large proportion of participants that have and have not received prior bicalutamide, the ERG have been unable to ascertain whether enzalutamide may replace bicalutamide in some instances. However, the ERG agree that, while the benefits of ADT in this setting are unclear, ADT is the only valid comparator for enzalutamide.

3.4 Outcomes

The outcomes stated in the NICE final scope are: metastasis-free survival (MFS) time to PSA progression, overall survival (OS), adverse effects of treatment and HRQOL. The company submission included all the outcomes listed in the NICE final scope and reports additional outcomes: time to next therapy for prostate cancer, time to treatment discontinuation, time to first use of cytotoxic chemotherapy, chemotherapy-free disease specific survival, chemotherapy-free survival, time to pain progression and PSA response rates.

3.5 Other relevant factors

The ERG agree with the company that they are no aware of any issues relating to equality for this submission.

4 Clinical effectiveness

4.1 Critique of the methods of review(s)

4.1.1 Searches

The CS provides details of the searches that were undertaken to identify the studies included in the clinical effectiveness review. The major relevant databases searched were: PubMed, Medline, Medline in Process, EMBASE, CDSR, CENTRAL and DARE. Searches were undertaken in November 2016 and updated in 2018. No restrictions were placed on timeframe, country or language. In addition, the company searched conference proceedings from seven major relevant organisations up to July 2018.

The search strategies are documented in full in Appendix D of the CS, document B, and are reproducible. The search strategies were considered fit for purpose, including both relevant controlled vocabulary and text terms with appropriate use of Boolean operators. The ERG notes that the company have not used the Cochrane Collaboration's RCT filter search, although the company have used major terms for RCTs in their searches so are unlikely to have missed any important studies. The ERG also notes that the abbreviation HRPC was included as a text word in the searches but not 'hormone-relapsed' in full for the clinical effectiveness searches. It is unclear if any additional studies have been missed because of this.

4.1.2 Inclusion criteria

The company conducted a systematic review to assess the clinical effectiveness of enzalutamide plus ADT. The company provided details of their inclusion criteria in Table 3 of the CS, document B, page 21 and reproduced by the ERG as Table 4 in this report. In line with the NICE final scope, the company considered only ADT as a relevant comparator for this submission. The company identified 11 eligible studies (27 publications) but stated that only two of these studies (9 publications) were relevant for their submission. At clarification, the company stated that the 27 publications were deemed irrelevant due to their having no relevant intervention and comparator.

Table 4 Selection criteria in the systematic literature review of clinical effectiveness

PICOS	Inclusion criteria	Exclusion criteria
Population of interest	Adult patients (≥18 year) with nmHRPC	Children
Interventions of interest	Enzalutamide	
Comparators of interest	ADT Anti-androgens: bicalutamide, flutamide, abiraterone, apalutamide, ODM-201 Docetaxel Sipuleucel-T Placebo/ active surveillance Denosumab	Therapies not yet at phase III setting in the nmHRPC setting
Outcomes of interest	Overall survival Progression-free survival Metastasis-free survival PSA response Time to PSA progression Time to chemotherapy initiation Time to opiate use for prostate cancer pain Time to pain progression Time to treatment discontinuation Adverse effects of treatment	
Study design of interest	Meta-analyses, systematic literature reviews, randomised controlled trials (RCTs), non-randomised studies, observational studies, case-cohort studies, registries	Preclinical and phase I studies, prognostic studies, case reports, reviews/ expert opinion, commentaries/ letters

The two studies included in the systematic review were the PROSPER trial [17] and the STRIVE trial. [18]

4.1.3 Critique of data extraction

The company state in document B, page 21, that "identification of relevant studies was conducted by two experienced specialists. Any discrepancies were discussed with a third specialist." It is unclear how many reviewers conducted data extraction.

4.1.4 Quality assessment

The company conducted quality assessment of the PROSPER and STRIVE trials using NICE quality criteria[19] for assessing the risk of bias and generalisability in parallel group RCTs and present their assessment in Appendix D of the CS. The ERG agrees with the company that both trials are of overall good quality with little risk of bias.

The ERG conducted a quality assessment of the methods used by the company for the systematic review of clinical evidence using the CRD criteria.[20] Results are presented in Table 5.

Table 5 Quality assessment of the company's systematic review of clinical effectiveness evidence

CRD quality item	Yes/No/Unclear
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all of the relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Are sufficient details of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

4.1.5 Evidence synthesis

The company provide evidence for the effectiveness of enzalutamide plus ADT from the PROSPER RCT, with data from the STRIVE RCT presented as supporting evidence. PROSPER is a manufacturer-sponsored, international, double-blind, phase 3 trial, comparing enzalutamide (at a dose of 160mg daily) versus placebo in people with nmHRPC. The primary end point was MFS, which was defined as the time from

randomisation to radiographic progression, or as the time to death without radiographic progression. STRIVE was a multicentre, phase 2 trial which was conducted in the US and compared enzalutamide versus bicalutamide in people with both metastatic and, high- and non-high risk, non-metastatic HRPC. The primary end point in STRIVE was progression free survival (PFS). The company did not include data from STRIVE in their economic model. Main reasons given for this are the smaller sample size of STRIVE compared to PROSPER, the fact that STRIVE was conducted in the US population, STRIVE and PROSPER differed in their assessed endpoints, OS data, in particular, was not collected in STRIVE, and the fact that bicalutamide was not included in the remit of the NICE final scope.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Characteristics and critique of the trials included in the systematic review of clinical effectiveness

The company present characteristics of the two trials in Table 4, document B of the CS on page 25, and this is reproduced by the ERG as Table 6 in this report. The CS refers to the intervention arm of PROSPER and STRIVE as the enzalutamide arm, however, the CS states that the treatment in this arm included:

- Enzalutamide and ADT in PROSPER
- Enzalutamide, ADT and bicalutamide placebo in STRIVE.

Similarly, the comparator arm of these two studies are referred to as the "placebo" and "bicalutamide" arms, respectively. The CS states that treatment in these arms included:

- Enzalutamide placebo and ADT in PROSPER
- Bicalutamide, ADT and enzalutamide placebo in STRIVE.

Table 6 PROSPER and STRIVE trial design

Study	PROSPER	STRIVE
Study design	Multinational, phase III, randomised, double-blind, placebo-controlled, efficacy and safety study	Multicentre, phase II, single country, l randomised, double-blind placebo-controlled, efficacy and safety study of enzalutamide versus bicalutamide in the United States
Population	nmHRPC with PSA doubling time ≤10 months (i.e., high risk)	Metastatic and nmHRPC. In the nmHRPC cohort, 83.0% had PSA doubling time ≤10 months (i.e., high risk)
Intervention(s)	The intervention was enzalutamide plus ADT Enzalutamide orally was given as a daily dose of 160 mg/day in 4 capsules (40 mg each) by mouth once daily Patients remained on ADT (by either receiving a GnRH agonist/antagonist or having a history of bilateral orchiectomy)	The intervention was enzalutamide, ADT and bicalutamide placebo Enzalutamide was given orally as 160 mg per day as four 40-mg capsules The bicalutamide placebo was administered orally as one placebo capsule ADT was maintained throughout the study; concurrent use of bisphosphonates and denosumab was permitted
Comparator(s)	The comparator was an enzalutamide-matched placebo plus ADT Placebo was administered orally as 4 capsules once daily Patients remained on ADT (by either receiving a GnRH agonist/antagonist or having a history of bilateral orchiectomy)	The comparator was bicalutamide, ADT and enzalutamide placebo Bicalutamide was given orally 50 mg per day as one capsule Enzalutamide placebo was given orally as four placebo capsules

Study	**PROSPER**		**STRIVE**
			ADT was maintained throughout the study, and concurrent use of bisphosphonates and denosumab was permitted
Indicate if trial supports application for marketing authorisation	Yes	X	X
	No		
Indicate if trial used in the economic model	Yes	X	
	No		X
Rationale for use/non-use in the model	The study provides evidence of efficacy and safety of enzalutamide plus ADT vs standard of care (i.e., ADT alone) in high risk nmHRPC patients		This study provides evidence of efficacy and safety of enzalutamide plus ADT vs ADT plus bicalutamide. However, the study included only 139 (35.1%) nmHRPC patients of which 112 (83.0%; missing data: n=4) were high risk. No STRIVE-related data are used in the economic model
Reported outcomes specified in the decision problem	**MFS (primary objective)** Time to PSA progression **Overall survival** **Quality of life** **Safety**		PFS (primary objective) Time to PSA progression Radiographic progression-free survival (metastatic only)
All other reported outcomes	Time to pain progression Chemotherapy-free disease-specific survival Chemotherapy-free survival		PSA Response rates

Study	PROSPER	STRIVE
	Time to first use of new antineoplastic therapy Time to first use of cytotoxic chemotherapy PSA response rates **Time to treatment discontinuation**	

Outcomes highlighted in the bold have been used in the cost effectiveness model.
ADT, androgen deprivation therapy; GnRH, gonadotropin-releasing hormone; MFS, metastasis-free survival; nmHRPC, non-metastatic hormone-relapsed prostate cancer; PFS, progression-free survival; PSA, prostate-specific antigen.

In PROSPER the sample size was determined as a total of 440 MFS events to provide 90% power to detect a target HR of 0.72 based on a two-sided log-rank test and an overall significance level of 0.05. Allowing for 10% loss to follow up, the target sample size was 1,440 (960 enzalutamide and 480 placebo). No interim analyses/stopping rules were pre-planned for any outcomes apart from overall survival. For overall survival, three interim and one final analysis was pre-specified at 135, 285, 440 and 596 death events respectively. At time of submission, the OS data are immature with only the first two interim analyses available (referred to as the IA1 and IA2 OS data cuts in the CS).

In STRIVE a minimum of 231 PFS events provided 90% power to detect a HR of 0.65 based on a two-sided log-rank test with 5% significance level. No interim analyses were planned.

The company present data in the CS from the PROSPER intention-to-treat (ITT) population (defined in the CS as "all randomised patients") for analyses of efficacy, disposition, demographics and baseline disease characteristics. A similar definition is given for the STRIVE ITT population. The PROSPER safety population is defined in the CS as "all patients in the randomised population who received any study medication." The company states that no safety population was defined for the STRIVE nmHRPC cohort.

The company present the baseline demographics and disease characteristics for PROSPER in Table 7 of the CS, document B on pages 38-39, this is reproduced by the ERG in Table 7 of this report. Treatment arms were balanced at baseline for the trial population as a whole (1401 participants).

[redacted]. The company state that these people could have been

determined to have metastatic disease after trial enrolment by the blinded independent central review (BICR).

Following clarification questions from the ERG, the company provided the baseline characteristics of the UK PROSPER participants in Table 2 of their clarification response, and this is reproduced by the ERG in Table 7. The ERG agrees with the company that the baseline characteristics are similar to the wider PROSPER population, with the following exceptions:

[redacted].

Following clarification from the ERG, the company confirmed that the percentage of participants who were exposed to bicalutamide prior to PROSPER trial entry in the UK PROSPER cohort was [redacted] and [redacted] for enzalutamide and placebo, respectively. In the overall trial population these percentages were [redacted] and [redacted], respectively.

Table 7 Demographic and baseline disease characteristics in PROSPER for the ITT population and the UK cohort

	ITT cohort		UK Cohort	
	Enzalutamide (n=933)	**Placebo (n=468)**	**Enzalutamide (n=47)**	**Placebo (n=23)**
Age (years)				
<65	121 (13.0%)	69 (14.7%)	[redacted]	[redacted]
65 to <75	368 (39.4%)	198 (42.3%)	[redacted]	[redacted]
≥75	444 (47.6%)	201 (42.9%)	[redacted]	[redacted]
Median (range)	74.0 (50.0, 95.0)	73.0 (53.0, 92.0)	[redacted]	[redacted]
Race				
American Indian or Alaskan Native	0 (0.0%)	0 (0.0%)	[redacted]	[redacted]
Asian	142 (15.2%)	88 (18.8%)	[redacted]	[redacted]
Black or African American	21 (2.3%)	10 (2.1%)	[redacted]	[redacted]
Native Hawaiian or Other Pacific Islander	3 (0.3%)	2 (0.4%)	[redacted]	[redacted]
White	671 (71.9%)	320 (68.4%)	[redacted]	[redacted]
Multiple	4 (0.4%)	4 (0.9%)	[redacted]	[redacted]
Other	15 (1.6%)	5 (1.1%)	[redacted]	[redacted]
Missing	77 (8.3%)	39 (8.3%)	[redacted]	[redacted]
Weight (kg)				
Mean (SD)	84.0 (15.87)	83.6 (16.21)	[redacted]	[redacted]
Median (min, max)	82.0 (43.1, 149.8)	82.0 (38.0, 167.0)	[redacted]	[redacted]
Missing	0	1	[redacted]	[redacted]
Baseline ECOG performance status				
0	747 (80.1%)	382 (81.6%)	[redacted]	[redacted]
1	185 (19.8%)	85 (18.2%)	[redacted]	[redacted]
>1	0 (0.0%)	0 (0.0%)	[redacted]	[redacted]
Missing	1 (0.1%)	1 (0.2%)	[redacted]	[redacted]
Disease status (by blinded independent central review)				
Non-metastatic	910 (97.5%)	454 (97.0%)	[redacted]	[redacted]
Metastatic	23 (2.5%)	14 (3.0%)	[redacted]	[redacted]
Baseline prior or concurrent use of BTA				
No (0)	828 (88.7%)	420 (89.7%)	[redacted]	[redacted]
Yes	105 (11.3%)	48 (10.3%)	[redacted]	[redacted]
1	103 (11.0%)	47 (10.0%)	[redacted]	[redacted]

	ITT cohort		UK Cohort	
	Enzalutamide (n=933)	**Placebo (n=468)**	**Enzalutamide (n=47)**	**Placebo (n=23)**
2	2 (0.2%)	1 (0.2%)	[redacted]	[redacted]
PSADT category				
<6 months	715 (76.6%)	361 (77.1%)	[redacted]	[redacted]
≥6 months	217 (23.3%)	107 (22.9%)	[redacted]	[redacted]
Missing	1 (0.1%)	0 (0.0%)	[redacted]	[redacted]
Stratification				
PSADT <6 months and no baseline BTA	642 (68.8%)	327 (69.9%)	[redacted]	[redacted]
PSADT <6 months and baseline BTA	73 (7.8%)	34 (7.3%)	[redacted]	[redacted]
PSADT ≥6 months and no baseline BTA	185 (19.8%)	93 (19.9%)	[redacted]	[redacted]
PSADT ≥6 months and baseline BTA	32 (3.4%)	14 (3.0%)	[redacted]	[redacted]
Missing	1 (0.1%)	0 (0.0%)	[redacted]	[redacted]
PSADT (months)				
Mean (SD)	4.3 (2.8)	4.3 (3.9)	[redacted]	[redacted]
Median (range)	3.8 (0.4, 37.4)	3.6 (0.5, 71.8)	[redacted]	[redacted]
Missing	1 (0.1%)	0 (0.0%)	[redacted]	[redacted]
Serum PSA (ng/mL)				
Mean (SD)	22.2 (46.1)	22.1 (41.1)	[redacted]	[redacted]
Median (range)	11.1 (0.8, 1071.1)	10.2 (0.2, 467.5)	[redacted]	[redacted]
Missing	0 (0.0%)	1 (0.2%)	[redacted]	[redacted]
Pain score as assessed by BPI-SF Question 3				
0-1	639 (68.5%)	336 (71.8%)	[redacted]	[redacted]
2-3	106 (11.4%)	52 (11.1%)	[redacted]	[redacted]
>3	142 (15.2%)	51 (10.9%)	[redacted]	[redacted]
Missing	46 (4.9%)	29 (6.2%)	[redacted]	[redacted]

Following clarification from the ERG, the company provided information for all inclusion and exclusion criteria violations in PROSPER and this is reproduced by the ERG as Table 8 in this report. Overall, [redacted] and [redacted] of participants in the enzalutamide and placebo arms, respectively, did not meet, or violated, at least one of the inclusion or exclusion criteria, with the largest proportion of participants violating

the following criteria:

[redacted]. The company state that none of the violations were considered to be major, and patients were not excluded from the ITT analysis. The company did not plan any per protocol analyses. The company clarified that none of the participants in the UK cohort violated any of the key selection criteria. The ERG agrees that, while these criteria have impact on treatment efficacy and/or safety, the numbers of participants with deviations were low and unlikely to bias any outcomes.

Table 8 Inclusion and exclusion criteria violations in PROSPER

Number of patients reporting at least 1	**Enzalutamide (N = 933)**	**Placebo (N = 468)**	**Total (N = 1401)**
Any Inclusion/Exclusion Criteria Deviations	[redacted]	[redacted]	[redacted]
Inclusion criteria			
Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation, signet cell, or small cell features	[redacted]	[redacted]	[redacted]
Testosterone ≤50 ng/dL (≤1.73 nmol/L) at screening	[redacted]	[redacted]	[redacted]
Progressive disease on androgen deprivation therapy at enrolment defined as a minimum of 3 rising PSA values (PSA1 <PSA2 <PSA3) assessed ≥1 week between each determination	[redacted]	[redacted]	[redacted]
The most recent local PSA and the screening PSA assessed by the central laboratory (central PSA) should be ≥2 mg/L (2 ng/mL). In the event of prior androgen receptor inhibitor use, the most recent local PSA and the central PSA assessed at screening must be obtained at least 4 weeks after the last dose of the androgen receptor inhibitor	[redacted]	[redacted]	[redacted]
PSA doubling time ≤10 months calculated by the sponsor	[redacted]	[redacted]	[redacted]
No prior or present evidence of metastatic disease as assessed by CT/MRI for soft tissue disease and	[redacted]	[redacted]	[redacted]

Number of patients reporting at least 1	**Enzalutamide (N = 933)**	**Placebo (N = 468)**	**Total (N = 1401)**
whole-body radionuclide bone scan for bone disease. If the screening one scan shows a lesion suggestive of metastatic disease, the patient will be eligible only if a second imaging modality (plain film, CT, or MRI) does not show bone metastasis. If the imaging results are equivocal or consistent with metastasis, the patient is not eligible for enrolment. Patients with soft tissue pelvic disease may be eligible if lesions do not qualify as target lesions (e.g., lymph nodes below aortic bifurcation are permissible if the short axis of the largest lymph node is <15 mm)			
Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1	[redacted]	[redacted]	[redacted]
Exclusion criteria			
Prior cytotoxic chemotherapy, aminoglutethimide, ketoconazole, abiraterone acetate, or enzalutamide for the treatment of prostate cancer or participation in a clinical trial of an investigational agent that inhibits the androgen receptor or androgen synthesis (unless treatment was placebo)	[redacted]	[redacted]	[redacted]
Treatment with hormonal therapy (e.g., androgen receptor inhibitors, oestrogens, 5-alpha reductase inhibitors) or biologic therapy for prostate cancer (other than approved bone-targeting agents and GnRH agonist/antagonist therapy) within 4 weeks of randomization	[redacted]	[redacted]	[redacted]
History of seizure or any condition that may predispose to seizure (e.g., prior cortical stroke or significant brain trauma). History of loss of consciousness or transient ischemic attack within 12 months of randomization	[redacted]	[redacted]	[redacted]
Clinically significant cardiovascular disease	[redacted]	[redacted]	[redacted]

The STRIVE trial enrolled 396 participants, of which 139 were nmHRPC patients, and 82.96% of these participants met the company's definition of high risk (PSADT < 10 months). The company present baseline data in Table 8 of the CS, document B,

page 41, and the ERG have reproduced data for the nmHRPC only subgroup in Table 9 of this report.

The ERG believes that the nmHRPC participants in the enzalutamide arm of the STRIVE trial are broadly comparable to the participants in the enzalutamide arm of the PROSPER trial. The PROSPER enzalutamide arm and the STRIVE nmHRPC enzalutamide arm were balanced for baseline data except for race due to a higher number of Black or African American participants in the STRIVE arm than the PROSPER arm. The incidence of prostate cancer is higher in African Americans than in Caucasians and mortality rates are 2.4 times higher. Similarly, the lower number of Black or African American participants in the UK PROSPER cohort may under-represent this demographic. Treatment arms were also unbalanced for mean (SD) weight, 84.0 (15.87) kg in PROSPER and 95.7 (27.29) kg in STRIVE and the Brief Pain Inventory – Short Form (BPI-SF) responses for question 3, with 68.5% of PROSPER participants compared with 84.3% of STRIVE participants self-reporting the least worst pain categories of 0-1. The ERG opinion is that these differences are unlikely to substantially bias the results.

Table 9 Demographic and baseline disease characteristics in PROSPER for the ITT population and the STRIVE nmHRPC cohort

	PROSPER		STRIVE nmHRPC only	
Outcomes	**Enzalutamide (n=933)**	**Placebo (n=468)**	**Enzalutamide (n=70)**	**Bicalutamide (n=69)**
Age (years)				
<65	121 (13.0%)	69 (14.7%)	11 (15.7%)	4 (5.8%)
65 to <75	368 (39.4%)	198 (42.3%)	25 (35.7%)	23 (33.3%)
≥75	444 (47.6%)	201 (42.9%)	34 (48.6%)	42 (60.9%)
Median (range)	74.0 (50.0, 95.0)	73.0 (53.0, 92.0)	73.5 (50.0, 92.0)	77.0 (58.0, 91.0)
Race				
American Indian or Alaskan Native	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asian	142 (15.2%)	88 (18.8%)	0 (0.0%)	0 (0.0%)
Black or African American	21 (2.3%)	10 (2.1%)	15 (21.4%)	9 (13.0%)
Native Hawaiian or Other Pacific Islander	3 (0.3%)	2 (0.4%)	0 (0.0%)	0 (0.0%)
White	671 (71.9%)	320 (68.4%)	53 (75.7%)	58 (84.1%)
Multiple	4 (0.4%)	4 (0.9%)	0 (0.0%)	0 (0.0%)
Other	15 (1.6%)	5 (1.1%)	2 (2.9%)	2 (2.9%)
Missing	77 (8.3%)	39 (8.3%)		
Weight (kg)				
Mean (SD)	84.0 (15.87)	83.6 (16.21)	95.7 (27.29)	89.5 (16.88)
Median (min, max)	82.0 (43.1, 149.8)	82.0 (38.0, 167.0)	91.0 (59.0-249.70	90.3 (45.8-145.3)
Missing	0	1		
Baseline ECOG performance status				
0	747 (80.1%)	382 (81.6%)	56 (80.0%)	53 (76.8%)
1	185 (19.8%)	85 (18.2%)	14 (20.0%)	16 (23.2%)
>1	0 (0.0%)	0 (0.0%)		
Missing	1 (0.1%)	1 (0.2%)		
Disease status				
Non-metastatic	910 (97.5%)	454 (97.0%)		
Metastatic	23 (2.5%)	14 (3.0%)		
Baseline prior/concurrent use for bone targeting agent				
No (0)	828 (88.7%)	420 (89.7%)		
Yes	105 (11.3%)	48 (10.3%)		
1	103 (11.0%)	47 (10.0%)		
2	2 (0.2%)	1 (0.2%)		
PSADT category				
<6 months	715 (76.6%)	361 (77.1%)		
≥6 months	217 (23.3%)	107 (22.9%)		
Missing	1 (0.1%)	0 (0.0%)		

	PROSPER		STRIVE nmHRPC only	
Outcomes	**Enzalutamide (n=933)**	**Placebo (n=468)**	**Enzalutamide (n=70)**	**Bicalutamide (n=69)**
Stratification				
PSADT <6 months and no baseline BTA	642 (68.8%)	327 (69.9%)		
PSADT <6 months and baseline BTA	73 (7.8%)	34 (7.3%)		
PSADT ≥6 months and no baseline BTA	185 (19.8%)	93 (19.9%)		
PSADT ≥6 months and baseline BTA	32 (3.4%)	14 (3.0%)		
Missing	1 (0.1%)	0 (0.0%)		
PSADT (months)				
Mean (SD)	4.3 (2.8)	4.3 (3.9)		
Median (range)	3.8 (0.4, 37.4)	3.6 (0.5, 71.8)		
Missing	1 (0.1%)	0 (0.0%)		
Serum PSA (ng/mL)				
Mean (SD)	22.2 (46.1)	22.1 (41.1)	13.8 (16.9)	13.1 (14.64)
Median (range)	11.1 (0.8, 1071.1)	10.2 (0.2, 467.5)	8.2 (1.8, 83.7)	6.9 (0.8, 71.5)
Missing	0 (0.0%)	1 (0.2%)		
Gleason Score				
Low (2-4)	21 (2.3%)	12 (2.6%)		
Medium (5-7)	491 (52.6%)	230 (49.1%)		
High (8-10)	381 (40.8%)	207 (44.2%)		
Unknown	40 (4.3%)	19 (4.1%)		
Pain score as assessed by BPI-SF Question #3				
0-1	639 (68.5%)	336 (71.8%)	59 (84.3%)	59 (85.5%)
2-3	106 (11.4%)	52 (11.1%)	11 (15.7%)	10 (14.5%)
>3	142 (15.2%)	51 (10.9%)		
Missing	46 (4.9%)	29 (6.2%)		

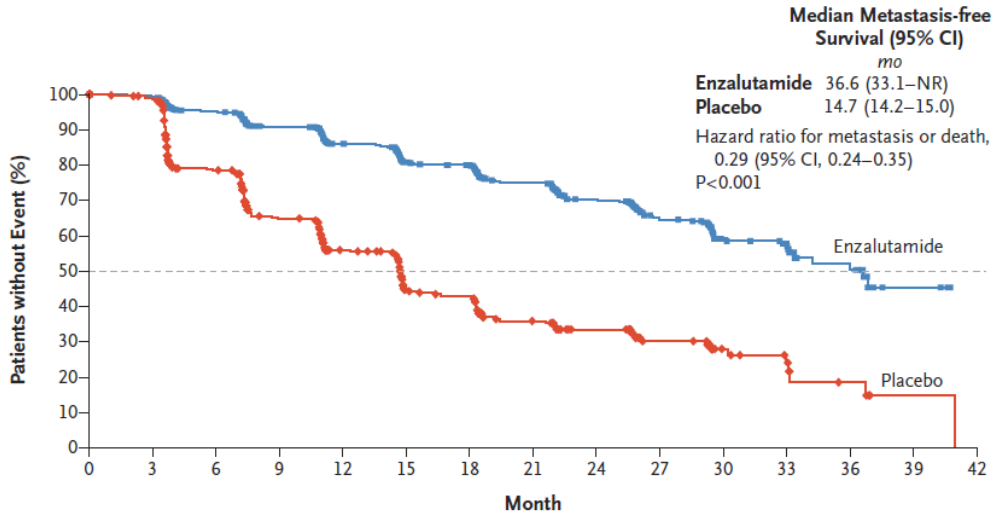
Source: Company submission and Medivation-Pfizer. Clinical Study Report - STRIVE: a multicenter phase 2, randomized, double-blind, efficacy and safety study of enzalutamide vs. bicalutamide in men with prostate cancer who have failed primary androgen deprivation therapy. 14 August 2015 [Unpublished data]

Metastasis-free survival

MFS was not considered by the STRIVE trial, therefore, the company present MFS data for PROSPER only. The company pre-specified in their protocol that the MFS analysis would be performed after 440 MFS events had occurred. At the time of the data analysis cut-off date of 28th June 2017, 447 patients (31.9% of the total population) experienced an event, 219 (23.5%) in the enzalutamide arm and 228 (48.7%) in the placebo arm. The company reports the results of the BICR MFS assessment: median (95% confidence interval [CI]) was 36.6 months (33.1, not reached) in the enzalutamide arm, and 14.7 months (14.2, 15.0) in the placebo group,

a difference of 21.9 months, and a statistically and clinically significant 70.8% risk reduction of an MFS event (hazard ratio [HR] 0.292, 95% CI [0.241, 0.352], p<0.0001) in favour of enzalutamide.

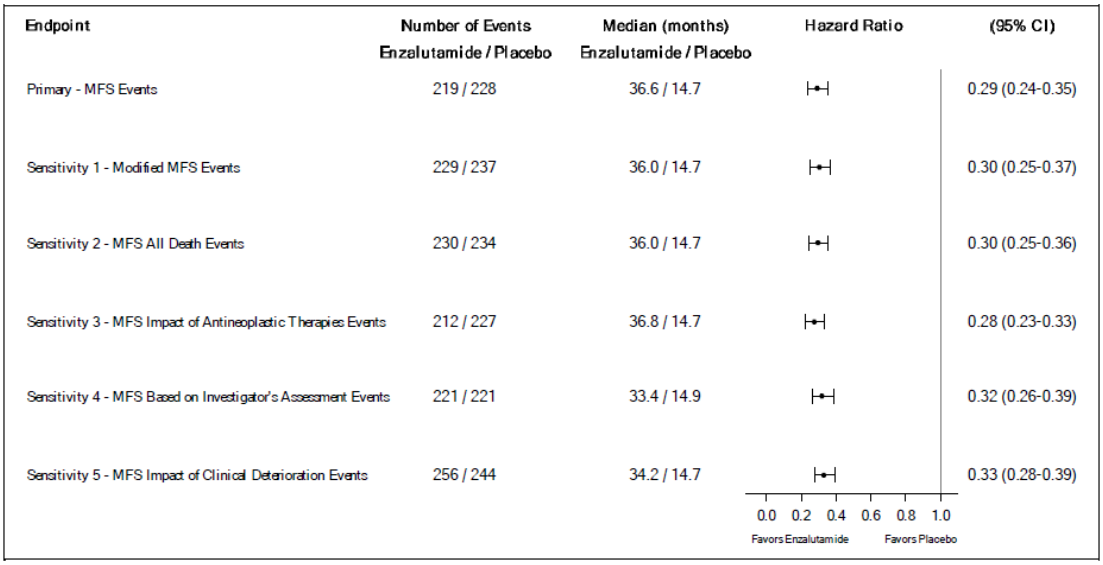
The company present the Kaplan-Meier estimates in Figure 6 of the CS, document B, on page 51 and the ERG have reproduced this as Figure 2 in this report.



p-value was based on a log-rank test stratified by PSADT (<6 months, ≥6 months) and prior or concurrent use of a bone-targeting agent (yes, no) as per IXRS.
Hazard ratio was based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and was relative to placebo with <1 favouring the enzalutamide group.
ITT, intent-to-treat; IXRS, Interactive voice/web recognition system; MFS, metastasis-free survival; PSADT, prostate-specific antigen doubling time

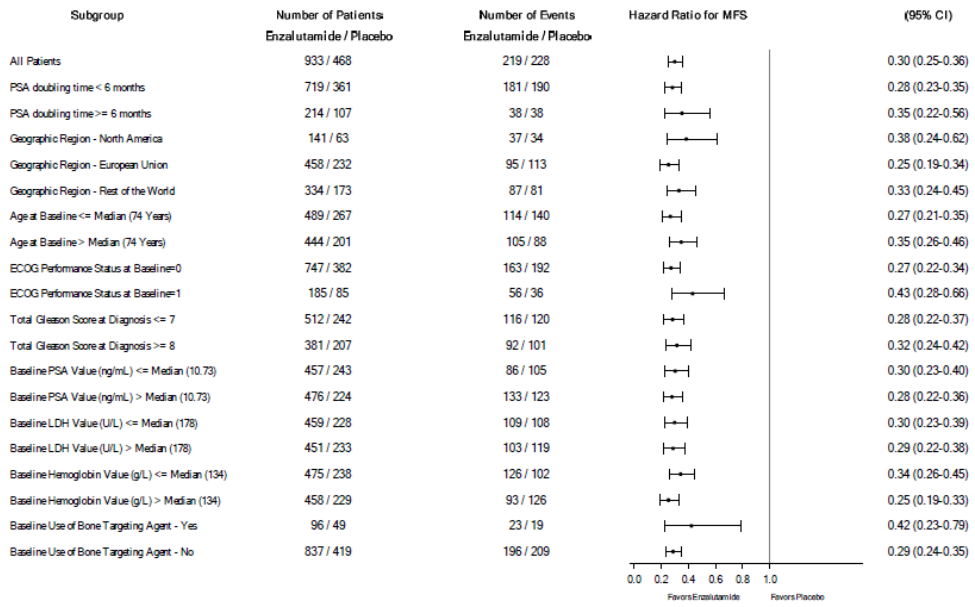
Figure 2 Kaplan-Meier curves for MFS (PROSPER intention-to-treat [ITT] population), reproduced by the ERG from the CS, document B

The company also present the results of sensitivity analyses in Figure 7 of the CS, document B, page 51 and Figure 18, document B, on page 78 and these are reproduced by the ERG as Figures 3 and 4 in this report. The results of the sensitivity analyses are in keeping with the primary analysis.



Numbers of patients included in this analysis were 933 for the enzalutamide group and 468 for the placebo group. Hazard ratios for all analyses were based on a Cox regression model (with treatment as the only covariate) stratified by PSADT (<6 months, ≥6 months) and prior or concurrent use of a bone-targeting agent (yes, no) as per IXRS.
Abbreviations. CI: confidence interval; ITT: intent-to-treat; IXRS: interactive voice/web recognition system; MFS: metastasis-free survival; PSADT: prostate-specific antigen doubling time

Figure 3 Forest plot of MFS – PROSPER primary and secondary analyses (ITT population), reproduced by the ERG from the CS, document B



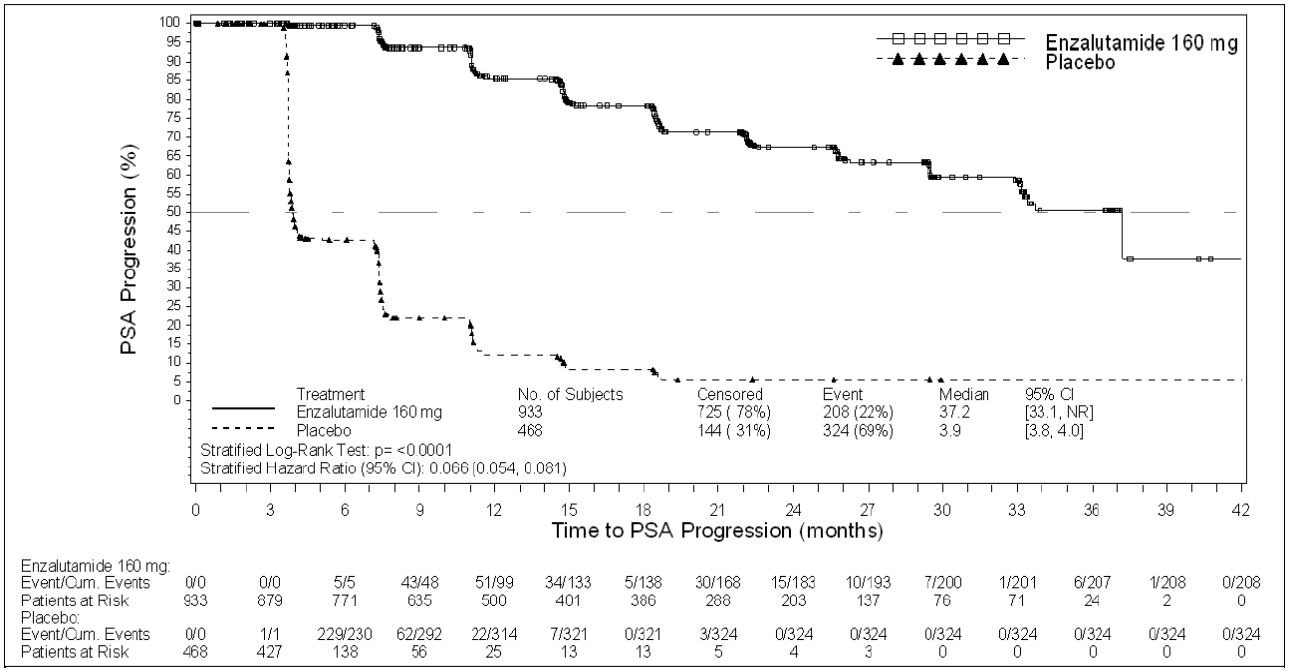
CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; ITT: intent-to-treat; LDH: Lactate dehydrogenase; MFS: metastasis-free survival; PSA=prostate-specific antigen

Figure 4 MFS in the PROSPER protocol predefined patient subgroups (ITT population), reproduced by the ERG from the CS, document B

The ERG considers there is strong evidence of a difference in MFS in PROSPER favouring enzalutamide and that the differences are consistent across predefined subgroups.

Time to PSA progression

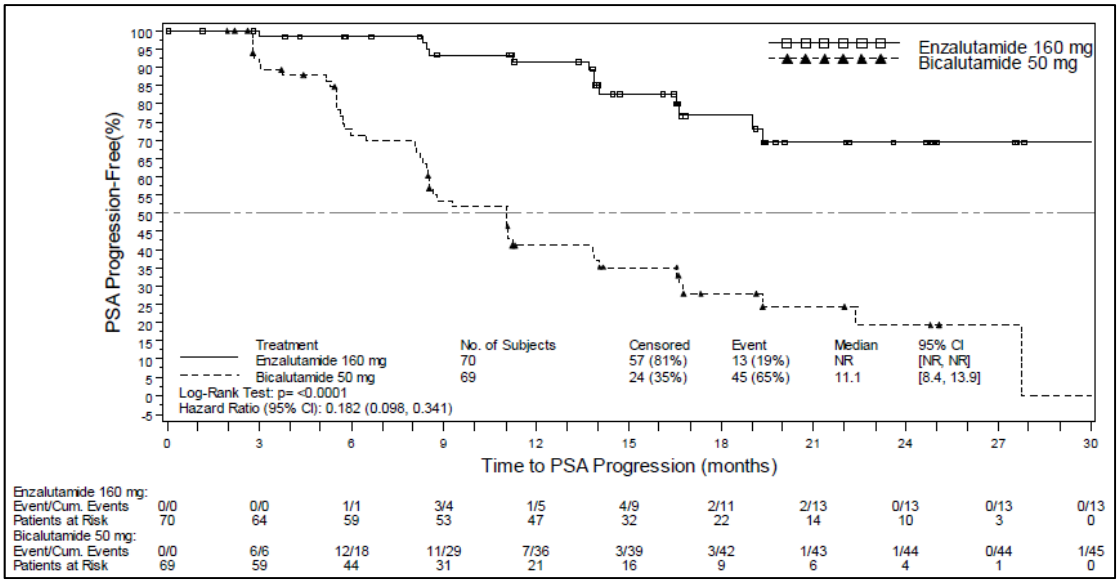
A higher number of patients in the PROSPER placebo arm (69.2%) experienced PSA progression than those in the enzalutamide arm (22.3%) and median time to PSA progression was also shorter in the placebo arm than the enzalutamide arm: 3.9 months (95% CI 3.8, 4.0) versus 37.2 months (95% CI 33.1, not reached). Treatment with enzalutamide was associated with a 93.4% reduction in risk of PSA progression (HR: 0.066, 95% CI: [0.054; 0.081], p<0.0001). The Kaplan-Meier estimates for time to PSA progression are presented as Figure 8 in the CS, document B, page 52 and reproduced by the ERG as Figure 5 in this report.



p-value was based on a log-rank test stratified by PSADT (<6 months, ≥6 months) and prior or concurrent use of a bone-targeting agent (yes, no) as per IXRS.
Hazard ratio was based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and was relative to placebo with <1 favouring the enzalutamide group.
CI: confidence interval; ITT: intent-to-treat; IXRS: interactive voice/web recognition system; PSADT: prostate-specific antigen doubling time.

Figure 5 Kaplan-Meier curves for time to PSA progression (PROSPER ITT population), reproduced by the ERG from the CS, document B

Similarly, in the STRIVE trial, 65.2% of the nmHRPC patients in the bicalutamide arm and 18.6% of nmHRPC patients in the enzalutamide arm experienced PSA progression. Enzalutamide reduced time to PSA progression compared with bicalutamide (HR: 0.182, 95% CI [0.098; 0.341]). Median time to PSA progression was not reached in the enzalutamide group versus 11.1 months in the bicalutamide group. The company present the Kaplan-Meier data for time to PSA progression in the nmHRPC STRIVE population in Figure 17 of the CS, document B, on page 75, and this is reproduced by the ERG as Figure 6 in this report.



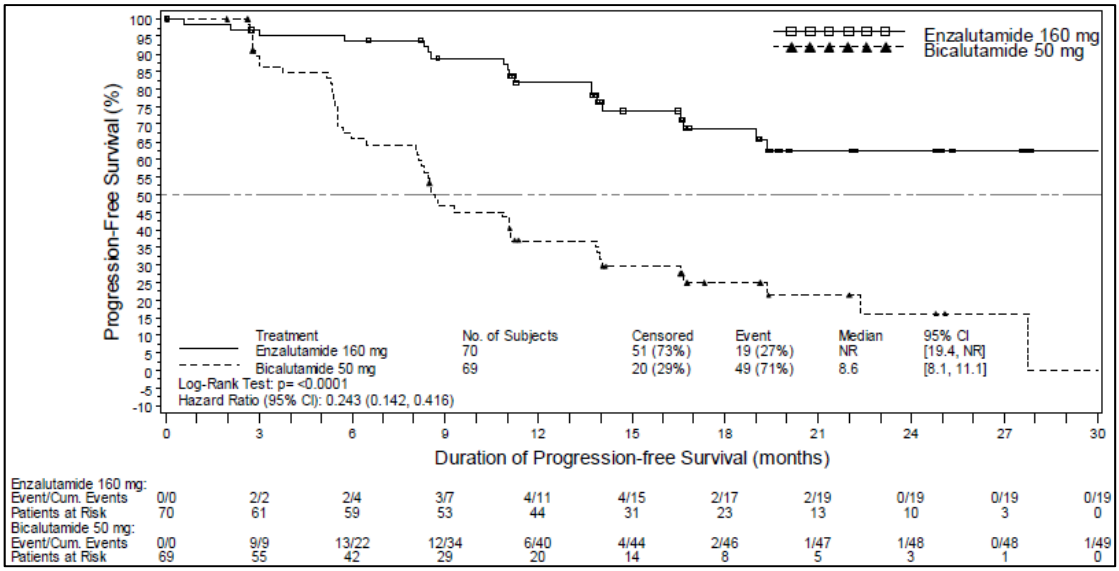
P-value is based on an unstratified log-rank test. Hazard ratio is based on an unstratified Cox regression model (with treatment as the only covariate) and is relative to bicalutamide with <1 favouring enzalutamide.
Cum, cumulative;
Abbreviations: ITT: intent-to-treat; NR: not reached; PSA: prostate-specific antigen

Figure 6 Kaplan-Meier curve for time to PSA progression (STRIVE nmHRPC ITT population), reproduced from the CS, document B

The ERG considers there is strong evidence of a difference in time to PSA progression in PROSPER and STRIVE favouring enzalutamide.

Progression free survival

PFS was not considered in the PROSPER trial. In the STRIVE nmHRPC population, enzalutamide was associated with a reduction in the risk of disease progression compared with bicalutamide (HR: 0.24, 95% CI [0.14, 0.42]). The median PFS was 8.6 months in the bicalutamide arm and was not reached in the enzalutamide arm. PSA progression was most frequently reported as the earliest component of PFS. The company present the Kaplan-Meir data for the STRIVE nmHRPC ITT population in Figure 16 of the CS, document B, page 74, and is reproduced by the ERG as Figure 7 in this report.

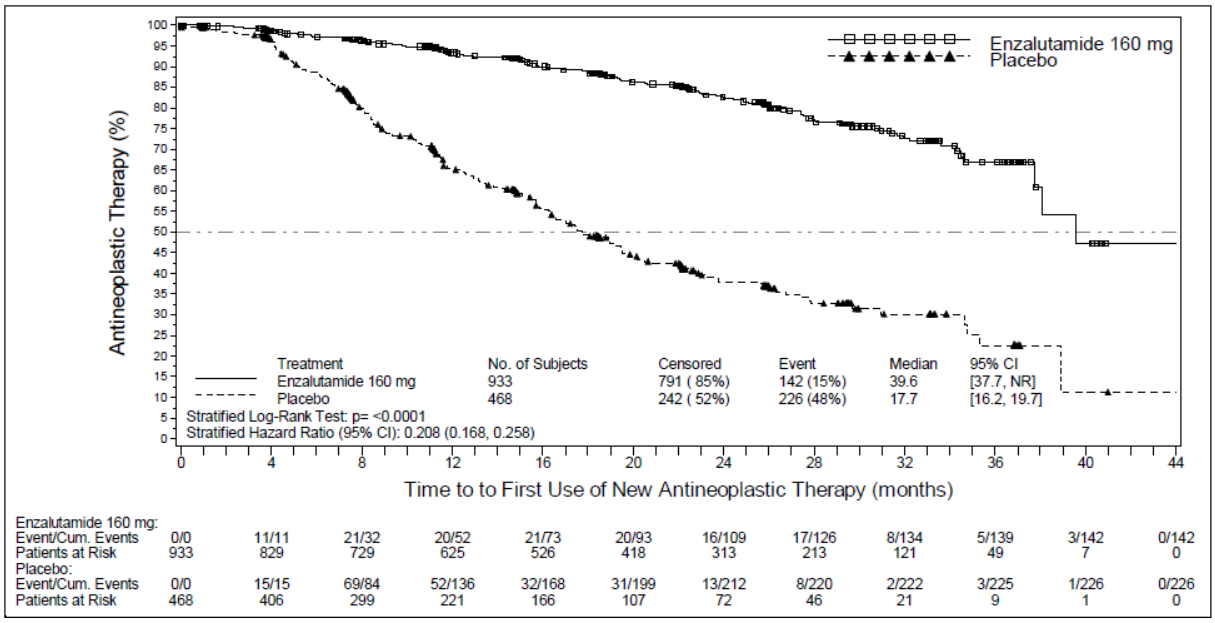


P-value is based on an unstratified log-rank test. Hazard ratio is based on an unstratified Cox regression model (with treatment as the only covariate) and is relative to bicalutamide with <1 favouring enzalutamide.
Abbreviations: Cum: cumulative; ITT: intent-to-treat; nmHRPC: non-metastatic hormone-relapsed prostate cancer; NR: not reached; PFS: progression-free survival

Figure 7 Kaplan-Meier curve for PFS (STRIVE nmHRPC ITT population)

Time to first use of new antineoplastic therapy

In total, 142 patients in PROSPER (15.2% of the enzalutamide arm and 48.3% of the placebo arm) received post-baseline first use of a new antineoplastic therapy. The median time to first use of a new antineoplastic therapy was 39.6 months (95% CI 37.7, not reported) in the enzalutamide arm and 17.7 months (95% CI 16.2, 19.7) in the placebo arm, a difference of 21.9 months (HR: 0.208, 95% CI: [0.168; 0.258], p value<0.0001). The company present the Kaplan-Meier data for time to first use of new antineoplastic therapy in Figure 9 of the CS, document B, page 54, and this is reproduced by the ERG as Figure 8 in this report. Abiraterone and docetaxel were the most frequently reported antineoplastic therapies received.



p-value was based on a log-rank test stratified by PSADT (<6 months, ≥6 months) and prior or concurrent use of a bone-targeting agent (yes, no) as per IXRS.
Hazard ratio was based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and was relative to placebo with <1 favouring the enzalutamide group.
CI: confidence interval; ITT: intent-to-treat; IXRS: interactive voice/web recognition system; PSADT: prostate-specific antigen doubling time

Figure 8 Kaplan-Meier curves for time to first use of new antineoplastic therapy (PROSPER ITT population), reproduced from the CS, document B

Overall survival

The company state that data for the final planned analysis for the PROSPER OS data are not available as the number of deaths specified for the final OS analysis (596 deaths) has not yet been reached. Data from the first two interim analyses are presented in the CS. The first interim analysis (IA1) occurred at total of 165 deaths (103/933 [11.0%] enzalutamide and 62/468 [13.2%] placebo) and did not show any statistically significant decrease in the risk of death for enzalutamide versus placebo treatment. The second interim analysis (IA2) was performed on 31st May 2018 when 288 deaths had occurred. The second interim analysis data included [redacted] deaths ([redacted] in the enzalutamide group and [redacted] deaths ([redacted] in the placebo group. The company present the OS and Kaplan-Meier data in Tables 13 and 14 and Figures 10 and 11 in the CS, document B, pages 58 and 59, and are reproduced by the ERG as Tables 10 and Figures 9 in this report. [redacted]

[redacted]

Table 10 Overall survival IA1 (ITT population)

Outcome	Enzalutamide (n=933)	Placebo (n=468)
Survival status		
Death	103 (11.0%)	62 (13.2%)
Censored[a]	830 (89.0%)	406 (86.8%)
Alive at data analysis cut-off date	808 (86.6%)	387 (82.7%)
Withdrew consent	19 (2.0%)	17 (3.6%)
Lost to follow-up	2 (0.2%)	0 (0.0%)
Other	1 (0.1%)	2 (0.4%)
Overall survival[b] (months)		
n	933	468
25th percentile	NR	34.0
Median [95% CI]	NR [NR; NR]	NR [NR; NR]
75th percentile	NR	NR
Treatment comparison: enzalutamide versus placebo		
Hazard ratio [95% CI][c]	0.795 [0.580; 1.089]	
p-value[c]	0.1519	
Probability of being event-free at:[b]		
Year 1 [95% CI]	0.98 [0.96; 0.98]	0.97 [0.95; 0.98]
Year 2 [95% CI]	0.91 [0.88; 0.93]	0.87 [0.82; 0.90]
Year 3 [95% CI]	0.77 [0.71; 0.81]	0.71 [0.62; 0.78]
Median follow-up time based on reverse Kaplan-Meier estimates for all patients (months)	23.8	23.0

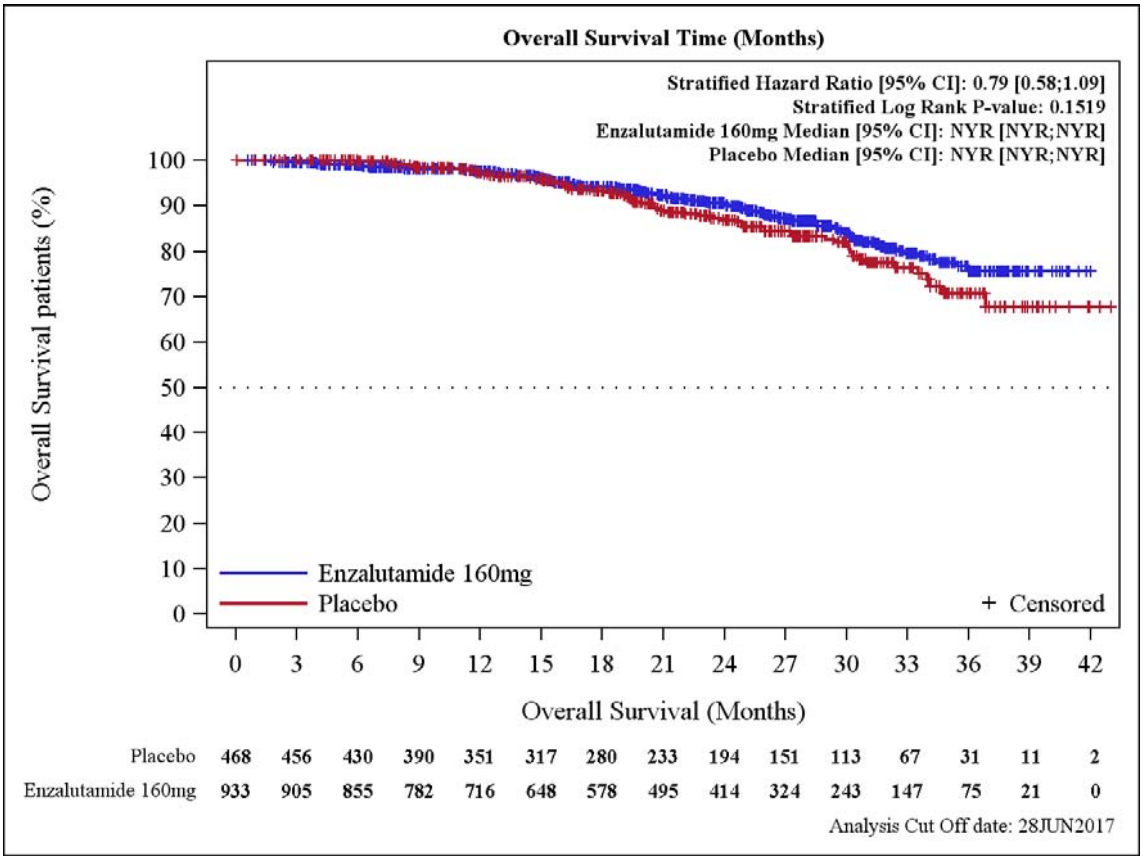
Source: PROSPER Clinical Study Report [Unpublished data]

a. Patients who were not known to have died at the analysis date were censored at the date last known alive or data analysis cut-off date, whichever occurred first.

b. Based on Kaplan-Meier estimates. Kaplan-Meier curves are provided in Figure .

c. P-value was based on a stratified log-rank test by PSADT (<6 months, ≥6 months) and prior or concurrent use of a bone-targeting agent (yes, no) as per IXRS. Hazard ratio was based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and was relative to the placebo group with <1 favouring the enzalutamide group.

Abbreviations: CI: confidence interval; IA1: interim analysis 1; ITT: intent-to-treat; IXRS: interactive voice / web recognition system; n: number of patients; NR: not reached; PSA: prostate-specific antigen.



Source: PROSPER Clinical Study Report [Unpublished data]

Note: p-value was based on a log-rank test stratified by PSA doubling time (<6 months, ≥6 months) and prior or concurrent use of a bone-targeting agent (yes, no) as per IXRS.

Hazard ratio was based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and was relative to placebo with <1 favouring the enzalutamide group.

Abbreviations: IA1: interim analysis 1; ITT: intent-to-treat; IXRS: interactive voice/web recognition system; OS: overall survival; PSADT: prostate-specific antigen doubling time.

Figure 9 Kaplan-Meier curves for duration of OS IA1 (ITT population)

Table 11 IA2 overall survival (ITT population), reproduced by the ERG from the CS, document B

Outcome	Enzalutamide (n=933)	Placebo (n=468)
Survival status		
Death	[redacted]	[redacted]
Censored[a]	[redacted]	[redacted]
Alive at data analysis cut-off date	[redacted]	[redacted]
Withdrew consent	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Other	[redacted]	[redacted]
Overall survival[b] (months)		
n	[redacted]	[redacted]
25th percentile	[redacted]	[redacted]
Median [95% CI]	[redacted]	[redacted]
75th percentile	[redacted]	[redacted]
Treatment comparison: enzalutamide versus placebo		
Hazard ratio [95% CI][c]	[redacted]	
p-value[c]	[redacted]	
Probability of being event-free at:[b]		
Year 1 [95% CI]	[redacted]	[redacted]
Year 2 [95% CI]	[redacted]	[redacted]
Year 3 [95% CI]	[redacted]	[redacted]
Median follow-up time based on reverse Kaplan-Meier estimates for all patients (months)	[redacted]	[redacted]

a. P-value is based on a stratified log-rank test.
b. Hazard ratio is based on a stratified Cox regression model (with treatment as the only covariate) and is relative to placebo with < 1 favouring enzalutamide. The 2 randomisation factors are PSA doubling time (< 6 months vs. >= 6 months) and prior or current use of a bone targeting agent.
CI: Confidence interval; HR: Hazard ratio; n: number of patients; NR: Not reached; SE: standard error.

IA2: interim analysis 2; ITT: intention to treat; OS: overall survival

Figure 10 is redacted – academic in confidence

Pre- and post- progression survival

The company used overall survival data from the PROSPER trial to inform the pre- (PrePS) post-progression survival (PPS) estimates used in the economic model. The company conducted a time-to-event analysis on the entire ITT population, censoring patients experiencing progression or were still alive at the cut-off date. The median follow-up time at IA1 was 18.5 months in the enzalutamide group and 15.1 months in the placebo group. At the first data cut of data, [redacted] PrePS events had occurred for enzalutamide and placebo respectively. The company state that the greater number of events in the enzalutamide arm is due to the longer time spent by these patients in the pre-progression stage. The mean time to a PrePS event was [redacted] months for enzalutamide and [redacted] months for placebo, resulting in an HR of a PrePS event of [redacted]. The company note

that results should be interpreted cautiously due to the low number of events in both treatment arms.

PPS was longer in the placebo group, with a mean time to event of [redacted] months versus [redacted] months. The company state that the shorter PPS was compensated by a longer MFS in the enzalutamide arm, resulting in a numerically longer OS in favour of enzalutamide.

The company present PrePS and PPS data in Table 41 of the CS, document B, on page 105 and this is reproduced by the ERG as Table 12 in this report.

Table 12 Pre- and post-progression survival (IA1, PROSPER ITT population), reproduced by the ERG from the CS, document B

Outcome	Enzalutamide (n=933)	Placebo (n=468)
PrePS		
Total number of patients	933	468
Number of patients with events	[redacted]	[redacted]
Number of censored cases	[redacted]	[redacted]
Mean time to events, months (SE)	[redacted]	[redacted]
Q1 [95% CI]	NR	NR
Median [95% CI]	NR	NR
Q3 [95% CI]	NR	NR
p-value[a]	[redacted]	
HR [95% CI][b]	[redacted]	
PPS		
Total number of patients	[redacted]	[redacted]
Number of patients with events	[redacted]	[redacted]
Number of censored cases	[redacted]	[redacted]
Mean time to events, months (SE)	[redacted]	[redacted]
Q1 [95% CI]	[redacted]	[redacted]
Median [95% CI]	[redacted]	[redacted]
Q3 [95% CI]	[redacted]	[redacted]
p-value[a]	[redacted]	
HR [95% CI][b]	[redacted]	

a. p-value is based on a stratified log-rank test.
b. Hazard ratio is based on a stratified Cox regression model (with treatment as the only covariate) and is relative to placebo with <1 favouring enzalutamide. The 2 randomisation factors are PSA doubling time (<6 months vs. ≥6 months) and prior or current use of a bone-targeting agent.
Abbreviations: CI: Confidence interval; HR: Hazard ratio; IA1: interim analysis 1; NR: Not reached; PPS: post-progression survival; PrePS: pre-progression survival; SE: standard error; TTD: time to treatment discontinuation

Antineoplastic therapy administered after treatment discontinuation

The company presents all post-progression therapies received by at least 1% of patients following treatment discontinuation for both IA1 and IA2 in Table 15 of the CS, document B, pages 59-60, and this is reproduced by the ERG as Table 13 in this report.

Table 13 Antineoplastic therapy administered to at least 1% of patients in either treatment group after treatment discontinuation in IA1 or IA2 (PROSPER safety population), reproduced by the ERG from the CS, document B

	IA1		IA2	
	ENZA 160 mg (N=930)	PLA (N=465)	ENZA 160 mg (N=930)	PLA (N=465)
Number of patients taking at least one posttreatment discontinuation antineoplastic	[redacted]	[redacted]	[redacted]	[redacted]
All other therapeutic products	[redacted]	[redacted]	[redacted]	[redacted]
Investigational drug	[redacted]	[redacted]	[redacted]	[redacted]
Antineoplastic agents	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]
Estramustine	[redacted]	[redacted]	[redacted]	[redacted]
Corticosteroids for systemic use	[redacted]	[redacted]	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]
Prednisolone	[redacted]	[redacted]	[redacted]	[redacted]
Dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]
Drugs for treatment of bone diseases	[redacted]	[redacted]	[redacted]	[redacted]
Denosumab	[redacted]	[redacted]	[redacted]	[redacted]
Zoledronic Acid	[redacted]	[redacted]	[redacted]	[redacted]
Endocrine therapy	[redacted]	[redacted]	[redacted]	[redacted]
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]
Bicalutamide	[redacted]	[redacted]	[redacted]	[redacted]
Leuprorelin	[redacted]	[redacted]	[redacted]	[redacted]
Goserelin	[redacted]	[redacted]	[redacted]	[redacted]
Triptorelin	[redacted]	[redacted]	[redacted]	[redacted]
Flutamide	[redacted]	[redacted]	[redacted]	[redacted]
Immunostimulants	[redacted]	[redacted]	[redacted]	[redacted]
Sipuleucel-T	[redacted]	[redacted]	[redacted]	[redacted]
BCG-vaccine	[redacted]	[redacted]	[redacted]	[redacted]
Lentinan	[redacted]	[redacted]	[redacted]	[redacted]
Sex hormones and modulators of the genital system	[redacted]	[redacted]	[redacted]	[redacted]
Antiandrogens	[redacted]	[redacted]	[redacted]	[redacted]
Therapeutic Radiopharmaceuticals	[redacted]	[redacted]	[redacted]	[redacted]

ENZA: enzalutamide; n: number of patients; OS: overall survival; PLA: placebo. Drugs were classified using the World Health Organisation Drug Dictionary

Following clarification from the ERG, the company provided additional details of the treatments received as second line therapies by participants after treatment discontinuation at IA1, and this table is reproduced by the ERG as Table 14 in this report. The ERG clinical advisor opinion is that the numbers receiving abiraterone following enzalutamide treatment ([redacted]) would unlikely be seen in UK practice, due to the lack of supportive evidence for abiraterone treatment at this stage of the care pathway; participants are more likely to continue with enzalutamide or receive docetaxel. The ERG notes that UK participants were a subset of the whole PROSPER population and this could reflect the difference in the type of treatments received as second line therapies. The ERG also notes that the company's economic model assumes that all participants receive either enzalutamide or abiraterone following progression. While Table 14 presents data for treatment discontinuation rather than progression, the data show similar distributions to data supplied by the company at clarification for first treatment after disease progression, and indicate that approximately half of the participants in the enzalutamide and placebo arms received either abiraterone or enzalutamide as a second line therapy.

Table 14 First therapy regimen participants received after study treatment discontinuation (PROSPER ITT, IA1)

	Enzalutamide	Placebo
	N (%)	N (%)
Subjects who discontinued treatment	296/933 (31.7%)	289/468 (61.8%)
Subjects who started any new anti-neoplastic treatment after treatment discontinuation	139/933 (14.9%)	222/468 (47.7%)
First regimen after study treatment discontinuation		
ABI ± BSC	[redacted]	[redacted]
ABI + DOC ± BSC	[redacted]	[redacted]
ABI + ENZA ± BSC	[redacted]	[redacted]
DOC ± BSC	[redacted]	[redacted]
ENZA ± BSC	[redacted]	[redacted]
Other chemotherapy* ± BSC	[redacted]	[redacted]
Other agents# ± BSC	[redacted]	[redacted]
Investigational drug ± BSC	[redacted]	[redacted]
None of the above (i.e., BSC)	[redacted]	[redacted]

ABI, abiraterone, BSC; best supportive care; ENZA, enzalutamide

Time to pain progression

The company defined pain progression as > 2 point increase from the baseline score for question 3 of the Brief Pain Inventory – Short Form (BPI-SF). Time to pain progression was comparable in both PROSPER treatment arms (HR: 0.959, 95% CI: [0.801; 1.149], p-value=0.6534). The median (95% CI) time to pain progression was 18.5 months (17.0, 22.1) in the enzalutamide group versus 18.4 months (14.8, 22.1) in the placebo group. The company suggest that this result indicates that pain was not related to the development of metastatic disease given that the median MFS was 36.6 months in the enzalutamide group and 14.7 months in the placebo group.

Time to first use of cytotoxic chemotherapy, chemotherapy-free survival and chemotherapy-free disease specific survival

The company provides the definitions of chemotherapy initiation-related endpoints in the PROSPER trial in Table 16 of the CS .and presents data for these endpoints in Table 17 of the CS document B, page 6. Table 17 is reproduced by the ERG as Table 15 in this report. Enzalutamide was associated with a statistically significant delay in the time to initiation of first use of cytotoxic chemotherapy (HR: [redacted] 95% CI [redacted]), and prolonged chemotherapy-free survival (HR: [redacted], 95% CI [redacted]) and chemotherapy-free disease-specific survival (HR: [redacted], 95% CI [[redacted])

Table 15 Time to first use of cytotoxic chemotherapy, chemotherapy-free disease specific survival and chemotherapy-free survival (PROSPER ITT population), reproduced by the ERG from the CS, document B

Outcome	Enzalutamide (n=933)	Placebo (n=468)
Status of chemotherapy and survival follow-up		
Event[a]	[redacted]	[redacted]
Initiated chemotherapy	[redacted]	[redacted]
Death	[redacted]	[redacted]
Death due to prostate cancer	[redacted]	[redacted]
Censored[b]	[redacted]	[redacted]
Treatment comparison: First Cytotoxic Therapy		
Hazard ratio [95% CI][c]	[redacted]	
p-value[c]	[redacted]	
Treatment comparison: Chemotherapy-Free Disease-Specific Survival		
Hazard ratio [95% CI][c]	[redacted]	
p-value[c]	[redacted]	
Treatment comparison: Chemotherapy-Free Survival		
Hazard ratio [95% CI][c]	[redacted]	
p-value[c]	[redacted]	

a. Based on the first post-baseline use of cytotoxic chemotherapy for prostate cancer.
b. Patients who had not initiated cytotoxic chemotherapy for prostate cancer at the time of analysis data cut-off were censored at date of last assessment prior to the analysis data cut-off date.
c. P-value was based on a stratified log-rank test by PSADT (<6 months, ≥6 months) and prior or concurrent use of a bone targeting agent (yes, no) as per IXRS. Hazard ratio was based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and was relative to the placebo group with <1 favouring the enzalutamide group.
Abbreviations: CI: confidence interval; ITT: intent-to-treat; IXRS: interactive voice / web recognition system; n: number of patients; PSADT: prostate-specific antigen doubling time

PSA response

Three different PSA-response rate were assessed in PROSPER: ≥50% decrease from baseline, ≥90% decrease and decrease to an undetectable level. The difference in response rates consistently favoured enzalutamide being significant for all levels of PSA reduction (p-value<0.0001).

Similarly, in the STRIVE trial, a higher proportion of patients in the enzalutamide group had confirmed >50% and >90% reduction in PSA from baseline than the bicalutamide arm (both p-value<0.0001).

Adverse reactions

The company present data for treatment emergent adverse event (TEAE) data from the PROSPER trial cut-off date of 28th June 2017, in the CS. The incidence of all grades of TEAEs was higher in the enzalutamide group than the placebo group. The company present summary data in Table 31 of the CS, document B, page 84 and this is reproduced by the ERG as Table 16 in this report.

Table 16 Overall summary of TEAEs (PROSPER safety population)

Outcome	Enzalutamide (n=930)	Placebo (n=465)
Patients with any TEAE	808 (86.9%)	360 (77.4%)
Any TEAE Grade 3 or higher	292 (31.4%)	109 (23.4%)
Any TEAE leading to death	32 (3.4%)	3 (0.6%)
Any serious TEAE	226 (24.3%)	85 (18.3%)
Any TEAE leading to study drug discontinuation	96 (10.3%)	35 (7.5%)
Any TEAE leading to dose reduction of study drug	94 (10.1%)	13 (2.8%)
Any TEAE leading to dose interruption of study drug	143 (15.4%)	40 (8.6%)
Patients with any TEAE related to study drug	581 (62.5%)	211 (45.4%)
Any TEAE Grade 3 or higher related to study drug	113 (12.2%)	25 (5.4%)
Any serious TEAE related to study drug	32 (3.4%)	12 (2.6%)

The company state "TEAEs involving impaired cognition and memory (terms within the MedDRA high level group term 'mental impairment disorders') were reported in 48 patients (5.2%) in the enzalutamide group and 9 patients (1.9%) in the placebo group (Table 35 of the CS and reproduced by the ERG as **Error! Reference source not found.**). A total of 28 patients (3.0%) in the enzalutamide group and 5 patients (1.1%) in the placebo group were considered to have a TEAE that was related to study drug. When events were adjusted for duration on treatment (events per 100 patient-years), the overall event rates were 3.8 in the enzalutamide group and 1.8 in the placebo group. Only 1 patient in the enzalutamide group and no patient in the placebo group experienced a Grade 3 or higher TEAEs of 'mental impairment'; the event was a Grade 3 cognitive disorder that led to study drug discontinuation. TEAEs of 'mental impairment' led to study drug discontinuation in a total of 5 patients (0.5%) in the enzalutamide group and 1 patient (0.2%)."

Table 17 Overall summary of TEAEs of special interest (PROSPER safety population)

TEAE of special interest	Enzalutamide (n=930)	Placebo (n=465)
Convulsion	3 (0.3%)	0 (0.0%)
Hypertension	114 (12.3%)	25 (5.4%)
Neutropenia	9 (1.0%)	1 (0.2%)
Memory impairment	48 (5.2%)	9 (1.9%)
Hepatic impairment	11 (1.2%)	9 (1.9%)
Major adverse cardiovascular event (MACE)	48 (5.2%)	13 (2.8%)
Posterior reversible encephalopathy syndrome (PRES)[a]	0 (0.0%)	0 (0.0%)

Patients treated with enzalutamide also had a higher incidence of ≥ Grade 3 TEAEs than the placebo group (31.4% vs 23.4% in the placebo group). ≥ Grade 3 TEAEs with at least a 1% higher incidence in the enzalutamide group included fatigue (2.9% enzalutamide vs 0.6% placebo), asthenia (1.2% vs 0.2%), and hypertension (4.6% vs 2.2%). In the placebo group, > Grade 3 TEAEs with at least a 1% higher incidence than the enzalutamide group include haematuria (1.7% vs 2.8%) and renal failure acute (0.4% vs 1.5%).

A higher number of participants in the enzalutamide group (10.3%) compared with the placebo group (7.5%) experienced a TEAE, of any grade, that led to study drug discontinuation. Of these TEAEs, only fatigue occurred in more than 1% of participants (2.2% of people in the enzalutamide arm and 0% in the placebo arm). TEAEs leading to death were also more frequent in the enzalutamide arm than the placebo arm (3.4% versus 0.6% respectively) and were most commonly cardiac disorders (1.0% enzalutamide vs 0.4% placebo), neoplasms benign, malignant and unspecified (0.6% enzalutamide vs 0.2% placebo), and general disorders and administration site conditions (0.5% enzalutamide vs 0.0% placebo).

[redacted]

[redacted] [Unpublished data])

The ERG notes that the safety events of enzalutamide in PROSPER and STRIVE are consistent with previous mHRPC studies. There was a higher incidence of TEAEs with enzalutamide primarily driven by hypertension, memory impairment and major adverse cardiac events.

HRQOL and other patient-reported outcomes

The PROSPER trial arms were balanced at baseline for health-related quality of life (HRQOL), and participants were either asymptomatic or had low symptom burden, good HRQOL and high functioning, except for sexual activity and sexual function. Data were collected up to week 97 and longitudinal changes from baseline were analysed by the company using a mixed model for repeated measures (MMRM) analysis and present this data in Table 20 of the CS, document B, page 65 (and reproduced by the ERG as Table 18 in this report). The company presented data for time to HRQOL deterioration in Table 21 of the CS, document B, page 66 (and reproduced by the ERG as Table 19 in this report). There were no statistically significant differences between the enzalutamide and placebo groups, with the

exception of hormonal treatment-related symptoms (measured by the EORTC QLQ PR25) and social wellbeing (measured by FACT-P) in favour of enzalutamide. Changes in pain scores favoured enzalutamide and median time to worsening of pain symptoms and pain progression was also longer in the enzalutamide arm than the placebo arm, as measured by the FACT-P and BPI-SF, although only the BPI-SF measure was statistically significant (HR: 0.75, 95% CI [0.57, 0.97]. Time to deterioration favoured enzalutamide over placebo for other HRQOL dimensions, with the exception of the physical wellbeing dimension of the FACT-P, although this was statistically non-significant, and time to worsening in hormonal treatment-related symptoms (33.15 vs 36.83 months; HR: 1.29, 95% CI [1.02, 1.63]). Statistically significant differences favouring enzalutamide were reported for EORTC-QLQ-PR25 bowel (33.15 vs 25.89 months; HR: 0.72, 95% CI [0.59, 0.89]).and urinary symptoms (36.86 vs 25.86 months; HR: 0.56, 95% CI [0.46, 0.72]), FACT-P emotional well-being (HR 0.69 [95% CI 0.55, 0.86]), physical composite score (HR 0.79 [95% CI 0.67, 0.93]), FACT P total score (HR 0.83 [95% CI 0.69, 0.99])., and the EQ-5D visual analogue scale(HR 0.75 [95% CI 0.63, 0.90]). The ERG notes that enzalutamide is associated with an earlier deterioration in HRQOL due treatment-related symptoms compared to placebo, for example hormonal treatment-related symptoms, but, overall, enzalutamide is associated with a delay in the worsening of HRQOL.

Table 18 Mean changes in PRO scores from baseline to week 97 (PROSPER MMRM)

Instrument	LS mean (SE)		LS mean difference [95% CI]
	Enzalutamide	Placebo	Enzalutamide vs placebo
BPI-SF			
Item 3: pain at its worst	0.52 (0.13)	0.73 (0.22)	-0.21 [-0.66, 0.24]
Pain severity	0.49 (0.10)	0.55 (0.16)	-0.06 [-0.40, 0.29]
Pain interference	0.65 (0.10)	0.85 (0.16)	-0.20 [-0.53, 0.13]
EORTC QLQ-PR25			
Bowel symptoms and function	[redacted]	[redacted]	[redacted]
Hormonal treatment-related symptoms	[redacted]	[redacted]	[redacted]
Urinary symptoms and problems	[redacted]	[redacted]	[redacted]
FACT-P			
Physical well-being	-2.26 (0.23)	-2.00 (0.36)	-0.26 [-1.00, 0.49]
Social well-being	0.30 (0.28)	-0.64 (0.44)	**0.94 [0.02, 1.85]**
Emotional well-being	-0.24 (0.20)	-0.58 (0.31)	0.34 [-0.30, 0.98]
Functional well-being	-2.44 (0.28)	-2.57 (0.44)	0.13 [-0.78, 1.05]
Prostate cancer scale	-2.61 (0.32)	-3.32 (0.51)	0.70 [-0.35, 1.75]
Prostate cancer pain scale	-0.93 (0.18)	-1.06 (0.28)	0.13 [-0.46, 0.71]
FACT-P total	-7.17 (0.92)	-9.20 (1.45)	2.04 [-0.97, 5.04]
EQ-5D-5L			
EQ-VAS	[redacted]	[redacted]	[redacted]

A negative contrast favours enzalutamide over placebo for BPI-SF scores and bowel symptoms and function, hormonal treatment-related symptoms, and urinary symptoms and problems, while a positive contrast favours enzalutamide over placebo for FACT-P scores, sexual activity and EQ-VAS.
Bolded contrast is significant at the $p<0.05$ level.
Abbreviations: BPI-SF: Brief Pain Inventory Short Form; EORTC QLQ-PR25: European Organisation for Research and Treatment of Cancer Quality of life Questionnaire; EQ-5D-5L: European Quality of Life-5 Dimensions-5 Levels health questionnaire; EQ-VAS: European Quality of Life-Visual Analogue Scale; FACT-P: Functional Assessment of Cancer Therapy-Prostate; LS: least squares; MMRM: mixed model repeated measures; SE: standard error.

Table 19 Time to confirmed symptoms progression and HRQoL deterioration (PROSPER ITT population)

Instrument	Median (95% CI) time, months		HR (95% CI)
	Enzalutamide	Placebo	
BPI-SF			
Item 3	34.69 [29.73, 36.86]	30.52 [22.11, NR]	0.82 [0.66, 1.03]
Pain severity	36.83 [34.69, NR]	NR	**0.75 [0.57, 0.97]**
Pain interference	33.15 [29.54, NR]	30.52 [22.11, NR]	0.94 [0.76, 1.18]
EORTC QLQ-PR25			
Bowel symptoms/function	33.15 [29.50, NR]	25.89 [18.43, 29.67]	**0.72 [0.59, 0.89]**
Hormonal treatment-related symptoms	33.15 [29.60, NR]	36.83 [29.47, NR]	**1.29 [1.02, 1.63]**
Urinary symptoms and problems	36.86 [33.35, NR]	25.86 [18.53, 29.47]	**0.56 [0.46, 0.72]**
FACT-P			
Physical well-being	18.56 [16.82, 22.18]	19.35 [18.33, 25.79]	1.15 [0.96, 1.38]
Social well-being	34.04 [29.60, NR]	29.50 [25.79, NR]	0.87 [0.71, 1.08]
Emotional well-being	36.73 [33.12, 38.21]	29.47 [22.18, 33.15]	**0.69 [0.55, 0.86]**
Functional well-being	18.60 [18.20, 22.14]	18.37 [14.78, 18.66]	0.94 [0.79, 1.13]
Prostate cancer scale	18.43 [14.85, 18.66]	14.69 [11.07, 16.20]	**0.79 [0.67, 0.93]**
Prostate cancer pain scale	25.76 [22.11, 29.47]	22.11 [18.40, 30.52]	0.94 [0.78, 1.14]
FACT-P total	22.11 [18.63, 25.86]	18.43 [14.85, 19.35]	**0.83 [0.69, 0.99]**
EQ-5D-5L			
EQ-VAS	[redacted]	[redacted]	[redacted]

Bolded contrast is significant at the p<0.05 level.
Abbreviations: BPI-SF: Brief Pain Inventory Short Form; CI=confidence interval; EORTC QLQ-PR25: European Organisation for Research and Treatment of Cancer Quality of life Questionnaire; EQ-5D-5L: European Quality of Life-5 Dimensions-5 Levels health questionnaire; EQ-VAS: European Quality of Life-Visual Analogue Scale; FACT-P: Functional Assessment of Cancer Therapy-Prostate; HR: hazard ratio; HRQoL: health-related quality of life; NR: not yet reached.

STRIVE CSR – median baseline FACT-P global score was 125.0 and similar between treatment groups (not presented in CSR table)

Similarly, there was no significant difference between the enzalutamide and bicalutamide treatment arms for time to degradation of FACT-P scores in the STRIVE trial. The median time to degradation was 8.4 months for the enzalutamide group and 8.3 months for the bicalutamide group (HR 0.910 [95% CI: 0.695, 1.192], p = 0.4945). (Medivation-Pfizer. Clinical Study Report - STRIVE: a multicenter phase 2, randomized, double-blind, efficacy and safety study of enzalutamide vs. bicalutamide in men with prostate cancer who have failed primary androgen deprivation therapy. 14 August 2015 [Unpublished data])

Time to treatment discontinuation

Time to study treatment discontinuation (TTD) was calculated by the company as treatment end date – treatment start date + 1 at both first and second interim analyses.

[redacted].

4.3 Critique of trials identified and included in the indirect comparison and/ or multiple treatment comparison

No trials in addition to those considered for the systematic literature review were considered for the network meta-analysis. The Company only included PROSPER and STRIVE in the indirect comparison and these have already been discussed. The ERG supports the justification provided by the Company for not including TARP and SPARTAN in the network meta-analysis. The ERG are unclear as to the rationale for conducting the network meta-analysis as bicalutamide is not a comparator in the decision problem.

4.4 Critique of the indirect comparison and/ or multiple treatment comparison

The ERG used the WINBUGS code provided by the Company and were able to reproduce the results of the fixed effects network meta-analysis. As the Company acknowledge, disease progression was assessed with metastases free survival in PROSPER while in STIVE radiographic progression free survival was used, the ERG suggest that a random effects model should therefore have been developed and the

results compared as a sensitivity check. The ERG ran a random effects model and obtained NMA results for Enzalutamide v placebo of [redacted] for MFS/rPFS and [redacted] for time to PSA progression. The results for Bicalutamide v placebo from the same model are [redacted] for MFS/rPFS and [redacted] for time to PSA progression.

4.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG intended to reproduce some of the Kaplan-Meier curves to examine the distributions selected for the extrapolation and this was the reason for requesting the survival data for Figures 22, 24 and 25 at clarification. The supplied data did not include all of the points which were plotted on the graph and so the ERG were only able to produce an approximation to each of these Kaplan-Meier graphs. These approximations did agree with the graphs presented in the Company's submission. The ERG therefore made use of the long-term progression graphs presented in appendix A of the company submission. In most cases the ERG agreed with the decision made by the Company for the choice of extrapolation distribution. The ERG do however have concerns regarding choosing the Weibull distribution for extrapolating pre-progression survival and would recommend that the log-normal is also considered for the cost effectiveness modelling.

4.6 Conclusions of the clinical effectiveness section

The ERG agree that the evidence on clinical effectiveness provided by the Company shows that there is a beneficial effect from enzalutamide compared to placebo. There is a large effect size on the primary outcome of metastases free survival and the difference between the experimental arm and the control arm are significant. The survival curves and summary statistics show a delay in the development of metastases.

The ERG also agree that the five secondary endpoints highlighted by the Company; time to prostate-specific antigen progression, time to first use of cytotoxic chemotherapy, chemotherapy free survival, chemotherapy-free disease specific survival and time to treatment discontinuation all show hazard ratios and significance levels which indicate a benefit for enzalutamide in comparison to placebo.

As stated above the ERG recognise that there is a beneficial effect on MFS from enzalutamide but would question the size of the anticipated overall survival benefit as stated at IA2 data analysis. The OS are immature and [redacted]

The ERG agrees that the safety of enzalutamide in PROSPER is consistent with previous mHRPC studies. There was a higher incidence of TEAEs with enzalutamide primarily driven by hypertension, memory impairment and major adverse cardiac events.

It is also the opinion of the ERG that while the network meta-analysis has been performed and interpreted correctly, the reasons for carrying out a network meta-analysis should have been explained as bicalutamide is not a comparator in the decision problem.

5 Cost effectiveness

5.1 ERG comment on company's review of cost-effectiveness evidence

5.1.1 State objectives of cost effectiveness review. Provide description of company's search strategy and comment on whether the search strategy was appropriate. If the company did not perform a systematic review, was this appropriate?

The company carried out a SLR to identify relevant economic evidence of enzalutamide and standard of care in managing nmHRPC.

Studies of cost effectiveness were sought by searching PubMed, MEDLINE, EMBASE, EconLit, Cochrane Databases of Systematic Review (CDSR, via Cochrane Library), HTA Database (via Cochrane Library), NHS Economics Evaluation Database (NHS EED, via Cochrane Library), HTA Accelerator (IQVIA proprietary database) and International Society of Pharmacoeconomics and Outcomes Research (ISPOR) Database in November 2016 and updated in July 2018. The searches were not restricted to language or timeframe. However, the PubMed search was restricted to a 10-year timeframe from 1 January 2006 to 24 November 2016. The search strategies are documented in Appendix G and partly in Appendix D of the company submission and are reproducible.

The PubMed/MEDLINE, EMBASE and Cochrane searches combined four search facets using the Boolean operator AND: prostate cancer; hormone-relapsed; non-metastatic; and economic evaluations, while in EconLit, two search facets using the Boolean operator AND: castration and prostate cancer.

The search strategies were considered fit for purpose, including both relevant controlled vocabulary and text terms with appropriate use of the Boolean operators. For the economic evaluation facets in both MEDLINE and EMBASE, the company used the NHS EED economics filter.

For health-related quality of life (HRQoL) studies, a separate SLR was conducted to identify reports of HRQoL and utility data for enzalutamide and standard of care in

managing nmHRPC. The company searched PubMed, MEDLINE, EMBASE, CDSR (via Cochrane Library), Cochrane Central Register of Controlled Trials (via Cochrane Library), Database of Abstracts of Reviews of Effects (via Cochrane Library), CEA Registry and HTA Accelerator in November 2016 and updated in July 2018. No restriction was applied. The PubMed search was only up to November 2016. The search strategies are documented in full in Appendix H of the submission and are reproducible.

The PubMed, MEDLINE, EMBASE and Cochrane searches combined four search facets using the Boolean operator AND: prostate cancer; hormone-refractory; non-metastatic; and HRQoL terms. The CEA Registry searched any terms related to the scope of HRPC and castration-relapsed prostate cancer (CRPC) which were appropriate.

The search strategies were considered fit for purpose, including both relevant controlled vocabulary and text terms with appropriate use of the Boolean operators.

5.1.2 State the inclusion/ exclusion criteria used in the study selection and comment on whether they were appropriate.

The company did not state the inclusion/exclusion criteria in the SLRs. However, the SLR included studies reporting the healthcare resource utilisation or direct and indirect costs associated with the management of adult patients with nmHRPC. For the SLR of HRQoL studies, the outcomes of interest were the impact of nmHRPC and its treatment on patients. No country, language or timeframe restrictions were imposed for both SLRs.

5.1.3 What studies were included in the cost effectiveness review and what were excluded? Where appropriate, provide a table of identified studies. Please identify the <u>most important</u> cost effectiveness studies.

Cost effectiveness studies

A poster presentation by Morote et al. 2013 on the costs of managing HRPC patients with high risk of developing bone metastases [22] was included. However, the company

indicates that it is not relevant to the UK setting as it reports the costs specific for Spain.

Quality of life studies

Three studies relevant to the utilities of nmHRPC and mHRPC were identified. These included:

- A poster presentation by Dawson et al. 2018 on nmHRPC, chemo-naïve mHRPC and during or post-chemo mHRPC in the US [23]
- A poster presentation by Hechmati et al. 2012 on high risk nmHRPC and mHRPC in the EU5[24]
- PROSPER HEOR report on high risk nmHRPC in Europe, North America and the rest of the world (Astellas. PROSPER HEOR report. Final version, January 2018. [unpublished data].).

The company considers the PROSPER HEOR report to be the most relevant source of evidence for their technology appraisal given the differences in elicitation method and study population in the 2 posters identified.

5.1.4 What does the review conclude from the data available? Does the ERG agree with the conclusions of the cost effectiveness review? If not, provide details.

The manufacturer stated that no previous cost-effectiveness studies were identified in the SLR. The ERG agrees that the study identified in the SLR is not directly relevant to the decision problem of the current appraisal. A detailed critique of the submitted model and economic evaluation follows below.

5.2 Summary and critique of company's submitted economic evaluation by the ERG Suggested research priorities

5.2.1 NICE reference case checklist (Table only)

Table 20 NICE reference checklist

Attribute	Reference case and TA methods guidance	Does the de novo economic evaluation match the reference case?
Comparator(s)	ADT	Yes
Patient group	As per NICE scope. *"Adults with nmHRPC"*	Partly. The model considers adults with high risk nmHRPC. High risk is defined as PSA doubling time (DT) ≤ 10 months and a PSA ≥ 2 ng/ml.
Perspective costs	Cost from an NHS and Personal Social Services (PSS) perspective	Partly. PSS does not appear to be included.
Perspective benefits	All direct health effects, whether for patients or, where relevant, carers	Partly. Health effects for carers are not considered.
Form of economic evaluation	Cost-effectiveness analysis expressed in terms of incremental cost per quality adjusted life year	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being assessed	Yes. A life-time horizon of up to 20 years is modelled from a starting age of 73.5 in the base case analyses.
Synthesis of evidence on outcomes	Evidence synthesis should be based on a systematic review	Yes. The model relies upon the findings from the PROSPER, PREVAIL, AFFIRM trials and a previous TA published in 2016. [8, 17, 25, 26]

Attribute	**Reference case and TA methods guidance**	**Does the de novo economic evaluation match the reference case?**
Outcome measure	Quality-adjusted life years	Yes.
Health states for QALY	Described using a standardized and validated instrument	The health status of patients at baseline was derived from the PROSPER trial. [17]Other utility values were taken from PREVAIL,[25] AFFIRM [26] and published literature using different methods (EQ-5D and direct preference elicitation methods).
Benefit valuation	Time-trade off or standard gamble	The nmHRPC and mHRPC utility are derived from EQ-5D-5L data in the PROSPER [17] and PREVAIL [25] trials respectively, via mapping to UK EQ-5D-3L values.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Partly. The nmHRPC, mHRPC and end-of-life utilities are estimated from the PROSPER and PREVAIL EQ-5D data. Values for the other health states of the model are estimated from the literature using various different methods (EQ-5D, direct TTO, SG). These were derived from representative samples of the public except the utility decrement for urinary retention which was based on a US study that elicited the value

Attribute	Reference case and TA methods guidance	Does the de novo economic evaluation match the reference case?
		using a SG with patients with benign prostate hyperplasia. [27]
Discount rate	An annual rate of 3.5% on both cost and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Probabilistic modelling	Probabilistic modelling	Yes.
Sensitivity analysis		Yes. The company presented one-way sensitivity analysis with the 15 most influential parameters reported. Several scenario analyses were also presented.

5.2.2 Models structure

The company developed a semi-Markov model coupled with a partitioned survival modelling approach. The model compares two treatments for high risk nmHRPC: enzalutamide with ADT versus ADT alone. The model utilises a monthly cycle and runs over a life-time horizon of 20 years, starting at the age of 73.5 years. Costs and QALYs are discounted at 3.5% per year as per NICE guidelines.

The model incorporates three mutually exclusive health states: “nmHRPC”, “mHRPC” and “Death” (Figure 11). Three Markov sub-health states are incorporated within the mHRPC health state: pre-chemo (PD1), during chemo (PD2) and post-chemo (PD3). The proportion of the cohort in the nmHRPC and mHRPC health states at each time point is determined by transition probabilities estimated by fitting parametric survival curves to metastasis-free survival (MFS) data from PROSPER.

Within the mHRPC health state, the proportion of the cohort in each sub-health state at each time point is derived by using transition probabilities estimated from the mean duration on specific treatments used in the progressive disease states. Survival is determined using the area under overall survival (OS) curve approach. However, the OS curve is separated into two curves - pre-progression survival (PrePS) and post-progression survival (PPS) and applied to nmHRPC and mHRPC patients, respectively. Thus the company describe the model as semi-Markov state transition model, with partitioned survival approach.

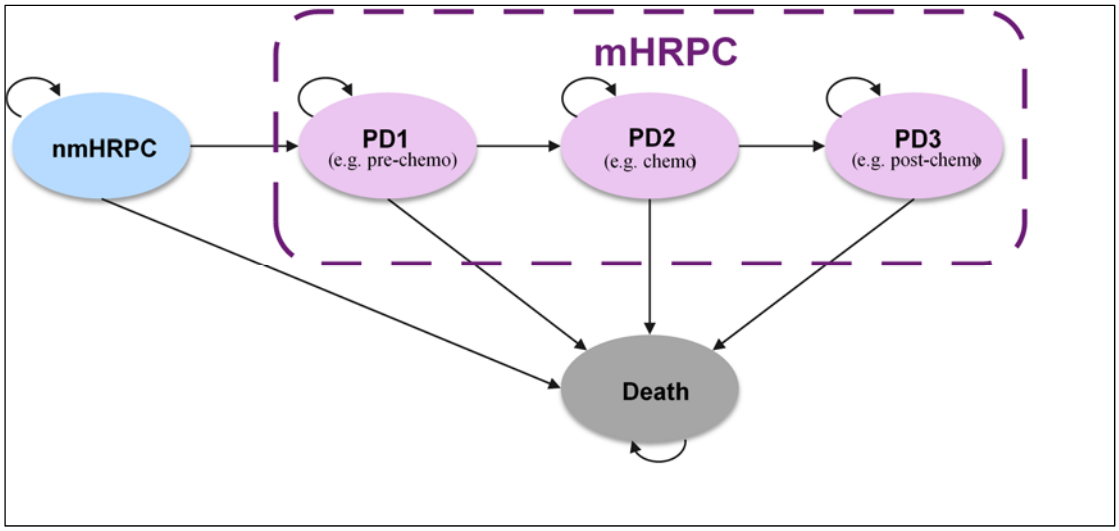


Figure 11 Model structure (Source: Figure 21, Company submission, document B)

All patients in the enzalutamide and ADT, and ADT alone arms of the model, start in the nmHRPC health state and a proportion progress to the mHRPC health state over time. Upon progression to PD1, the model assumes that those in the enzalutamide arm discontinue enzalutamide but remain on ADT alone for a period of time. For those in the ADT alone arm, the company base case assumes that all patients commence enzalutamide treatment upon progression to PD1. Subsequently, in PD2, it is assumed, in both arms of the model, that 40% of patients receive docetaxel chemotherapy while the remaining receive ADT alone. In PD3, all patients receive best supportive care.

The model also incorporates treatment-related AEs, and skeletal related events associated progression to mHRPC. These incur cost and quality of life impacts.

In general the ERG believe that the company model captures the progressive nature of the disease. One potentially problematic issue relates to the reliance on PPS survival data that does not vary across the PD sub-states (1-3); i.e. the probability of death does not vary by PD sub-state. If mortality is increases with progression through the PD state, then the model may underestimate life years in PD1, and overestimate life years spent in PD3. Further uncertainties relate to a number of model parameters inputs and assumptions which are discussed in the relevant sections below.

5.2.3 Population

The population is as per the PROSPER trial entry criteria - adults with high risk non-metastatic prostate cancer; high risk is defined as having a baseline PSA level ≥ 2 ng/ml and a PSA doubling time (PDT) ≤ 10 months.

Several parameters related to the mHRPC health state of the model rely on data from the PREVAIL trial,[25] which compared enzalutamide to placebo in patient with mHRPC prior to chemotherapy (equivalent to stage PD1 in the company's model). The ERG had some concerns regarding the comparability of the progressed PROSPER population and the baseline PREVAIL population, given that those in the PROSPER trial were defined as high risk. At clarification, the company agreed with the ERG that there is uncertainty on the similarity between these populations. However, based on the progressed PROSPER population having a similar prevalence of soft tissue metastases and similar HRQoL compared to the baseline PREVAIL population, the company suggests that the progressed PROSPER population is comparable to the PREVAIL population at baseline. The ERG agrees that there is no evidence suggesting that the PROSPER population progresses at a different rate to the PREVAIL population following progression to metastasis.

However, the ERG had a remaining concern that the proportion of bone metastases among patients with metastases differed between the PROSPER population at time of progression and the PREVAIL population at baseline; [redacted] whilst 41-42% had bone metastasis at time of progression in PROSPER (Table 11, Company submission, document B). Given that skeletal-related events (SREs) incorporated in the company model were derived from

the PREVAIL trial, and are associated with bone metastases, the ERG was initially concerned that the SRE rate derived from PREVAIL might overestimate the rate for the progressed PROSPER population. However, in response to a clarification question on this issue, the company performed a scenario analysis removing all SREs, and the impact on the ICER was minimal.

5.2.4 Interventions and comparators

Intervention

The submission describes enzalutamide for the treatment of adults with high risk nmHRPC. It is administered as a single daily oral dose of 160 mg (as 4 four x 40 mg soft capsules). ADT is also modelled to continue in all patients on enzalutamide, and following progression to metastasis over the entire model time horizon.

Comparator

As there are no nmHRPC specific treatments currently recommended by NICE, ADT alone was applied as the comparator treatment in the model. This is line with the final scope for the appraisal and the comparator arm of the PROSPER trial.

The model compares enzalutamide with ADT to ADT alone for the treatment of nmHRPC. In the ADT alone arm, all patients receive enzalutamide as their second line treatment on progression to metastasis (PD1). In the enzalutamide arm, ADT alone is assumed to be the 2nd line treatment. Thereafter, in PD2, patients in both arms of the model receive 3rd line docetaxel (40%) or ADT alone (60%), reflecting the observation that some patients will refuse or be unsuitable for chemotherapy. Finally, in PD3, all patients receive BSC which is assumed to include continued use of ADT in the model. Thus, the model compares the following treatment pathways for nmHRPC:

- 1st enzalutamide and ADT → 2nd ADT alone → 3rd docetaxel or ADT → 4th BSC
- 1st ADT alone → 2nd enzalutamide and ADT → 3rd docetaxel or ADT → 4th BSC

Whilst the company have modelled a few alternative scenarios regarding the downstream treatment pathway, including the use of abiraterone rather than enzalutamide as the second line treatment in the ADT arm, the ERG is concerned that the company has not explored the impact of assuming that a proportion of patients may also receive other available treatments (e.g. radium 223 or cabazitaxel at PD2 and PD3. Furthermore, the ERG are uncertain about the validity of the assumption that patients in the enzalutamide arm will receive ADT alone upon progression. Whilst the impact on the treatment pathway is uncertain, it is possible that moving enzalutamide up the treatment pathway will also lead to a shift in current subsequent treatments up the clinical pathway, such that docetaxel is provided at PD1, and alternative active drugs are provided at PD2 and PD3. The ERG explore the potential impact of this in sensitivity analyses.

5.2.5 Perspective, time horizon and discounting

The perspective is that of the patient for health effects, and that of the NHS/PSS for costs. A 20-year horizon is adopted, which is in effect a lifetime horizon with 99% of the cohort modelled to have died by 12.25 years in the enzalutamide arm and 9.17 years in the standard care arm. Health benefits and costs are discounted at 3.5%.

5.2.6 Treatment effectiveness and ***extrapolation***

The difference in treatment effect between enzalutamide and ADT is incorporated in the company model primarily through survival curves for MFS, pre-progression survival (PrePS) and post-progression survival (PPS). These survival curves are derived from the PROSPER trial. [17] PrePS is applied by treatment arm in the nmHRPC health state, and PPS is applied by treatment arm across all sub-states of the mHRPC health state. Thus modelled treatments following progression to metastasis affect cost and utility via progression through the metastatic sub-states, but not mortality. Data inputs for AEs and SREs were derived from PROSPER, PREVAIL, and Tannock et al. [17, 25, 28]

Metastasis-free survival (MFS)

The proportion of patients transitioning from the nmHRPC to mHRPC (PD1) is determined by time dependent transition probabilities derived from the MFS curves fitted to the observed Kaplan Maier data from the PROSPER trial. The curve fitting

approach was performed according to NICE DSU guidance. [29] Among the six evaluated individual parametric distributions, the generalised gamma provided the best statistical and visual fit. However, the company rejected it on grounds of questionable validity; large deviations from the Kaplan Meier median were noted, implying that the curves seemed to underestimate the observed median MFS in both the ADT and enzalutamide arms of the PROSPER trial (Figure 22, Company submission, document B). The company stated that this was confirmed by clinical experts who noted that the extrapolations were questionable (Astellas. Minutes of the validation interview with a UK clinical expert. 2018. [Unpublished data]; Astellas. Enzalutamide in M0CRPC extrapolation validation meeting with medical expert. March 2018. [Unpublished data])

The company therefore considered spline-based and piecewise survival models. Of several specifications assessed, a spline model (2 knots, hazard scale) offered the most clinically valid extrapolation, with 3-year MFS estimates closest to the observed PROSPER data (Figure 12). Of alternative piecewise models assessed, the fit with log-logistic tail was judged to provide the most plausible extrapolations. Given that fewer assumptions were involved in the spline model, and to avoid the 'tail' seen with log-logistic curves, MFS in the base case model was extrapolated using the 2 knot spline model. The piecewise extrapolation with log-logistic tails was assessed in a scenario analysis.

The ERG agrees that the spline model provides a good visual fit to the observed MFS data which is relatively mature, particularly in the ADT arm, and that it is appropriate for extrapolation.

Figure 12 is redacted – academic in confidence

Overall survival

Overall survival data from the PROSPER trial was used to inform PrePS and PPS curves in the model. The company undertook the approach of splitting OS into PrePS and PPS, to improve the lack of face validity of utilising a single OS curve to estimate mortality across all states in the model, and better represent the survival difference between asymptomatic nmHRPC patients and progressed mHRPC patients. Data from the first two interim OS analyses (IA1 and IA2) are reported in the company submission. Despite the availability of the more mature IA2 OS data, the company have opted to use the data from IA1 (corresponding the primary analysis point for MFS) in their base-case analysis. The rationale provided by the company was a preference for using the MFS data to model progression to metastasis, which was not analysed at IA2 and so could not be used to split the IA2 OS data by progression status. The company also provided a scenario where they used the more mature IA2 OS data, but in this analysis they used time to treatment discontinuation (from the IA2 data cut) as a proxy for progression to metastasis.

(i) Pre-progression survival (PrePS)

Pre-progression survival was analysed by treatment group, treating progression to metastasis as a censoring event. A comparison of the Pre-PS data showed a low mortality rate in both arms and no statistically significant difference between groups (Company submission, document B, Table 41). However, separate parametric curves were fitted by treatment arm, with a Weibull model (Figure 13) chosen for each arm based on a combination of visual and statistical criteria, and comparison with age specific general population mortality. [30] (Astellas. Minutes of the validation interview with a UK clinical expert. 2018 [Unpublished data]; Astellas. Minutes of the validation interview with a UK health economist expert. 2018 [Unpublished data]) The ERG had concerns regarding the validity of the long-term extrapolations of PrePS based on the Weibull curves (Figure 13). [redacted]), the ERG questioned the validity of applying treatment arm specific rates at the clarification stage. The company noted that they had also provided a scenario analysis in their submission which utilised age specific general population mortality to model pre-progression survival, and that this had a minimal impact on the ICER. The reason for this is that most of the cohort in the ADT arm of the model have progressed by the time the PrePS curves diverge. The ERG acknowledge this.

Figure 13 is redacted – academic in confidence

(ii) Post-progression survival (PPS)

It is the ERG's understanding that PPS was assessed starting from the time of progression to metastasis.

since it is upon progression to metastatic disease that the placebo (ADT) group receive active treatment and the enzalutamide group cease treatment;

For PPS based on the IA1 data cut, a Weibull parametric model was chosen for both arms based on the visual fit and statistical criteria (Figure 14). [25 31] The Weibull curves were further noted to provide the best match to external OS reference data from the PREVAIL trial, which compared enzalutamide to placebo in pre-chemotherapy patients with mHRPC (equivalent position to PD1 in the current model). ERG have checked the fitted curves and are in agreement that the fitted Weibull PPS curves, provide a reasonable match to observed OS in the placebo and

enzalutamide arms of PREVAIL.[25] If anything, the fitted PPS curves may overestimate the observed difference in OS between enzalutamide and placebo in PREVAIL, which could be conservative in favour ADT in the current appraisal.

Figure 14 is redacted – academic in confidence

Although the ERG agrees with the approach of using PrePS and PPS in the model, the validity of the long-term model projection using the IA1 data cut is questionable, potentially leading to overestimation of the survival benefit for enzalutamide. The ERG believes that it would be more appropriate to use the more mature IA2 OS data to inform pre- and post-TD mortality in the base case analysis, but then a question remains as to

whether this should be used in conjunction with the MFS curves (only available for the IA1 data cut) to model the transition to mHRPC, or the TTD curves which are available for the IA2 data cut. The company provided a scenario in their original submission based on the latter approach, and provided a further scenario using the former combination in response to the clarification letter.

Figure 15 is redacted – commercial in confidence

Figure 16 is redacted – academic in confidence

Treatments in PD1

Upon entering PD1 sub-state, the model assumes that all patients in the ADT arm receive second-line enzalutamide. However, there is a mismatch between the modelled second line treatment and the actual second line treatments that were received by patients in PROSPER. This was confirmed by the company's response to the clarification letter, which indicated that of those who had commenced second line treatment following progression on ADT, [redacted] had initiated treatment with enzalutamide, whereas [redacted], BSC and docetaxel respectively (Table 21). The company provided a further scenario analysis based on this alternative PD1 treatment distribution for the ADT arm as part of their response, and this change had a moderate impact on the ICER.

The company were also asked to comment on any differences that the distribution of second line treatment in the placebo arm of PROSPER might have in comparison to enzalutamide (the assumption in the company model). In response, they noted that a network meta-analysis using PREVAIL,[25] COU-AA-302[31] and TAX327[28] [redacted] (Systematic Review and Mixed Treatment Comparison of Enzalutamide for Chemotherapy Naïve Castration-Resistant Prostate Cancer Final Report Astellas. January 2015 [unpublished data]). Therefore, since [redacted] of patients appear to have received ADT (BSC) alone upon progression in PROSPER, it could be argued that that PPS in the company model should have been adjusted upward to reflect the assumption of 100% enzalutamide treatment at PD1 following progression on ADT. However, as noted above, the extrapolation of PPS applied in the model has in fact been externally validated against the PREVAIL OS data, which is relevant to a pre-chemotherapy mHRPC population treated with 100% enzalutamide versus ADT alone.

It was similarly noted that the distribution of first antineoplastic treatments following disease progression on enzalutamide in PROSPER was inconsistent with the model assumption of docetaxel (40%) or ADT alone (60%) at PD2 in the enzalutamide arm of the model. Table 3 in fact indicates that of those who initiated a second line treatment following progression on enzalutamide, [redacted] initiated abiraterone and [redacted] appear to have been re-challenged with enzalutamide. It is unclear to ERG why this is the case, but the ERG acknowledge that in the UK NHS patients would not be considered for either abiraterone or retreatment with enzalutamide following progression on enzalutamide. It is also clear from Table 3 that docetaxel was the second most commonly prescribed second line treatment ([redacted]) in the enzalutamide arm, which is in line with the NHS treatment pathway. The ERG are generally satisfied that extrapolation of the PROSPER trial is suitable for the economic modelling, despite the described discrepancies in post-progression treatments compared to the modelled pathway.

Table 21 First treatment after disease progression in the enzalutamide and placebo arm (IA1; ITT) (Source: reproduce from company response to clarification questions, Table 8 and 10)

	Enzalutamide	Placebo
	N (%)	N (%)
Subjects who started any new anti-neoplastic treatment after disease progression	107/933 (11.5%)	169/468 (36.1%)
First regimen after study treatment discontinuation		
ABI ± BSC	[redacted]	[redacted]
ABI + ENZA ± BSC	[redacted]	[redacted]
DOC ± BSC	[redacted]	[redacted]
ENZA ± BSC	[redacted]	[redacted]
Other chemotherapy* ± BSC	[redacted]	[redacted]
Other agents# ± BSC	[redacted]	[redacted]
Investigational drug ± BSC	[redacted]	[redacted]
None of the above (i.e., BSC)	[redacted]	[redacted]

Abbreviations: ABI: abiraterone; BSC: best supportive care; DOC: docetaxel; ENZA: enzalutamide. §Median days between disease progression and initiation of first antineoplastic therapy. *Includes any chemotherapy other than docetaxel as well as any targeted therapy. #It includes Sipuleucel-T and ubenimex.

A further issue that the ERG queried at the clarification stage, was the expected duration of treatment on ADT alone (at PD1) following progression on enzalutamide. In the model, the company assumed a median duration of 7.2 months, based on extrapolation of data on the time to discontinuation from the placebo arm of the PREVAIL trial. [25]They then used this to generate a constant probability of progression to PD2. The ERG had some doubts about the applicability of this value to the PROSPER population which was defined as at high risk of progression to metastasis at baseline. The ERG therefore requested a scenario analysis utilising the median time from progression to initiation of subsequent antineoplastic therapy. In response, the company clarified that the median time from radiographic progression to next antineoplastic therapy initiation was [redacted] in enzalutamide arm of PROSPER, implying a shorter time spent in PD1 for those progressed on enzalutamide (Table 22). The company provided the scenario analysis using this median duration, resulting in quicker progression to PD2 and earlier docetaxel initiation. This resulted in a modest increase in the ICER in (results presented in section 5.2.9.

The median durations of other subsequent lines of therapy, which are used to govern the rate of progression through the PD sub-states in the model, are further critiqued in section 5.2.8 on resource use and costs.

Table 22 First treatment after disease progression in the enzalutamide arm and time from disease progression to initiation of first antineoplastic (IA1; ITT) (Source: Table 8, Company response to clarification questions)

	Enzalutamide	
	N (%)	Median days (min; max) §
Subjects who started any new anti-neoplastic treatment after disease progression	107/933 (11.5%)	[redacted]
First regimen after study treatment discontinuation		
ABI ± BSC	[redacted]	[redacted]
ABI + ENZA ± BSC	[redacted]	[redacted]
DOC ± BSC	[redacted]	[redacted]
ENZA ± BSC	[redacted]	[redacted]
Other chemotherapy* ± BSC	[redacted]	[redacted]
Other agents# ± BSC	[redacted]	[redacted]
Investigational drug ± BSC	[redacted]	[redacted]
None of the above (i.e., BSC)	[redacted]	[redacted]

Abbreviations: ABI: abiraterone; BSC: best supportive care; DOC: docetaxel; ENZA: enzalutamide. §Median days between disease progression and initiation of first antineoplastic therapy. *Includes any chemotherapy other than docetaxel as well as any targeted therapy. #It includes Sipuleucel-T and ubenimex.

5.2.7 Health related quality of life

The model incorporates health state-specific utility weights and utility decrements associated with adverse events. A baseline utility weight is applied to nmHRPC health state. Upon progression from nmHRPC to the mHRPC PD1 state, a lower health state utility is applied for the duration of time spent in that state. Health state utility is further reduced as disease progresses through PD2 and PD3. Utility decrements are applied for AEs based on the frequency of different AEs associated with enzalutamide, ADT and docetaxel. The AEs included in the model are those of grade 3 and 4 severity, those reported in ≥ 2% of patients and AEs of special interest (see Table 46 of the company submission, document B). Utility decrements associated with SREs are also applied in the mHRPC health states based on event rates derived from PREVAIL. An end-of-life utility is also applied for the 3 months preceding death.

Utility values: nmHRPC and mHRPC

The company relied on EQ-5D data from the PROSPER, PREVAIL, and AFFIRM[26] (Astellas. PROSPER HEOR report. Final version, January 2018. [Unpublished data] Medivation. Clinical Study Report - PREVAIL. 2014 [Unpublished data]) trials for their health state utility values.

In the PROSPER trial, EQ-5D-5L data were collected at baseline and at 16 week intervals thereafter, including during the follow-up period. In line with current NICE position,[29] the company mapped the EQ-5D-5L response data to the UK EQ-5D-3L utility values using the 'cross-walk' method, developed by van Hout et al.[32] The mapped baseline utility value for the overall PROSPER cohort was used as the utility value for the nmHRPC health state, and mean mapped utility value at the first post-progression assessment was used as for the PD1 state. The health state utility value for PD2 was derived from the PREVAIL trial, as the mean of first post-progression EQ-5D values, and the PD3 value was derived from the AFFIRM trial, which the company reports is in line with the post chemotherapy health state value used in the NICE submission for enzalutamide in pre-chemotherapy mHRPC patients. [8]

The base case values, which are reported in Table 44 of the company submission, are [redacted] for nmHRPC, [redacted] for PD1, [redacted] for PD2 and [redacted] for PD3. For the remaining 3 months before death, an end-of-life utility value of [redacted] is applied in the model, based on the final utility value observed within 90 days of death in PREVAIL trial participants (Medivation. Clinical Study Report - PREVAIL. 2014 [Unpublished data]).

The ERG has some concern that the utility value for the progressed state (PD1) represents a mean value at first assessment following progression which was not adjusted for baseline. However, in response to the clarification letter the company suggested that using the first post-progression utility value can be considered conservative, since health state utility may deteriorate over time within state PD1 as a result of exposure to treatment or disease progression. The ERG acknowledge this, but would suggest that the same could be true for the nmHRPC utility value, for which the company have relied on a baseline measure which would have been taken before any treatment had been initiated. Thus, the ERG has some remaining

uncertainty about the true difference in utility values between the nmHRPC health state and PD1 mHRPC sub-state. Since the company model assumes that the cohort of subjects progressing in the PROSPER trial is comparable to the PREVAIL population at baseline, the ERG explore the impact of applying a health state utility value derived from PREVAIL (0.844), which was used for people with stable disease on BSC at the equivalent point to entry into state PD1 in the company's previous submission for enzalutamide in pre-chemotherapy mHRPC patients.[8]

Utility values: Adverse events and skeletal-related events

The disutilities for AEs are taken from a range of published literature. These utilities are elicited in the context of various types of metastatic cancer from a representative sample of the public using a number of different methods. For urinary retention, the value appears to have been adapted from a study reported by Armstrong et al, [27]which utilised a value from a sample of US patients with benign prostate hyperplasia. [33] Of note, the utility value reported by Armstrong et al[27] had been adjusted for total symptom score and for the presence of incontinence to be applied in the context of benign prostate enlargement. Despite the uncertainty surrounding the utility values applied in the model, the company did not discuss on the appropriateness of these values for the indication population in the current submission.

The durations for which adverse event utiity decrements are applied are based on previous reviews of enzalutamide and abiraterone and a number of assumptions.[34] The utility values and for AEs and the durations for which they are applied in the company model, are presented in Table 23. One issue that the ERG would highlight is the relatively small utility value applied to MACE events, and in particular the short duration for which this value is applied. However, it is not possible within the model structure to apply chronic disutility associated with cardiovascular morbidity, and with a small difference in the rate of these events between treatment arms, doing so would be unlikely to have a substantial impact on the ICER.

The utilities related to SREs are derived from the PREVAIL trial[17] and Botterman et al.[35] The duration of each SRE is assumed to last for 30.42 days, based on the ERG reports for NICE TA377 and TA259 (Table 23).[34, 36]

Table 23 Duration and disutilities of AEs (Source: adapted from Table 47, Company submission, document B)

AE	Disutility	Duration of disutility (days)
Anaemia	-0.119	10.5
Asthenia	-0.131	91.25
Back pain	-0.069	10.5
Bone pain	-0.069	10.5
Deterioration in general physical health	-0.131	91.25
Fall	-0.069	10.5
Fatigue	-0.131	91.25
Febrile neutropenia	-0.120	10.5
Haematuria	No (dis-)utilities available	10.5
Hypertension	-0.153	10.5
Major cardiovascular adverse event (MACE)	-0.153	10.5
Neutropenia	-0.090	10.5
Pulmonary embolism	-0.145	10.5
Urinary retention	-0.110	10.5
SREs		
Spinal cord compression	-0.237	30.42
Pathological bone fracture	-0.201	30.42
Radiation to the bone	-0.056	30.42
Surgery to the bone	-0.056	30.42

Abbreviations: AE: adverse event; ERG: evidence review group; TA: technology appraisal.

Rate of adverse events and skeletal-related events

The company applies the rate of AEs for enzalutamide and ADT arms in the nmHRPC and mHRPC health states based on the PROSPER and PREVAIL trials, respectively. For AEs specific to docetaxel, the corresponding rates are obtained from a study by Tannock et al,[28] a randomised controlled trial comparing docetaxel (given either every three weeks or weekly) plus daily prednisone with mitoxantrone plus prednisone for patients with mHRPC. All the rates are calculated based on the number of events and patient years over the treatment emergent period of the studies (Table

46, Company submission, document B).The rates for SREs are taken from the PREVAIL trial.

5.2.8 Resources and costs

The company's model incorporated direct medical costs associated with the intervention and comparator, and future health care costs associated with HRPC. The company note that their SLR did not identify any resource use studies specific to nmHRPC, and so the pre-progression costs for the model were derived primarily from the PROSPER trial. Health care resource use following progression to metastasis was based on previous NICE enzalutamide technology appraisals and experience from its use in routine clinical practice.

Health state unit costs

The company note that the following costs were represented in the model: outpatient treatment, drug therapies and concomitant medications, administrations costs, monitoring costs, hospitalisation costs, follow-up treatment costs, and nursing care costs. The company note that the costs applied in the model were validated with a UK Clinical expert and that they are largely in line with those in the ERG report for the appraisal of enzalutamide for chemotherapy naïve mHRPC. [34]

Health state costs

Table 49 of the company submission (document B) summarises the health care visit and testing assumptions applied in the model by health state and treatment received. In general, visits and testing are assumed less frequent (every 8 weeks) for patients on enzalutamide than they are for patients on ADT alone (every 6 weeks). The company have not specifically justified why this is the case in the current submission. The same issue was identified and discussed in TA377 (enzalutamide versus BSC for pre-chemo mHRPC),[8] with the FAD for TA377 [37] noting that the company's rational was that clinicians would monitor patients on BSC who have failed on ADT more closely than they would patients who are stable on active treatment. However, the FAD for TA377 also noted that the committee considered that clinicians would also monitor enzalutamide patients for adverse events, and they concluded that the frequency of long-term monitoring with best supportive care and enzalutamide would be similar. The view was shared by the ERGs clinical expert, and so on this basis the ERG

explored the impact of equalising the visit and testing schedules for enzalutamide and ADT alone as per Table 24 below. In addition, the ERG identified a number of discrepancies between the visit and testing resource use inputs listed in Table 49 of the company submission, and some of the values actually applied in the model. The ERG therefore assessed the impact of revising the model based parameters in line with those reported in the company submission. This had minimal impact of the ICER. The unit costs for health care visits and tests were taken from the Unit Costs of Health and Social Care (PSSRU 2017) or the NHS reference costs (NHS Reference Costs 2016-2017).

The lists of relevant concomitant medications that are included in the company model are provided in Table 52 of the company submission (document B). The percentage of patients receiving these on enzalutamide and ADT were derived from the frequency of use reported in PROSPER for nmHRPC (Table 50 of the company submission, document B), and from PREVAIL for mHRPC (Table 51 of the company submission, document B). Unit costs for the concomitant medications were obtained primarily from the eMit database. These costs contribute only a small amount to the overall difference in cost between the Enzalutamide and ADT arms of the model.

Intervention and comparator costs

With respect to enzalutamide acquisition costs, the list NHS pack price of £2,734.67 was sourced from the BNF online. A pack contains 112 40mg tablets or soft capsules. The company state that the dose in the license application for nmHRPC is a daily oral dose of 160mg. Thus, a pack provides a 28 day supply of the drug, and the daily cost of treatment comes to £97.67 per day. A PAS discount is applied in the model, giving a daily cost of [redacted] The total nmHRPC enzalutamide acquisition cost in the enzalutamide arm of the model is a function of the daily price and time on treatment, which in the company base case is based on the MFS curve less pre-progression mortality. Since the company model works on a monthly cycle rather than a four week cycle, the daily cost is multiplied by the average number of days per month and applied to the proportion of the cohort remaining on active treatment in each cycle of the model.

The cost of ADT is applied in a similar way based on the unit price of non-proprietary luteinizing hormone releasing hormone combined with the average daily dose and average number of days per month. It is applied equally in both treatment arms throughout the model; i.e. ADT treatment is assumed to continue in 100% of patients across the entire time horizon of the model.

Subsequent treatment costs (following progression to mHRPC)

In the comparator arm of the model (ADT alone), the company base case assumes that 100% of patients receive treatment with enzalutamide upon progression to PD1. The same enzalutamide daily unit cost is applied to the proportion of the cohort surviving in that state. The time in state PD1 (in the comparator arm) is governed by a constant transition probability to PD2 (assumed exponential distribution) derived from the median time to enzalutamide discontinuation based on data from PREVAIL (Table 43 of the company submission, document B). The company note that the applied treatment duration was derived from the parametric gamma distribution fitted to the PREVAIL June 2014 data cut used in their previous submission to support enzalutamide for pre-chemo mHRPC.[8] However, there is a discrepancy between the value of 23.7 months reported in Table 43 of the company submission, and the value of 20.7 months which is applied in the model. The 20.7 months closely matches the reported median progression free survival reported for PREVAIL, [25] and so the ERG have assumed this is correct.

Similarly, following progression to PD1 in the enzalutamide arm of the model, the cohort is assumed to proceed on ADT alone for a period. The time in PD1 (on ADT alone) is based on a transition probability, which the company report as being derived from the extrapolated median treatment duration for the placebo arm of PREVAIL (June 2014 data cut) – using the company's preferred Weibull function from TA377 (see Table 43 of the company submission, document B). However, the applied value of 7.2 months is longer than the median progression free survival reported by Beer et al.[25] The ERG are therefore uncertain if the value of 7.2 months represents mean or median time on treatment. If it is a mean value, this may overestimate time in PD1 in the model, since the formula used to calculate the transition probability requires the median time to treatment discontinuation.

Table 24 ERG revised visits and testing included as health care resource use (Source: Adapted from Table 49 of the company submission, Document B)

Service	nmHRPC state		mHRPC state	
	Patients on ENZ	Patients on ADT	Patients on ENZA (PD1)	Patients on ADT (PD1 – PD2)
Outpatient visit consultant	1 every 6 weeks for 50% of patients	1 every 6 weeks for 50% of patients	1 every 6 weeks for 50% of patients	1 every 6 weeks for 50% of patients
Outpatient visit nurse	1 every 6 weeks for 50% of patients	1 every 6 weeks for 50% of patients	1 every 6 weeks for 50% of patients	1 every 6 weeks for 50% of patients
Community nurse visit	1 every 6 weeks for 100% of patients	1 every 6 weeks for 100% of patients	1 every 6 weeks for 100% of patients	1 every 6 weeks for 100% of patients
CT scan	3 every 36 weeks for all patients	3 every 36 weeks for all patients	3 every 36 weeks for all patients	3 every 36 weeks for all patients
Radiographic/MRI scan	None	None	None	None
ECG	None	None	None	None
Ultrasound	None	None	None	None
Bone scan	1 every 20 weeks for 20% of patients	1 every 20 weeks for 20% of patients	1 every 20 weeks for 20% of patients	1 every 20 weeks for 20% of patients
Full blood count	1 every 8 weeks for 100% of patients	1 every 8 weeks for 100% of patients	1 every 8 weeks for 100% of patients	1 every 8 weeks for 100% of patients
Liver function test	1 every 8 weeks for 100% of patients	1 every 8 weeks for 100% of patients	1 every 8 weeks for 100% of patients	1 every 8 weeks for 100% of patients
Kidney function test	1 every 8 weeks for 100% of patients	1 every 8 weeks for 100% of patients	1 every 8 weeks for 100% of patients	1 every 8 weeks for 100% of patients
PSA	1 every 8 weeks for 100% of patients	1 every 8 weeks for 100% of patients	1 every 8 weeks for 100% of patients	1 every 8 weeks for 100% of patients

Abbreviations: ADT: androgen deprivation therapy; BSC: basic standard of care; CT: Computer tomography ECG: electrocardiogram; ENZA: enzalutamide; ERG: evidence review group; nmHRPC: non-metastatic hormone-relapsed prostate cancer; PD: progressed disease; PSA: prostate-specific antigen; pts: patients.

Following progression to PD2 in both arms of the model, 40% of the cohort are assumed to receive docetaxel, which is costed as per the non-proprietary list price, with time in state governed by the median treatment duration reported in TAX 327. For the 60% who receive ADT alone in state PD2, the time in state is assumed equal; i.e. there is no modelled benefit of treatment with docetaxel compared with ADT alone at this position in the model. The 40% receiving docetaxel in PD2 appears to be in line with the view expressed by clinical experts who were present at the committee meeting for TA377. [37]

Further, since the appraisal of enzalutamide in pre-chemotherapy mHRPC, a number of further treatments have been approved for use in patients with mHRPC. These include radium-223 for people with symptomatic bone metastasis and no know visceral metastasis (either after docetaxel or if docetaxel is contraindicated or not suitable) (TA412),[38] and cabazitaxel in people whose disease has progressed during or after docetaxel chemotherapy (TA391). [39]The company have disregarded these treatment options in the model, based on market research suggesting they are not used by a majority of patients in the UK. (Kantar-Health. Market Research on CRPC in the UK. 2018 [Unpublished data]).

Adverse event and skeletal related event costs

The company also incorporated costs associated with the adverse events included in their model, using HRG based reference costs where available. These are provided in Table 54 of the company submission (document B). The ERG cross checked the reported HRG codes, and are generally satisfied that they are appropriate and consistent with those applied in the model for TA377. However, the ERG checked the cost applied for MACE events (£759), which appeared quite low given the nature of these events. This value was based on the weighted average of the non-elective short stay costs for HRG AA35 (A-F) (Stoke with complications and comorbidity 0-16). The ERG can replicate the figure, but are unclear why the non-elective short stay (NES) costs were chosen for this relatively severe event. Examination of the reference costs showed that only 36% of all AA35 activity was coded as NES, with the majority (63%) coded as non-elective long stay. The ERG therefore explored the impact of costing MACE events based on the reference costs for total AA35 HRG activity rather than the NES data alone. This resulted in a cost of £3,279 per event,

which may still underestimate the true cost to the NHS of a MACE event since it only captures the initial hospital episode associated with stroke.

The company also incorporated skeletal related events (SREs) associated with progression of bone metastasis, and included costs for these events based on the same HRG codes used in the previous submission for enzalutamide in pre-chemotherapy mHRPC.[8] The ERG are satisfied that the unit costs are appropriate and consistent with the previous submission. However, the ERG were concerned that the rates of SREs, applied upon progression to mHRPC, were derived from the PREVAIL trial where a greater percentage of mHRPC patients had bone metastasis at baseline compared to those in PROSPER at the time of progression to metastasis. The company provided a scenario analysis in response to this concern at the clarification stage, which showed that omitting SREs from the model had a minimal impact on the ICER.

Overall, the ERG are generally satisfied that the unit costs applied in the model are appropriate for the resource use events included. The ERGs primary concerns relate more to some of the resource use inputs and assumptions that govern the costs incurred within the different health states of the model. The ERG conducts further exploratory analysis to address this in section 5.3.

5.2.9 Cost effectiveness results

Base-case results

The company's base-case cost-effectiveness results are presented in Table 25. It demonstrates that enzalutamide is associated with a cost increase of [redacted] and [redacted] QALY gain, as compared to ADT. The ICER comes to £28,853 per QALY gained.

Table 25 Base-case cost-effectiveness results (Source: Table 60, Company submission, document B)

Outcome	Enzalutamide	ADT
Technology acquisition cost (first line)*	[redacted]	[redacted]
Subsequent lines treatment costs	[redacted]	[redacted]
Other costs	[redacted]	[redacted]
Total costs	[redacted]	[redacted]
Incremental costs	[redacted]	
LYG	[redacted]	[redacted]
Incremental LYG	[redacted]	
QALYs	[redacted]	[redacted]
QALYs gained	[redacted]	
ICER (incremental cost/QALY gained)	**£28,853**	

*Note: enzalutamide technology acquisition cost are based on the UK list price and no PAS has been taken into account.

The disaggregated cost and QALY outcomes are presented in Table 26. Treatment costs in nmHRPC health state are the largest contributor to overall costs in the enzalutamide arm, whilst treatment costs in PD1 sub-state are the largest cost contributor in the ADT arm. The high PD1 treatment cost in ADT arm is attributable to the fact that 100% of patients receive active treatment with enzalutamide in this state. Similarly, the majority of QALYs accrue in the nmHRPC state in the enzalutamide arm, whilst more QALYs accrue in the PD1 state in the ACT arm.

The incremental QALY gain is driven by the high QALYs gained in the enzalutamide arm in nmHRPC health state [redacted]. This offsets the lower QALYs gained in PD1 sub-health state [redacted].

Table 26 Base-case cost and QALY outcomes (discounted) (Source: reproduced from Tables 58 and 59, Company submission, document B)

Outcome	Enzalutamide	ADT
A. Cost		
nmHRPC treatment costs	[redacted]	[redacted]
PD1 treatment costs	[redacted]	[redacted]
PD2 treatment costs	[redacted]	[redacted]
PD3 treatment costs	[redacted]	[redacted]
nmHRPC Health state cost	[redacted]	[redacted]
PD1 Health state cost	[redacted]	[redacted]
PD2 Health state cost	[redacted]	[redacted]
PD3 Health state cost	[redacted]	[redacted]
nmHRPC Conmed costs	[redacted]	[redacted]
PD1 Conmed costs	[redacted]	[redacted]
PD2 Conmed costs	[redacted]	[redacted]
PD3 Conmed costs	[redacted]	[redacted]
nmHRPC AEs	[redacted]	[redacted]
PD1 AEs	[redacted]	[redacted]
PD2 AEs	[redacted]	[redacted]
PD3 AEs	[redacted]	[redacted]
PD1 SREs	[redacted]	[redacted]
PD2 SREs	[redacted]	[redacted]
PD3 SREs	[redacted]	[redacted]
Terminal care costs	[redacted]	[redacted]
Subtotal nmHRPC	[redacted]	[redacted]
Subtotal PD1	[redacted]	[redacted]
Subtotal PD2	[redacted]	[redacted]
Subtotal PD3	[redacted]	[redacted]
Terminal care	[redacted]	[redacted]
Total costs	[redacted]	[redacted]
B. QALY		
nmHRPC	[redacted]	[redacted]
PD1	[redacted]	[redacted]
PD2	[redacted]	[redacted]
PD3	[redacted]	[redacted]
End-of-life disutility	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]

Efficacy outcome

Markov traces of each health state over time for enzalutamide and ADT are presented in Figure 17. As discussed in section 5.2.6, the model projects an OS benefit in favour of enzalutamide. The difference in mean and median OS for the two arms is [redacted] and [redacted] months, respectively. The traces further illustrate that the enzalutamide cohort spends a longer in the nmHRPC health state, and less time in the PD1 health state compared to the ADT cohort.

[redacted]Abbreviations: ADT: androgen deprivation therapy; nmHRPC: non-metastatic hormone-relapsed prostate cancer; OS: overall survival; PD: progressed disease.

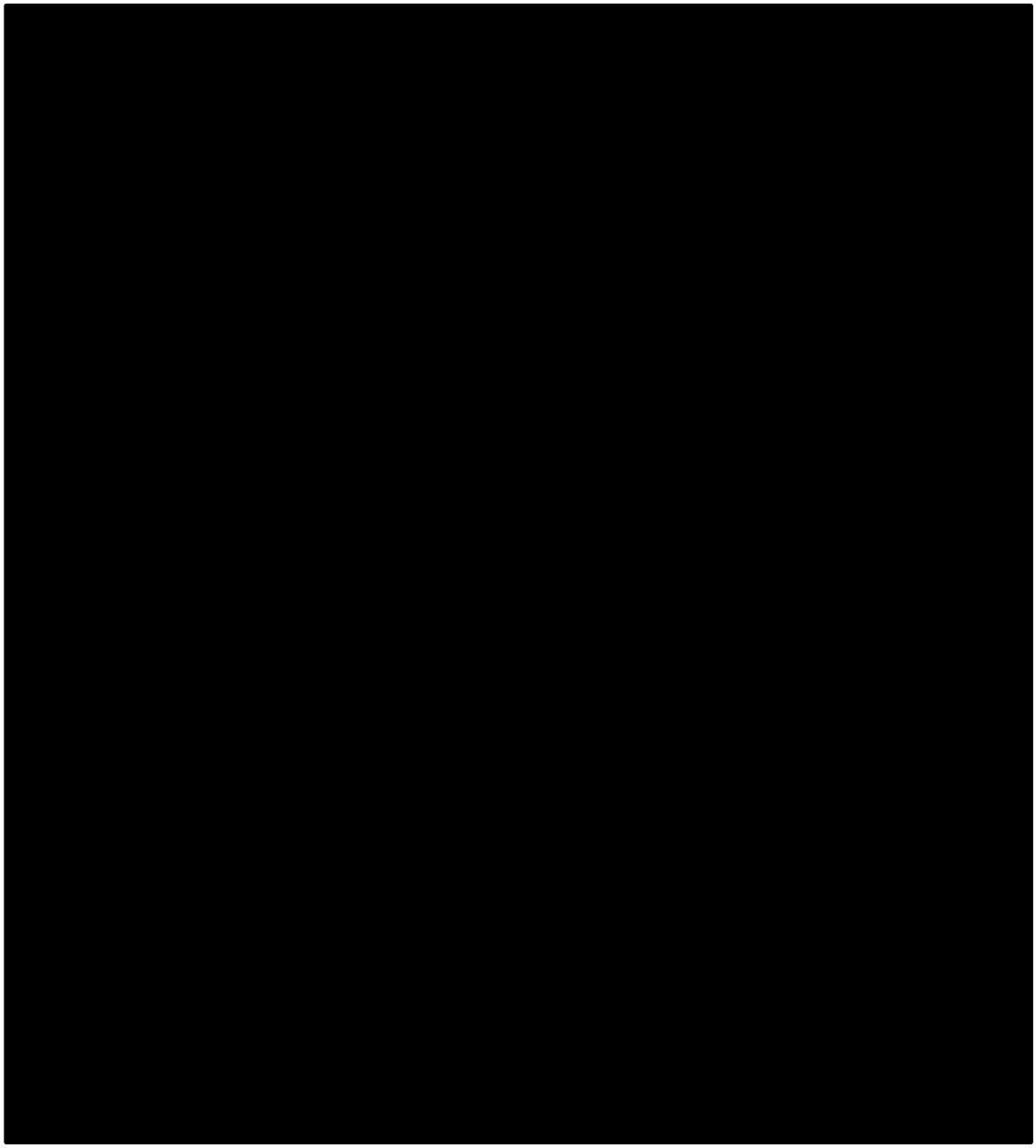


Figure 17 is commercial in confidence

5.2.10 Sensitivity analyses

One-way sensitivity analyses

Results of one-way sensitivity analyses for the 15 most important drivers of the ICER are presented Table 27. The corresponding tornado diagram is provided in Figure 27 of the company submission, document B. The model is sensitive to the parametric curves of MFS, PrePS and PPS. Other drivers are age at baseline, discount rate for effects and cost, health state costs in nmHRPC, PD1 median duration and PD1 utility value.

Table 27 One-way SA results for enzalutamide vs. ADT (Source: Table 61, Company submission, document B)

Parameter	Model Input (BC)	Low	High	ICER Low	ICER High
Base-case	NA	NA	NA	£28,853	
Parametric uncertainty (Gamma parameter) of fitted Spline curve to PROSPER MFS placebo data	[redacted]	[redacted]	[redacted]	£99,582	£13,523
Average age at baseline	[redacted]	[redacted]	[redacted]	£29,206	£52,160
Parametric uncertainty (intercept parameter) of fitted Weibull curve to PROSPER PPS placebo data	[redacted]	[redacted]	[redacted]	£24,448	£44,180
Parametric uncertainty (Gamma0 parameter) of fitted Spline curve to PROSPER MFS enzalutamide data	[redacted]	[redacted]	[redacted]	£22,965	£3,282
Parametric uncertainty (intercept parameter) of fitted Weibull curve to PROSPER PrePS enzalutamide data	[redacted]	[redacted]	[redacted]	£39,957	£25,922
Parametric uncertainty (intercept parameter) of fitted Weibull curve to PROSPER PPS enzalutamide data	[redacted]	[redacted]	[redacted]	£36,033	£24,236
Parametric uncertainty (intercept parameter) of fitted Weibull curve to PROSPER PrePS placebo data	[redacted]	[redacted]	[redacted]	£24,789	£32,247
Discount rate for effects	[redacted]	[redacted]	[redacted]	£24,557	£30,836
Parametric uncertainty (scale parameter) of fitted Weibull curve to PROSPER PrePS enzalutamide data	[redacted]	[redacted]	[redacted]	£27,346	£31,201
Median treatment duration of ADT in PD1	[redacted]	[redacted]	[redacted]	£30,217	£27,397
Median treatment duration of enzalutamide in PD1	[redacted]	[redacted]	[redacted]	£29,749	£27,130
Discount rate for costs	[redacted]	[redacted]	[redacted]	£30,654	£28,205
Health state costs for patients on enzalutamide in nmHRPC	[redacted]	[redacted]	[redacted]	£28,029	£29,760
Health state costs for patients on ADT in nmHRPC	[redacted]	[redacted]	[redacted]	£29,606	£28,023
Health state utility value in PD1	[redacted]	[redacted]	[redacted]	£28,120	£29,595

Abbreviations: ADT: androgen deprivation therapy; BC: base-case; ICER: incremental cost-effectiveness ratio; nmHRPC: non-metastatic hormone-relapsed prostate cancer; PD: progressed disease; PPS: post-progression survival; PrePS: pre-progression survival; QALY: quality-adjusted life years; SA: sensitivity analysis

Probabilistic sensitivity analysis

The company's PSA results are presented in Table 28. The probabilistic ICER is slightly higher than the deterministic base case ICER at 30,175 per QALY gained. The scatter plot and cost-effectiveness acceptability curves are reproduced in Figures 18 and 19 respectively. At the WTP threshold of £30,000/QALY, the probability of enzalutamide being cost-effective is [redacted], compared to ADT.

Table 28 Probabilistic SA statistical results (probabilistic cost-effectiveness outcomes) (Source: Table 62, Company submission, document B)

	Enzalutamide		ADT		Incremental		
	Costs	**QALYs**	**Costs**	**QALYs**	**Costs**	**QALYs**	**CE ratio**
Deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,853
Probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,175
StDev	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,994
# values	10,000	10,000	10,000	10,000	10,000	10,000	10,000
Min Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£19,064
Max Limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,970
95% LCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,919
95% UCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£106,757

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

Figure 18 is redacted – commercial in confidence

Figure 19 is redacted – commercial in confidence

Scenario analyses

The results of a range of scenario analyses presented in the company submission, and of the additional scenarios provided in response to the ERG clarification questions, are presented in Table 29.

The company submission describes how in scenario 1 (Table 29), data from the IA2 data cut were used. Time to treatment discontinuation was used to inform the progression from nmHRPC to mHRPC, since MFS was not analysed at this time point, and the OS data was split treatment discontinuation; i.e. pre-treatment discontinuation (PreTD) and post treatment discontinuation (PTD) survival, which were applied to the nmHRPC and mHRPC health states respectively. TTD is a proxy for progression to metastasis as some patients may discontinue treatment prior to progression, and the ERG are uncertain to what extent some patients may have remained on treatment for a period after first metastases occurred and until a decision was made on the next subsequent treatment. The company's extrapolations of TTD, and PreTD and PostTD survival are illustrated in Figures 20 to 22 below. The curve fitting followed a similar approach to that followed for MFS, PrePS and PPS described in section 5.2.6. A 2 knot spline was chosen to model TTD (Figure 20), a Weibull distribution was chosen for PreTD survival (Figure 21), and a gamma was chosen for PTD survival (Figure 22). The company also explained how scenario 2 (Table 29 below) was implemented based on an extrapolation of the IA1 TTD data using a generalised gamma model.

Table 29 Results of scenario analyses (Source: reproduce from Table 67, company submission, document B and Table 9, 11-13, Company response to clarification questions)

Model scenario		Cost ENZA	Cost ADT	QALY ENZA	QALY ADT	ICER
	Base-case	[redacted]	[redacted]	[redacted]	[redacted]	£28,853
1	PROSPER IA2 data	[redacted]	[redacted]	[redacted]	[redacted]	£24,874
2	TTD for nmHRPC PD1 transition	[redacted]	[redacted]	[redacted]	[redacted]	£30,456
3	MFS piecewise survival model	[redacted]	[redacted]	[redacted]	[redacted]	£27,852
4	No PCa mortality in nmHRPC	[redacted]	[redacted]	[redacted]	[redacted]	£28,859
5	PREVAIL PPS reference curve	[redacted]	[redacted]	[redacted]	[redacted]	£26,237
6	PROSPER PPS log-logistic guided by COU-AA-302 abiraterone OS	[redacted]	[redacted]	[redacted]	[redacted]	£30,394
7	Single OS curve	[redacted]	[redacted]	[redacted]	[redacted]	£26,829
8	'England value set' utilities	[redacted]	[redacted]	[redacted]	[redacted]	£28,138
9	Earlier chemotherapy after enzalutamide in nmHRPC	[redacted]	[redacted]	[redacted]	[redacted]	£30,937
10	No patients opt-out of chemo	[redacted]	[redacted]	[redacted]	[redacted]	£29,794
11	Treatment interruptions	[redacted]	[redacted]	[redacted]	[redacted]	£24,712
12	Abiraterone in PD1 (ADT/AS arm)	[redacted]	[redacted]	[redacted]	[redacted]	£24,303
13	PD1 duration in PROSPER	[redacted]	[redacted]	[redacted]	[redacted]	£31,671
14	PD1 treatments in PROSPER	[redacted]	[redacted]	[redacted]	[redacted]	£33,863
15	No SREs	[redacted]	[redacted]	[redacted]	[redacted]	£28,878
16	IA1 MFS and IA2 OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADT: androgen deprivation therapy; AS: active surveillance; ENZA: enzalutamide; ICER: incremental cost-effectiveness ratio; MFS: metastasis-free survival; OS: overall survival; PCa: prostate cancer; PPS: post-progression survival; TTD: time to treatment discontinuation; WTP: willingness to pay.

Figure 20 is redacted – academic in confidence

Figure 21 is redacted – academic in confidence

Figure 22 is redacted – academic in confidence

As for scenario 16, IA1 MFS and IA2 OS data were used.

Table 30 Comparison of cost-effectiveness results scenario 1 and scenario 16 (Source: reproduce from Table 64, Company submission, document B and Table 13, Company response to clarification question)

Outcome	Base-case		Scenario 1		Scenario 16	
	Enzalutamide	ADT	Enzalutamide	ADT	Enzalutamide	ADT
Technology acquisition cost (first line)*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent lines treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs	[redacted]		[redacted]		[redacted]	
LYG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental LYG	[redacted]		[redacted]		[redacted]	
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs gained	[redacted]		[redacted]		[redacted]	
ICER (change from base case)	**£28,853**		**£24,874 (-£3,979)**		[redacted]	

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year.

5.2.11 Model validation and face validity check

In the submission, the company state that a series of face-to-face advisory boards were held to validate the model and its inputs, including an extrapolation validation meeting, one advisory board meeting, and individual one-on-one interviews with clinical and economic experts. Furthermore, the assumptions employed in the model are made to be consistent with the published literature and previous NICE TAs. The model fits and the plausibility of clinical outcomes for all extrapolations were validated by UK clinical and health economic experts.

The ERG has checked the input parameters and calculations in the company model, and conducted additional tests to check for any errors following the checklist by Tappenden and Chilcott. [40] The outcomes of this exercise are presented in Table 31. The company model predicted results that were in line with the checklist verification criteria. In addition, the model was checked for accuracy by comparing data included in the report with the corresponding data entered in the economic model. All checks

were applied to the company's revised economic model submitted in response to the clarification letter. The ERG does not have any major concerns with respect to the internal consistency of the model at this stage.

Table 31 ERG conducted 'black-box' verification tests applied to the company submitted model

Model component	Model test	Unequivocal criterion for verification	Issues identified in company model
Clinical trajectory	Set relative treatment effect (odds ratios, relative risks or hazard ratios) parameter(s) to 1.0 (including adverse events)	All treatments produce equal estimates of total LYGs and total QALYs	None
	Sum expected health state populations at any model time point (state transition models)	Total probability equals 1.0	None
	Sum expected probability of terminal nodes (decision-tree models)	Total probability equals 1.0	Not applicable
QALY estimation	Set all health utility for living states parameters to 1.0	QALY gains equal LYGs	None
	Set QALY discount rate to 0	Discounted QALYs = undiscounted QALYs for all treatments	None
	Set QALY discount rate equal to very large number	QALY gain after time 0 tend towards zero	None
Cost estimation	Set intervention costs to 0	ICER is reduced*	None
	Increase intervention cost	ICER is increased*	None
	Set cost discount rate to 0	Discounted costs = undiscounted costs for all treatments	None, after error rectification. A minor error related to assigning the health benefit discount rate to the discounted cost calculations. There was no implication on the original findings presented in the submission as no differential discounting was applied.
	Set cost discount rate equal to very large number	Costs after time 0 tend towards zero	None

Input parameters	Produce n samples of model parameter m	Range of sampled parameter values does not violate characteristics of statistical distribution used to describe parameter (e.g., samples from beta distribution lie in range [0-1] etc.)	None. Although the ERG notes this is highly unlikely given the assumed SD of the sampling distribution for a number of parameters included in the PSA is equal to mean value x 10%.
General	Set all treatment-specific parameters equal for all treatment groups	Costs and QALYs equal for all treatments	None. The nmHRPC treatment costs is noted to be doubled for enzalutamide arm compared to ADT arm due to the additional ADT received in enzalutamide arm. This applies to the PD1 treatment costs for ADT arm when they received additional enzalutamide.
	Amend value of each individual model parameter*	ICER is changed	None.
	Switch all treatment-specific parameter values*	QALYs and costs for each option should be switched	None (except those already identified above)
ICER incremental cost-effectiveness ratio, LYG life-years gained, QALY quality-adjusted life-year * Note this assumes that the parameter is part of the total cost function and/or total QALY function			

5.3 Exploratory and sensitivity analyses undertaken by the ERG

Additional work and analyses undertaken by the ERG and their associated impact on the ICER findings are reported in this section. The ERG has conducted all these analyses based on a revised version of the economic model submitted by the company in response to the clarification letter (dated: October 11th, 2018).

5.3.1 ERG exploratory scenario analyses

The ERG additional exploratory analyses are described in Table 32 below, with justification and reference to the relevant section of the ERG report which discusses the issue being addressed. The results of these analyses are presented in Table 33.

The scenarios (1, 10 and 11) which explore the impact of modifying the downstream clinical treatment pathway, in line with the ERGs expert advice, are presented here using the list price for radium-223 and cabazitaxel. These scenarios were incorporated using functionality and parameter input values that were available in the company model, although not utilised in scenarios presented in the company submission. Since a patient access scheme is available for both of these treatments on the NHS in England, the results are not suitable for informing decision making. A separate confidential appendix will be provided utilising the appropriate discounted prices. These should also be treated with caution since it is not possible to adjust post-progression mortality for the different treatment sequences. Nevertheless, it can be noted that the modelled changes increase the ICER for enzalutamide.

In terms of the ERG change of equalising visit and monitoring costs between enzalutamide and ADT (scenario 2), this results in a modest increase in the ICER. The change to the cost of MACE evens (scenario 3) has only a minor impact. Changing the utility value applied in state PD1 to 0.844 (based on TA377 for chemotherapy naïve patients), also results in a modest increase in the ICER for enzalutamide. When these three changes are made in combination, the ICER for enzalutamide increases to £32,132 (scenario 6).

The ICER increases further in scenario 7 when the time in sub-state PD1 is based on the data from PROSPER, as per the company scenario provided in response to the clarification letter. When IA2 data are used to model progression (based on TTD) and

pre and post TD survival, in conjunction with all the changes applied in scenario 7, the ICER comes to £31,210 (scenario 8). However, if the MFS data from IA1 are used to model progression, in conjunction with the IA2 pre- and post-TD survival curves (and the changes described in scenario 7), then the ICER for enzalutamide increases to £56,168 (scenario 9).

Table 32 Additional scenario analyses, including justifications, performed by the ERG

<table>
<tr><th></th><th>Parameter / Analysis</th><th>Base case Assumption</th><th>Scenario explored</th><th>Justification</th><th>Table / section reference in ERG report</th></tr>
<tr><td>BC</td><td colspan="3">Company preferred base case analysis (All ERG exploratory analyses are conducted relative to this base case)</td><td></td><td>Table 12</td></tr>
<tr><td colspan="6">Treatment pathway</td></tr>
<tr><td>1</td><td>Treatment pathway in PD1-3</td><td>Company preferred treatment pathway (PD1-PD3)</td><td>ERG exploratory treatment pathway:
<table><tr><th>HS</th><th>Enza arm</th><th>ADT arm</th></tr><tr><td>nmHRPC</td><td>Enza (100%)</td><td>ADT (100%)</td></tr><tr><td>PD1</td><td>Docetaxel (60%)
ADT alone (40%)</td><td>Enza (100%)</td></tr><tr><td>PD2</td><td>R223 (60%)
ADT alone (40%)</td><td>Docetaxel (50%)
ADT alone (50%)</td></tr><tr><td>PD3</td><td>Cabazitaxel (10%)
BSC (90%)</td><td>R223 (40%)
BSC (60%)</td></tr></table></td><td>Based on the ERG's clinical expert advice, the shifting of enzalutamide up the treatment pathway may result in a shift in subsequent lines of treatment up the clinical pathway, creating more space for further subsequent treatment. R223 and cabazitaxel are two NICE recommended treatment options in the post docetaxel setting.</td><td>5.2.4</td></tr>
<tr><td colspan="6">Costs</td></tr>
<tr><td>2</td><td>Health state cost for nmHRPC and PD1-3</td><td>Company model monitoring frequency</td><td>Equalise monitoring and testing frequency for both arms.</td><td>Based on the ERG's clinical expert advice, it seems reasonable to assume that patients on ADT alone would be monitored at the same frequency as those on</td><td>5.2.8 (Table 24)</td></tr>
<tr><td>3</td><td>Setting visits and tests equal to the values presented in Table 49 of the</td><td>Company model monitoring frequency</td><td>Apply health care visit and testing frequencies as presented in Table 49 of the company submission</td><td>A number of discrepancies were observed between the company reported health care visit and testing frequencies and the values applied in</td><td>5.2.8</td></tr>
</table>

	company submission			the company model. The ERG are uncertain which values the company intended to use.	
4	Revised cost of MACE events	Non elective short stay reference cost for HRG AA35 (£759.30)	Overall reference cost for HRG AA35 (£3,279)	It is unclear to the ERG why the company based the cost of this serious adverse event on short stay hospital activity only.	5.2.8
Utilities					
5	PD1 utility value	Company preferred utility value derived from PROSPER ([redacted])	Baseline utility value applied for chemotherapy naïve mHRPC patients in NICE TA377 (0.844), derived from the PREVAIL trial	There is some uncertainty regarding the lack of adjustment for baseline in the company derived estimate for PD1. The PREVAIL population at baseline provides an alternative source for PD1 utility and is reflective of what the company used in their previous submission.	5.2.7
Plausible combinations of analyses					
6	Combined changes in 2, 4, and 5	See above	See above	The ERG believe it is plausible to assume a scenario which combines these changes to the company base case	As above
7	As per 6 + median duration in PD1 following progression on enzalutamide	The company base case assumes a median duration of 7.2 months on	Changes as per scenario 6, and median duration of 3.8 months on ADT alone in PD1 following progression on enzalutamide (based on post-progression data from PROSPER provided by the company)	The ERG has some uncertainty about the value of 7.2 months which has been used to represent the median treatment duration on ADT alone following progression on enzalutamide, since it is longer than the median rPFS reported for the	5.2.6 and 5.2.8

	based on data from PROSPER	ADT alone in PD1 following progression on enzalutamide		PREVAIL trial (5.4 month). The ERG are also uncertainty about the generalizability of the PREVAIL median duration on placebo to the progressed PROPSPER cohort.	
8	As per 7 + IA2 data used for progression (TTD), and PreTD and Post TD survival	The company base case uses IA1 MFS data for progression and IA1 PrePS and PPS data for survival	Changes as per scenario 7, in combination with the company's scenario that utilised data from IA2 to inform progression (TTD) and preTD and postTD survival	The ERG believe that the more mature survival data are more informative, but have some uncertainty over the preferred source of progression data (TTD from IA2 or MFS from IA1)	5.2.6 5.2.9 (Table 29)
9	As per 7 + IA2 data for PreTD and Post TD survival, MFS for progression.	As above	Changes as per scenario 7, in combination with the ERG requested scenario that utilised data from IA2 to inform preTD and postTD survival, but MFS data from IA1 for progression.	The ERG believe that the more mature survival data are more informative, but have some uncertainty over the preferred source of progression data to use in combination with it (TTD from IA2 or MFS from IA1)	5.2.6 5.2.9 (Table 29)
10	6 + 1	As above	Combined changes described in scenario 1 and scenario 6	To explore the potential impact of changes in the downstream treatment pathway in combination with other changes to the company base case	See above
11	9 + 1	As above	Combined changes described in scenario 1 and scenario 9	To explore the potential impact of changes in the downstream treatment pathway in combination with other changes to the company base case	See above

Key: ADT: androgen deprivation therapy; AE: adverse events; BC: base case; Enza: enzalutamide; R223: Radium-223; ERG: Evidence Review Group; ICER: incremental cost-effectiveness ratio; MACE: major adverse cardiovascular event; QALY: quality adjusted life year.

Table 33 Impact of alternative scenario analyses on cost-effectiveness results

			Enzalutamide		ADT					
Analysis		**Description**	**Cost**	**QALY**	**Cost**	**QALY**	**Inc. Cost**	**Inc. QALY**	**Deterministic ICER**	**% change in the ICER**
	Company submitted model (response to clarification)									
BC		Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,853	0%
	ERG explored analyses (All applied relative to company base case)									
	Treatment pathway									
1		ERG exploratory treatment pathway[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,198	+60.12%
	Costs									
2		Equalise monitoring and testing frequency for both arms.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,435	+5.49%
3		Apply health care visit and testing frequencies as presented in Table 49 of the company submission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,207	-2.24%
4		MACE cost = overall reference cost for HRG AA35 (£3,279)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,058	+0.71%
	Utilities									
5		Baseline utility value for chemotherapy naïve mHRPC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,257	+4.87%

			Enzalutamide		ADT					
Analysis		**Description**	**Cost**	**QALY**	**Cost**	**QALY**	**Inc. Cost**	**Inc. QALY**	**Deterministic ICER**	**% change in the ICER**
		patients from NICE TA377 (0.844)								
	Combined analyses									
6		Combined changes in scenarios 2, 4, and 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,132	+11.36%
7		As per 6 + Median duration in PD1 following progression on enzalutamide = 3.8 months (based in PROSPER)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,628	+23.48%
8		As per 7 + PROSPER IA2 data for TTD and PreTD and Post TD survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,210	+8.17%
9		As per 7 + IA2 data for PreTD and Post TD survival, MFS for progression.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£56,168	+94.67%
10		7 + 1[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,376	+74.59%
11		10 + 1[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£92,202	+219.56%

a; List price applied to downstream treatment with radium-223 and cabazitaxel (not suitable for informing decision making).

5.3.2 Reflection of the ERG preferred assumptions

The ERG preferred set of assumptions are incorporated in scenario 7 (Table 33). The ERG believe the changes to the visit and monitoring costs are justified based on the discussions recorded in the FAD for TA377, which appeared to support the assumption of similar visit and monitoring costs for enzalutamide and ADT in the mHRPC chemotherapy naïve setting. The ERG's own expert advice also supports this assumption in the nmHRPC setting. The ERG also believe the increased cost for MACE events is justified given the potential severity of these events. Further, since long-term cost and utility implications of cardiovascular morbidity cannot be incorporated within the company's model structure, the impact of these events may still be under-estimated.

Regarding the ERG change to the utility value for the PD1 sub-state, the ERG are concerned that the value applied in the company model, based on the first post-progression assessment, has not been adjusted for baseline. Furthermore, given the 16 week measurement schedule for the EQ-5D in PROSPER, it is not clear what the company base case value represents; i.e. it may include patients up to 16 weeks post progression, by which time some may have progressed to PD2. For consistency with the approach of using baseline utility form PROSPER for the nmHRPC health state, the ERG prefer to use the adjusted baseline value for chemotherapy naïve mHRPC patients from TA377 (based on PREVAIL EQ-5D data). In addition, the ERG prefer to use the available data from PROSPER suggesting that patients who progressed on enzalutamide may have spent a shorter period of time on ADT alone (3.8 months) compared to the median time of 7.2 months applied in the company base case.

On balance the ERG also have a preference for the more mature survival data from IA2 rather than IA1. There is then the question of whether it is more appropriate to combine this with progression based on the MFS data which are only available for the IA1 data cut, or to utilise the TTD data from IA2 as a proxy for progression to mHRPC. The latter is justified by the company on grounds that they had to use this TD data to split the IA2 survival data. However, the ERG are concerned that the TTD data is only a proxy for progression to mHRPC, which may be susceptible to bias; i.e. if patients are more likely to discontinue placebo as opposed to active treatment prior to radiographic progression, then the TTD curves may overestimate the rate of progression to mHRPC for ADT patients. Alternatively, if patients are less likely to discontinue enzalutamide immediately following progression to metastasis, then the TTD may underestimate true progression in the enzalutamide arm.

Therefore, the ERG has a preference towards the analysis which uses the MFS data from IA1 and the preTD and postTD survival data from IA2. Whilst the ERG recognise that there is an inconsistency between the measure used for progression (MFS), and the measure used to split the survival data in this scenario, the ERG prefer it because: 1) it uses the more robust measure of progression to metastasis; 2) [redacted]

Thus the ERG believe the ICER may be as high as £56,168, assuming that the company's modelled subsequent treatment pathway is realistic. Based on exploratory analyses that assume earlier treatment with enzalutamide results in docetaxel being initiated earlier at PD1, with further subsequent treatment with radium-223 and cabazitaxel being initiated for a proportion of patients post docetaxel, the ERG believe that the ICER for enzalutamide could possibly be higher.

5.4 Conclusions of the cost effectiveness section

The company's submitted economic model captures progression from nmHRPC to mHRPC (incorporating three sub-states that capture subsequent treatment lines following progression to mHRPC). The lack of a link between progression through the PD sub-states and mortality is a limitation of the model structure.

The company base case utilised MFS data from the primary analysis data cut of the PROSPER trial, corresponding to interim analysis one (IA1) for the analysis of overall survival, to model progression from nmHRPC to mHRPC. The ERG are satisfied that this outcome based on radiographic assessment accurately captures the progression event of interest and that the approach to extrapolation is robust. The company also used OS data from the PROSPER IA1 data cut to model pre and post progression survival based on the same definition of progression used in the MFS outcome. With respect to post-progression treatment sequences, the company assumed a period of ADT alone following progression on enzalutamide (PD1), followed by docetaxel (40%) or ADT alone (60%) at PD2, then BSC at PD3. In the control arm, 100% were modelled to receive enzalutamide at PD1, followed by the same sequence at PD2 and PD3 as in the enzalutamide arm.

The company base case ICER comes to £28, 853. One-way sensitivity analysis showed the ICER to be most sensitivity to variation in the parameters of the parametric curves assigned for MFS, PrePS and PPS. The company also provided a range of 12 scenario analyses, in which the ICER increased just above £30,000 in three of these. The ERG requested further scenario analyses at the clarification stage, asking the company to explore the impact of 1) using the observed distribution of second line treatment in the placebo arm of PROSPER to estimate the cost of treatment at PD1 in the ADT arm of the model; 2) using the observed median time from progression to initiation of first antineoplastic therapy in PROSPER, to model the transition from PD1 to PD 2 in the enzalutamide arm of the model; and 3) using the MFS for progression in combination with the more mature IA2 OS data from PROSPER to inform pre and post progression mortality. These three analyses increased the ICER for enzalutamide to £31,671, £33,863, and [redacted] respectively. The ERG consider the latter issue to be one of the most significant uncertainties in the model. Whilst the ERG acknowledge the inconsistency is using MFS to model the transition to mHRPC, in combination with preTD and postDT survival data from IA2, the ERG believe this is still a plausible scenario. Ideally, the ERG would have liked to have seen IA2 OS data split radiographic progression status, and combined the IA2 MFS data. However, the company indicated that the MFS analysis was not available for the IA2 data cut.

Further sources of uncertainty in the model relate to:

1. The modelled downstream treatment pathways in the enzalutamide and ADT arms of the model.
2. The cost of monitoring and testing patients on enzalutamide and ADT alone
3. The utility value associated with progression to sub-state PD1 in the model.

6 Overall conclusions

The ERG agree that the evidence on clinical effectiveness provided by the Company shows that there is a beneficial effect from enzalutamide compared to placebo. There is a large effect size on the primary outcome of metastases free survival and the difference between the experimental arm and the control arm are significant. The survival curves and summary statistics show a delay in the development of metastases.

The ERG also agree that the five secondary endpoints highlighted by the Company; time to prostate-specific antigen progression, time to first use of cytotoxic chemotherapy, chemotherapy free survival, chemotherapy-free disease specific survival and time to treatment discontinuation all show hazard ratios and significance levels which indicate a benefit for enzalutamide in comparison to placebo.

The ERG recognise that there is a beneficial effect on MFS from enzalutamide but would question the size of the anticipated overall survival benefit as stated at interim analysis 2. The OS data are immature and not statistically significant by second interim analysis.

The ERG agrees that the safety of enzalutamide in PROSPER is consistent with previous mHRPC studies. There was a higher incidence of TEAEs with enzalutamide primarily driven by hypertension, memory impairment and major adverse cardiac events.

It is the ERG opinion that the biggest weakness with the effectiveness data is that the PROSPER study does not closely match the decision problem because the post progression treatments in PROSPER do not match UK treatment pathways.

The company's cost-effectiveness evidence is based on a semi-Markov model with three main states: nmHRPC, mHRPC and death. The mHRPC state incorporates three sub-states (PD1-PD3) to capture progression through subsequent treatment lines for mHRPC, but which are not separately linked to with survival in the model. The company base case ICER for enzalutamide in nmHRPC patients was £28,853. The ICER ranged from £24,236 to £38,918 in alternative scenario analyses provided by

the company in their original submission or in response to the clarification letter. Key uncertainties relate to:

- The choice of data for modelling progression to mHRPC (MFS or TTD), and the measure of progression that us used to split overall survival by progression status (MFS from the IA1 data cut or TTD from the IA2 data cut).
- The modelled downstream treatment pathways in the enzalutamide and ADT arms of the model, in terms of:
    - Differences between the modelled pathway of subsequent treatments and the subsequent treatments received in the PROSPER trial.
    - Duration of ADT treatment following progression to mHRPC on enzalutamide.
    - The applicability of the modelled treatment pathway to the NHS in England.
- The cost of monitoring and testing patients on enzalutamide and ADT alone.
- The utility value associated with progression to sub-state PD1 in the model.

Combing alternative assumptions leads to significant upward uncertainty in the ICER.

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National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report
Enzalutamide for treating non-metastatic hormone-relapsed prostate cancer [ID1359]

You are asked to check the ERG report from Aberdeen HTA Group to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on 16 November** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Table of abbreviations being incomplete and not consistent with text

Description of problem	Description of proposed amendment	Justification for amendment	Comments
On page xii: The table of abbreviations is not complete (e.g., mHRPC and PTD are missing) and there are inconsistencies (e.g., TTD in the list of abbreviations but TD in the report)	The Table of abbreviations should be completed and either modify inconsistencies (e.g., TTD vs TD) in the text or add both abbreviations in the Table of abbreviations	It is confusing to have two different abbreviations for the same word (e.g., TTD in the clinical-effectiveness critique vs TD in the economic section)	Not a factual error. The ERG believes the current text does not pose any problem in terms of appropriateness or transparency. The proposed revision is not accepted.

Issue 2 Post-enzalutamide treatment pathway

Description of problem	Description of proposed amendment	Justification for amendment	Comments
The ERG states at different sections that the treatment pathway the company has modelled does not reflect the current treatment pathway. The ERG proposes several changes to the pathway in scenario 1 and related scenarios. However, the ERG does not provide any source of the evidence behind the new treatment pathway. On the ERG scenario 1, both radium 223 and cabazitaxel are	The ERG should provide sources for the applied proportion of patients who receive radium 223 and cabazitaxel in scenario 1.	It is not clear what evidence drives the changes to the treatment pathway in ERG's scenario 1.	The ERG have noted the source of the applied proportions in Table 32 of the ERG report. These were based on the ERGs own expert opinion.

given to a high proportion of patients but based on Market Research in the UK, they are not commonly prescribed to mHRPC patients. In addition, it should be noted that the company included a scenario (number 9) in their submission where it is assumed that all patients who progressed on enzalutamide will receive docetaxel immediately after treatment discontinuation. This is aligned with the ERG proposed changes to the treatment pathway.			

Issue 3 Enzalutamide SmPC

Description of problem	Description of proposed amendment	Justification for amendment	Comments
On page 19, the ERG state: *"The company state that "interactions with certain medicinal products that are eliminated through metabolism or active transport are expected" and "these products should be avoided or used with caution. The risk for liver injury after paracetamol administration is*	This text was not quoted in the Company submission. The company propose for the text to be replaced with the following: *The **enzalutamide SmPC** state that "interactions with certain medicinal products that are eliminated through metabolism or active transport are expected" and "these products should be avoided or used with caution. The risk for liver injury after paracetamol administration is suspected to be*	The text was not quoted in any of the company's submission documents	The proposed amendment is accepted.

suspected to be higher in patients concomitantly treated with enzyme inducers"." However, this text was not quoted in the Company submission but it is mentioned in the Xtandi SmPC.	*higher in patients concomitantly treated with enzyme inducers".*		

Issue 4 Pain score in the PROSPER UK cohort

Description of problem	Description of proposed amendment	Justification for amendment	Comments
On page 31, the ERG states: "*A lower proportion of UK subjects with a pain score of 0-1 in the placebo arm*." However, it should read "a higher proportion".	The statement should be replaced with: "*A **higher** proportion of UK subjects with a pain score of 0-1 in the placebo arm*"	The proportion of patients with a baseline pain score of 0-1 was 87.0% (n=20) of UK patients vs 71.8% (n=336) of patients in the overall cohort (see Table 7)	The ERG copied this statement from the Company's response to Clarification question A2. The proposed amendment is accepted.

Issue 5 Incorrect Table number

Description of problem	Description of proposed amendment	Justification for amendment	Comments
on page 82, the ERG states: "*Table 3 in fact indicates that of those who initiated a second line treatment following progression on enzalutamide* [redacted] *initiated abiraterone and* [redacted] *appear to have been re-challenged with enzalutamide*" and "*It is also clear*	The text should be modified and replaced with: "*It is also clear from Table **21** that docetaxel was the second most commonly prescribed second line treatment*" "*Table **21** in fact indicates that of those who initiated a second line treatment following progression on enzalutamide,* [redacted] *initiated*	Incorrect cross-reference	The proposed amendment is accepted.

from Table 3 that docetaxel was the second most commonly prescribed second line treatment" however the correct table that should be referenced is Table 21.	*abiraterone and* [redacted] *appear to have been re-challenged with enzalutamide*"		

Issue 6 Proportion of patients on docetaxel

Description of problem	Description of proposed amendment	Justification for amendment	Comments
On pages 7, 71, 73, 82, 92, 117, the ERG highlight that the Company have assumed that in the corresponding health states, 40% of patients receive docetaxel and the remaining 60%, ADT. The ERG have not questioned this assumption but have assumed 60% on docetaxel and 40% on ADT in their adapted model (page 111).	It seems that the ERG do not query the proportion of patients who receive docetaxel (i.e., 40% as many patients will not be eligible and others will opt out from being exposed to chemotherapy). In that case, the ERG should modify the treatment pathway stated in Table 32 (page 111) and update the relevant scenarios accordingly (i.e., scenarios 1, 10 and 11)	Given the advanced age of the PROSPER patients and number of comorbidities, assuming that 60% of progressed patients will receive docetaxel is an overestimation	The ERGs clinical expert advisor was of the opinion that for the NHS cohort of patients with mHRPC, a larger proportion of patients would be expected to receive docetaxel than 40%, particularly if offered further up the treatment pathway as explored in ERG scenarios 1, 9 and 10. The ERG acknowledge that this is subject to uncertainty, and that clinical opinion will vary. It is not a factual inaccuracy.

Issue 7 MFS definition

Description of problem	Description of proposed amendment	Justification for amendment	Comments
On page 3, the ERG report does not provide the full MFS definition.	Please replace with:	To highlight the timeframe of death	Not a factual error. The proposed revision is not

The ERG report states: *"The primary end point was MFS, which was defined as the time from randomization to radiographic progression, or as the time to death without radiographic progression*"	"*The primary end point was MFS, which was defined as the time from randomization to radiographic progression, or as the time to death* ***within 112 days of treatment discontinuation*** *without evidence of radiographic progression*."		accepted.

Issue 8 Random effects model for the NMA

Description of problem	Description of proposed amendment	Justification for amendment	Comments
On pages 17, 74 and 75, the ERG suggests that the Company should have applied a random effects model to the NMA. The related sections are: - On page 17, the ERG states "*a random effects model should therefore have been developed and the results compared as a sensitivity check*" - On pages 74-75, the ERG states "*As the Company acknowledge, disease progression was assessed with metastases free survival in PROSPER while in STIVE radiographic progression free survival was used, the ERG suggest that a random effects model should therefore have been developed and the results compared as a sensitivity check*"	The Company does not agree that a random effects model would be applicable in this case. The Company would like that all references to the random effects model are deleted from the ERG report.	The Company did not conduct a random effects model because a random effect model requires an estimate of the between-study standard deviation (SD) and the network of evidence in our case consists of 1 study per treatment comparison. In case when the number of studies is small, and especially with only 1 study per comparison, using a standard vague /weakly informative prior distribution for the between-study SD will give implausible posterior distribution [1]. Looking at the credible intervals of the results provided by the ERG, it can be seen that these credible intervals are extremely large. The ERG does not provide any information on what priors have been used in the analyses. Based on the literature, the choice of prior is critical, in particular if the number of studies is small [2,3,4]. For the case of two studies and in the absence of relevant external data, information about between-trial	

		heterogeneity is clearly very small. Cited references [1] Gelman A. Prior distributions for variance parameters in hierarchical models. Bayesian Anal. 2006;1(3):515–33. [2] Dias S, Sutton AJ, Welton NJ, Ades AE. (2012). Heterogeneity: subgroups, meta-regression, bias and bias-adjustment. NICE DSU Technical Support Document 3, National Institute for Health and Clinical Excellence (NICE). [3] Dias S, Sutton AJ, Welton NJ, Ades AE. (2014). A generalized linear modelling framework for pairwise and network meta-analysis of randomized controlled trials. NICE DSU Technical Support Document 2, National Institute for Health and Clinical Excellence (NICE). [4] Turner RM, Jackson D, Wei Y, Thompson SG, Higgins PT. (2015). Predictive distributions for between-study heterogeneity and simple methods for their application in	

		Bayesian meta-analysis. Statistics in Medicine 34, 984–998.	

Issue 9 95% credible intervals

Description of problem	Description of proposed amendment	Justification for amendment	Comments
On pages 5 and 63, there is no separation between the lower and higher credible intervals (CrI) in any of the 95% CrI. The text in the ERG report is: *The ERG ran a random effects model and obtained NMA results for enzalutamide v placebo of [redacted] for MFS/rPFS and [redacted] for time to PSA progression. The results for Bicalutamide v placebo from the same model are [redacted] for MFS/rPFS and [redacted] for time to PSA progression.*	The text should be removed as the random effects model does not apply. But if the text is maintained, then a space should be added between the lower and upper bound: *The ERG ran a random effects model and obtained NMA results for enzalutamide v placebo of [redacted] for MFS/rPFS and [redacted] for time to PSA progression. The results for Bicalutamide v placebo from the same model are [redacted] for MFS/rPFS and [redacted] for time to PSA progression.*	See Issue 8	

Issue 10 How the treatment arms in PROSPER and STRIVE are referred to

Description of problem	Description of proposed amendment	Justification for amendment	Comments
On page 26, the ERG have stated:	The text should be replaced with: *The company present characteristics of the two*	The way it is written suggests that the Company mistakenly refer to the intervention and comparator	This is not a factual error and is in keeping with phrasing used by the company on pages 23

The company present characteristics of the two trials in Table 4, document B of the CS on page 25, and this is reproduced by the ERG as Table 6 in this report. The CS refers to the intervention arm of PROSPER and STRIVE as the enzalutamide arm, however, the CS states that the treatment in this arm included: *• Enzalutamide and ADT in PROSPER* *• Enzalutamide, ADT and bicalutamide placebo in STRIVE.* *Similarly, the comparator arm of these two studies are referred to as the "placebo" and "bicalutamide" arms, respectively. The CS states that treatment in these arms included:* *• Enzalutamide placebo and ADT in PROSPER* *• Bicalutamide, ADT and enzalutamide placebo in STRIVE.*	*trials in Table 4, document B of the CS on page 25, and this is reproduced by the ERG as Table 6 in this report. The* ***Company highlights that in the CS the intervention arm of PROSPER and STRIVE is referred to as the enzalutamide arm, but the arm includes****:* *• Enzalutamide and ADT in PROSPER* *• Enzalutamide, ADT and bicalutamide placebo in STRIVE.* *Similarly, the* ***Company state that the*** *comparator arm of these two studies are referred to as the "placebo" and "bicalutamide" arms, respectively but the arm includes:* *• Enzalutamide placebo and ADT in PROSPER* *• Bicalutamide, ADT and enzalutamide placebo in STRIVE.*	arms	and 24 in document B of the Company's submission.

Issue 11 No patients receiving radium 223 or cabazitaxel in the model

Description of problem	Description of proposed amendment	Justification for amendment	Comments
On page 92, the ERG states that: *"The company have disregarded these treatment options in the model, based on market research suggesting they are not used by a majority of patients in the UK. (Kantar-Health. Market Research on CRPC in the UK. 2018 [Unpublished data])."*	The text should be removed or be replaced by: *The company **included radium 223 and cabazitaxel in the model but considered that 0% of patients received these options** based on market research suggesting they are not used by a majority of patients in the UK. (Kantar-Health. Market Research on CRPC in the UK. 2018 [Unpublished data]).*	The Company did consider radium 223 and cabazitaxel but based on the low proportion of patients receiving these two drugs in the UK in the market research outcomes (i.e., [redacted]), it was decided to set them as 0%.	This statement is not factually inaccurate. It reflects the company's wording on page 100 of their submission.

Issue 12 Missing word

Description of problem	Description of proposed amendment	Justification for amendment	Comments
On page 111, a word is missing in the following text: *Based on the ERG's clinical expert advice, it seems reasonable to assume that patients on ADT alone would be monitored at the same frequency as those on*	Add "enzalutamide": *Based on the ERG's clinical expert advice, it seems reasonable to assume that patients on ADT alone would be monitored at the same frequency as those on **enzalutamide***	Incomplete sentence	Accepted. A new page has been provided in the erratum document.

Issue 13 Incorrect description of the impact of enzalutamide to PROs

Description of problem	Description of proposed amendment	Justification for amendment	Comments
On pages 5 and 59, the ERG summarises incorrectly the PROSPER patient reported outcomes (PROs). *There were no statistically significant differences between the enzalutamide and placebo groups, with the exception of hormonal treatment-related symptoms (measured by the EORTC QLQ PR25) and social wellbeing (measured by FACT-P) in favour of enzalutamide.* *The ERG notes that enzalutamide is associated with an earlier deterioration in HRQOL due treatment-related symptoms compared to placebo, for example hormonal treatment-related symptoms, but, overall, enzalutamide is associated with a delay in the worsening of HRQOL.*	The two paragraphs should be replaced with the following: *Enzalutamide demonstrated significant improvements over ADT in terms of time to confirmed deterioration for FACT-P total score, FACT-P emotional well-being and FACT-P prostate cancer scale, the EQ-5D VAS score, and the EORTC-QLQ-PR25 urinary and bowel symptoms score. In contrast, enzalutamide was associated with an earlier deterioration of the EORTC QLQ-PR25 hormonal treatment-related symptoms score. There were no statistically significant differences between the enzalutamide and placebo groups for the mean change from baseline (MMRM analysis) for any PRO, with the exception of hormonal treatment-related symptoms (measured by the EORTC QLQ PR25) which favoured ADT and social wellbeing (measured by FACT-P) in favour of enzalutamide.* *Overall, enzalutamide delayed worsening of HRQoL.*	ERG statement on enzalutamide's effect on PROs is not accurate; it implies that enzalutamide worsens HRQoL and this does not reflect the overall impact of enzalutamide on HRQoL of nmHRPC patients. It should be noted that the Company made an error in page 67 of Document B. The last paragraph should be: "*This difference in median time to deterioration reached statistical significance for emotional wellbeing (HR 0.69 [95% CI 0.55, 0.86]),* ***prostate cancer scale*** *(HR 0.79 [95% CI 0.67, 0.93]) and FACT P total score (HR 0.83 [95% CI 0.69, 0.99]).*"	The ERG does not agree that the text implies that enzalutamide worsens overall HRQOL or that the text is factually incorrect. The proposed amendment is not accepted.

Issue 14 ICER of scenarios 1, 10 and 11

Description of problem	Description of proposed amendment	Justification for amendment	Comments
On page 109, the ERG reports: *A separate confidential appendix will be provided utilising the appropriate discounted prices. These should also be treated with caution since it is not possible to adjust post-progression mortality for the different treatment sequences. Nevertheless, it can be noted that the modelled changes increase the ICER for enzalutamide*	Replace with: *A separate confidential appendix will be provided utilising the appropriate discounted prices. These should also be treated with caution since it is not possible to adjust post-progression mortality for the different treatment sequences. Nevertheless, it can be noted that the modelled changes **decrease** the ICER for enzalutamide*	When applying the PAS to radium 223 and cabazitaxel, the ICER will decrease	The ERG accepts that the wording is a bit ambiguous. The ERG was referring to general point fact that the modifications to treatment pathway would increase the ICER relative to the company's base case. A clean page with amended text has been added to the erratum document.

Issue 15 Pain being due to other causes than MFS

Description of problem	Description of proposed amendment	Justification for amendment	Comments
On page 54, the ERG states: *The company suggest that this result indicates that pain was not related to the development of metastatic disease given that the median MFS was 36.6 months in the enzalutamide group and 14.7 months in the placebo group*	Suggest replacing with: *The **results may suggest** that pain was not related to the development of metastatic disease given that the median MFS was 36.6 months in the enzalutamide group and 14.7 months in the placebo group*	The Company did not state the assumption	The wording in the ERG report reflects the wording used by the Company on page 61 of submission document B: "These results suggest that pain was not related to the development of metastases given that median MFS was 36.6 months (95% CI: [33.1;

			not reached]) in the enzalutamide group and 14.7 months (95% CI: [14.2; 15.0]) in the placebo group." The proposed amendment is not accepted.

Issue 16 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	Comments
On the ERG report, there are several typos: • In page 5, 62: "STIVE" should be "**STRIVE**" • In page 15, "Ennzalutamide" should be "**Enzalutamide**" • In page 86, "utiity" should be "**utility**" • In page 89, "*These costs contribute only a small amount to the overall difference in cost between the Enzalutamide and ADT arms of the model"* should	Typographical errors should be amended	Typographiical errors	These are minor typographical errors that do not affect meaning. No changes required.

be "***enzalutamide***" • In page 92, "stoke" should be "**stroke**" • In page 105, *The company model predicted results **that** were in line with the checklist verification criteria* – "**that**" should be removed • In page 116, "form PROSPER" should be "**from** PROSPER" • In page 118, "£28, 853" should be "**£28,853**"			

Issue 17 Company's typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	Comments
On page 90, the ERG states: *However, there is a discrepancy between the value of 23.7 months reported in Table 43 of the company submission, and the value of 20.7 months which is applied in the model*	None	The value of 23.7 months in Table 43 of the company submission was a typo	Acknoweldged

Issue 18 Duplicated abbreviation in Table of abbreviations

Description of problem	Description of proposed amendment	Justification for amendment	Comments
On page 12 (Table of abbreviations), PFS is mentioned twice	Remove one PFS	Duplicated abbreviation	Not a factual error. The proposed amendment is not accepted.

Issue 19 Stated order of ICERs

Description of problem	Description of proposed amendment	Justification for amendment	Comments
On page 118, the ERG states: *The ERG requested further scenario analyses at the clarification stage, asking the company to explore the impact of 1) using the observed distribution of second line treatment in the placebo arm of PROSPER to estimate the cost of treatment at PD1 in the ADT arm of the model; 2) using the observed median time from progression to initiation of first antineoplastic therapy in PROSPER, to model the transition from PD1 to PD 2 in the enzalutamide arm of the model; and 3) using the MFS for progression in combination with the more mature IA2 OS data*	The text should be replaced with: *The ERG requested further scenario analyses at the clarification stage, asking the company to explore the impact of 1) using the observed distribution of second line treatment in the placebo arm of PROSPER to estimate the cost of treatment at PD1 in the ADT arm of the model; 2) using the observed median time from progression to initiation of first antineoplastic therapy in PROSPER, to model the transition from PD1 to PD 2 in the enzalutamide arm of the model; and 3) using the MFS for progression in combination with the more mature IA2 OS data from PROSPER to inform pre and post progression mortality. These three analyses increased the ICER for enzalutamide to* ***£33,863, £31,671,*** *and* [redacted] *respectively*	The order of the ICERs do not match the scenarios	The ERG acknoweldge the error and have provided a revised page in the erratum document.

from PROSPER to inform pre and post progression mortality. These three analyses increased the ICER for enzalutamide to £31,671, £33,863, [redacted] *respectively*			

Issue 20 Redundant word

Description of problem	Description of proposed amendment	Justification for amendment	Comments
On page 119, the ERG states: *The mHRPC state incorporates three sub-states (PD1-PD3) to capture progression through subsequent treatment lines for mHRPC, but which are not separately linked **to** with survival in the model*	[redacted]	Redundant word	Not a factual error. The proposed amendment is required.

Aberdeen HTA Group

Enzalutamide for treating non-metastatic hormone-relapsed prostate cancer [ID1359]

Erratum

Completed November 2018

This document is intended to replace pages 19, 31, 82, 109, 111, Table 33 (p 114-115) and page 118 of the original ERG assessment report for *Enzalutamide for treating non-metastatic hormone-relapsed prostate cancer,* which contained a few inaccuracies. The amended pages follow in order of page number below. The changes to Table 33 relate to the descriptions of scenarios 9 and 10, and changes to the results in scenarios 1, 9 and 10. These three scenarios involve 10% of patients receiving cabazitaxel as the final line of treatment in the enzalutamide arm. The ERG noticed that when producing the confidential appendix for these scenarios, the model had assumed the incorrect vial size (40 mg as opposed to 60mg). Therefore, the ERG have revised the results for these scenarios (at list price) in this erratum document.

symptoms improve to < Grade 2, then resumed at the same or reduced dose of 120 mg or 80 mg. The concomitant use of strong CYP2C8 inhibitors should be avoided, or enzalutamide should be reduced to a 80 mg daily dose if the avoidance of co-administration is not possible. Co-administration with warfarin and coumarin-like anticoagulants should be avoided. Patients receiving enzalutamide and anticogaulants metabolised by CYP2C9 should receive additional International Normalised Ration monitoring.

The SmPC state that "interactions with certain medicinal products that are eliminated through metabolism or active transport are expected" and "these products should be avoided or used with caution. The risk for liver injury after paracetamol administration is suspected to be higher in patients concomitantly treated with enzyme inducers". The SmPC lists the following medicinal products that can be affected, but are not limited to:

- Analgesics (e.g. fentanyl, tramadol)
- Antibiotics (e.g. clarithromycin, doxycycline)
- Anticancer agents (e.g. cabazitaxel)
- Antiepileptics (e.g. carbamazepine, clonazepam, phenytoin, primidone, valproic acid)
- Antipsychotics (e.g. haloperidol)
- Antithrombotics (e.g. acenocoumarol, warfarin, clopidogrel)
- Betablockers (e.g. bisoprolol, propranolol)
- Calcium channel blockers (e.g. diltiazem, felodipine, nicardipine, nifedipine, verapamil)
- Cardiac glycosides (e.g. digoxin)
- Corticosteroids (e.g. dexamethasone, prednisolone)
- HIV antivirals (e.g. indinavir, ritonavir)
- Hypnotics (e.g. diazepam, midazolam, zolpidem)
- Immunosuppressant (e.g. tacrolimus)
- Proton pump inhibitor (e.g. omeprazole)
- Statins metabolised by CYP3A4 (e.g. atorvastatin, simvastatin)
- Thyroid agents (e.g. levothyroxine)

determined to have metastatic disease after trial enrolment by the blinded independent central review (BICR).

Following clarification questions from the ERG, the company provided the baseline characteristics of the UK PROSPER participants in Table 2 of their clarification response, and this is reproduced by the ERG in Table 7. The ERG agrees with the company that the baseline characteristics are similar to the wider PROSPER population, with the following exceptions:

- [redacted].

Following clarification from the ERG, the company confirmed that the percentage of participants who were exposed to bicalutamide prior to PROSPER trial entry in the UK PROSPER cohort was [redacted] and [redacted] for enzalutamide and placebo, respectively. In the overall trial population these percentages were [redacted] and [redacted], respectively.

The company were also asked to comment on any differences that the distribution of second line treatment in the placebo arm of PROSPER might have in comparison to enzalutamide (the assumption in the company model). In response, they noted that a network meta-analysis using PREVAIL,[25] COU-AA-302[31] and TAX327[28] demonstrated no significant difference in OS between enzalutamide and abiraterone (HR 0.94, 95% CI 0.72; 1.23) or between enzalutamide and docetaxel (HR 1.00, 95% CI 0.72; 1.39), but significantly longer OS with enzalutamide vs placebo (Systematic Review and Mixed Treatment Comparison of Enzalutamide for Chemotherapy Naïve Castration-Resistant Prostate Cancer Final Report Astellas. January 2015 [unpublished data]). Therefore, since 26% of patients appear to have received ADT (BSC) alone upon progression in PROSPER, it could be argued that that PPS in the company model should have been adjusted upward to reflect the assumption of 100% enzalutamide treatment at PD1 following progression on ADT. However, as noted above, the extrapolation of PPS applied in the model has in fact been externally validated against the PREVAIL OS data, which is relevant to a pre-chemotherapy mHRPC population treated with 100% enzalutamide versus ADT alone.

It was similarly noted that the distribution of first antineoplastic treatments following disease progression on enzalutamide in PROSPER was inconsistent with the model assumption of docetaxel (40%) or ADT alone (60%) at PD2 in the enzalutamide arm of the model. Table 21 in fact indicates that of those who initiated a second line treatment following progression on enzalutamide, [redacted] initiated abiraterone and [redacted] appear to have been re-challenged with enzalutamide. It is unclear to ERG why this is the case, but the ERG acknowledge that in the UK NHS patients would not be considered for either abitaterone or retreatment with enzalutamide following progression on enzalutamide. It is also clear from Table 21 that docetaxel was the second most commonly prescribed second line treatment ([redacted]) in the enzalutamide arm, which is in line with the NHS treatment pathway. The ERG are generally satisfied that extrapolation of the PROSPER trial is suitable for the economic modelling, despite the described discrepancies in post-progression treatments compared to the modelled pathway.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

Additional work and analyses undertaken by the ERG and their associated impact on the ICER findings are reported in this section. The ERG has conducted all these analyses based on a revised version of the economic model submitted by the company in response to the clarification letter (dated: October 11th, 2018).

5.3.1 ERG exploratory scenario analyses

The ERG additional exploratory analyses are described in Table 32 below, with justification and reference to the relevant section of the ERG report which discusses the issue being addressed. The results of these analyses are presented in Table 33.

The scenarios (1, 10 and 11) which explore the impact of modifying the downstream clinical treatment pathway, in line with the ERGs expert advice, are presented here using the list price for radium-223 and cabazitaxel. These scenarios were incorporated using functionality and parameter input values that were available in the company model, although not utilised in scenarios presented in the company submission. Since a patient access scheme is available for both of these treatments on the NHS in England, the results are not suitable for informing decision making. A separate confidential appendix will be provided utilising the appropriate discounted prices. These should also be treated with caution since it is not possible to adjust post-progression mortality for the different treatment sequences. Nevertheless, it can be noted that the modelled changes at list prices increase the ICER for enzalutamide relative to the company base case.

In terms of the ERG change of equalising visit and monitoring costs between enzalutamide and ADT (scenario 2), this results in a modest increase in the ICER. The change to the cost of MACE evens (scenario 3) has only a minor impact. Changing the utility value applied in state PD1 to 0.844 (based on TA377 for chemotherapy naïve patients), also results in a modest increase in the ICER for enzalutamide. When these three changes are made in combination, the ICER for enzalutamide increases to £32,132 (scenario 6).

The ICER increases further in scenario 7 when the time in sub-state PD1 is based on the data from PROSPER, as per the company scenario provided in response to the clarification letter. When IA2 data are used to model progression (based on TTD) and

Table 32 Additional scenario analyses, including justifications, performed by the ERG

<table>
<tr><th></th><th>Parameter / Analysis</th><th>Base case Assumption</th><th>Scenario explored</th><th>Justification</th><th>Table / section reference in ERG report</th></tr>
<tr><td>BC</td><td colspan="3">Company preferred base case analysis (All ERG exploratory analyses are conducted relative to this base case)</td><td>Table 12</td></tr>
<tr><td colspan="6">Treatment pathway</td></tr>
<tr><td>1</td><td>Treatment pathway in PD1-3</td><td>Company preferred treatment pathway (PD1-PD3)</td><td>ERG exploratory treatment pathway:
<table><tr><th>HS</th><th>Enza arm</th><th>ADT arm</th></tr><tr><td>nmHRPC</td><td>Enza (100%)</td><td>ADT (100%)</td></tr><tr><td>PD1</td><td>Docetaxel (60%)
ADT alone (40%)</td><td>Enza (100%)</td></tr><tr><td>PD2</td><td>R223 (60%)
ADT alone (40%)</td><td>Docetaxel (50%)
ADT alone (50%)</td></tr><tr><td>PD3</td><td>Cabazitaxel (10%)
BSC (90%)</td><td>R223 (40%)
BSC (60%)</td></tr></table></td><td>Based on the ERG’s clinical expert advice, the shifting of enzalutamide up the treatment pathway may result in a shift in subsequent lines of treatment up the clinical pathway, creating more space for further subsequent treatment. R223 and cabazitaxel are two NICE recommended treatment options in the post docetaxel setting.</td><td>5.2.4</td></tr>
<tr><td colspan="6">Costs</td></tr>
<tr><td>2</td><td>Health state cost for nmHRPC and PD1-3</td><td>Company model monitoring frequency</td><td>Equalise monitoring and testing frequency for both arms.</td><td>Based on the ERG’s clinical expert advice, it seems reasonable to assume that patients on ADT alone would be monitored at the same frequency as those on enzalutamide.</td><td>5.2.8 (Table 24)</td></tr>
<tr><td>3</td><td>Setting visits and tests equal to the values presented in Table 49 of the</td><td>Company model monitoring frequency</td><td>Apply health care visit and testing frequencies as presented in Table 49 of the company submission</td><td>A number of discrepancies were observed between the company reported health care visit and testing frequencies and the values applied in</td><td>5.2.8</td></tr>
</table>

Table 33 Impact of alternative scenario analyses on cost-effectiveness results

			Enzalutamide		ADT					
Analysis		**Description**	**Cost**	**QALY**	**Cost**	**QALY**	**Inc. Cost**	**Inc. QALY**	**Deterministic ICER**	**% change in the ICER**
	Company submitted model (response to clarification)									
BC		Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,853	0%
	ERG explored analyses (All applied relative to company base case)									
	Treatment pathway									
1		ERG exploratory treatment pathway[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,648	58.31%
	Costs									
2		Equalise monitoring and testing frequency for both arms.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,435	+5.49%
3		Apply health care visit and testing frequencies as presented in Table 49 of the company submission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,207	-2.24%
4		MACE cost = overall reference cost for HRG AA35 (£3,279)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,058	+0.71%
	Utilities									
5		Baseline utility value for chemotherapy naïve mHRPC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,257	+4.87%

			Enzalutamide		ADT					
Analysis		**Description**	**Cost**	**QALY**	**Cost**	**QALY**	**Inc. Cost**	**Inc. QALY**	**Deterministic ICER**	**% change in the ICER**
		patients from NICE TA377 (0.844)								
	Combined analyses									
6		Combined changes in scenarios 2, 4, and 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,132	+11.36%
7		As per 6 + Median duration in PD1 following progression on enzalutamide = 3.8 months (based in PROSPER)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,628	+23.48%
8		As per 7 + PROSPER IA2 data for TTD and PreTD and Post TD survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,210	+8.17%
9		As per 7 + IA2 data for PreTD and Post TD survival, MFS for progression.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£56,168	+94.67%
10		6 + 1[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£49,799	72.60%
11		9 + 1[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£90,985	215.34%

a; List price applied to downstream treatment with radium-223 and cabazitaxel (not suitable for informing decision making).

The company base case ICER comes to £28, 853. One-way sensitivity analysis showed the ICER to be most sensitivity to variation in the parameters of the parametric curves assigned for MFS, PrePS and PPS. The company also provided a range of 12 scenario analyses, in which the ICER increased just above £30,000 in three of these. The ERG requested further scenario analyses at the clarification stage, asking the company to explore the impact of 1) using the observed distribution of second line treatment in the placebo arm of PROSPER to estimate the cost of treatment at PD1 in the ADT arm of the model; 2) using the observed median time from progression to initiation of first antineoplastic therapy in PROSPER, to model the transition from PD1 to PD 2 in the enzalutamide arm of the model; and 3) using the MFS for progression in combination with the more mature IA2 OS data from PROSPER to inform pre and post progression mortality. These three analyses increased the ICER for enzalutamide to £33,863, £31,671, and [redacted] respectively. The ERG consider the latter issue to be one of the most significant uncertainties in the model. Whilst the ERG acknowledge the inconsistency is using MFS to model the transition to mHRPC, in combination with preTD and postDT survival data from IA2, the ERG believe this is still a plausible scenario. Ideally, the ERG would have liked to have seen IA2 OS data split radiographic progression status, and combined the IA2 MFS data. However, the company indicated that the MFS analysis was not available for the IA2 data cut.

Further sources of uncertainty in the model relate to:

1. The modelled downstream treatment pathways in the enzalutamide and ADT arms of the model.
2. The cost of monitoring and testing patients on enzalutamide and ADT alone
3. The utility value associated with progression to sub-state PD1 in the model.