Enzalutamide for treating non-metastatic hormone-relapsed prostate cancer

Produced by Aberdeen HTA Group

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Declared competing interests of the authors

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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.

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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]	

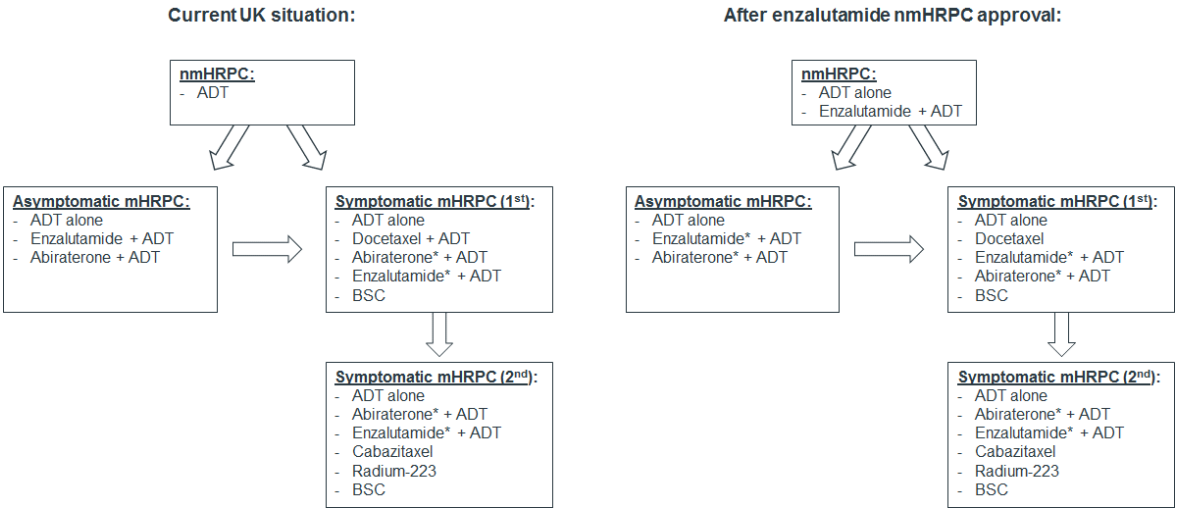
HRPC, hormone-relapsed prostate cancer; M, million; nm, non-metastatic; ONS, office for national statistics; PCa, prostate cancer.

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 $\leq$10 months and a PSA $\geq$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%)		

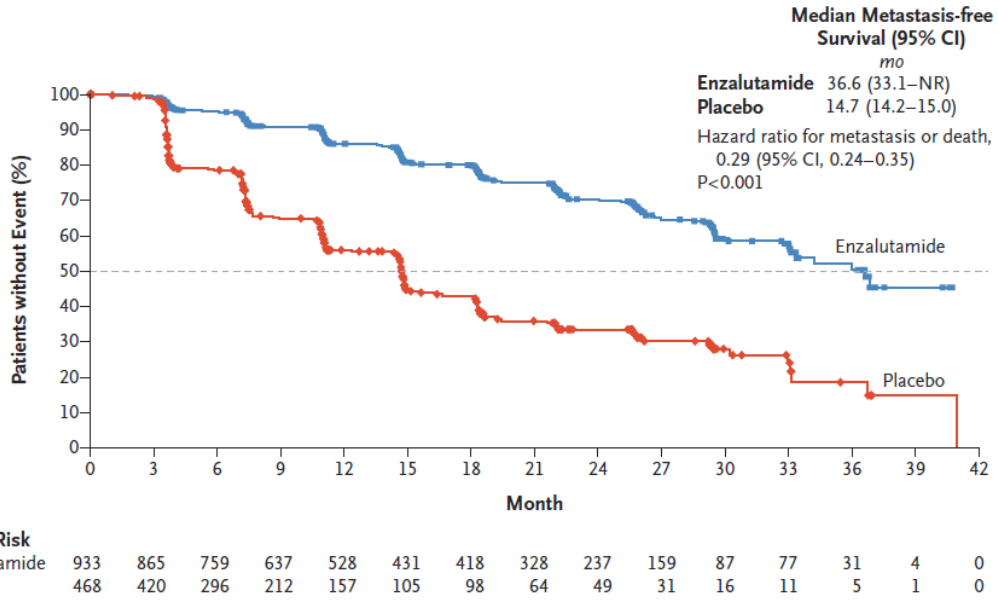
Source: Company submission and Medivation-Pfizer. Clinical Study Report - STRIVE: a multicenter phase 2, randomized, double-blind, efficacy and safety study of enzalutamide vs. bicalutamide in men with prostate cancer who have failed primary androgen deprivation therapy. 14 August 2015 [Unpublished data]

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.

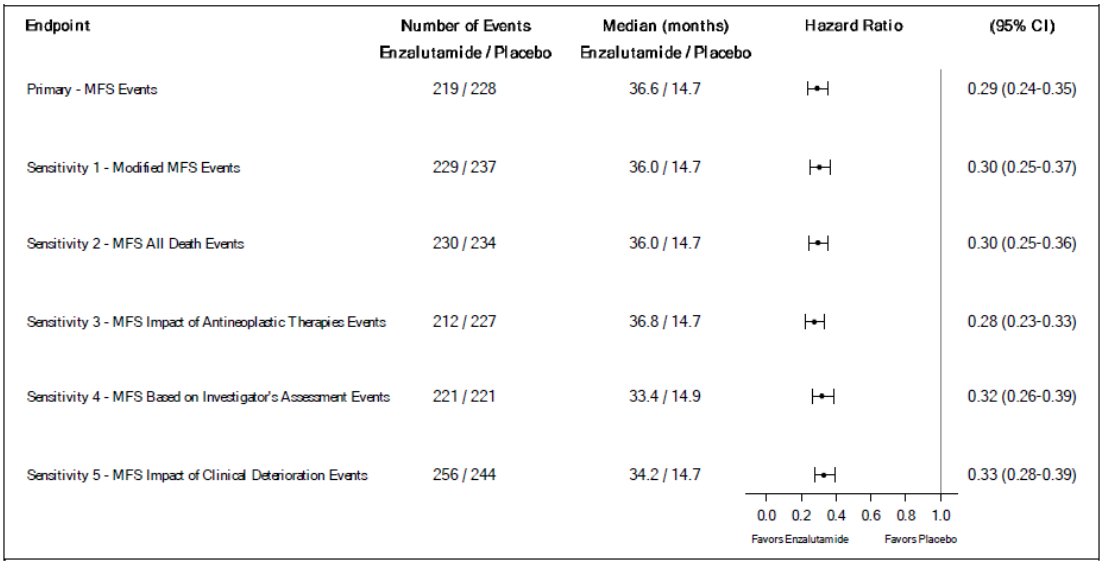
The company present the Kaplan-Meier estimates in Figure 6 of the CS, document B, on page 51 and the ERG have reproduced this as Figure 2 in this report.



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

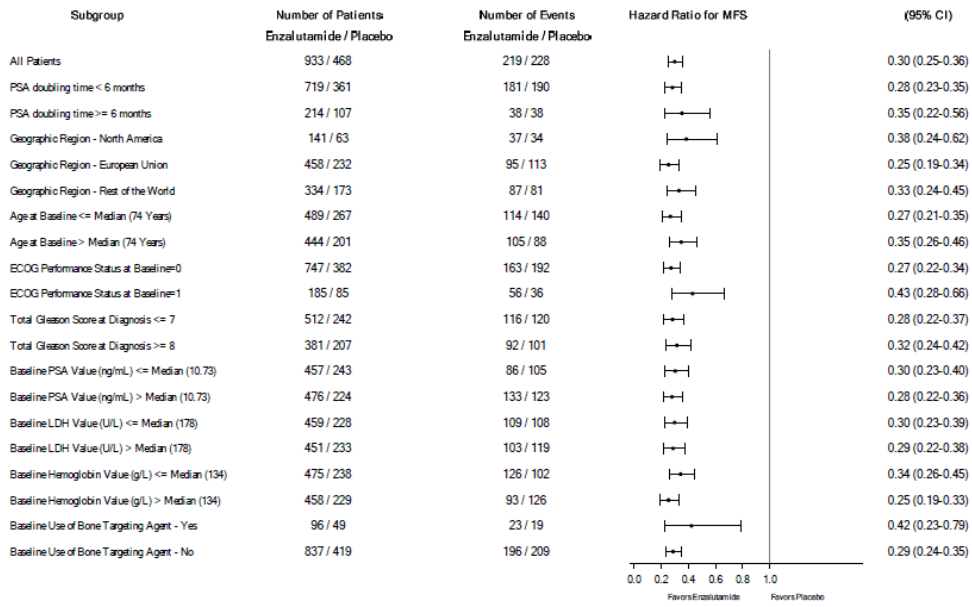
Figure 2 Kaplan-Meier curves for MFS (PROSPER intention-to-treat [ITT] population), reproduced by the ERG from the CS, document B

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



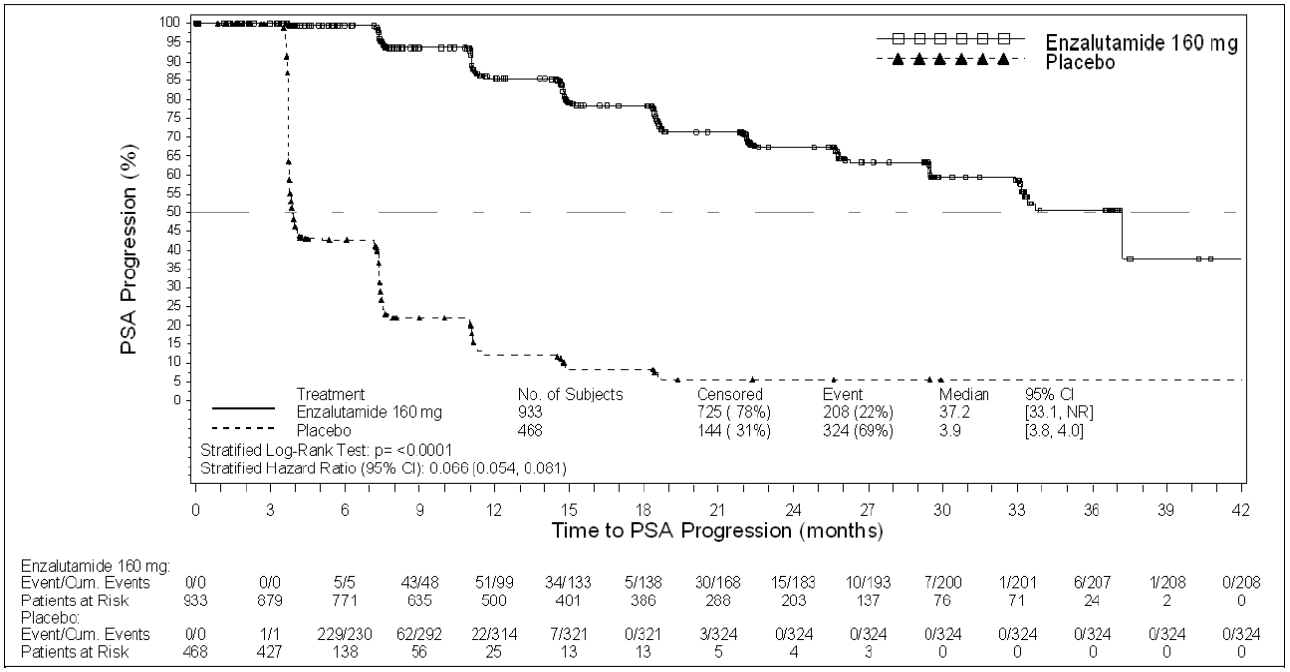
CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; ITT: intent-to-treat; LDH: Lactate dehydrogenase; MFS: metastasis-free survival; PSA=prostate-specific antigen

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

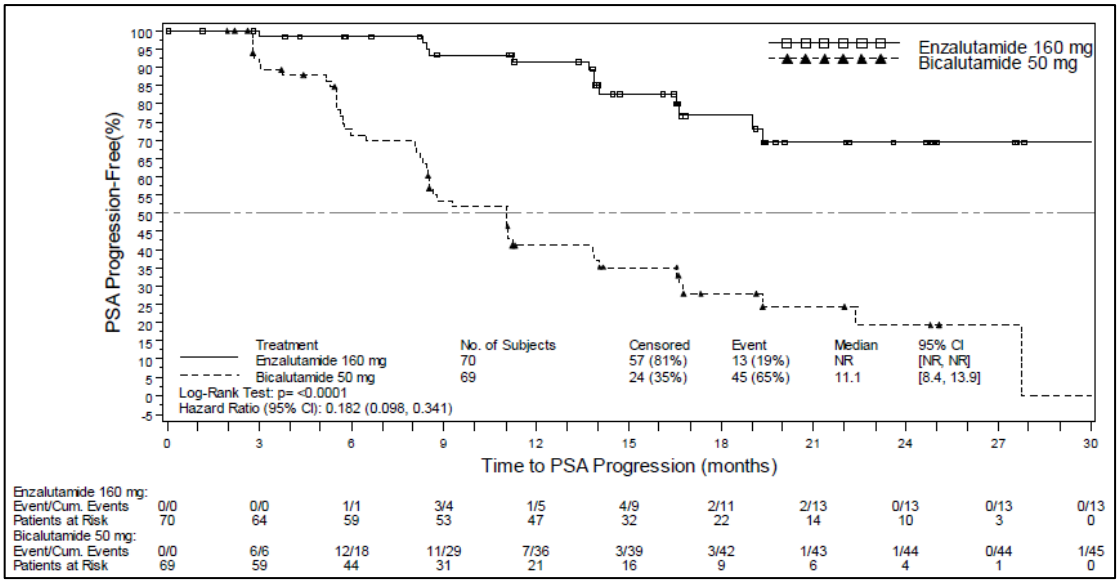
A higher number of patients in the PROSPER placebo arm (69.2%) experienced PSA progression than those in the enzalutamide arm (22.3%) and median time to PSA progression was also shorter in the placebo arm than the enzalutamide arm: 3.9 months (95% CI 3.8, 4.0) versus 37.2 months (95% CI 33.1, not reached). 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.



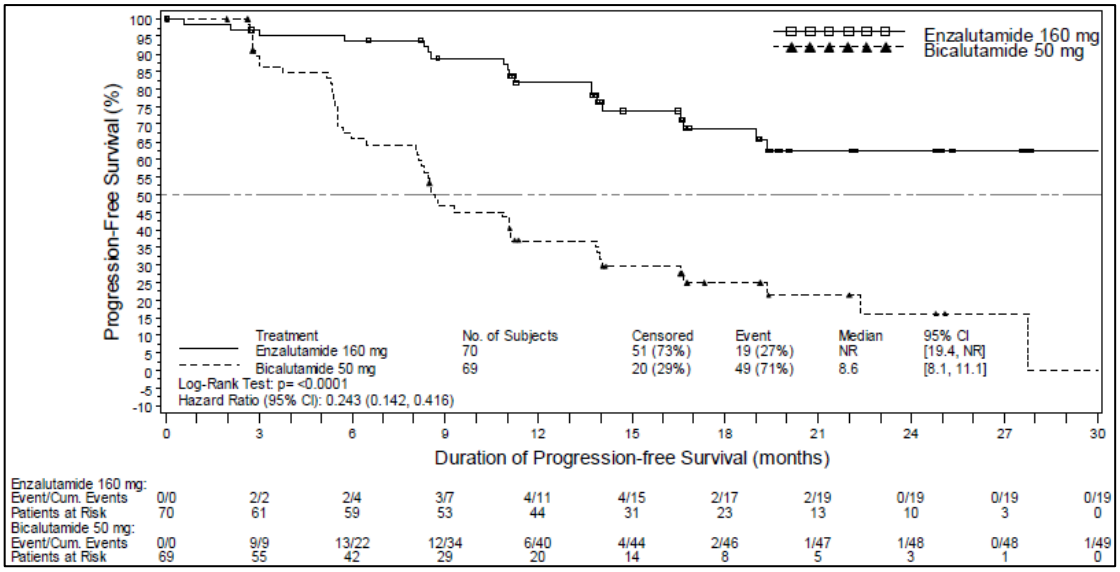
P-value is based on an unstratified log-rank test. Hazard ratio is based on an unstratified Cox regression model (with treatment as the only covariate) and is relative to bicalutamide with <1 favouring enzalutamide.
Cum, cumulative;
Abbreviations: ITT: intent-to-treat; NR: not reached; PSA: prostate-specific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

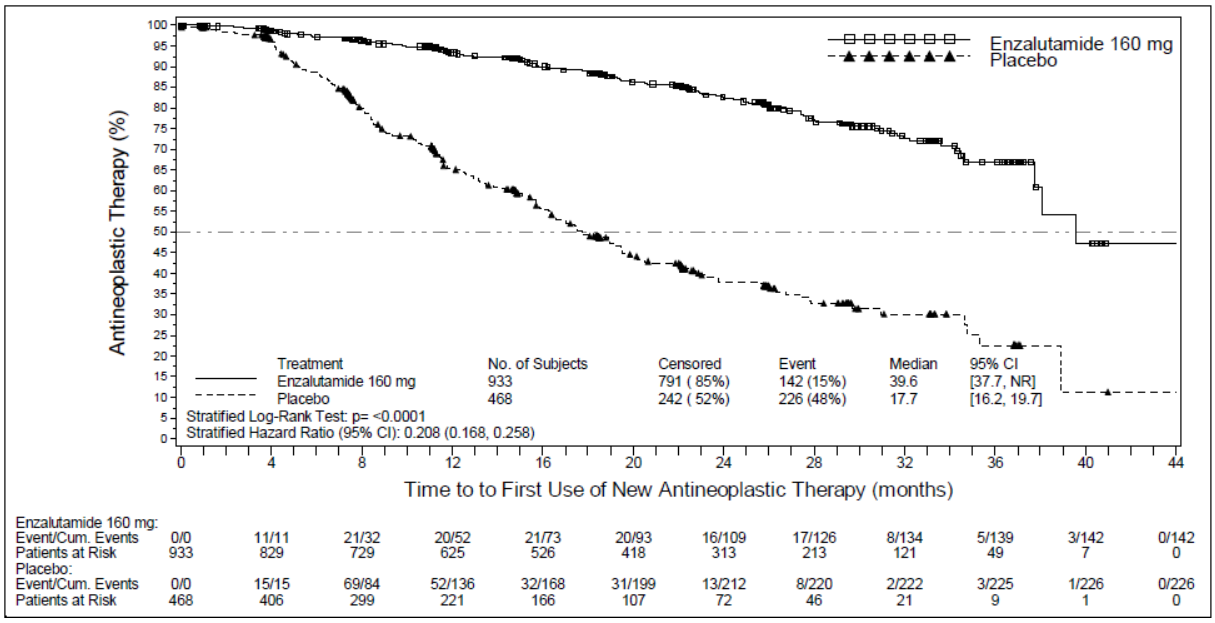


P-value is based on an unstratified log-rank test. Hazard ratio is based on an unstratified Cox regression model (with treatment as the only covariate) and is relative to bicalutamide with <1 favouring enzalutamide.
Abbreviations: Cum: cumulative; ITT: intent-to-treat; nmHRPC: non-metastatic hormone-relapsed 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

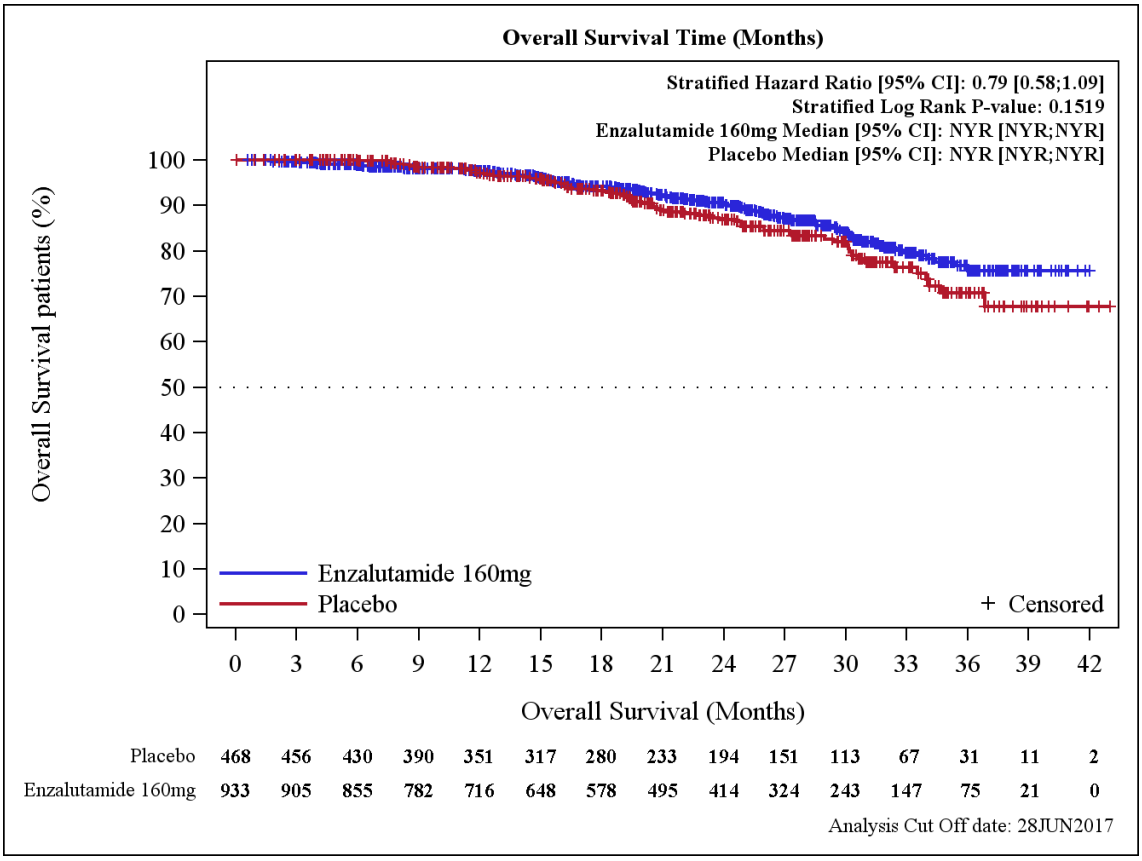
Source: PROSPER Clinical Study Report [Unpublished data]

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 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.



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 Table 17). 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.

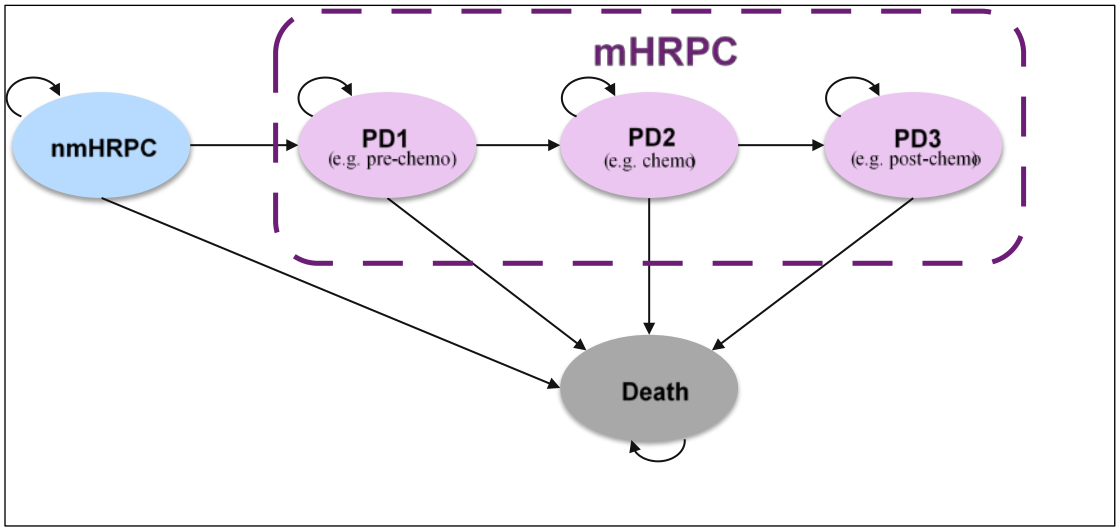


Figure 11 Model structure (Source: Figure 21, Company submission, document B)

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.

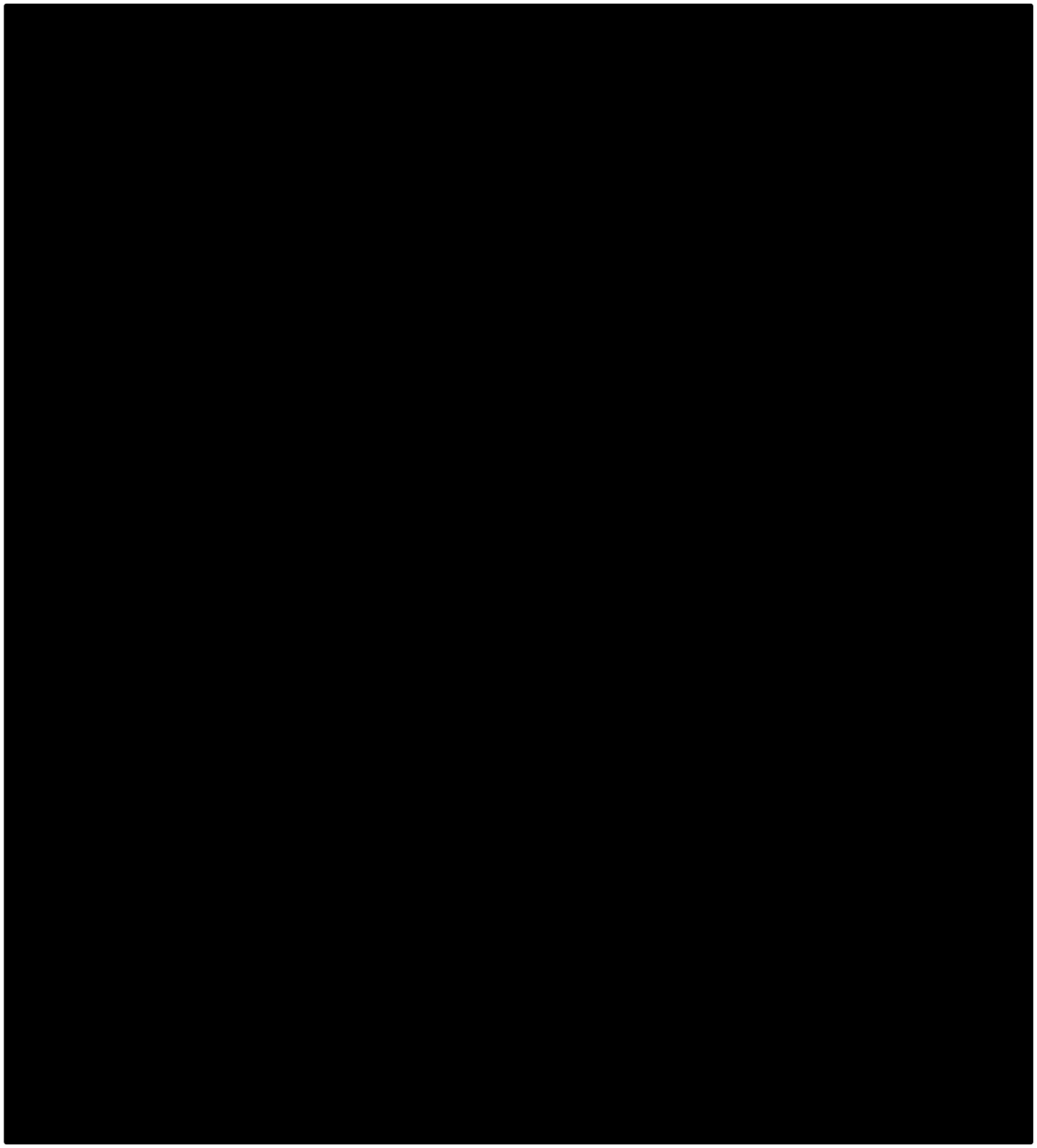


Figure 17 is commercial in confidence

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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