Enzalutamide for treating metastatic hormone-relapsed prostate cancer not previously treated with chemotherapy

Produced by Aberdeen HTA Group

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Rider on responsibility for report

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

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Contribution of authors

Clare Robertson acted as systematic reviewer, critiqued the clinical effectiveness methods. Shona Fielding acted as statistician, critiqued the statistical methods presented in the submission, checked all the numerical results, tables, and figures related to the review of the clinical effectiveness evidence, conducted further statistical analyses. Ewen Cummins acted as health economist, critiqued and reviewed the cost-effectiveness evidence presented in the submission, checked and rebuilt the economic model, and carried out further sensitivity analyses. Cynthia Fraser acted as information scientist, critiqued the methods used for identifying relevant studies in the literature and conducted additional searches. Thomas Lam acted as clinical expert, provided clinical advice and general guidance. Craig Ramsay acted as project lead for this appraisal, critiqued and reviewed the clinical and cost effectiveness methods, and supervised the work throughout the project. All authors contributed to the writing of the report and approved its final version.

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ADT	androgen deprivation therapy
AE	adverse event
AR	androgen receptor
AWMSG	All Wales Medicines Strategy Group
BPI-SF	Brief pain inventory short form
BSC	best supportive care
CDF	cancer drug fund
CI	confidence interval
CS	company submission
DMC	data monitoring committee
DSU	decision support unit
ECOG	Eastern Cooperative Oncology Group (performance status)
EQ5D	EuroQuol 5-Dimension
ERG	evidence review group
FACT-P	Functional Assessment of Cancer Therapy – Prostate
FDA	Food and Drug Administration
HR	hazard ratio
HRPC	hormone relapsed prostate cancer
IPCW	inverse probability of censoring weight
ITT	intention to treat
LDH	lactate dehydrogenase
LHRH	Luteinising Hormone Releasing Hormone
LS	least squares
mHRPC	metastatic hormone relapsed prostate cancer
NICE	national institute for health and clinical
OS	overall survival
NYR	not yet reached
PSA	Prostate specific antigen
QALY	Quality Adjusted Life Year
QoL	quality of life

rPFS	radiographic progression free survival
SAE	serious adverse event
SMC	Scottish Medicines Consortium
SRE	skeletal related event
TTD	time to treatment discontinuation
VAS	visual analogue scale

1 SUMMARY

This report provides a review of the evidence submitted by Astellas in support of enzalutamide (trade name Xtandi) for the treatment of adult men with asymptomatic or mildly symptomatic metastatic hormone relapsed prostate cancer (mHRPC) after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated. It considers the original company's submission (CS) received by the ERG on 9th February 2015 and the company's responses to clarification requests received on 13th March 2015.

1.1 Critique of the decision problem in the company's submission

The population, intervention, comparators and outcomes are in line with the final NICE scope. The population considered by the company is "adult men with mHRPC who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated." The intervention is enzalutamide and the comparators were best supportive care and abiraterone. In addition to the outcomes listed in the final scope, the CS presents data on time to treatment discontinuation (TTD) as the company claims that clinicians find TTD is a more accurate reflection of clinical practice than progression free survival. The company states that this end point has previously been accepted by NICE. The ERG agree with the company as ERG clinical advice states that it is standard UK practice to stop treatment once progression is diagnosed.

1.2 Summary of clinical effectiveness evidence submitted by the company

The company presented the results of a single trial (PREVAIL) for the comparison of enzalutamide (160mg once daily) versus placebo (once daily). The patient population was those with asymptomatic or mildly symptomatic mHRPC and in whom immediate chemotherapy was not yet clinically indicated, with ECOG status of zero or one. In total 1717 patients were randomised (ITT population), 872 to enzalutamide and 845 to placebo with 1715 receiving at least one dose of study drug (safety population, N = 871 enzalutamide, N = 844 placebo).

Following presentation of interim data on 16th September 2013, the data monitoring committee (DMC) halted the study allowing patients randomised to placebo to receive

enzalutamide. Therefore the interim analysis was considered the final analysis. For economic modelling purposes an additional data cut of 30 June 2014 was undertaken.

For the 16 September 2013 analysis, 241 (27.6%) deaths had occurred in the enzalutamide arm and 299 (35.4%) deaths in the placebo arm. Median overall survival was 32.4 months for enzalutamide and 30.2 for placebo. Enzalutamide was found to significantly reduce the risk of mortality by 29.4% compared to placebo (unstratified HR = 0.706 with 95% CI (0.596 to 0.837), log-rank test p < 0.001). In the 30 June 2014 cut-off, [redacted] and [redacted] deaths occurred in the enzalutamide and placebo arms respectively. Median OS was [redacted] months with enzalutamide and [redacted] months with placebo (unstratified HR: [redacted]; p<0.001). When adjusting for treatment switching using the inverse probability of censoring weight (IPCW) method, the hazard ratio was [redacted] with 95% CI [redacted].

Treatment with enzalutamide resulted in a statistically significant reduction in risk of radiographic progression (as determined by central review) or death compared with placebo (hazard ratio 0.186; 95% CI (0.149, 0.231); p < 0.0001). Treatment with enzalutamide was associated with a reduction in the risk of first skeletal related event (SRE) (HR = 0.718, 95% CI 0.610 to 0.844).

Patients receiving enzalutamide were at a reduced risk of initiation of cytotoxic therapy (HR = 0.349, 95% CI 0.303 to 0.403) with median time of 28 months for enzalutamide compared with median of 10.8 months for placebo. The most common cytotoxic therapy was docetaxel and this was received by 90.5% of patients who initiated cytotoxic chemotherapy.

Median time to PSA progression was longer for enzalutamide (median = 11.2 months) compared to placebo (median = 2.8 months) resulting in a reduced risk for PSA progression in the enzalutamide arm (HR = 0.169, 95% CI 0.147 to 0.195).

A much higher proportion of placebo patients (76.0%) received a post-baseline antineoplastic therapy compared to the enzalutamide group (43.8%) with HR = 0.273 (95% CI 0.240 to 0.311). The median time to receipt of this therapy was 22.8 months in the enzalutamide group compared to 7.4 months in the placebo group.

The BPI-SF was used to assess several pain-related outcomes. Results for the different definitions of pain progression all show a significant reduction in the risk for enzalutamide patients relative to placebo patients.

Time to first QoL deterioration (defined as a greater than 10 point decrease in FACT-P total score) was longer for enzalutamide (median = 11.3 months) compared to placebo (median = 5.6 months) and HR = 0.625 (95% CI 0.542, 0.720).

Median time to TTD at the 16 September 2013 cut off was 17.71 months for enzalutamide and 4.55 months for placebo.

The overall incidence of adverse events (AEs) with enzalutamide was similar to that of placebo within PREVAIL (96.9% in enzalutamide, 93.2% on placebo). Fatigue and nausea were the most commonly reported drug-related AEs in both arms. A similar proportion of patients in both treatment arms experienced an AE that led to a permanent treatment discontinuation (enzalutamide, n= 49 (5.6%); placebo N = 51 (6.0%).

Only two studies were deemed relevant for inclusion in an indirect comparison. The COU-AA-302 trial compared abiraterone plus prednisone versus prednisone plus placebo and PREVAIL for enzalutamide. The two trials were similar in terms of the patient population except all patients in COU-AA-302 were on a corticosteroid (100% in COU-AA-302; 30.2% in PREVAIL, but only 4% at baseline).

The OS in COU-AA-302 trial resulted in HR of 0.79 95% CI (0.66, 0.95) in favour of abiraterone compared to placebo; HR 0.52 95% CI (0.45, 0.61) for risk of radiographic progression and HR 0.62 95% CI (0.51, 0.72) for time to initiation of cytotoxic therapy. The resultant indirect treatment effects for enzalutamide versus abiraterone (where <1 favours enzalutamide) were [redacted] 95% CI ([redacted]) for OS, [redacted] 95% CI ([redacted]) for risk of radiographic progression and [redacted] 95% CI ([redacted]) for time to initiation of cytotoxic therapy.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The evidence provided by the company for the comparison of enzalutamide versus placebo (representing best supported care) comes from a single trial (PREVAIL). However, the trial was large (N = 1717) and multi-centre throughout the world. Around 10% of the patients were from the UK. There is good evidence of a benefit of enzalutamide with acceptable safety profile for the population of patients.

No head to head trial was found for enzalutamide to the comparator of abiraterone. One trial, COU-AA-302 was found to compare abiraterone (plus prednisone) versus prednisone alone. The differences in the control groups (different use of corticosteroids) of these trials meant that any indirect comparison should be treated with caution. The company undertook an indirect comparison and found for OS there was no significant difference between enzalutamide and abiraterone. For risk of radiographic progression, time to cytotoxic chemotherapy and time to PSA progression there was a significant advantage of enzalutamide over abiraterone.

The results of these indirect comparisons were not used in the economic modeling by the company because of the concerns over the comparability of the control groups in PREVAIL and COU-AA-302.

1.4 Summary of cost effectiveness submitted evidence by the company

A de novo Markov model with a weekly cycle length is developed by the company. All patients start on a 1st line treatment. A proportion of those modelled as ceasing the 1st line treatment receive 2nd line docetaxel, with the remainder proceeding straight to palliative care. The model has the facility for a proportion of those ceasing 2nd line docetaxel to receive a 3rd line treatment, with the remainder proceeding to palliative care. Those ceasing 3rd line treatment proceed to palliative care. An equal probability of death is applied to all health states.

The model compares three treatment sequences. For all the modelling presented within the company submission, the model compares:

1st enzalutamide	2nd docetaxel	3rd palliative,
1st abiraterone	2nd docetaxel	3rd palliative,
1st BSC	2nd docetaxel	3rd enzalutamide → 4th palliative

with transitions to palliative care being possible from 1st line enzalutamide and 2nd line docetaxel, and within the BSC arm from 3rd line enzalutamide as well.

The main model inputs are the overall survival (OS) curves and time to treatment discontinuation (TTD) curves for the 1st line treatments. These are derived for each of the 1st line treatments which are modelled:

- Enzalutamide
- Abiraterone
- BSC

The 1st line treatment's overall survival curve provides the probability of death in each cycle, this probability being applied equally to all the model health states. As a consequence, the modelling of treatments subsequent to the 1st line treatment has no impact upon the modelled overall survival. The modelling of treatments subsequent to the 1st line treatment only affects which health states patients pass through subsequent to 1st line treatment, with these health states being associated with their own costs and quality of life.

For a given 1st line treatment, its TTD curve determines the proportion of patients that continue to receive it and remain progression free through time.

The company extrapolation report rejected proportionate hazards and as a consequence individual parameterised curves were separately fitted to the arms of PREVAIL. Two data cuts were available: September 2013 and June 2014 with PREVAIL having been unblinded in December 2013 for ethical reasons. Due to cross-over and PREVAIL permitting a number of 2nd line treatments that would not be usual practice in the UK the company adjusted the overall survival data using the IPCW method, though an alternative two stage method was also explored.

The company preferred the June 2014 data cut due to the fuller data. Weibull parameterisations were used for overall survival mainly due to their face validity, while gamma parameterisations were used for the TTD curves.

For abiraterone a naïve indirect comparison was performed. The Kaplan Meier OS and PFS curves from the COU-AA-302 3rd interim analysis were digitized, the Guyot method employed and parametric models fitted.

2nd and 3rd line treatments had exponential TTD curves fitted to them, based upon the median treatment durations reported in the literature. The proportions of patients receiving 2nd and 3rd line treatments were derived from PREVAIL data.

Quality of life for those on 1st line treatments was drawn from a mixed model repeated measures analysis of the PREVAIL EQ-5D data of weeks 1 to 61. The BSC arm was assumed to have the PREVAIL baseline quality of life of 0.844, while the net treatment effect of 0.021 was added to this for enzalutamide. Abiraterone was assumed to have the same quality of life as enzalutamide.

Quality of life values for 2nd and 3rd line treatments of 0.658 and 0.612 were derived by averaging values within the literature. A quality of life value for palliative care of 0.500 was drawn from the Sandblom *et al* reference.[1]

Enzalutamide and abiraterone were not associated with any explicit administration costs but routine monitoring costs were included. Abiraterone was assumed to require twice the routine monitoring frequency of enzalutamide. BSC was assumed to require CT scans three times as frequently as abiraterone. This resulted in annualised routine monitoring costs of £1,087 for enzalutamide, £1,886 for abiraterone and £1,897 for BSC.

2nd line docetaxel was assumed to be administered every 3 weeks and was associated with an administration cost of £302. Routine monitoring costs for 2nd and 3rd line treatments were an annualised £3,841 for 2nd line docetaxel and £1,291 for 3rd line enzalutamide.

Treatments were also associated with SREs and with AEs, these having cost and quality of life impacts.

BSC was estimated to result in an undiscounted overall survival of 2.745 years, 1.657 QALYs and total costs of £36,296. Abiraterone was estimated to result in an undiscounted overall survival of 3.003 years, 2.120 QALYs and total costs of £80,672. Enzalutamide was estimated to result in an undiscounted overall survival of 3.238 years, 2.274 QALYs and total costs of £84,840.

The net gain of 0.618 QALYs at a net cost of £48,543 resulted in a cost effectiveness estimate for enzalutamide compared to BSC of £78,587 per QALY. The net gain of 0.154 QALYs at a net cost of £4,168 resulted in a cost effectiveness estimate for enzalutamide compared to abiraterone of £27,076 per QALY.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

ERG expert opinion suggests that those in the enzalutamide arm and the abiraterone arm would receive a 3rd line treatment after 2nd line docetaxel.

The ERG is also critical of the implied cost effectiveness of 3rd line enzalutamide compared to palliative care within the model. The company cost per QALY estimates for this are very large and well in excess of those it submitted for the evaluation of enzalutamide post-chemotherapy [TA316]. This tends to improve the cost effectiveness estimate for 1st line enzalutamide pre-chemotherapy compared to BSC. The effect of this is more marked in the company base case due to only the BSC arm incorporating a 3rd line of treatment.

Overall survival is extrapolated from Kaplan Meier curves which even for the June 2014 data cut have a considerable proportion of patients still alive. The degree of extrapolation required is therefore large which increases the uncertainty associated with the final estimates. Sensitivity analyses around the company base case curves as suggested by the NICE methods guide have not been presented.

There remain some concerns around the selection of the June 2014 data cut for the adjusted overall survival curves. The impact of applying the adjusted overall survival curves of the September 2013 data cut is large and detrimental to the cost effectiveness estimates.

It may be more reasonable to apply the pre-unblinding September 2013 data cut TTD curves, since unblinding may have a direct effect upon the probability of discontinuation.

It is not clear that the naïve indirect comparison with abiraterone would provide a sound base for the cost effectiveness estimates.

The PREVAIL EQ-5D quality of life values appear to have been inappropriately handled, with this improving the cost effectiveness estimates. The ERG is of the opinion that each arm's change from baseline should be applied to the baseline value.

The company summary of the quality of life literature is incomplete. It also does not consider the EQ-5D quality of life values that the company used for its submission for the STA of enzalutamide post-chemotherapy [TA316]. These values when applied within the modelling worsen the cost effectiveness estimates.

Since the company draws quality of life values for the health states of the model from a range of disparate sources, in the opinion of the ERG the references which could provide a single source of estimates for the different health states of the model should be given greater consideration. These could help identify whether the quality of life differences between the health states that are applied within the company modelling are reasonable. To the ERG, they seem to suggest that these differences may be exaggerated.

The rationale for the extent of the differences in routine monitoring resource use for the 1st line treatments does not appear to be presented. These differences are quite marked, with abiraterone being assumed to have twice the routine monitoring of enzalutamide.

If the modelled probability of dying exceeds that of discontinuing 1st line treatment, patients no longer progress through the model health states but are held on 1st line treatment for their remaining survival. This mainly applies to abiraterone and may mean that the model structure is biased against it.

The model structure assumes that at a given time point patients have the same life expectancy regardless of whether they are on 1st line treatment or are in palliative care. The ERG has some sympathy with the constraints of modelling. The impact of alternative assumptions would require a significant model revision and might lean slightly too far in the opposite direction. There is no obvious direction of bias that might arise from this consideration.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Strengths of the effectiveness data are:

- Robustly designed and analysed multinational RCT.
- Clearly summarised effectiveness data.

Strengths of the economics of the company submission are:

- A well written submission that outlines the broad model structure, provides the company rationale for most of the choices that are made and clearly identifies the parameter inputs values.
- A well-documented extrapolation report with adjustments to overall survival that are in line with the relevant DSU report.
- The availability of the PREVAIL EQ-5D data, and a pre-specified statistical analysis plan for its analysis.
- A reasonable model structure, with the possible exception of the handling of deaths.

1.6.2 Weaknesses and areas of uncertainty

Weaknesses of the company submission are:

- No exploration of the possibility of a post-chemotherapy 3rd line treatment within the enzalutamide and abiraterone arms.
- Questionable use of the PREVAIL EQ-5D data to exaggerate the gains from remaining on 1st line treatments, particularly 1st line enzalutamide treatment and 1st line abiraterone treatment.
- Only the values of the mixed model repeated measures EQ-5D analysis being presented with no consideration of the pattern mixed model EQ-5D analysis.

- An apparently much worse implied cost effectiveness estimate for 3rd line enzalutamide than the company submitted for the post-chemotherapy STA [TA316], with this tending to bias the company analysis against BSC.
- An incomplete summary of the quality of life values available in the literature, with this summary not presenting the EQ-5D values derived from the AFFIRM study that the company submitted for the post-chemotherapy STA [TA316].
- Questionable differentiation of the costs of routine monitoring for the 1st line treatments, this applying with particular force between 1st line enzalutamide and 1st line abiraterone.
- Patients within the model having the same life expectancy at a given time point regardless of whether they are receiving 1st line treatment or are in palliative care.

Areas of uncertainty within the company submission are:

- The estimated additional survival due to the incompleteness of the PREVAIL overall survival curves and the resulting degree of extrapolation that is required.
- No sensitivity analyses around the extrapolated overall survival for the curves of the base case despite this being suggested within the NICE methods guide.
- The estimated additional survival being sensitive both to the adjustment method employed for overall survival data to account for subsequent treatments and to whether the September 2013 data cut or the June 2014 data cut is used.
- The quality of life values for the different health states of the model being taken from disparate sources with no sensitivity analysis using values from a single source for the pre-chemotherapy, chemotherapy and post-chemotherapy health states.
- An apparently arbitrary curtailment of the EQ-5D data at week 61 despite the main purpose of this data being to model the mean change from baseline in quality of life by arm among those remaining on 1st line treatment.
- The estimated net costs and net QALYs for the comparison with abiraterone due to the naïve indirect comparison.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG made a number of revisions to the company model, the main ones being as follows:

- Assuming that after 1st line enzalutamide and 2nd line docetaxel patients could receive 3rd line abiraterone, while after 1st line abiraterone and 2nd line docetaxel patients could receive 3rd line enzalutamide.
- Applying the Sep 2013 data cut for the TTD curves.
- Applying the PREVAIL quality of life estimates for the changes from baseline to the PREVAIL baseline quality of life value to derive the quality of life values for 1st line treatments.
- Applying the AFFIRM baseline quality of life value for 3rd line treatments.
- Assuming that dosing for enzalutamide and abiraterone was from the start of cycle and four weekly.
- Assuming the same routine monitoring costs across the 1st line treatments.

These revisions worsen the cost effectiveness estimates. For the comparison of enzalutamide with BSC the cost effectiveness estimate worsens from £78,587 per QALY to £113k per QALY. For the comparison of enzalutamide with abiraterone the cost effectiveness estimate worsens from £27,076 per QALY to £40,776 per QALY.

A range of sensitivity analyses are also presented by the ERG.

Applying the September 2013 IPCW Weibull overall survival curve rather than the June 2014 IPCW Weibull overall survival curve reduces the net costs but reduces the net QALY gain more, so worsens the cost effectiveness estimate compared to BSC to £143k per QALY and compared to abiraterone to £92,092 per QALY. The 2 stage June 2014 Weibull shows a similar pattern, worsening the cost effectiveness estimate compared to BSC to £129k per QALY and compared to abiraterone to £67,238 per QALY.

Applying the PFS TTD Weibull and the COU-AA-302 PFS Weibull, given that the COU-AA-302 curves are based upon PFS, worsens the cost effectiveness estimate compared to abiraterone to £47,856 per QALY.

Assuming that those in the enzalutamide arm and the abiraterone arm cannot receive 3rd line treatment after 2nd line docetaxel improves the cost effectiveness estimate compared to BSC to £109k per QALY, but worsens it compared to abiraterone to £43,363 per QALY.

Applying the same quality of life for those remaining on 1st line treatment from week 62 has only a limited impact upon results. The cost effectiveness estimate compared to BSC worsens to £118k per QALY, while the cost effectiveness estimate compared to abiraterone only worsens to £41,292 per QALY. The impact of applying the company preferred quality of life estimate for those on 3rd line treatment is similarly muted, improving the cost effectiveness estimate compared to BSC to £110k per QALY and the cost effectiveness estimate compared to abiraterone to £40,299 per QALY.

The quality of life estimates of Diels et al[2] have a larger impact, worsening the cost effectiveness estimate compared to BSC to £134k per QALY and the cost effectiveness estimate compared to abiraterone to £43,896 per QALY.

Retaining the company 1st line resource use improves the cost effectiveness compared to BSC to £110k per QALY, and improves it compared to abiraterone quite dramatically to £26,135 per QALY. Applying the PPRS 2015 rebate also improves the cost effectiveness estimates, to [redacted] per QALY compared to BSC and to [redacted] per QALY compared to abiraterone.

2 BACKGROUND

2.1 Critique of company's description of underlying health problems

The company's description of prostate cancer in terms of prevalence, symptoms and complications is accurate and appropriate to the decision problem. The company describes hormone-relapsed prostate cancer (HRPC) as an advanced stage of prostate cancer, which shows signs of disease progression despite castrate levels of testosterone. Early stage prostate cancer is localised to the prostate and driven by androgens.[3] At this stage the disease may be treated with surgery, radiotherapy or conservative management (active surveillance) depending on the risks/benefits associated with treatment. Prostate cancer that is unsuitable for, or has failed, curative interventions is usually initially androgen sensitive and can respond beneficially to androgen deprivation therapy (ADT), thus, men diagnosed with inoperable locally advanced or metastatic disease, or who have inoperable recurrent disease, are initially treated with ADT. As the disease progresses, the tumour ceases to respond to ADT and becomes hormone-relapsed. Despite low/undetectable levels of androgen, androgen receptor (AR) signalling remains active and continues to drive the disease.[4] At the point of diagnosis, 84% of HRPC patients will have metastatic disease (mHRPC). Of those non-metastatic patients, 33% will develop metastases within two years.[5]

The company states that HRPC tumours may respond to anti-androgen therapy (or anti-androgen withdrawal), androgen inhibitors and estrogenic agents, although treatment response is limited and some therapies are associated with cardiotoxicity and related mortality. Most men receive two or more hormonal manipulations and are then offered chemotherapy (usually docetaxel).[6] Asymptomatic men receive best supportive care (BSC) or abiraterone, the latter currently only available via the cancer drug fund (CDF) in England for the pre-chemotherapy setting.[7] Chemotherapy is usually given to symptomatic men.

The company states that, because many hormone-relapsed tumours over-express ARs, second generation anti-androgen therapies, such as enzalutamide, have been found to be effective in treating patients who have failed ADT. Enzalutamide is indicated for the treatment of adult men with mHRPC whose disease has progressed on or after

docetaxel therapy (post-chemotherapy setting), and for the treatment of asymptomatic or mildly symptomatic adult men with mHRPC after ADT failure but in whom chemotherapy is not yet clinically indicated. It is the latter indication that is considered by the company submission (CS).

Data on the epidemiology of mHRPC are limited.[8] The company has assumed an annual prevalence of mHRPC in England[9] and Wales[10] of 12,172 in 2015, rising to 12,642 by 2020 (Table 1). Of these men, 60% are estimated to be chemotherapy-naïve.[11] Of these chemotherapy-naïve patients, 76% are estimated to be asymptomatic or mildly symptomatic with a Brief Pain Inventory-Short Form (BPI) score $\leq$3.[12] The company estimates that the number of chemotherapy-naïve men who would be eligible for enzalutamide in its indication as a first line therapy for mHRPC is approximately 3000 in 2014 and, in its indication extension, is considered to be approximately 1362 men in 2015 and 5616 men in 2019. The company based these estimates on annual prevalence and population projections for England and Wales.

The company suggests that, if enzalutamide were made available at the end of quarter 3 in 2015, 25% of new chemotherapy-naïve mHRPC cases in that year would be eligible for treatment (* in Table 1). As all these figures are based on estimates, it is uncertain how accurate this data are.

Table 1 Eligible patient population for treatment of adult men with asymptomatic or mildly symptomatic mHRPC in whom chemotherapy is not yet indicated

	2015	2016	2017	2018	2019	2020
Male population in England and Wales	28,480,411	28,709,686	28,931,107	29,153,465	29,368,865	29,582,107
Estimated number of new mHRPC patients	12,172	12,270	12,364	12,459	12,551	12,642
Chemo-naïve	7,303	7,362	7,419	7,476	7,531	7,585
Asymptomatic or mildly symptomatic patients	5,446	5,585	5,628	5,671	5,713	5,755
Eligible patient population	**1,385***	**5,585**	**5,628**	**5,671**	**5,713**	**5,755**

The company states that no life-expectancy data are available for chemotherapy-naïve patients in England and Wales. The company, therefore, presents median overall survival (OS) data from the most mature cut-off analysis (775 events) from the PREVAIL trial, a randomised controlled trial comparing enzalutamide and placebo in men with asymptomatic or mildly symptomatic metastatic HRPC, in whom chemotherapy is not yet clinically indicated. The company reports median OS for enzalutamide and placebo as 32.4 and 30.2 months respectively for the September 2013 data cut-off and [redacted] and [redacted] months respectively for the June 2014 data cut-off. (Astellas Pharma, 2015)

2.2 Critique of company's overview of current service provision

Sections 2.4 to 2.6 of the CS present an overview of current treatment options within the NHS. It is the opinion of the Evidence Review Group (ERG) that this description is accurate at the time of submission.

The company cites NICE guidance CG 175 for prostate cancer diagnosis and treatment, noting that, while chemotherapy (docetaxel) is recommended for men with

mHRPC and a Karnofsky performance status ≥60%, the guidance does not provide specific recommendations for asymptomatic or mildly symptomatic mHRPC patients for whom chemotherapy is not yet clinically indicated. The guideline recommends dexamethasone (0.5mg daily) following ADT and anti-androgen therapy but does not incorporate any statements regarding the use of abiraterone, enzalutamide or sipuleucel-T in patients who have failed to respond to ADT and for whom chemotherapy is not yet indicated.[13] Similarly, European Association of Urology (EAU) guidelines[14] do not provide clear guidance for asymptomatic HRPC patients. Symptomatic mHRPC patients who have failed ADT are recommended chemotherapy with docetaxel every three weeks.[14]

The company states that 40% of men with mHRPC will progress to docetaxel chemotherapy and it is estimated that 70-75% of these patients may be candidates for further post-chemotherapy treatment.[11] The CS queries whether exposure to enzalutamide or abiraterone in the chemotherapy-naïve setting may alter the post-chemotherapy care pathway in the UK. Under current practice, patients receive docetaxel therapy when they become symptomatic and, if it can be tolerated, remain on this treatment until their disease progresses, whereupon they move to the post-chemotherapy setting and are treated with enzalutamide or abiraterone.[13] It is uncertain whether administering enzalutamide and abiraterone in the chemotherapy-naïve setting will replace their use in the post-chemotherapy setting.

The CS states that Abiraterone and sipuleucel-T are European approved therapies for asymptomatic or mildly symptomatic chemotherapy-naïve mHRPC patients. Both are currently under review by NICE,[15] (and hence unavailable, although abiraterone is available in England through the CDF. NICE is currently assessing radium-223 dichloride as a second line therapy for mHRPC following docetaxel therapy. At the time of writing the CS, cabazitaxel was available to post-chemotherapy patients via the CDF, although the company notes that it is expected to be de-listed from the fund in March 2015.[7] The current treatment pathway was summarised diagrammatically by the CS and is reproduced below in Figure 1.

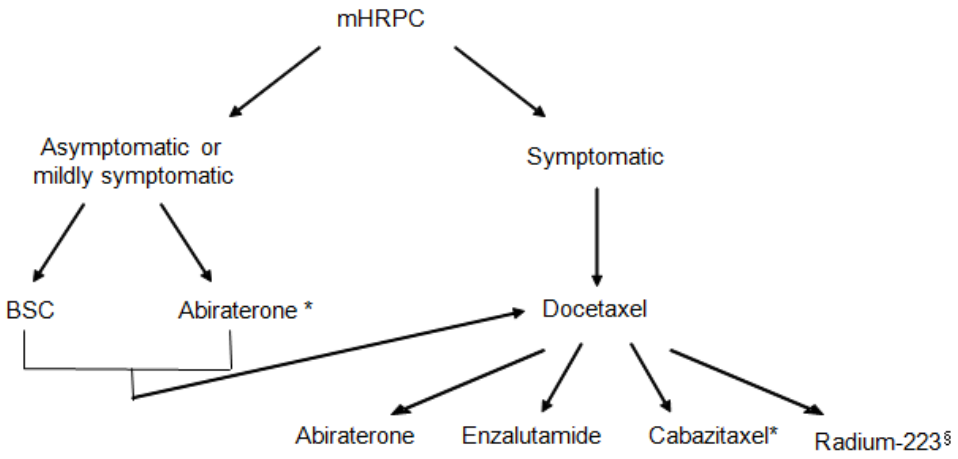


Figure 1 Current treatment algorithm of mHRPC in England clinical practice

Source: CS

*Following a negative NICE recommendation, cabazitaxel in the post-chemotherapy setting are available through the CDF on a case by case basis, in England, although this is due to change from March 2015. Abiraterone is widely used in England via the CDF; the NICE appraisal is ongoing §NICE has given preliminary recommendations for radium 223 to be given to symptomatic patients in the post-chemotherapy setting.[16]

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

3.1 Population

The population considered by the company is "adult men with mHRPC who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated." This is in keeping with the population addressed by the final NICE scope.

3.2 Intervention

The submitted technology is enzalutamide which is in line with the final NICE scope. Brief summary details of mechanism of action, dosage, drug interactions and approval status is given below.

3.2.1 Mechanism of action

The submitted technology is enzalutamide. Enzalutamide is a novel oral AR signalling inhibitor specifically selected for activity in models of mHRPC. The company states that enzalutamide blocks the AR signalling pathway at three different levels, thus acting as a pure AR antagonist, unlike other AR inhibitors which can act as partial agonists: (see Figure 2)[11,15,17]

1. Competitively inhibits binding of androgens to ARs in the interior of prostate cells (cytosol)
2. Inhibits the nuclear translocation of activated receptors
3. Inhibits the association of the activated AR with DNA even when AR is over-expressed and in prostate cells resistant to anti-androgens

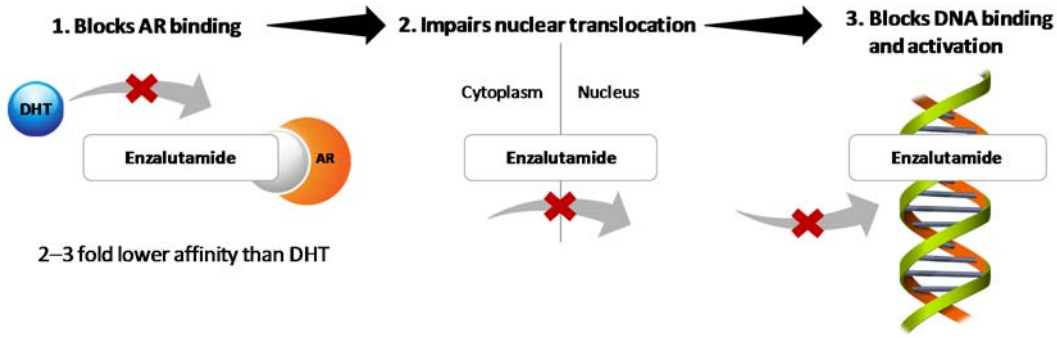


Figure 2 Signalling steps inhibited by enzalutamide[18,19]

The action of enzalutamide on AR signalling reduces expression of AR-dependent genes, decreases growth of prostate cancer cells, induction of cancer cell death and tumour regression.

Enzalutamide can be administered with or without steroids, thus allowing the option of avoiding steroid-related side-effects. (Astellas Pharma, 2015)

3.2.2 Dosage

The recommended dose of enzalutamide is 160 mg (four 40 mg capsules) administered orally by the patient once daily. Capsules are white to off-white oblong soft gelatine capsules imprinted in black ink with ENZ. No special facilities are required for drug administration and product-specific monitoring (e.g. liver function tests or cardiovascular monitoring) is also not required. (Astellas Pharma, 2015)
Enzalutamide can be taken with or without food. If a patient experiences a ≥ Grade 3 toxicity or an intolerable side effect, dosing should be withheld for one week or until symptoms improve to ≤ Grade 2, then resume at the same or a reduced dose (120 mg or 80 mg), if warranted.[20] Enzalutamide is administered until disease progression. (Astellas Pharma, 2015)

Elderly patients

There are no dose adjustments necessary for elderly patients.[20]

Patients with renal impairment

No initial dosage adjustment is necessary for patients with mild to moderate renal impairment. Caution is advised in the use of enzalutamide in patients with severe renal impairment and end-stage renal disease.[20]

Patients with hepatic impairment

No initial dosage adjustment is necessary for patients with baseline mild or moderate hepatic impairment. Use of enzalutamide in patients with severe hepatic impairment is not recommended.[20]

3.2.3 Drug interactions

Co-administration of enzalutamide may alter the pharmacological effects of some drugs during the first month of treatment. The use of strong CYP2C8 inhibitors should be avoided. Enzalutamide dosage should be reduced to 80mg if strong CYP2C8 are administered, and should be returned to the prior dose upon inhibitor discontinuation.

3.2.4 Regulatory approval

Enzalutamide has regulatory approval in Europe, USA, Canada and Australia for use in the treatment of mHRPC in the post-chemotherapy setting. The Food and Drug Administration (FDA) approved its use in the chemotherapy-naïve setting in the USA in September 2014. UK marketing authorisation was granted on 28th November 2014. At the time of writing this report, enzalutamide was under assessment by the All Wales Medicines Strategy Group (AWSUBMISSIONG) and the Scottish Medicines Consortium (SMC) (submission dates were 14th January 2015 and 2nd February 2015 respectively). (Astellas Pharma, 2015) Enzalutamide in the chemotherapy-naïve setting has been available in England via the CDF since October 2014.

3.3 Comparators

The comparators considered by the CS are best supportive care (BSC) and abiraterone. These comparators are in line with the NICE final scope. The manufacture's definition of BSC includes: luteinising hormone-releasing hormone (LHRH) analogues in men who have not been surgically castrated, corticosteroids, blood transfusion, bisphosphonates, radiotherapy, analgesics and palliative surgery to treat skeletal-related events (SREs). Abiraterone inhibits synthesis of androgens but does not have any subsequent effect on the AR signalling pathway. At the time of the submission, abiraterone is currently available in the chemotherapy-naïve setting via the CDF in England only. The company estimates that 53% of eligible patients in England are receiving abiraterone via the CDF. Abiraterone must be taken with food to avoid increasing systemic exposure and must be administered with steroids to reduce the effects of mineralocorticoid excess. Regular monitoring for liver toxicity, hypokalaemia and fluid retention is required.

3.4 Outcomes

The ERG is of the opinion that the outcomes considered in the CS are in line with those detailed in the NICE final scope. The considered outcomes are: Overall survival; radiographic progression-free survival (rPFS); time to initiation of cytotoxic chemotherapy; time to PSA progression; PSA response (decrease in ≥50% and ≥90%); best overall soft tissue response; adverse events; health-related quality of life (HRQOL), measured by FACT-P, EQ-5D and BPI. In addition to the outcomes listed in the final scope, the CS presents data on time to treatment discontinuation (TTD) as the company claims that clinicians find TTD is a more accurate reflection of clinical practice than rPFS. The company states that this end point has previously been accepted by NICE. The ERG agree with the company as ERG clinical advice states that it is standard practice to stop treatment once progression is diagnosed. The company also presents data for time to first skeletal-related event (SRE); time to first post-baseline antineoplastic therapy.

3.5 Other relevant factors

The company states that they are unaware of any equality issues and, therefore, have not considered equality in their submission.

Table 2 Differences between the final scope issued by NICE and the decision problem addressed in the company submission

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Adult men with mHRPC who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated	As per the final scope	Not applicable
Intervention	Enzalutamide	Enzalutamide once daily 160 mg (four x 40 mg) capsules	Not applicable
Comparator(s)	• Abiraterone in combination with prednisone or prednisolone • BSC (this may include radiotherapy, radiopharmaceuticals, analgesics, bisphosphonates, further hormonal therapies, and corticosteroids).	As per the final scope	Not applicable
Outcomes	The outcome measures to be considered include: • Overall survival (OS) • Progression-free survival (radiographic and prostate specific antigen response) • Time to initiation of chemotherapy • Response rate • Adverse effects of treatment • Health-related quality of life (HRQL).	In addition to the outcomes listed in the final scope, the company wish to present data on time to treatment discontinuation (TTD)	TTD is considered a more accurate reflection of what happens to mHRPC patients in clinical practice than rPFS. This end point has previously been accepted by NICE.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access scheme for the intervention or comparator technologies should be taken into account.	As per the final scope	
Subgroups to be considered	None	None	
Special considerations, including issues related to equity or equality	None	None	

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

The company undertook comprehensive searches to identify relevant clinical effectiveness data and the strategies are reproduced in full in Appendix 10.2.4 of the submission. Sources searched were extensive and included relevant conference proceedings and trials registers. The search strategies used were designed to include information for the EMA submission and were therefore broader than the scope of this submission, including additional interventions and not restricting by study design (apart from the Embase search) or outcomes. A comprehensive range of controlled vocabulary and free text terms were used and combined appropriately using Boolean logic. The ERG believes that all relevant data were retrieved by these searches.

4.1.2 Inclusion criteria

The inclusion and exclusion criteria applied by the company for the systematic review of clinical effectiveness are detailed in Table 3. The ERG believes the criteria are comprehensive and in keeping with the NICE final scope.

Table 3 Eligibility criteria for inclusion in the clinical effectiveness systematic review

	Clinical effectiveness
Inclusion criteria	Population: • Studies in adults (over the age of 18) with asymptomatic, or mildly symptomatic, mHRPC AND who have not received prior chemotherapy, were eligible for inclusion in the review[a] Interventions: • The interventions were enzalutamide, abiraterone, docetaxel, radium-223 dichloride and sipuleucel-T. However, only studies including enzalutamide or abiraterone as an intervention or comparator are described here Outcomes: • The outcomes included in the systematic literature review included OS, PFS, rPFS, response rate, PSA response, time to chemotherapy initiation, time to antineoplastic therapy (cytotoxic or hormonal), time to SRE, time to PSA progression, best overall response, adverse effects of treatment, HRQL including time to pain progression, time to increase in analgesia and time to decline in performance status. • Of the outcomes listed above, only OS, rPFS, time to chemotherapy initiation, time to SRE, time to PSA progression and overall best response were to be included in the ITC. Study design: • Phase II and III, RCTs of any size and duration were eligible for inclusion in the clinical effects and safety review • Crossover RCTs were eligible if data were presented at crossover • Non-randomised comparative and uncontrolled studies were

[a] Studies assessing mixed populations (i.e. where some patients had received chemotherapy and some had not) were included in the indirect treatment comparison for comparators where studies of chemotherapy naïve populations did not exist. However, the only study included for the indirect comparison vs abiraterone had enrolled chemo-naïve patients only.

	eligible for inclusion if they reported relevant clinical effectiveness or safety data for enzalutamide • Studies published as abstracts or conference presentations, as well as data from unpublished RCTs, were eligible for inclusion in the review if adequate data were provided. Systematic reviews were eligible for inclusion as a source of references to primary studies Language restrictions • Studies reported in languages other than English were identified and listed for information only
Exclusion criteria	Population: • Studies reporting on patients described as 'hormone sensitive' or 'castration sensitive' were not eligible for inclusion. Similarly, studies reporting on patients who had received prior chemotherapy were excluded Interventions • Studies that did not include any of the interventions listed in the inclusion criteria Outcomes • Studies that did not include any of the outcomes listed in the inclusion criteria Study design • Single arm studies except if they provided relevant clinical effectiveness or safety data for enzalutamide Language restrictions • No study reported in any language other than English was reviewed or included in the indirect treatment comparison

The PRISMA flow chart detailing the number of studies included and excluded by the company is presented as Figure 3. After reasonable exclusions, the company identified one, triple-blind phase III randomised controlled trial (RCT) of enzalutamide compared with placebo, the PREVAIL trial.[21] The PREVAIL trial was sponsored by the company and conducted at 207 sites in 22 countries from North America, Europe, Australia and Asia, with 153 patients recruited from the UK.

The company did not identify any head-to-head RCTs of enzalutamide and an eligible comparator, although the company states that, for the purposes of the CS, the placebo arm in the PREVAIL trial could be considered equivalent to BSC.

One relevant non-RCT was identified. [20,22] This is a dose escalation study of enzalutamide, which includes a mixed population of chemotherapy-naïve (n=12) and post-chemotherapy (n=12) patients. The study does not report data separately for the two different patient groups. The study was excluded from the indirect treatment comparison.

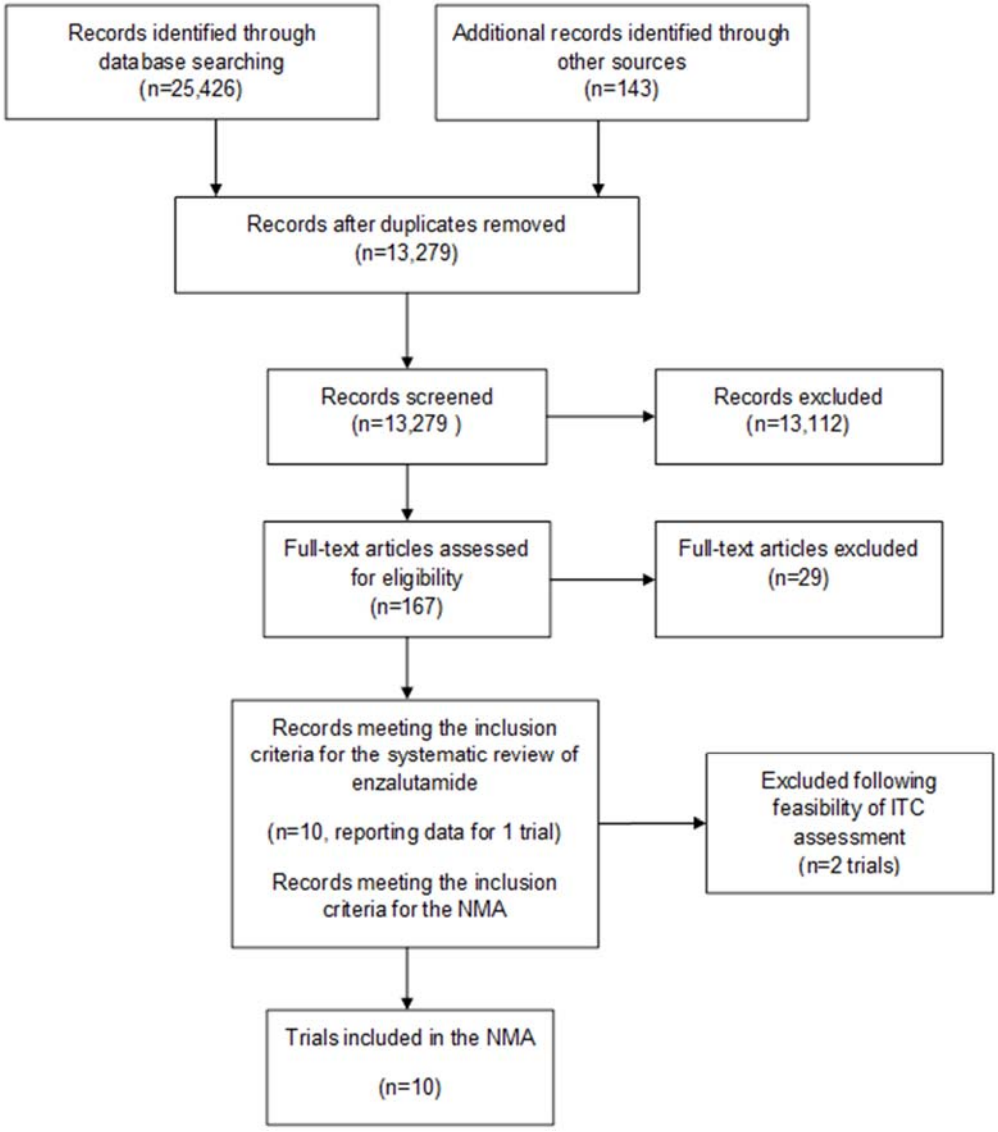


Figure 3 PRISMA flow diagram with the efficacy and safety studies of enzalutamide identified through the systematic literature review

ERG notes that although Figure 3 states 10 trials included in NMA, the submission actually only reports two studies and the others were excluded because they were not relevant comparators for this submission.

4.1.3 Critique of data extraction

The methods used to identify and data extract current evidence are considered appropriate. Two independent reviewers screened the abstracts and full text articles identified by the literature searches. One reviewer conducted data extraction using a data extraction form designed for the review, while a second reviewer checked a sample of the data extraction. Any disagreements were resolved by a third reviewer. The company followed NICE STA guidance to conduct the risk of bias assessment. The CS details the information and data extracted from the included study and are considered to be generally accurate by the ERG.

4.1.4 Quality assessment

The ERG performed a quality assessment of the company's systematic review using the York Centre for Reviews and Dissemination (CRD) criteria (Table 4). The quality of the systematic review was generally good.

Table 4 Quality assessment of the company's review

CRD quality item	Score
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

As only one RCT was identified by the systematic review, the company could not undertake any meta-analyses.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The company presented the results of a single trial (PREVAIL) for the comparison of enzalutamide (160mg once daily) versus placebo (once daily). Use of glucocorticoids was allowed but not required. The patient population was those with asymptomatic or mildly symptomatic mHRPC and in whom immediate chemotherapy was not yet clinically indicated, with ECOG status of zero or one. In total 1717 patients were randomised (ITT population), 872 to enzalutamide and 845 to placebo with 1715 receiving at least one dose of study drug (safety population, N = 871 enzalutamide, N = 844 placebo).

The co-primary end points were overall survival (OS) and radiographic progression free survival (rPFS). OS was defined as time from randomisation to death from any cause in the ITT population (all randomised patients). Survival time of living patients was censored at the last date a patient was known to be alive or lost to follow-up. rPFS was defined as time from randomisation date to the first objective evidence of radiographic disease progression assessed by centre radiology review or death due to any cause within 168 days after treatment discontinuation, whichever was first.

The secondary outcomes included in PREVAIL consisted of the following:

- Time to first documented skeletal related event (SRE) defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain
- Time to initiation of cytotoxic chemotherapy defined as the time from randomisation to the date of initiation of cytoxic chemotherapy
- Time to prostate specific antigen (PSA) progression where PSA progression was defined according to consensus guidelines of the PCWG2.
- PSA response defined as >= 50% reduction in PSA from baseline to lowest post-baseline PSA value which required confirmation by a consecutive assessment at least 3 weeks later
- Best overall soft tissue response on the basis of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

PREVAIL also included a number of exploratory outcomes which were pre-specified in the study protocol:

- Quality of life maintenance as assessed by functional assessment of cancer therapy – prostate (FACT-P) and EQ5D
- Brief pain inventory short form (BPI-SF) questionnaire
- Time to first post-baseline antineoplastic therapy (cytotoxic, hormonal or investigational)
- PSA response, defined as a 90% or more decrease from baseline

Patients in PREVAIL remained on their allocated study drug until confirmed radiographic disease progression or a SRE and either the initiation of cytotoxic chemotherapy or an investigational agent for the treatment of prostate cancer. After permanent discontinuation of study drug, patients continued to be monitored in long-term follow-up for radiographic disease progression (unless disease progression already confirmed), SREs (unless SRE already documented), additional antineoplastic treatments for prostate cancer, and survival.

During the treatment phase, subjects had a safety assessment at Day1/Week1 visit, the week 2 visit, every 4 weeks starting from week 5 through to week 25 and then every 12 weeks thereafter. Efficacy assessments were performed at weeks 13 and 25 and then every 12 weeks thereafter. The visit schedule for those patients in long-term follow-up was the same as on treatment patients (every 4 weeks to week 49 and every 12 weeks thereafter. Inclusion and exclusion criteria for the trial along with patient characteristics are shown in Table 5 and 6 respectively.

The ERG is of the opinion that the population inclusion and exclusion criteria does represent a UK pre-chemotherapy population. The ERG clinical expert opinion was that there were no obvious subgroups of patients that would have been eligible for docetaxel in the UK at the start of the trial.

Table 5 Eligibility criteria in the PREVAIL trial

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
PREVAIL	• Age 18 or older and willing and able to provide informed consent • Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features • Ongoing ADT defined as a GnRH analogue or bilateral orchiectomy • Patients who had not had a bilateral orchiectomy, had to have a plan to maintain effective GnRH analogue therapy for the duration of the trial • Serum testosterone level ≤ 1.73 nmol/L (50 ng/dL) at the screening visit • Patients on bisphosphonate therapy had to have been on stable doses for ≥4 weeks • Progressive disease at study entry defined as ≥1 of the following criteria while being on ADT: - PSA progression defined by a minimum of 2 rising PSA levels with an interval of ≥1 week between each determination. Patients who received an antiandrogen had to have had progression after withdrawal. The PSA value at the screening visit had to be ≥2 µg/L (2 ng/mL)	• Severe, concurrent disease, infection, or comorbidity that, in the judgement of the investigator, would make the patient inappropriate for enrolment • Known or suspected brain metastasis or active leptomeningeal disease • History of another malignancy within the previous 5 years other than curatively treated nonmelanoma skin cancer • Absolute neutrophil count < 1500/µL, or platelet count < 100,000/µL, or haemoglobin < 5.6 mmol/L (9 g/dL) at the screening visit • Total bilirubin, ALT or AST > 2.5-times the upper limit of normal at the screening visit • Creatinine > 177 µmol/L (2 mg/dL) at the screening visit • Albumin < 30 g/L (3.0 g/dL) at the screening visit • History of seizure or any condition that may predispose to seizure. Also, history of loss of consciousness or transient ischemic attack within 12 months of enrolment (day 1 visit) • Clinically significant cardiovascular disease including myocardial infarction within 6 months; uncontrolled angina within 3 months; congestive heart failure New York Heart

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
	- Soft tissue disease progression defined by RECIST 1.1 - Bone disease progression defined by PCWG2 with 2 or more new lesions on bone scan • Metastatic disease documented by bone lesions on bone scan or by measurable soft tissue disease by CT/MRI. Patients whose disease spread was limited to regional pelvic lymph nodes were not eligible • No prior cytotoxic chemotherapy for prostate cancer • Asymptomatic or mildly symptomatic from prostate cancer (i.e., < 4 on BPI question 3) • ECOG performance status 0–1 • Estimated life expectancy ≥6 months • Able to swallow the study drug and comply with study requirements	Association class III or IV, or patients with history of congestive heart failure New York Heart Association class III or IV in the past, unless a screening echocardiogram or multi-gated acquisition scan performed within 3 months results in a left ventricular ejection fraction that is ≥ 45%; history of clinically significant ventricular arrhythmias; history of Mobitz II second degree or third degree heart block without a permanent pacemaker in place; hypotension as indicated by systolic blood pressure < 86 mm Hg at the screening visit; bradycardia as indicated by a heart rate of < 50 beats per minute on the screening ECG; uncontrolled hypertension as indicated by systolic blood pressure > 170 mm Hg or diastolic blood pressure > 105 mm Hg at the screening visit • Gastrointestinal disorder affecting absorption (e.g., gastrectomy, active peptic ulcer disease within last 3 months) • Major surgery within 4 weeks of enrolment (day 1 visit) • Use of opiate analgesics for pain from prostate cancer within 4 weeks of enrolment (day 1 visit) • Radiation therapy for treatment of the primary tumour within 3 weeks of enrolment (day 1 visit) • Radiation or radionuclide therapy for treatment of metastasis • Treatment with flutamide, 5-α reductase inhibitors, estrogens, cyproterone, systemic biologic therapy for prostate cancer (other than approved bone targeted agents and GnRH analogue therapy) or other agents with antitumor activity within 4 weeks

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
		of enrolment (day 1 visit) or with bicalutamide or nilutamide within 6 weeks of enrolment (day 1 visit) • History of prostate cancer progression on ketoconazole • Prior use, or participation in a clinical trial, of an investigational agent that blocks androgen synthesis or blocks the androgen receptor • Participation in a previous clinical trial of enzalutamide • Use of an investigational agent within 4 weeks of enrolment (day 1 visit) • Use of herbal products that may have hormonal antiprostate cancer activity and/or are known to decrease PSA levels or systemic corticosteroids greater than the equivalent of 10 mg of prednisone per day within 4 weeks of enrolment (day 1 visit) • Any condition or reason that, in the opinion of the investigator, interfered with the ability of the patient to participate in the trial, which placed the patient at undue risk, or complicates the interpretation of safety data

The majority of men recruited to the PREVAIL trial were white (76.7% of enzalutamide participants and 77.5% of placebo patients) with mean ages of 71.3 years (range 43.0 to 93.0) and 71.2 years (range 42.0 to 93.0) for the enzalutamide and placebo arms respectively. Both arms were balanced in terms of demographics, baseline disease characteristics and medical history. The majority of men in both arms had an ECOG status of 0 (enzalutamide 67.0%; placebo 69.2%). The baseline characteristics of the PREVAIL trial participants are detailed in Table 6.

Table 6 Baseline characteristics of participants in the PREVAIL trial

PREVAIL	ENZA (N=872)	PLA (N=845)
Age (years)		
Mean	71.3 (8.51)	71.2 (8.42)
Median	72.0	71.0
Range	43.0, 93.0	42.0, 93.0
Race		
White	669 (76.7%)	655 (77.5%)
Black or African American	21 (2.4%)	13 (1.5%)
Asian	85 (9.7%)	82 (9.7%)
American Indian/Alaskan	1 (0.1%)	0 (0.0%)
Native Hawaiian or other Pacific Islander	1 (0.1%)	1 (0.1%)
Other	95 (10.9%)	94 (11.1)
Baseline ECOG performance		
0	584 (67.0%)	585 (69.2%)
1	288 (33.0%)	260 (30.8%)
2	0 (0.0%)	0 (0.0%)
PSA (ng/ml)		
Median	54.1	44.2
Range	0.1, 3182.0	0.3, 3637.0
Time (months) from Initial Diagnosis of Prostate Cancer to Randomisation		
Mean (SD)	78.6 (59.12)	76.2 (55.73)
Median	62.7	64.6
Gleason Score at Diagnosis		
2–4	7 (0.8%)	7 (0.9%)
5–7	407 (48.6%)	378 (46.8%)

PREVAIL	ENZA (N=872)	PLA (N=845)
8–10	424 (50.6%)	423 (52.4%)
Missing	34	37
Baseline use of corticosteroids > 7 days[a]	35 (4.0%)	36 (4.3%)
Disease Localisation at Screening		
Bone only	348 (39.9%)	335 (39.6%)
Soft tissue only	124 (14.2%)	149 (17.6%)
Both bone and soft tissue	393 (45.1%)	355 (42.0%)
None	7 (0.8%)	6 (0.7%)
Type of Disease Progression at Study Entry		
PSA progression only	375 (43.0%)	369 (43.7%)
Radiographic progression with PSA progression	349 (40.0%)	344 (40.7%)
Radiographic progression with no PSA progression	126 (14.4%)	107 (12.7%)
No disease progression per protocol	22 (2.5%)	25 (3.0%)
Measurable Soft Tissue Disease at Screening	396 (45.4%)	381 (45.1%)
Distribution of Disease at Screening		
Bone	741 (85.0%)	690 (81.7%)
Lymph node	437 (50.1%)	434 (51.4%)
Visceral disease (lung or liver)	98 (11.2%)	106 (12.5%)
Visceral liver	40 (4.6%)	34 (4.0%)
Visceral lung	64 (7.3%)	75 (8.9%)
Visceral lung and liver	6 (0.7%)	3 (0.4%)
Other soft tissue	113 (13.0%)	105 (12.4%)
Number of Bone Metastases at Screening		
0	131 (15.0%)	155 (18.3%)
1	97 (11.1%)	85 (10.1%)
2–4	213 (24.4%)	186 (22.0%)
5–9	146 (16.7%)	147 (17.4%)
10–20	140 (16.1%)	122 (14.4%)
> 20	145 (16.6%)	150 (17.8%)

Abbreviations: ECOG: Eastern Cooperative Oncology Group; ENZA: enzalutamide; PLA: placebo; PSA: prostate specific antigen; SD: Standard Deviation.

[a] Includes all steroid use for prostate cancer on the date of first dose of study drug and with continuous exposure for at least 7 days.

The company submission utilises data from a number of data cuts (pre-planned interim and final analyses) for OS and rPFS. The pre-planned analysis for OS was to be after around 516 events and was undertaken on 16 September 2013 (with 540 events). For OS, subsequent data cut offs were obtained on 15 January 2014 (656 events) and 30 June 2014 (775 events). Data for January 2014 were not presented in the current company submission. For rPFS, the pre-planned interim analysis was to be after around 410 centrally confirmed events and the data cut occurred on 6 May 2012 (with 439 events). A later data cut off was undertaken on 16 September 2013 with 889 investigator assessed events.

The co-primary endpoints were analysed for a number of pre-defined subgroups as follows:

- ECOG performance status at study entry (0 or 1)
- Age (< 75 versus ≥75 years)
- Geographic regions (North America versus Europe versus rest of world)
- Gleason scores at diagnosis (≤ 7 versus ≥ 8)
- Type of progression at study entry (PSA progression only versus radiographic progression with or without PSA progression)
- Visceral disease at study entry (yes versus no)
- Baseline PSA value (≤ median versus > median)
- Baseline lactate dehydrogenase (LDH) value (≤ median versus > median)
- Baseline haemoglobin value (≤ median versus > median)

In addition, a post-hoc analysis on time to treatment discontinuation (TTD) was undertaken as TTD was deemed relevant for the health economic model. Also, a post-hoc adjustment of OS data was conducted to take into account of treatments received second line by patients that differed from the treatments these patients would have received in clinical practice.

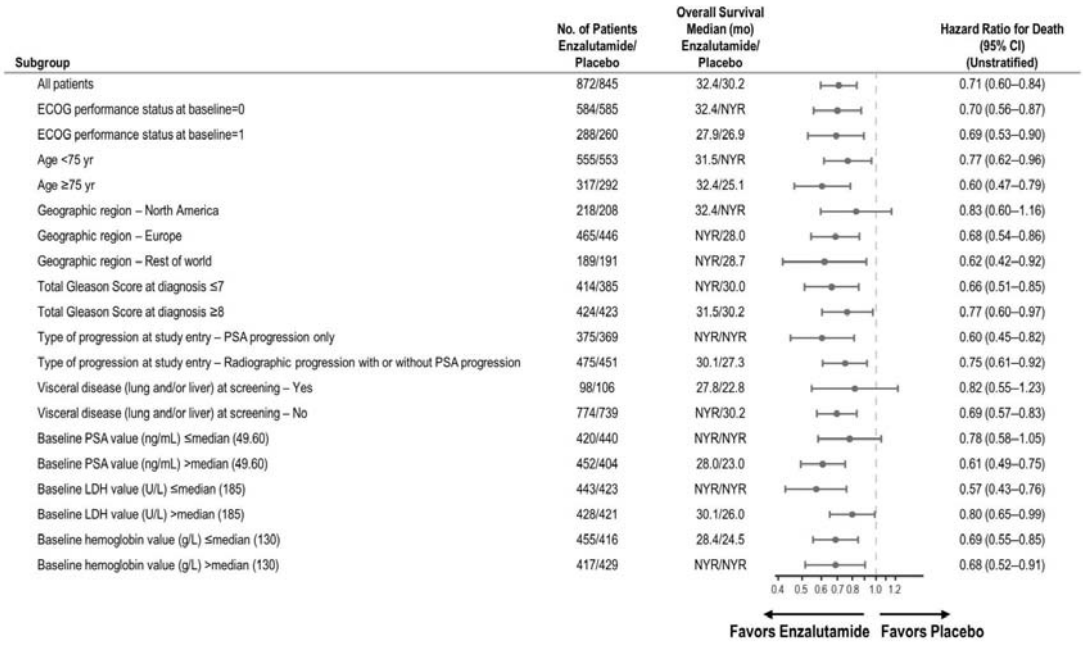
The following subsections now describe the results of the PREVAIL trial for relevant outcomes for the comparison of enzalutamide with placebo.

4.2.1 Overall survival

An interim analysis was planned after approximately 516 deaths and the data cut was taken on 16 September 2013 with 540 deaths. Following presentation of this data to the data monitoring committee (DMC) the blinded portion of the study was halted allowing patients randomised to placebo to receive enzalutamide. Therefore the interim analysis was considered the final analysis. For economic modelling purposes an additional data cut of 30 June 2014 was undertaken.

For the 16 September 2013 analysis, 241 (27.6%) deaths had occurred in the enzalutamide arm and 299 (35.4%) deaths in the placebo arm. Median (95% confidence interval) overall survival was 32.4 (30.1 to not yet reached) for enzalutamide and 30.2 (28.0 to not yet reached) for placebo. Enzalutamide was found to significantly reduce the risk of mortality by 29.4% compared to placebo (unstratified HR = 0.706 with 95% CI (0.596 to 0.837), log-rank test $p < 0.001$).

Using the most recent data-cut (30 June 2014), [redacted] deaths had occurred in the enzalutamide arm and [redacted] deaths in the placebo arm. Median (95% confidence interval) overall survival was [redacted] for enzalutamide and [redacted] for placebo. Enzalutamide was found to significantly reduce the risk of mortality by [redacted] compared to placebo ([redacted]). Therefore, enzalutamide significantly prolongs overall survival compared to placebo.



Source: Figure B4, CS and Beer at al

Figure 4 Subgroup analyses of overall survival

Analysis of OS in the pre-specified sub groups showed a sustained benefit of enzalutamide over placebo (Figure 4). However, the benefit did not quite reach statistical significance for the North America geographic region, visceral disease at screening and baseline PSA value ≤ median.

4.2.2 Overall survival (adjusted)

The standard ITT analysis is likely to underestimate the true survival benefit because of treatment switching. Methods to discuss treatment switching are discussed in the NICE Decision Support Unit (DSU) technical support document 16.[20] In the submission, the company provided some background on the different methods and selected to undertake the inverse probability of censoring weight (IPCW) and two-stage method with the former considered the primary analysis for the economic model and the latter used a scenario analysis.

For information, in brief the IPCW method involves censoring patients at the point of treatment switch and then controlling for this potentially informative censoring by weighting the follow-up information for patients who remain at risk of the event such that they not only account for themselves but also for patients with similar characteristics whose follow-up was censored by informative censoring. The method

relies on the 'no unmeasured confounders' assumption, that is data are available on all baseline and time dependent prognostic factors for mortality that independently predict informative censoring (switching).

The two-stage method involves estimating a treatment effect specific to switching patients and then uses this to derive a counterfactual dataset unaffected by switching. This method also has the 'no unmeasured confounders' assumption but can only be applied if a secondary baseline exists and unless all switching occurs soon after the secondary baseline, it will be prone to time-dependent confounding. Full details of how these methods were applied in PREVAIL are presented in section 6.3.6.6 of the company submission.

In PREVAIL at the final data cut (30 June 2014) [redacted] of patients in the placebo arm and [redacted] in the enzalutamide arm received a second line treatment that differed from those they would have received in clinical practice. At the interim data analysis of 16 September 2013 these percentages had been [redacted] and [redacted] respectively. Within the CS, it was stated that the time between treatment discontinuation and starting the second line therapy was about two to two and half months in PREVAIL. The ERG views this delay as an important consideration for the economic modelling.

The post-study treatment received 2nd line in PREVAIL are shown Table 7.

Table 7 Post-study treatment received 2nd line in PREVAIL

	September 2013 cut-off		June 2014 cut-off	
	Placebo (N=845)	**Enzalutamide (N=872)**	**Placebo (N=845)**	**Enzalutamide (N=872)**
Docetaxel	401 (47.5%)	228 (26.1%)	[redacted]	[redacted]
Hormonal treatments	16 (1.9%)	11 (1.3%)	[redacted]	[redacted]
Lutamide	45 (5.3%)	14 (1.6%)	[redacted]	[redacted]
Enzalutamide	**0 (0.0%)**	**1 (0.1%)**	[redacted]	[redacted]
Abiraterone	**90 (10.7%)**	**61 (7.0%)**	[redacted]	[redacted]
Cabazitaxel	**22 (2.6%)**	**14 (1.6%)**	[redacted]	[redacted]
Sipuleucel –T	**9 (1.1%)**	**10 (1.1%)**	[redacted]	[redacted]
Investigational	**43 (5.1%)**	**28 (3.2%)**	[redacted]	[redacted]
Other chemotherapy for prostate cancer cytotoxic	**14 (1.7%)**	**14 (1.6%)**	[redacted]	[redacted]
Other chemotherapy for prostate cancer non-cytotoxic	**2 (0.2%)**	**1 (0.1%)**	[redacted]	[redacted]

Source: Table B23 company submission; Bold indicates treatments for which OS was adjusted for

The ERG note that the company state that the treatment pathway for the current population is to receive enzalutamide until progression, then docetaxel followed by a third line treatment. According to the trial protocol, this third line treatment should not be enzalutamide if they received it pre-docetaxel. However as described in Table B14 (CS), nine patients who received first line enzalutamide then went on to receive enzalutamide again post-docetaxel. This is considered by the ERG to be a contradiction. The ERG queried this at clarification but the company confirmed that these nine patients did indeed receive enzalutamide post-docetaxel. This in the opinion of the ERG adds further evidence that third line treatments do need to be considered in any economic modelling and is discussed further in section 5.3.4.

The results of the two adjustment methods for each of the data cut-offs are shown in Table 8 along with the original unadjusted estimate.

Table 8 Adjusted OS using IPCW and two-stage methods

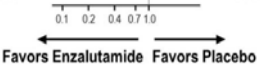
	HR (95% CI)	
	16 September 2013	**30 June 2014**
Unadjusted OS	0.706 (0.595, 0.837)	[redacted]
Adjusted OS using IPCW	[redacted]	[redacted]
Adjusted OS using two-stage	[redacted]	[redacted]

Results of the two adjustment methods were similar and showed a greater benefit of enzalutamide on overall survival than the original unadjusted analysis. It is important to note that the hazard ratios from the IPCW method are adjusted for baseline covariates while for the two-stage method and original unadjusted analysis they are not. The ERG consider the choice of model (IPCW) by the company to be appropriate for estimating the true effect of treatment on survival.

4.2.3 Radiographic progression free survival (rPFS)

The primary analysis of rPFS was pre-specified to be based on at least 410 centrally determined rPFS events observed. This resulted in a data cut of 6 May 2012 with 439 centrally determined events (enzalutamide 118/832 = 14.2% and placebo 321/801 = 40.1%). Patients randomised after the data cut-off date (N = 84) were not included in the analysis. Treatment with enzalutamide resulted in a statistically significant reduction in risk of radiographic progression (as determined by central review) or death compared with placebo (hazard ratio 0.186; 95% CI (0.149, 0.231); $p < 0.0001$). Radiographic progression was also assessed in the previously defined subgroups and in all cases the estimates favoured enzalutamide over placebo (Figure 5).

Subgroup	No. of Patients Enzalutamide/ Placebo	rPFS Median (mo) Enzalutamide/ Placebo	Hazard Ratio for rPFS (95% CI) (Unstratified)
All patients	832/801	NYR/3.9	0.19 (0.15–0.23)
ECOG performance status at baseline=0	557/549	NYR/3.7	0.15 (0.11–0.20)
ECOG performance status at baseline=1	275/252	14.1/4.0	0.27 (0.19–0.37)
Age <75 yr	529/517	NYR/4.6	0.20 (0.15–0.26)
Age ≥75 yr	303/284	NYR/3.7	0.17 (0.12–0.24)
Geographic region – North America	214/204	NYR/4.8	0.17 (0.12–0.25)
Geographic region – Europe	456/435	13.8/3.8	0.21 (0.15–0.28)
Geographic region – Rest of world	162/162	NYR/3.7	0.14 (0.08–0.25)
Total Gleason Score at diagnosis ≤7	401/370	14.1/5.3	0.16 (0.11–0.22)
Total Gleason Score at diagnosis ≥8	399/394	NYR/3.7	0.23 (0.17–0.31)
Type of progression at study entry – PSA progression only	348/341	NYR/5.6	0.16 (0.11–0.24)
Type of progression at study entry – Radiographic progression with or without PSA progression	464/435	14.1/3.7	0.18 (0.14–0.24)
Visceral disease (lung and/or liver) at screening – Yes	97/101	NYR/3.6	0.28 (0.16–0.49)
Visceral disease (lung and/or liver) at screening – No	735/700	14.1/4.0	0.17 (0.14–0.22)
Baseline PSA value (ng/mL) ≤median (51.10)	395/411	NYR/5.5	0.16 (0.11–0.23)
Baseline PSA value (ng/mL) >median (51.10)	437/389	13.8/3.6	0.18 (0.14–0.24)
Baseline LDH value (U/L) ≤median (185)	427/402	14.1/4.0	0.14 (0.10–0.20)
Baseline LDH value (U/L) >median (185)	404/398	NYR/3.8	0.23 (0.17–0.31)
Baseline hemoglobin value (g/L) ≤median (130)	429/388	14.1/3.7	0.24 (0.18–0.31)
Baseline hemoglobin value (g/L) >median (130)	403/413	NYR/5.3	0.13 (0.09–0.19)
Baseline bisphosphonate or denosumab use – Yes	215/222	13.8/5.6	0.27 (0.18–0.41)
Baseline bisphosphonate or denosumab use – No	617/579	NYR/3.7	0.16 (0.12–0.21)



Source: Figure B6, CS and Beer at al

Figure 5 Subgroup analyses of rPFS

The company undertook a series of sensitivity analyses using various censoring rules such as including all deaths, requirement for soft tissue confirmation and other analyses censoring for clinical progression (Table 9). In all cases the results favoured enzalutamide with HRs ranging from 0.174 to 0.234 and all statistically significant ($p < 0.0001$).

Sensitivity analysis 6 used investigator assessed rPFS at 16 September 2013 and therefore included the largest number of patients. The company indicated this was their reason for use of these data in the economic model.

Table 9 Summary of sensitivity analysis for rPFS (ITT)

	N events (%)		
	Enzalutamide (N = 832)	Placebo (N = 801)	HR (95% CI)[#]
Primary analysis: central review	118 (14.2%)	321 (40.1%)	0.186 (0.149, 0.231)
Sensitivity analysis 1	117 (14.1%)	296 (37.0%)	0.219 (0.176, 0.273)
Sensitivity analysis 2	121 (14.5%)	326 (40.7%)	0.186 (0.150, 0.231)
Sensitivity analysis 3	171 (20.6%)	450 (56.2%)	0.184 (0.153, 0.221)
Sensitivity analysis 4	118 (14.2%)	321 (40.1%)	0.185 (0.149, 0.231)
Sensitivity analysis 5	108 (13.0%)	245 (30.6%)	0.234 (0.186, 0.296)
Sensitivity analysis 6	387/872 (44.4%)	502/845 (59.4%)	0.307 (0.267, 0.353)
Sensitivity analysis 7	128 (15.4%)	354 (44.2%)	0.178 (0.144, 0.220)
Sensitivity analysis 8	178 (21.4%)	480 (59.9%)	0.174 (0.146, 0.209)

[#] All p <0.0001
1: based on investigator review
2: included all deaths during cut-off rather than deaths within 168 days of treatment discontinuation
3: considered new SREs, any radiation therapy for prostate cancer, or new antineoplastic therapy
4: considered date of next scheduled visit as the date of progression if progression was determined at an unscheduled visit
5: required confirmation of soft tissue progression before week 13
6: based on investigator assessments using cut off date of interim OS (16 September 2013)
7: considered patients discontinuing for clinical progression as rPFS events
8: considered patients discontinuing treatment for any reason as rPFS events

The company were unclear in their definitions of rPFS in relation to the differences between central review and investigator assessed. Estimates from the latter were used in the indirect comparison and economics but the rationale for this choice by the company was unclear to the ERG. Upon clarification, it is now the understanding of the ERG that the first 439 events (in the 6 May 2012 data cut) were assessed by a central review team. After that time any additional progression events were identified by the investigator rather than the central review team. The later data cut (16 September 2013) provided additional events because of the longer follow-up and the data from this cut were used in the economic modelling. In the opinion of the ERG, this change is unlikely to have caused any substantive bias.

4.2.4 Secondary outcomes

All results in this section relate to the data cut-off of 16 September 2013. Table 10 shows the results for the secondary and exploratory outcomes. Treatment with enzalutamide was associated with a significant reduction in risk of experiencing an

SRE although the median time to first SRE was similar in both groups (about 31 months). The majority of SREs experienced were radiation to the bone (65.1% enzalutamide and 67.3% placebo). Treatment with enzalutamide was associated with a reduction in the risk of first SRE (HR = 0.718, 95% CI 0.610 to 0.844). This effect was consistently favourable across the pre-specified subgroups.

Patients receiving enzalutamide were at a reduced risk of initiation of cytotoxic therapy (HR = 0.346, 95% CI 0.303 to 0.403) with median time of 28 months for enzalutamide compared with median of 10.8 months for placebo. The most common cytotoxic therapy was docetaxel and this was received by 90.5% of patients who initiated cytotoxic chemotherapy.

Median time to PSA progression was longer for enzalutamide (median = 11.2 months) compared to placebo (median = 2.8 months) resulting in a reduced risk for PSA progression in the enzalutamide arm (HR = 0.169, 95% CI 0.147 to 0.195).
A much higher proportion of placebo patients (76.0%) received a post-baseline antineoplastic therapy compared to the enzalutamide group (43.8%) with HR = 0.273 (95% CI 0.240 to 0.311). The median time to receipt of this therapy was 22.8 months in the enzalutamide group compared to 7.4 months in the placebo group.

Table 10 Summary of results for secondary outcomes/exploratory outcomes

	N events (%)			
	Enzalutamide	**Placebo**	**HR (95% CI)**	**p-value**
Time to first SRE	278 (31.9%)	309 (36.6%)	0.718 (0.610, 0.844)	<0.0001
Time to initiation of cytotoxic chemotherapy	308 (35.3%)	5151 (60.9%)	0.349 (0.303, 0.403)	<0.0001
Time to PSA progression	532 (61.0%)	548 (64.9%)	0.169 0.147, 0.195)	<0.0001
Time to 1st post-baseline antineoplastic therapy	382 (43.8%)	642 (76.0%)	0.273 (0.240, 0.311)	<0.0001

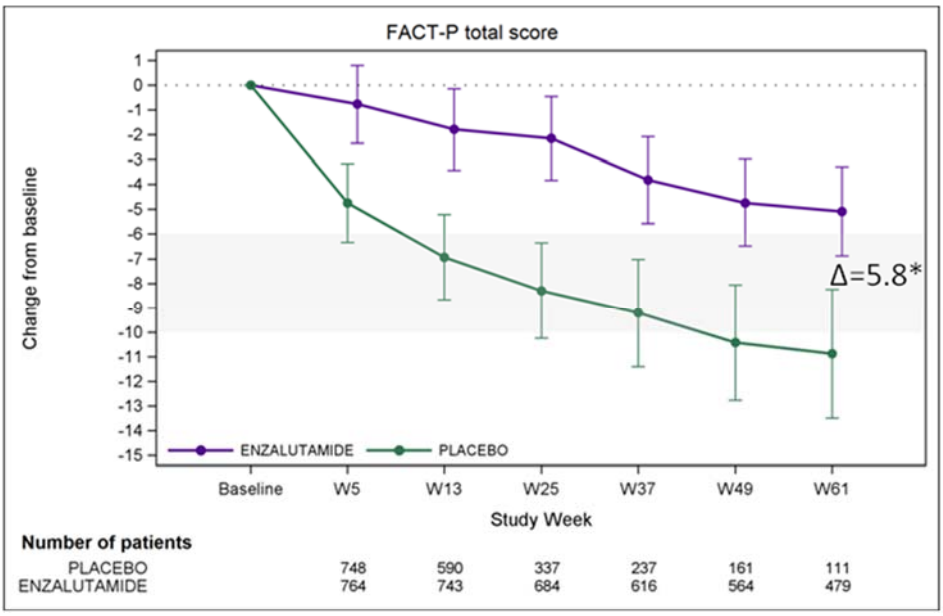
PSA response was defined as ≥ 50% reduction in PSA from baseline to the lowest post-baseline value. In the enzalutamide group, 78% had PSA response compared to 3.5% in the placebo arm (p <0.0001). The objective response rate was defined as

proportion of patients with complete or partial response as best tumour response was statistically significantly higher with enzalutamide (58.8%) compared with placebo (5.0%), p <0.0001.

4.2.5 Exploratory outcomes

FACT-P

A number of exploratory outcomes were assessed relating to quality of life and pain. A higher proportion of enzalutamide patients had a positive QoL response (FACT-P) than placebo irrespective of whether it was confirmed at two consecutive assessments. Within the enzalutamide group 20.6% had confirmed response compared to 8.9% in placebo patients (p < 0.001). However, the proportion of patients with confirmed QoL deterioration at some stage in the study was also higher for enzalutamide (25.3%) compared to placebo (15.8%), p <0.001. QoL deterioration was defined by a 10-point decrease in the FACT-P score. The company comment that the higher proportion of patients with QoL deterioration is likely to be due to the QoL data being collected for longer in the enzalutamide group than placebo group. The ERG agree with this comment.



Source: Figure B12, CS

Figure 6 Adjusted mean change from baseline in FACT-P total score (ITT)

The change from baseline in FACT-P score was greater in the placebo group than enzalutamide (Figure 6). Differences between arms for the FACT-P sub domains were found at most visits for all domains, with a few minor exceptions (see Figure B13, company submission).

Time to first QoL deterioration (defined as a greater than 10 point decrease in FACT-P total score) was longer for enzalutamide (median = 11.3 months) compared to placebo (median = 5.6 months) and HR = 0.625 (95% CI 0.542, 0.720).

Pain-related outcomes

The BPI-SF was used to assess several pain-related outcomes. Pain progression was assessed using the worst pain (item number 3 of BPI), the pain severity composite score and the pain preference composite score. Results of the analysis between enzalutamide and placebo are shown in Table 11. Results for the different definitions of pain progression all show a significant reduction in the risk for enzalutamide patients relative to placebo patients.

Table 11 Pain related outcomes

	N events (%)			
	Enzalutamide	**Placebo**	**HR (95% CI)**	**p-value**
Time to pain progression (worst pain)	330 (41.0%)	317 (50.5%)	0.62 (0.53, 0.74)	<0.001
Time to pain progression (average pain)	[redacted]	[redacted]	0.60 (0.51, 0.71)	<0.001
Time to pain progression (pain interference)	247 (31.3%)	255 (41.6%)	0.57 (0.48, 0.69)	<0.001

Changes in pain severity were assessed using the BPI-SF. Severity of pain increased in both treatment groups but the increase between baseline and week 25 was significantly greater in the placebo arm (Table 12). Similarly a significant increase in level of pain interference with daily activities was observed in both arms but significantly higher with placebo (Table 12).

Table 12 Changes in pain severity and pain interference between baseline and week 25

	Adjusted LS mean (SE)			
	Enzalutamide	Placebo	Treatment difference	p-value
Change in pain severity	0.52 (0.34, 0.70)	0.79 (0.59, 1.00)	-0.28 (-0.46, -0.10)	0.002
Change in pain interference	0.58 (0.36, 0.80)	0.99 (0.75, 1.23)	-0.41 (-0.63, -0.19)	<0.001

EQ5D

A post-hoc analysis of EQ5D was undertaken by the company. About 98% of patients had a baseline EQ5D available with 93.8% of enzalutamide and 74.6% of placebo patients having baseline and at least one post-baseline value.

A mixed model was used to compare differences between treatment arms. The treatment effect on the EQ5D utility favoured enzalutamide at week 61 (LS mean 0.03+/-0.02) but did not reach statistical significance (p = 0.080). However, a lower decrease in the VAS score by week 61 was observed for patients treatment with enzalutamide compared to placebo (LS mean: 4.58 +/- 1.39, p = 0.001). Time to EQ5D deterioration was also assessed, defined as reduction of 0.14 in utility score, or reduction of 11 points on the VAS score. Median time to deterioration of the utility score was 19.2 months on enzalutamide and 11.1 months on placebo, and HR = 0.62 (0.52, 0.73), p <0.001. In the case of the VAS, median time to deterioration was 22.1 months on enzalutamide and 13.8 months on placebo, and HR = 0.67 (0.56, 0.80), p <0.001. The treatment effect of enzalutamide over the whole study was analysed using the mixed model and showed a utility gain of 0.02. Data beyond week 61 were not included in the model by the company because of the low numbers in the placebo arm (falling below 10%). The company did not state, and the ERG cannot identify, any obvious methodological reason why data should be excluded if fewer than 10% patients returned data.

Time to treatment discontinuation (TTD)

The company commented that clinicians consider TTD as the most appropriate endpoint to assess for disease progression. The ERG agree with the company as it is standard practice to stop treatment once progression is diagnosed. Median TTD at the 16 September 2013 cut off was 17.71 months for enzalutamide and 4.55 months for placebo. The company comments that these values were comparable with median rPFS at the same data cut.

The company fit survival curves to both the 16 September 2013 and June 2014 data cuts for TTD to use the latter in the economic modelling. However the ERG are concerned at the use of the June 2014 data because unblinding occurred on 3rd December 2013 and this may have influenced the decision to stop (or indeed continue with) study treatment. In terms of finding a suitable curve, using the same processes as OS and rPFS, the generalised Gamma was chosen to be the most plausible clinically and showed a good model fit with AIC and BIC. In the opinion of the ERG the choice of curve is acceptable but the September 2013 data cut should be used instead for economic modelling.

The CS also noted that there was an average of two months between TTD and starting 2nd line treatment in the PREVAIL study, though this was similar between enzalutamide and placebo groups.

4.2.6 Safety outcomes

Safety data of enzalutamide versus placebo were available for PREVAIL and the company presented results using the 16 September 2013 data cut off.

Adverse events

The overall incidence of adverse events (AEs) with enzalutamide was similar to that of placebo within PREVAIL. It is to be expected for the patient population who have advanced prostate cancer to have adverse events and nearly all patients experience at least one AE in PREVAIL (96.9% in enzalutamide, 93.2% on placebo). Table 13 gives a summary of the adverse events in PREVAIL.

Table 13 Summary of adverse events in PREVAIL

Number of patients reporting ≥ 1	ENZA (N=871)	PLA (N=844)
Adverse Event (AE)	844 (96.9%)	787 (93.2%)
AE associated with study drug discontinuation	148 (17.0%)	216 (25.6%)
AE as primary reason for study drug discontinuation	49 (5.6%)	51 (6.0%)
AE leading to dose reduction of study drug	18 (2.1%)	8 (0.9%)
AE leading to temporary interruption of study drug dosing	98 (11.3%)	88 (10.4%)
AE leading to death	37 (4.2%)	32 (3.8%)
Serious adverse event	279 (32.0%)	226 (26.8%)
Median time to first SAE (months) [95%CI]	NYR [28.3, NYR]	23.3 [16.1, NYR]
Grade 3 or higher AE	374 (42.9%)	313 (37.1%)
Median time to first grade ≥ 3 AE (months) [95%CI]	22.3 [19.0, 28.3]	13.3 [11.1, 18.2]

Source: Table B34 company submission; NYR – not yet reached

In the enzalutamide group, 374 (42.9%) had any grade ≥ 3 AE, with 114 (30%) of these occurring within first 90 days increasing to 47.6% within 180 days and 74.6% within first 365 days. For placebo, 313 (37.1%) had any grade ≥ 3 AE with 55.3% in the first 90 days, up to 80.2% within first 180 days and 94.6% within first 365 days. Time to first Grade 3 or higher AE was longer in the enzalutamide group (Table 13).

Table 14 Adverse events reported in ≥ 5% of patients in any arm with a ≥2% absolute difference

	Overall incidence, n (%)			Events per 100-patient years of reporting N (event rate)	
AE	**ENZA (N=871)**	**PLA (N=844)**	**RR [95% CI]**	**ENZA (N=871)**	**PLA (N=844)**
Fatigue	310 (35.6%)	218 (25.8%)	1.38 [1.19, 1.59]	353 (29.9)	233 (43.0)
Back pain	235 (27.0%)	187 (22.2%)	1.22 [1.03, 1.44]	279 (23.6)	230 (42.5)
Constipation	193 (22.2%)	145 (17.2%)	1.29 [1.06, 1.57]	218 (18.5)	154 (28.4)
Arthralgia	177 (20.3%)	135 (16.0%)	1.27 [1.04, 1.56]	219 (18.6)	160 (29.5)
Decreased appetite	158 (18.1%)	136 (16.1%)	1.13 [0.91, 1.39]	175 (14.8)	146 (27.0)
Diarrhoea	142 (16.3%)	119 (14.1%)	1.16 [0.92, 1.45]	180 (15.3)	153 (28.3)
Hot flush	**157 (18.0%)**	**65 (7.7%)**	2.34 [1.78, 3.08]	**160 (13.6)**	**66 (12.2)**
Asthenia	113 (13.0%)	67 (7.9%)	1.63 [1.23, 2.18]	149 (12.6)	72 (13.3)
Weight decreased	100 (11.5%)	71 (8.4%)	1.36 [1.02, 1.82]	102 (8.6)	74 (13.7)
Oedema peripheral	92 (10.6%)	69 (8.2%)	1.29 [0.96, 1.74]	105 (8.9)	72 (13.3)
Hypertension	**117 (13.4%)**	**35 (4.1%)**	3.24 [2.25, 4.67]	**127 (10.8)**	**36 (6.6)**
Headache	91 (10.4%)	59 (7.0%)	1.49 [1.09, 2.05]	117 (9.9)	67 (12.4)
Fall	**101 (11.6%)**	**45 (5.3%)**	2.17 [1.55, 3.05]	**128 (10.8)**	**48 (8.9)**
Dizziness	76 (8.7%)	53 (6.3%)	1.39 [0.99, 1.95]	83 (7.0)	57 (10.5)
Haematuria	73 (8.4%)	49 (5.8%)	1.44 [1.02, 2.05]	105 (8.9)	60 (11.1)
Insomnia	70 (8.0%)	47 (5.6%)	1.44 [1.01, 2.06]	74 (6.3)	47 (8.7)
Nasopharyngitis	62 (7.1%)	42 (5.0%)	1.52 [1.04, 2.23]	71 (6.0)	45 (8.3)
Dysgeusia	**66 (7.6%)**	**31 (3.7%)**	2.06 [1.36, 3.13]	**68 (5.8)**	**31 (5.7)**
Upper respiratory tract infection	53 (6.1%)	30 (3.6%)	1.71 [1.11, 2.65]	65 (5.5)	38 (7.0)

Source: Table B35, company submission and company clarification report.
NB: the RRs presented in table B35 were incorrect but were corrected upon clarification

The AEs that were reported in ≥ 5% of patients in any arm with a ≥ 2% absolute difference are shown in Table 14. When the longer exposure to study drug in the enzalutamide arm is taken into account, only hot flush, hypertension, fall and dysgeusia were more common in the enzalutamide arm. Table 15 shows the number and percentage of patients who had grade ≥ 3 AEs that were reported in ≥ 1% of patients in any arm. The most common grade ≥ 3 AEs were hypertension, renal and urinary disorders, spinal cord compression and musculoskeletal and connective tissue disorders. Significant differences between enzalutamide and placebo were found for

eye disorders (in particular cataract), vascular disorders (including hypertension) with more of those events in the enzalutamide group than placebo.

Table 15 Adverse events grade ≥3 reported in ≥1% of patients in either group by system organ class (safety set)

AE	ENZA (N=871)	PLA (N=844)	RR [95% CI]
Patients with any grade ≥3 AE	374 (42.9%)	313 (37.1%)	1.16 [1.03; 1.30]
Blood and lymphatic system disorders	37 (4.2%)	31 (3.7%)	1.16 [0.72; 1.85]
Anaemia	29 (3.3%)	25 (3.0%)	1.12 [0.66; 1.90]
Eye disorders	14 (1.6%)	2 (0.2%)	6.78 [1.55; 29.76]
Cataract	**11 (1.3%)**	**1 (0.1%)**	10.66 [1.38; 82.38]
Gastrointestinal disorders	37 (4.2%)	25 (3.0%)	1.43 [0.87; 2.36]
Nausea	**9 (1.0%)**	**4 (0.5%)**	2.18 [0.67; 7.05]
General disorders and administration site conditions	58 (6.7%)	49 (5.8%)	1.15 [0.79; 1.66]
Fatigue	16 (1.8%)	16 (1.9%)	0.97 [0.49; 1.93]
General physical health deterioration	**18 (2.1%)**	**10 (1.2%)**	1.74 [0.81; 3.76]
Asthenia	11 (1.3%)	8 (0.9%)	1.33 [0.54; 3.30]
Infections and infestations	45 (5.2%)	37 (4.4%)	1.18 [0.77; 1.80]
Urinary tract infection	13 (1.5%)	11 (1.3%)	1.15 [0.52; 2.54]
Pneumonia	**11 (1.3%)**	**7 (0.8%)**	1.52 [0.59; 3.91]
Injury, poisoning, and procedural complications	29 (3.3%)	19 (2.3%)	1.48 [0.84; 2.62]
Fall	**12 (1.4%)**	**6 (0.7%)**	1.94 [0.73; 5.14]
Musculoskeletal and connective tissue disorders	68 (7.8%)	78 (9.2%)	0.90 [0.66; 1.23]
Back pain	22 (2.5%)	25 (3.0%)	0.85 [0.48; 1.50]
Bone pain	12 (1.4%)	20 (2.4%)	0.58 [0.29; 1.18]
Arthralgia	12 (1.4%)	9 (1.1%)	1.29 [0.55; 3.05]
Pathological fracture	9 (1.0%)	7 (0.8%)	1.25 [0.47; 3.33]
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	52 (6.0%)	38 (4.5%)	1.33 [0.88; 1.99]
Metastatic pain	14 (1.6%)	16 (1.9%)	0.85 [0.42; 1.73]

AE	ENZA (N=871)	PLA (N=844)	RR [95% CI]
Nervous system disorders	73 (8.4%)	53 (6.3%)	1.33 [0.95; 1.88]
Spinal cord compression	**33 (3.8%)**	**24 (2.8%)**	1.33 [0.79; 2.23]
Syncope	**14 (1.6%)**	**8 (0.9%)**	1.70 [0.72; 4.02]
Renal and urinary disorders	49 (5.6%)	68 (8.1%)	0.70 [0.49; 1.00]
Urinary retention	8 (0.9%)	14 (1.7%)	0.55 [0.23; 1.31]
Hydronephrosis	5 (0.6%)	16 (1.9%)	0.30 [0.11; 0.82]
Haematuria	9 (1.0%)	11 (1.3%)	0.79 [0.33; 1.90]
Urinary tract obstruction	9 (1.0%)	9 (1.1%)	0.97 [0.39; 2.43]
Vascular disorders	69 (7.9%)	26 (3.1%)	2.57 [1.65; 4.00]
Hypertension	**59 (6.8%)**	**19 (2.3%)**	3.01 [1.81; 5.00]

Drug-related AEs

Fatigue and nausea were the most commonly reported drug-related AEs in both arms. There was a significantly higher incidence in the enzalutamide group compared to placebo for the following adverse events related to study medication: constipation, fatigue, oedema peripheral, pain in extremity, dysgeusia, headache, psychiatric disorders, dyspnoea, dry skin, hot flush, hypertension and flushing (Table B38, company submission). The AEs reported for enzalutamide in PREVAIL were in line with the adverse reactions listed on the summary of product characteristics.

Death and causes of death

It has already been reported that enzalutamide was associated with a significant improvement in survival with a 29% decrease in the risk of death (HR = 0.706, 95% CI [0.596, 0.837]). A lower proportion of patients died due to disease progression in the enzalutamide arm (27.6%) than the placebo arm (35.4%) with RR (95% CI) = 0.78 (0.66, 0.93). However a comparable proportion suffered an AE that led to their death (4.2% versus 3.8%).

Serious adverse event

Overall 32% (N = 279) in the enzalutamide arm and 26.8% (N = 226) in the placebo arm experienced at least one SAE of any grade or causality. For enzalutamide, of the 279 patients, 20% had the first SAE within 90 days, 40% within 180 days and 69%

within 365 days compared to the placebo groups (N = 226), with 51%, 74% and 90% respectively. Events with a higher incidence for enzalutamide than placebo were: anaemia (1.6% vs. 0.9%), coronary artery disease (0.5% vs. 0.0%), fatigue (0.5% vs. 0.0%), femoral neck fracture (0.6% vs. 0.0%), pathological fracture (1.1% vs. 0.6%), syncope (0.7% vs. 0.0%), cauda equine syndrome (0.5% vs. 0.0%) and hypertension (0.5% vs. 0.0%). The incidence of all other events was comparable between groups or indeed more common on placebo.

AEs leading to treatment discontinuation

A similar proportion of patients in both treatment arms experiences an AE that led to a permanent treatment discontinuation (enzalutamide, n= 49 (5.6%); placebo N = 51 (6.0%). The adverse events reported in more than one patient were:

- Nausea (0.3% vs. 0.4%)
- Dysphagia (0.0% vs. 0.4%)
- Vomiting (0.0% vs. 0.2%)
- Fatigue (0.2% vs. 0.9%)
- Subdural haemotama (0.0% vs. 0.2%)
- Hepatic enzyme increased (0.0% vs. 0.2%)
- Cerebrovascular accident (0.2% vs. 0.1%)
- Lethargy (0.0% vs. 0.2%)
- Syncope (0.2% vs. 0.0%)
- Renal failure acute (0.2% vs. 0.1%)

4.3 Critique of trials identified and included in the indirect comparison and/ or multiple treatment comparison

The search undertaken by the company identified ten studies conducted with enzalutamide or abiraterone but also docetaxel, radium-223, dichloride and sipuleucel-T. Only two studies were deemed relevant for this submission and inclusion in the indirect comparison. The COU-AA-302 trial compared abiraterone plus prednisone versus prednisone plus placebo[23] and PREVAIL for enzalutamide as previously discussed.[21] The two trials were similar in terms of the patient population except all patients in COU-AA-302 were on a corticosteroid (100% in COU-AA-302, 30.2% in PREVAIL (but only 4% at baseline). The company argue that this use of

prednisone in COU-AA-302 meant the control arms of the two trials were not directly comparable for inclusion in an indirect comparison as the common treatment arm. Patient characteristics between PREVAIL and COU-AA-302 were similar although PREVAIL had a higher proportion of white patients compared to COU-AA-302, which the ERG interpret as being a function of COU-AA-302 not containing any study sites in Asia. Having visceral metastases was an exclusion criteria in COU-AA-302 but allowed in PREVAIL so COU-AA-302 contains 0% patients with visceral disease while PREVAIL had 11.9% patients with visceral disease. Both studies recruit patients of ECOG = 0 or ECOG = 1 only, but PREVAIL had a higher proportion with ECOG = 1 (31.9% versus 24.5% in COU-AA-302). The baseline characteristics of men in both trials are presented in Table 16.

The outcomes considered in the indirect comparison were:

- Overall survival
- rPFS
- time to cytotoxic chemotherapy initiation
- time to PSA progression
- best overall response (complete or partial)
- best overall response (progressive disease)

Data from PREVAIL were taken from the June 2014 data cut off for overall survival and the September 2013 cut-off for other outcomes. Data for COU-AA-302 were taken predominantly from the interim (IA3) cut off and an additional final analysis for OS. Table 17 summarises the results of each trial and the indirect comparison for the outcomes described. Data for PREVAIL for rPFS was investigator assessed rather than central review.

Odds of best overall response (complete or partial) was higher for enzalutamide than abiraterone ([redacted]). But no difference was observed for progressive disease as best overall response (Table 18). The company commented that these estimates were provided for information but were not included in the economic analysis for the reasons described above.

Table 16 Baseline characteristics of men in PREVAIL and COU-AA-302 trials

	COU-AA-302		PREVAIL	
	ABI + PRED (N=546)	**PLA + PRED (N=542)**	**ENZA (N=872)**	**PLA (N=844)**
Age				
Median (range)	71 (44-95)	70 (44-90)	72 (43-93)	71 (42-93)
≥75 years	185 (34%)	165 (30%)	317 (29.2)	364 (34.6)
Ethnicity				
American Indian or Alaska Native	-	-	1 (0.1%)	0 (0.0%)
Asian	(0.7)	(1.7)	85 (9.7%)	82 (9.7%)
Black or African American	(2.8)	(2.4)	21 (2.4%)	13 (1.5%)
Native Hawaiian or other Pacific Islander	(0.0)	(0.4)	1 (0.1%)	1 (0.1%)
White	(95.4)	(94.4)	669 (76.7%)	655 (77.5%)
Other, multiple, unknown	(1.1)	(1.1)	95 (10.9%)	94 (11.1)
Time since diagnosis (years)*				
Median (range)	5.5 (<1-28)	5.1 (<1-28)	5.2 (<1; 27.2)	5.4 (<1; 23)
Extent of disease				
N	542	540		
Bone only	274 (51%)	267 (49%)	348 (39.9%)	335 (39.6%)
Soft tissue or node	267 (49%)	271 (50%)	Soft tissue: 124 (14.2%) Node: 437 (50.1%)	Soft tissue: 149 (17.6%) Node: 434 (51.4%)
Visceral (lung or liver)	0 (0%)	0 (0%)	98 (11.2%)	106 (12.5%)
ECOG performance status				
0	413 (75.6)	409 (75.5)	584 (67.0%)	585 (69.2%)
1	133 (24.4)	133 (24.5)	288 (33.0%)	260 (30.8%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

	COU-AA-302		PREVAIL	
	ABI + PRED (N=546)	**PLA + PRED (N=542)**	**ENZA (N=872)**	**PLA (N=844)**
PSA				
Number of patients	470	454		
Median, ng/mL	22.3	21.0	54.1	44.2
Gleason score at initial diagnosis	488	508	838	808
≤7	225 (46%)	254 (50%)	414 (49.4)	385 (47.6%)
≥8	263 (54%)	254 (50%)	424 (50.6%)	423 (52.4%)
Missing				
Previous cancer therapy	544	542	872	845
Surgery	256 (47%)	244 (45%)	453 (51.9%)	419 (49.6%)
Radiotherapy	283 (52%)	303 (56%)	392 (45.0%)	380 (45.0%)
Hormonal	544 (100%)	542 (100%)	865 (99.2%)	838 (99.2%)
Other	82 (15%)	63 (12%)		
Screening BPI-SF pain score (worst pain over last 24 hours)				
N	532	522	859	840
0–1	353 (66%)	336 (64%)	569 (66.2%)	567 (67.5%)
2–3	169 (32%)	170 (33%)	275 (32.0%)	262 (31.2%)
≥4	10 (2%)	16 (3%)	15 (1.7%)	11 (1.3%)
Baseline LDH (ng/mL)				
Number of patients	543	536	871	844
Median (range)	187 (60; 871)	184 (87; 781)	185 (52; 1861)	185 (67; 2321)

Source:Ryan at al, PREVAIL Clinical Study Report
ABI: abiraterone; ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; PLA: placebo; PRED: prednisone; PSA: prostate-specific antigen; SD: standard deviation.
*Time since diagnosis for patients in the PREVAIL study has been recalculated; original data are provided in months (enzalutamide: 62.7 months; 95% CI [0.2; 326.6]; placebo: 64.6 months; 95% CI [0.1; 275.4]).

Table 17 Results of the indirect comparison as presented by the company

	Enzalutamide vs placebo		Abiraterone vs placebo		ITC: ENZA vs ABI
	Source	HR (95% CI)	Source	HR (95% CI)	HR (95% CI)
OS	June 2014 (unadjust)	[redacted]	IA3	0.79 (0.66, 0.95)	[redacted]
OS	June 2014 (IPCW)	[redacted]	IA3	0.79 (0.66, 0.95)	[redacted]
OS	June 2014 (unadjust)	[redacted]	Final	0.80 (0.69, 0.93)	[redacted]
OS	June 2014 (IPCW)	[redacted]	Final	0.80 (0.69, 0.93)	[redacted]
rPFS	September 2013	0.307 (0.267, 0.353)	IA3	0.52 (0.45, 0.61)	[redacted]
Time to cytotoxic chemo	September 2013	0.349 (0.303, 0.403)	IA3	0.62 (0.51, 0.72)	[redacted]
Time to OSA progression	September 2013	0.169 (0.147, 0.195)	IA3	0.50 (0.43, 0.58)	[redacted]

*Corrected result after clarification

Table 18 Results of indirect comparison for best overall response

	ENZA vs placebo	ABI vs placebo	OR (95% CI) ENZA vs ABI
Best overall response (CR+PR)	233/396 vs 19/381	79/220 vs 35/218	[redacted]
Best overall response (PD)	21/396 vs 124/381	4/220 vs 33/218	[redacted]

4.4 Critique of the indirect comparison and/ or multiple treatment comparison

There are limited data on which to undertake an indirect comparison as only one trial exists for each of the enzalutamide versus placebo (PREVAIL) and abiraterone versus placebo (COU-AA-302). The company argue that the use of prednisone in COU-AA-302 meant the control arms of the two trials were not directly comparable for inclusion in an indirect comparison as the common treatment arm. As a result of this assumption, the indirect comparison results are not applied to the base case economic model, but only presented here by the company for information. The ERG accepts that the treatment in the control groups are different, but it is by no means clear that completely ignoring the indirect results in favour of a naïve single group comparison of the active treatment arms of the two trials will give more accurate results.

The company indicated they used a fixed effects model for the indirect comparison, however the detail in the main submission was lacking. The ERG asked the company at clarification if they had used the Bucher Method. The company responded saying no, the Bucher method was not used and the results of the network meta-analysis were from a fixed effects model. They provided the Appendix to reference 46. The ERG were not provided reference 46 in the reference pack but on review of the appendix to this report the ERG interpretation was the company had undertaken a larger NMA including studies with treatments other than enzalutamide and abiraterone. In the opinion of the ERG, the company have obtained the estimates for enzalutamide versus abiraterone from this larger network, rather than undertaking a two trial network comparison. The ERG checked the results of the company using the standard Bucher Method (see section 4.5). The ERG obtained comparable estimates for enzalutamide versus abiraterone, so although we are concerned about the transparency of the methods employed by the company, the ERG are happy that the estimates obtained

are accurate. However they come with the caveat of whether it is sensible to undertake an indirect comparison in the first place because of the differences in the control arms of the two trials.

The company provided incorrect results for two of the indirect comparison results in the main submission. The ERG queried these and upon clarification the company indicated they had used data from the wrong data cut for PREVAIL. These were corrected and the ERG agreed with the updated results.

The ERG were also unsure why data from the investigator assessed rPFS was used instead of central review and have repeated the analysis using the latter (Section 4.5). Upon clarification, the company indicated that in PREVAIL, centrally reviewed PFS was only planned for the first 410 centrally reviewed events. It was conducted on the 6 May 2012 data cut off with 439 events. Investigator assessed PFS was evaluated for the entire duration of follow-up and included 889 events for the 16 September 2013 data cut off. The ERG interpret this to mean, that the first 439 events were assessed by a central review team, but thereafter for the remaining events the onsite investigator made the decision as to whether progression had occurred. Although this distinction is not made that clear by the company, the ERG agree that utilising longer follow-up data cut is the more appropriate. However the ERG are not clear why central review was not used for all events, and what impact that may have had on the numbers defined as progressed/not progressed.

4.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG was concerned by the lack of transparency of the indirect comparison undertaken by the company. As such the ERG undertook a Bucher comparison of the PREVAIL and COU-AA-302 trials to obtain an estimate for enzalutamide versus abiraterone. The results are presented in Table 19 alongside the relevant result presented by the company.

Table 19 ERG results for indirect comparison of enzalutamide vs. abiraterone

	Data Cut	ERG Bucher HR (95% CI)	Company NMA HR (95% CI)
OS	June 2014 (unadjust):IA3	[redacted]	[redacted]
OS	June 2014 (IPCW):IA3	[redacted]	[redacted]
OS	June 2014 (unadjust):final	[redacted]	[redacted]
OS	June 2014 (IPCW):final	[redacted]	[redacted]
rPFS	September 2013	[redacted]	[redacted]
Time to cytotoxic chemo	September 2013	[redacted]	[redacted]
Time to PSA progression	September 2013	[redacted]	[redacted]

Although some slight numerical differences between the ERG estimates and the company NMA, the results are extremely comparable. In all of the overall survival analyses no differences are shown between enzalutamide and abiraterone. An advantage of enzalutamide over abiraterone was shown for radiographic PFS, time to cytotoxic chemotherapy and time to PSA progression.

For completeness the ERG have undertaken the indirect comparison using the results from the various sensitivity analysis of rPFS (Table 20). The magnitude of effect is similar whichever definition is used, all the 95% CIs are below one indicating a benefit of enzalutamide over abiraterone for radiographic progression free survival.

Table 20 ERG results for indirect comparison of enzalutamide vs. abiraterone using sensitivity analyses for PREVAIL

rPFS definition	ERG Bucher HR (95% CI)
Central review (6 May 2012)	0.36 (0.27, 0.47)
Investigator assessed (6 Sep 2013)	0.59 (0.48, 0.73)
Sensitivity analysis 1	0.42 (0.32, 0.55)
Sensitivity analysis 2	0.36 (0.27, 0.47)
Sensitivity analysis 3	0.35 (0.28, 0.45)
Sensitivity analysis 4	0.36 (0.27, 0.47)
Sensitivity analysis 5	0.45 (0.34, 0.60)
Sensitivity analysis 6	0.59 (0.48, 0.73)
Sensitivity analysis 7	0.34 (0.26, 0.45)
Sensitivity analysis 8	0.33 (0.26, 0.43)

4.6 Conclusions of the clinical effectiveness section

Clinical effectiveness data were presented for a single trial (PREVAIL) for the comparison of enzalutamide versus placebo in adults with asymptomatic or mildly symptomatic mHRPC in whom immediate chemotherapy is not yet clinically indicated. PREVAIL showed that enzalutamide led to:

- significantly longer overall survival despite a higher proportion of placebo patients being able to switch to other therapies will survival benefit
- significantly longer rPFS
- superior treatment effect for radiographic tumour response, PSA response, pain palliation and quality of life (FACT-P and EQ5D)

In the case of OS and rPFS, all favourable outcomes were maintained in the pre-specified sub groups.

In PREVAIL for the safety outcomes the overall incidence of AEs was comparable between enzalutamide and placebo. The overall incidence of ≥ 3 AEs and SAEs was greater with enzalutamide than placebo, but lower within the first year of treatment. The most commonly reported treatment –related AEs observed with enzalutamide were fatigue and nausea but after adjustment for treatment exposure, incidence was lower with enzalutamide.

Overall, the ERG believes the results of PREVAIL show a significant benefit with a good safety profile of enzalutamide over placebo for this patient population.

No head to head trial was found for enzalutamide to the comparator of abiraterone. One trial, COU-AA-302 was found to compare abiraterone (plus prednisone) versus prednisone alone. The differences in the control groups of these trials meant that any indirect comparison should be treated with caution. The company undertook an indirect comparison and found for OS there was no significant difference between enzalutamide and abiraterone. For rPFS, time to cytotoxic chemotherapy and time to PSA progression there was a significant advantage of enzalutamide over abiraterone.

The results of these indirect comparisons were not used in the economic modeling by the company because of the concerns over the comparability of the control groups in PREVAIL and COU-AA-302.

5 COST EFFECTIVENESS

5.1 ERG comment on manufacturer's review of cost-effectiveness evidence

5.1.1 State objective of cost effectiveness review. Provide description of manufacturers search strategy and comment on whether the search strategy was appropriate. If the manufacturer did not perform a systematic review, was this appropriate?

The searches for cost-effectiveness are included in Appendix 10.2.4 since the broad searches used for the major databases were suitable for identifying economic evaluations. In addition the appropriate specialist economic databases: NHS NEED , HEED, Econlit , CEA Registry and HTA sources were searched.

Separate searches were undertaken for the measurement and valuation of health effects and are replicated in full in Appendix 10.12. Sources searched were extensive, including the major general health and economic databases. These search strategies were designed to retrieve utilities data for metastatic prostate cancer, combining an appropriate range of controlled vocabulary and free text terms.

5.1.2 State the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

No details were available to the ERG.

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 most important cost effectiveness studies.

Cost effectiveness studies

A brief summary of the submission for the STA of abiraterone for asymptomatic and mildly symptomatic chemotherapy naïve mHRPC patients [ID503] is included in table B44 of the submission.[11]

Quality of life studies

A brief summary of the quality of life values identified in the literature by the company is included in table B66 of the submission.

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.

Cost effectiveness studies

The summary of the submission for the STA of abiraterone notes that the cost effectiveness estimate was £46,777 per QALY inclusive of the abiraterone PAS.

The summary is partial because it does not include a review of the evaluation report or the FAD of the abiraterone STA. The ERG made a number of revisions to the base case of the model that resulted in an ERG exploratory base case cost effectiveness estimate of £57,558 per QALY. Revising the survival curve associated with 2nd line docetaxel use further increased the cost effectiveness estimate to £65,515 per QALY. The committee concluded that all the cost effectiveness estimates were substantially above the range normally considered to be cost effective. The committee did not recommend abiraterone in this indication.

Quality of life studies

Table B66 on page 174 of the submission presents the company summary of the relevant quality of life studies. From this summary, the reports of Bahl et al,[24] Diels et al,[2] Sandblom et al,[1] Winquist et al[25] and Wolff et al[26] appear likely to be the most relevant.

The values of the company modelling are drawn from Wolff et al, Diels et al and Sandblom et al.[1,2,26]

The literature is used to inform the quality of life values for patients in three health states of the model:

- Patients on 2nd line docetaxel
- Patients on 3rd line treatment
- Patients in palliative care

but the literature values for those pre-docetaxel are obviously relevant as a cross check of the PREVAIL 0.844 EQ-5D baseline value used by the company in its modelling

Note that the company submission for the STA of abiraterone for the same indication [ID503] undertook a survey among 163 mCRPC patients at the various stages of the disease that correspond with the current company modelling. Regrettably, all these values are redacted from the publicly available documents presumably on grounds of them being AIC, which means that a level playing field cannot be guaranteed between the current assessment and ID503[b].

1st line baseline quality of life

The summary presented in table B66 suggests that Wolf et al[26] and Diels et al[2] might provide quality of life estimates for the pre-docetaxel subgroup. Unfortunately, the data summarised in table B66 do not appear to be in line with the references supplied for Wolf et al[26] and Diels et al[2] was only supplied as an abstract.[27]

The ERG has been able to source Wolf et al 2012[28] as an abstract, the values of which are in line with table B66 of the company submission: EQ-5D utility values of 0.81 (n=33) for no previous chemotherapy, 0.64 (n=31) for ongoing chemotherapy and 0.66 (n=37) for post-chemotherapy. The 0.810 value of table B66 is below the 0.844 baseline value that the company estimates from PREVAIL EQ-5D data.

The company summary of Diels et al[2] of table B66 only presents the mean EQ-5D and mean FACT-P mapping predicted values by country. The company supplied Diels et al abstract[27] only reports the mean EQ-5D quality of life value of 0.67 across the 43% with no previous chemotherapy, 32% with ongoing chemotherapy, 24% with previous chemotherapy. The full paper, Diels et al,[2] provides more detail and mean EQ-5D values of 0.70 for chemotherapy naïve patients (n=236), 0.66 for those undergoing chemotherapy (n=223) and 0.60 for post-chemotherapy (n=143). The Diels et al[2] value of 0.70 for pre-chemotherapy patients is considerably below the 0.844 baseline value that the company estimates from PREVAIL EQ-5D data.

[b] http://www.nice.org.uk/guidance/gid-tag434/documents/prostate-cancer-metastatic-hormone-relapsed-not-treated-with-chemotherapy-abiraterone-acetate-with-prednisolone-id503-evaluation-report2

The weighted average for chemotherapy naïve patients across Wolff et al[28] and Diels et al[2] is 0.71. Again, this is somewhat below the 0.844 baseline value that the company estimates from PREVAIL EQ-5D data.

2nd line docetaxel quality of life

The company summary of Wolff et al[28] suggests a value of 0.660 which is in line with the 0.658 of the company modelling.

Diels et al[2] provide a value of 0.66 which is in line with the company modelling. The economic modelling draws a value of 0.658 for those on 2nd line docetaxel from Wolff et al[28] and Diels et al[2] which is in line with the values and patient numbers.

Post 2nd line docetaxel and 3rd line treatment

The economic modelling draws a value of 0.612 for those about to receive 3rd line treatment from Wolff et al[28] and Diels et al.[2] Table B66 suggests a value of 0.640 from Wolff et al.[28] Diels et al[2] suggests a value of 0.60.

Bahl et al[24] analyse EQ-5D data in the post-docetaxel setting for those receiving cabazitaxel. Quality of life is 0.698 at baseline with this improving to between 0.730 and 0.817 while on treatment, and remaining at 0.695 after 10 cycles of treatment.

James et al[29] is also supplied as an abstract, deriving an EQ-5D utility of 0.63 among patients progressing during or after docetaxel therapy. The open ended nature of the estimate for progressing on or after docetaxel therapy means that this estimate is difficult to apply to the health states of the company model.

Winquist et al[25] is also supplied as an abstract, deriving a mean baseline EQ-5D utility of 0.713 among 55 patients about to receive cabazitaxel. This used the Canadian tariff, and it is not clear whether all patients had received prior chemotherapy.

Surprisingly, the company summary of quality of life values for 3rd line treatment does not summarise the EQ-5D values of the company submission for enzalutamide post-docetaxel. Values provided at clarification show a mean EQ-5D value of [redacted]

at baseline in the AFFIRM trial which is broadly in line with that of Bahl et al[24] and somewhat above the 0.612 applied within the model.

The economic modelling draws a value of 0.612 for those on 2nd line docetaxel from Wolff et al[28] and Diels et al[2] which is in line with the values and patient numbers.

The remaining references and values suggest that the value used for the modelling may be too low relative to the value applied for 1st line treatment. This is in line with the weighted averages from Wolff et al[28] and Diels et al[2] which suggest values of 0.713 for the chemotherapy naïve, 0.658 for those on chemotherapy and 0.612 for those post-chemotherapy.

A smaller difference between these values worsens the cost effectiveness estimate for enzalutamide compared to BSC.

Palliative care

The company applies a 0.500 quality of life to palliative care, citing Sandblom et al.[1] The company summary of Sandblom et al[1] presented in Table B66 only presents the 0.770 EQ-5D value for the majority of prostate cancer patients who remained alive over the course of the study.

Sandblom et al[1] estimated the quality of life among men with prostate cancer in the last 16 months of life using the EQ-5D. There was a gradual decline from around 0.58 12 to 16 months prior to death to around 0.46 in the last four months of life. Table 1 of Sandblom et al[1] suggests that among the 66 patients who died of prostate cancer during the study period the mean EQ-5D utility was 0.538. The ERG has not been able to source the 0.500 quality of life estimate within Sandblom et al,[1] though the estimates for the last eight months of life would approximately correspond to this.

Quality of life: summary

The Wolff et al abstract cited by the company did not contain quality of life data.[26] The ERG has sourced a Wolff et al abstract[28] which is in line with the company summary of Table B66.

The Diels et al[2] full paper suggests EQ-5D quality of life values of 0.70 for pre-chemotherapy, 0.66 for chemotherapy and 0.60 for post-chemotherapy. This is the only paper available to the ERG which provides estimates relevant to the different health states of the model using a single data set. It suggests that the baseline value for 1st line treatment taken from PREVAIL may be out of line with the other estimates used within the modelling, and that there may be too large a quality of life difference modelled between the 1st line and subsequent lines of treatment. The possibility of this receives further support from the PREVAIL and AFFIRM baseline EQ-5D values which show a smaller difference than that applied in the company modelling. Reasonable sensitivity analyses that are suggested by the above are:

- Using the baseline values of PREVAIL and AFFIRM.
- Assuming that the value for 2nd line docetaxel is the average of those of the 1st line and 3rd line values.
- Using the values of Diels et al.[2]

5.2 Summary and critique of manufacturer's submitted economic evaluation by the ERG

5.2.1 NICE reference case checklist

Table 21 NICE reference case checklist

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	The comparators are best supportive care (BSC) and abiraterone. These are as per the NICE scope.
Patient group	As per NICE scope. " *Adults with asymptomatic or mildly symptomatic metastatic hormone-relapsed prostate cancer in whom chemotherapy is not yet clinically indicated* "	Yes.
Perspective costs	NHS & Personal Social Services	Yes.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-effectiveness analysis	Yes. Cost utility analysis.
Time horizon	Sufficient to capture differences in costs and outcomes	10 years. This is effectively a lifetime horizon.
Synthesis of evidence on outcomes	Systematic review	The main analysis comparing enzalutamide with BSC relies upon evidence from the main PREVAIL trial. Independent overall survival curves and time to treatment discontinuation curves are estimated for each arm due to proportionate hazards having been rejected. The comparison with abiraterone relies upon independent curves estimated for the abiraterone arm of COU-AA-302.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	Partial. The main health states for 1st line treatments and SRE utility decrements

		are estimated from the PREVAIL EQ-5D data. But the values for the other health states of the model have been estimated from values within the literature. How these values have been arrived at is not entirely transparent.
Benefit valuation	Time-trade off or standard gamble	The PREVAIL EQ-5D data is estimated using the standard UK tariff. Time-trade off.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Yes. At least for the values for 1st line treatments.
Discount rate	An annual rate of 3.5% on both costs 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. The base cases are modelled deterministically and probabilistically. The company notes that due to the IPCW adjustment method the uncertainty around the clinical effectiveness parameters is likely to have been underestimated.
Sensitivity analysis		A wide range of univariate sensitivity analyses are undertaken, with the electronic model reporting the 15 most influential parameters. A number scenario analyses are also presented.

5.2.2 Model structure

A de novo Markov model with a weekly cycle length is developed by the company.

All patients start on a 1st line treatment. A proportion of those modelled as ceasing the

1st line treatment receive 2nd line docetaxel, with the remainder proceeding straight to palliative care. The model has the facility for a proportion of those ceasing 2nd line docetaxel to receive a 3rd line treatment, with the remainder proceeding to palliative care. Those ceasing 3rd line treatment proceed to palliative care. An equal probability of death is applied to all health states.

Treatments are also associated with SREs and with AEs, these having cost and quality of life impacts.

The main model inputs are the overall survival (OS) curves and time to treatment discontinuation (TTD) curves for the 1st line treatments. These are derived for each of the 1st line treatments which are modelled:

- Enzalutamide
- Abiraterone
- BSC

The 1st line treatment's overall survival curve provides the probability of death in each cycle, this probability being applied equally to all the model health states. As a consequence, the modelling of treatments subsequent to the 1st line treatment has no impact upon the modelled overall survival. The modelling of treatments subsequent to the 1st line treatment only affects which health states patients pass through subsequent to 1st line treatment, with these health states being associated with their own costs and quality of life.

For a given 1st line treatment, its TTD curve determines the proportion of patients that continue to receive it and remain progression free through time.

5.2.3 Population

The population is as per the PREVAIL trial entry criteria, chemotherapy treatment naïve asymptomatic and mildly symptomatic mHRPC patients.

5.2.4 Interventions and comparators

The model does not just compare the three 1st line treatments of enzalutamide, abiraterone and BSC. It compares three treatment sequences. For all the modelling presented within the submission, the model compares:

- 1st enzalutamide 2nd docetaxel → 3rd palliative,
- 1st abiraterone 2nd docetaxel → 3rd palliative,
- 1st BSC 2nd docetaxel → 3rd enzalutamide → 4th palliative

with transitions to palliative care being possible from 1st line enzalutamide and 2nd line docetaxel, and within the BSC arm from 3rd line enzalutamide as well.

In the light of this, for the company base case the model structure presented in Figure B17 on page 137 of the submission is slightly misleading. Patients in the enzalutamide arm and abiraterone arm may receive PP1, but PP2 does not exist for them. Only patients in the BSC may receive both PP1 and PP2, as noted in the company submission:

> *Upon progression following docetaxel treatment only patients in the BSC can receive another active treatment. This is in line with clinical practice in the UK where prescription of enzalutamide or abiraterone is not recommended if patients have received any of these two treatments previously.*

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 ten year horizon is adopted, which is in effect a lifetime horizon. Health benefits and costs are discounted at 3.5%.

5.2.6 Treatment effectiveness and extrapolation

1st line treatment effectiveness

The company extrapolation report rejected proportionate hazards and as a consequence individual parameterised curves were separately fitted to the arms of PREVAIL. Two data cuts were available: September 2013 and June 2014 with PREVAIL having been unblinded in December 2013 for ethical reasons. Due to cross-over and PREVAIL permitting a number of 2nd line treatments that would not be usual practice in the UK the company adjusted the overall survival data using the IPCW method, though an alternative two stage method was also explored.

For abiraterone the Kaplan Meier OS and PFS curves from the COU-AA-302 3rd interim analysis were digitized, the Guyot method employed and parametric models fitted.

The best fitting curves for both the PREVAIL June 2014 IPCW overall survival data and the COU-AA-302 3rd interim analysis data applied the gamma distribution as outlined below.

Table 22 Goodness of fit estimates: PREVAIL June 2014 IPCW and COU-AA-302: OS

	Placebo		Enzalutamide		Abiraterone	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	943.0	947.3
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	860.6	869.2
Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]	861.5	870.1
Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]	859.3	867.9
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	858.8	867.4

But for the PREVAIL data the resulting gamma parametric OS curves were deemed clinically implausible due to the implied survival rates.

Table 23 Estimated five year and ten year survival rates

	Placebo		Enzalutamide		Abiraterone[c]	
	5 year	10 year	5 year	10 year	5 year	10 year
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	..	..
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	11.53%	0.02%
Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]	..	..
Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]	23.09%	6.06%
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	19.91%	1.68%

Firstly, the placebo and enzalutamide gamma OS curves cross before the year 5 point, with 5 year survival rates of [redacted] in the placebo arm and [redacted] in the enzalutamide arm. The PREVAIL weibull OS curves also crossed but much later at around [redacted] months when virtually no patients are modelled as surviving in either arm. Given

[c] These values are taken from the company model, which only implements the Weibull, log-logistic and gamma functional forms.

visual inspection of the parameterised curves compared to the Kaplan Meier curves, the similarity of the information criteria for the gammas and the Weibulls and expert opinion the Weibulls were selected for the base case. Given the recommendations of the DSU technical support document 14, the Weibull was also selected for abiraterone.

Rather than model radiographic progression (rPFS) the company chose to model the time to treatment discontinuation (TTD). The reasons for this were that the fixed scan intervals in PREVAIL were protocol determined and that rPFS would not reflect how disease progression would be identified in clinical practice. TTD has also been used in previous NICE assessments of treatments for prostate cancer. Treatment discontinuation in PREVAIL only occurred once a patient had progression confirmed either through rPFS or an SRE and was scheduled to initiate another antineoplastic therapy.

The company also chose the June 2014 data cut for the base case TTD estimates, with the following goodness of fit parameters.

Table 24 Goodness of fit estimates: PREVAIL June 2014 and COU-AA-302: TTD

	Placebo		Enzalutamide		Abiraterone	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	1,285.21	1,289.51
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	1,273.87	1,282.48
Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]	1,247.55	1,256.16
Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]	1,255.55	1,264.15
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	1,246.96	1,255.57

As for overall survival, the proportions of patients modelled as surviving on treatment were also considered.

Table 25 Estimated 3 year and 5 year proportions remaining on treatment: June 2014

	Placebo		Enzalutamide		Abiraterone[d]	
	3 year	5 year	3 year	5 year	3 year	5 year
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	..	..
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	17.33%	3.95%
Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]	22.52%	11.29%
Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]	21.36%	11.02%
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	23.58%	12.78%

Visual inspection of the Kaplan Meier curves suggested that all curves other than the exponential provided a reasonable fit. Company expert opinion suggested that the [redacted] estimate for the proportion of patients remaining on 1st line enzalutamide at year 5 as per the best fitting log-logistic curve was implausible, particularly in the light of the OS weibull suggesting that only [redacted] would remain alive at this point. It was felt that the gamma distribution provided a more reasonable estimate of [redacted] remaining on treatment at the 5 year point.

This results in the following OS and TTD modelled curves being applied (Figure 7).

Figure 7 Base case OS Weibull and TTD gamma curves

Unadjusted hazard ratios relative to the PREVAIL placebo arm were also estimated for overall survival and TTD, with these being available for sensitivity analyses.

[d] These values are taken from the company model, which only implements the Weibull, log-logistic, log-normal and gamma functional forms.

Table 26 Unadjusted hazard ratios present within the economic model

	OS	TTD
Abiraterone	[redacted]	[redacted]
Enzalutamide Jun 2014 data cut	[redacted]	[redacted]
Enzalutamide Sep 2013 data cut	[redacted]	[redacted]

Applying the hazard ratios to the unadjusted PREVAIL placebo OS Weibulls and gammas results in the following 5 year and 10 year survival rates.

Table 27 OS estimates from hazard ratios applied to PREVAIL unadjusted placebo curves

	Placebo		Enzalutamide		Abiraterone	
	5 year	10 year	5 year	10 year	5 year	10 year
Weibull Jun 2014 unadjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull Sep 2013 unadjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

As would be expected, in contrast to the estimates of the parameterised curves the hazard ratios suggest that overall survival in the abiraterone arm is much closer to that in the enzalutamide arm than to that in the placebo arm at 5 years and at 10 years.

Applying the hazard ratios to the weibull TTD and gamma TTD curves that are presented within the electronic model result in the following estimated proportions remaining on 1st line treatment at 3 years and at 5 years.

Table 28 Estimated three year and five year proportions remaining on treatment from HRs

	Placebo		Enzalutamide		Abiraterone	
	3 year	5 year	3 year	5 year	3 year	5 year
Weibull TTD Jun 2014	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma TTD Jun 2014	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull TTD Sep 2014	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma TTD Sep 2013	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Compared to the individual gamma TTD curves, the hazard ratios when applied to the PREVAIL placebo gamma TTD curves suggest rather fewer remaining on 1st line treatment at 5 years in the abiraterone arm than in the enzalutamide arm. But the

proportions remaining on 1st line treatment in the enzalutamide arm exceed the proportions modelled as surviving at 5 years when using the June 2014 IPCW Weibulls. Much the same is true when applying the hazard ratios to the PREVAIL placebo weibull TTD curves, though the disparity with the proportions modelled as surviving at 5 years is less.

2nd line docetaxel, 3rd line enzalutamide and 3rd line abiraterone

Among those ceasing 1st line treatment who cease for reasons other than death, 84.5% are assumed to move on to receive 2nd line docetaxel with the remaining 16% moving to palliative care. This is based upon PREVAIL data from the BSC arm: of the [redacted] who ceased 1st line therapy or switched to enzalutamide, [redacted] went on to receive a 2nd line antineoplastic therapy though among these due to trial design only [redacted] received docetaxel.

Within the enzalutamide arm and the abiraterone arm, those ceasing 2nd line docetaxel for reasons other than death move to palliative care. But within the BSC arm those, 80.9% of those ceasing treatment for reasons other than death move on to receive 3rd line enzalutamide. Note that the model also has the facility for 3rd line abiraterone[e]. The 80.9% estimate is similarly based upon PREVAIL data from the BSC; of the 387 patients who ceased 2nd line docetaxel 313 went on to receive a 3rd line treatment.

For 2nd line docetaxel and 3rd line enzalutamide and abiraterone the TTD curves are assumed to be exponential. For 2nd line docetaxel a per cycle discontinuation probability of 2.04% is derived from a median number of administrations of 9.5, as reported in Tannock et al,[30] with these being 3 weeks apart suggesting a median treatment duration of 28.5 weeks. For 3rd line enzalutamide and abiraterone the median number of administrations of 8.3 and 7.4, as reported in Scher et al[17] and Fizazi et al[31] respectively, coupled with these being monthly or 4.3 weeks apart suggests median treatment durations of 36.0 weeks and 32.1 weeks. These are used to derive per cycle discontinuation probabilities of 1.91% and 2.14% respectively. These give rise to the following TTD curves for 2nd line docetaxel and 3rd line enzalutamide

[e] There are also other options at 2nd line, such as radium-223, and at 3rd line such as docetaxel and cabazitaxel. Given expert opinion, the ERG has concentrated upon 3rd line enzalutamide and abiraterone.

and abiraterone. Note that these apply from the start of 2nd line treatment and the start of 3rd line treatment, rather than from the first cycle of the model.

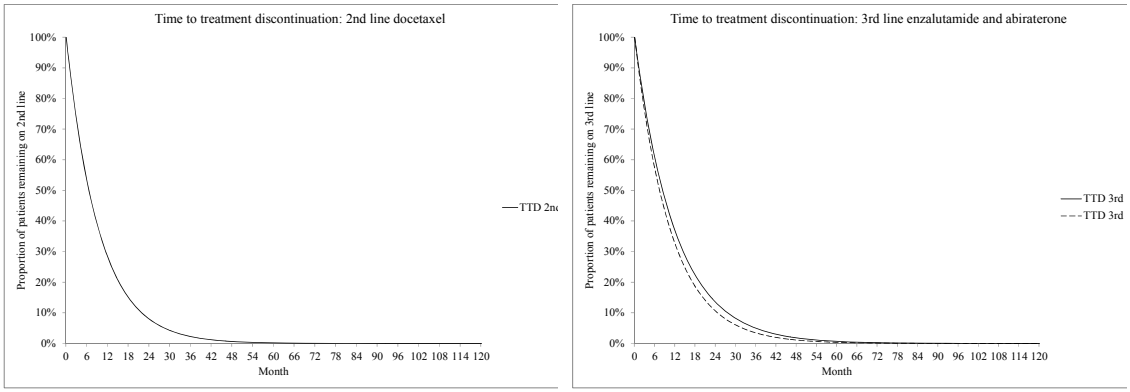


Figure 8 TTD curves for 2nd line and 3rd line treatments

SREs: 1st line treatments

The number of SREs observed in PREVAIL during stable disease, this having the same definition as that used for the construction of the TTD curves, from the interim September 2013 data cut was converted to a rate using the treatment emergent periods of [redacted] years for 1st line enzalutamide and [redacted] years for BSC. 1st line abiraterone was assumed to have the same SRE profile as 1st line enzalutamide due to a lack of data in the pre-chemotherapy setting.

For treatments subsequent to 1st line the pooled PREVAIL post-progression number of events was converted to a rate using the pooled treatment emergent period of [redacted] years.

This resulted in the following SRE rates.

Table 29 SRE rates: September 2013 data cut

	Enza.		BSC		Progressed	
	n	Annual	n	Annual	n	Annual
Spinal cord compression	38	[redacted]	21	[redacted]	176	[redacted]
Pathologic bone fractures	41	[redacted]	15	[redacted]	100	[redacted]
Radiation to bone	130	[redacted]	83	[redacted]	586	[redacted]
Surgery to bone	15	[redacted]	9	[redacted]	39	[redacted]
Total	224	[redacted]	128	[redacted]	901	[redacted]

While the company model used the September data cut to estimate SRE rates, data from the June 2014 data cut suggested similar estimates with treatment emergent periods of [redacted] years for 1st line enzalutamide and [redacted] years for BSC.

Table 30 SRE rates: June 2014 data cut

	Enza.		BSC	
	n	Annual	n	Annual
Spinal cord compression	44	[redacted]	22	[redacted]
Pathologic bone fractures	48	[redacted]	16	[redacted]
Radiation to bone	142	[redacted]	85	[redacted]
Surgery to bone	17	[redacted]	9	[redacted]
Total	251	[redacted]	132	[redacted]

Serious adverse events

The number of adverse events within PREVAIL was conditioned by the patient years in the treatment period, [redacted] years for enzalutamide and [redacted] years for BSC, to derive the mean number of adverse events in each cycle of the model.

The number of adverse events from COU-AA-302 was taken from Rathkopf et al[32] and the FDA label for abiraterone. Due to the treatment period not being given, these were assumed to be the same as in PREVAIL: [redacted] years for abiraterone and [redacted] years for BSC. This was used to calculate an absolute rate difference for abiraterone compared to BSC, which was then summed with the BSC PREVAIL adverse event rate to provide an estimate for abiraterone within the model. It seems likely that summation was used rather than a relative risk due to the adverse event rates reported for COU-AA-302 not being aligned with those reported in PREVAIL and so the BSC arm in PREVAIL having a zero rate for a number of the COU-AA-302 adverse events. But it also means that PREVAIL BSC rates have been assumed to apply to abiraterone where none were reported in COU-AA-302

The rates of adverse events for docetaxel were taken from Tannock et al,[30] with a 183 years treatment period.

This resulted in the following estimates.

Table 31 Serious adverse events: numbers of patients with event and annualised rates

	PREVAIL data				COU-AA-302 data					ITC	TAX 327	
	Enza.		BSC		Abir.		BSC		Net	Abir.	Doc.	
	n	Annual	n	Annual	n	Annual	n	Annual	Annual	Annual	n	Annual
Anaemia	29	2.46%	25	4.62%							17	9.31%
Arthralgia					11	0.93%	11	2.03%	-1.10%			
Back pain	22	1.86%	25	4.62%						4.62%		
Bone pain	12	1.02%	20	3.69%						3.69%		
Deterioration	18	1.53%	10	1.85%								
Dyspnoea					13	1.10%	5	0.92%	0.18%	0.18%		
Fatigue					13	1.10%	10	1.85%	-0.74%	0.00%	17	9.31%
Feb. neutropenia											10	5.48%
Hypertension	59	5.00%	19	3.51%	23	1.95%	17	3.14%	-1.19%	2.32%		
Hypokalaemia					14	1.19%	10	1.84%	-0.66%	0.00%		
Fluid retention					5	0.42%	9	1.66%	-1.24%	0.00%		

The adverse event rates for 3rd line enzalutamide and 3rd line abiraterone were assumed to be the same as for 1st line treatment.

5.2.7 Health related quality of life

Quality of life for 1st line treatments

EQ-5D data was collected in PREVAIL at week 1, and 12 weekly thereafter among those remaining on the study drug. The company conducted a mixed model repeated measures (MMRM) analysis of this data, having established a final statistical analysis plan on 15 Nov 2013 prior to the data base being locked. The data analysis report is dated 19 Sep 2014.

Only one analysis was undertaken for the main quality of life states required for the model. This controlled for baseline score, treatment, investigation site, the ECOG pain score at baseline, fatigue severity at baseline, pain at baseline, age, time, time and treatment arm interaction and time and baseline value interaction. EQ-5D data was rejected for weeks 73 and onwards due to less than 10% of the original reporting population remaining in the BSC arm.

The mean baseline quality of life value was 0.844. The least squares estimates for changes from baseline were a loss of 0.042 for enzalutamide and a loss of 0.064 for placebo. This resulted in a treatment effect estimate of a gain of 0.021 from enzalutamide over placebo.

The model assumed that patients in on 1st line BSC had the mean baseline quality of life of 0.844. Patients in the enzalutamide arm who had not discontinued and progressed to 2nd line had the mean baseline quality of life of 0.844 plus the treatment effect of 0.021, resulting in a quality of life of 0.866.

Quality for life for 2nd and 3rd line treatments

The submission appears to state that weighted averages of the values of Wolff et al,[28] 0.66 for post-chemotherapy and 0.64 for those receiving chemotherapy, and Diels et al,[2] 0.69, were used to derive quality of life values for 2nd and 3rd line treatments of 0.658 and 0.612.

Quality of life for palliative care

A quality of life value of 0.506 was drawn from Sandblom et al.[1]

Quality of life: SREs

The quality of life disutilities for SREs were taken from a stand-alone analysis of the PREVAIL EQ-5D data, pooled across the arms. Two analyses were undertaken, one that examined the impact of the first SRE upon quality of life and another that examined the impact of the most severe SRE upon quality of life.

The impact of an SRE upon quality of life was undertaken in two steps. Each patient's longitudinal quality of life before the SRE was modelled using a linear effects mixed model with an intercept and slope for time, with a range of other covariates including investigation site, baseline ECOG status, whether pain was present at baseline, the severity of fatigue at baseline and whether the patient was older than 65. A treatment adjusted mean change was then estimated based upon the difference between the predicted longitudinal quality of life of the linear effects mixed model and the post SRE value that was actually observed.

Table 32 SRE quality of life impacts by event type

	Disutility by SRE	
	First	Most Sev.
Spinal cord compression	-0.237	[redacted]
Radiation to bone	-0.056	[redacted]
Surgery to bone	-0.056	[redacted]
Pathologic bone fractures	-0.201	[redacted]

The company submission selected the impact of the 1st SRE analysis rather than the most severe SRE analysis. The reasons for this are not given and the company submission does not itemise the disutilities of the most severe analysis. SREs were assumed to last for one month based upon Botteman et al.[33] This resulted in the following SRE quality of life impacts by treatment.

Table 33 SRE quality of life impact by treatment

	QALY per SRE	Prob per cycle	QALY per cycle
1st line enzalutamide	-0.0094	0.0037	0.0000
1st line abiraterone	-0.0094	0.0037	0.0000
1st line BSC	-0.0086	0.0050	0.0000
Subsequent to 1st line	-0.0090	0.0110	-0.0001

Quality of life: serious adverse events

The disutilities for adverse events were drawn from a range of sources. Their duration was mainly assumed to be 10.5 days; i.e. between 7 and 14 days, but asthenia, deterioration in general, fatigue and leukopenia were assumed to last for 3 months. These durations were drawn from the ERG report to the STA of abiraterone post-chemotherapy STA [TA259].[34]

Table 34 Serious adverse event disutilities by event

	Disutility	Source
Anaemia	-0.119	Swinburn[35]
Arthralgia	-0.069	Doyle[36]
Back pain	-0.069	Doyle et al[36]
Bone pain	-0.069	Doyle et al[36]
Deterioration	-0.131	Assumed equal to fatigue
Dyspnoea	-0.050	Doyle[36]
Fatigue	-0.131	Lloyd et al[37], Nafees et al[38] Swinburn[35]
Feb. neutropenia	-0.120	Lloyd et al[37] and Nafees et al[38]
Hypertension	-0.153	Swinburn[35]
Hypokalaemia		None available
Neutropenia	-0.090	Nafees et al[38]
Fluid retention		None available

This resulted in the following adverse event quality of life decrements for each treatment.

Table 35 Serious adverse event quality of life impact by treatment

	QoL per event	Prob per cycle	QoL per cycle	Annualised
1st line enzalutamide	-0.0073	0.0023	-0.00002	-0.0009
1st line abiraterone	-0.0025	0.0021	-0.00001	-0.0003
1st line BSC	-0.0059	0.0035	-0.00002	-0.0011
2nd line docetaxel	-0.0061	0.0158	-0.00010	-0.0051
3rd line enzalutamide	-0.0073	0.0023	-0.00002	-0.0009
3rd line abiraterone	-0.0025	0.0021	-0.00001	-0.0003
Palliative care	-0.0059	0.0035	-0.00002	-0.0011

5.2.8 Resources and costs

Direct drug costs and administration costs

The list price of enzalutamide is £2,735 for a 28 day pack and the list price of abiraterone is £2,930 for a 30 day pack resulting in effectively the same daily cost of £97.67.

2nd line docetaxel was costed assuming 3 weekly administration with one 160mg 8ml vial being required at a cost of £47.30 as drawn from the CMU EMIT database.

It was assumed that there are no administration costs for enzalutamide, abiraterone or BSC. Only 2nd line docetaxel is associated with an administration cost as drawn from NHS reference costs: £301.56 SB15Z Simple parenteral subsequent administration.

Health state costs

These costs include all the routine visits and monitoring associated with treatment. The unit costs of these and their sources are outlined below.

Table 36 Monitoring visit unit costs

Service	Cost	Source: PSSRU or reference costs
OP consultant	£139.00	section 15.5 PSSRU
OP nurse	£42.00	section 10.4 PSSRU
CT scan	£106.45	DIAGIMOP RA10Z medical oncology
MRI scan	£241.85	DIAGIMOP RA03Z medical oncology
ECG	£140.16	OPROC EA47Z Clinical Oncology
Ultrasound < 20 min	£62.37	DIAGIMOP RA23Z medical oncology
Bone scan	£192.90	DIAGIMOP RA36Z medical oncology

Monitoring during the first three months of enzalutamide and abiraterone is typically assumed to be twice as frequent as thereafter.

Table 37 Health state costs for 1st line treatments

	% pts	Weeks between appointments				
		Enzalutamide		Abiraterone		BSC
Months		1,2,3	4+	1,2,3	4+	All
OP consultant	50%	4	8	2	4	6
OP nurse	50%	4	8	2	4	6
CT scan	100%	27	27	22	22	7
Bone scan	20%	12	12	12	12	12
Cost per cycle		£34.66	£20.91	£64.55	£36.26	£36.47
Annualised cost		£1,803	£1,087	£3,356	£1,886	£1,897

For reasons of space the above does not outline the blood counts (£3.01 for 1 test: DAPS05), liver function tests (£6.23 for 5 tests: DAPS04), kidney function tests (£12.46 for 10 tests: DAPS04), and PSA tests (£1.25 per test: DAPS04). In general, during the first three months these tests are 4 weekly for enzalutamide and 2 weekly

for abiraterone. Thereafter they are 8 weekly for enzalutamide and 4 weekly for abiraterone, and throughout are 6 weekly for BSC. The costs of these tests are included in the total costs presented above.

The health state costs for 1st line enzalutamide treatment during the first three months at an annualised cost of £1,803 are somewhat less than those for 1st line abiraterone treatment where these have an annualised cost of £3,356. This cost difference lessens thereafter, but 1st line enzalutamide still has lower annualised health state costs of £1,087 compared to £1,886 for 1st line abiraterone. Despite BSC having less frequent outpatient visits than 1st line abiraterone, the higher frequency of CT scans in the BSC arm results in a health state costs of £1,897 which is roughly in line with the long terms health state cost for 1st line abiraterone of £1,886 and somewhat above the long term health state cost for 1st line enzalutamide of £1,087.

The parallel health state costs for 2nd line docetaxel, 3rd line enzalutamide and 3rd line abiraterone are outlined below.

Table 38 Health state costs for subsequent treatments

	% pts and weeks between appointments					
	2nd docetaxel		3rd enzalutamide		3rd abiraterone	
	% pts	wks	% pts	wks	% pts	wks
OP consultant	100%	3	100%	8	100%	4
OP nurse	100%	10	5%	8	5%	8
CT scan	10%	12	5%	8	5%	8
OP nurse	5%	6	5%	8	5%	8
CT scan	5%	6	5%	8	5%	8
Bone scan	20%	12	5%	8	5%	8
Cost per cycle	£73.87		£24.82		£44.48	
Annualised cost	£3,841		£1,291		£2,313	

Costs: SREs

Pathological bone fractures were assumed to be 50% non-vertebral fractures and 50% vertebral fractures. 61% of non-vertebral fractures were also assumed to require 3 months outpatient follow up at a 2008 cost of £5,073 based upon Ross et al.[39] Uprating this by the CPI to £5,847 resulted in an average outpatient cost per non-

vertebral fracture of £3,566. The remaining SREs were costed using NHS reference costs as below.

Table 39 SRE unit cost by event

	Cost	Source
Spinal cord compression	4,688	Non-elective long stay: HC28D
Radiation to bone	683	All HRGs: SC21Z-SC28Z: 5 fractions
Surgery to bone	£3,568	Non-elective long stay: HD39E
Pathologic bone fractures	5,351	See below
Vertebral	£3,568	All HRGs: HD39D-H
Non-vertebral	£3,568	All HRGs: HD39D-H
Non-vertebral OP	£3,566	Ross et al[39] : 61% of £5,847

This resulted in the following SRE costs by treatment.

Table 40 SRE costs by treatment

	Mean per event	Prob per cycle	Mean per cycle	Annualised
1st line enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]
1st line abiraterone	[redacted]	[redacted]	[redacted]	[redacted]
1st line BSC	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent to 1st line	[redacted]	[redacted]	[redacted]	[redacted]

Costs: serious adverse events

The unit costs of adverse events and their sources are as below. These are based upon the (A) NHS reference costs 2012-13 and (B) the ERG report to the STA of abiraterone post-chemotherapy STA [TA259].[34]

Table 41 Serious adverse event unit costs by event

	Cost	Source
Anaemia	£1,779	(A) Non-elective long stay: SA04G-L
Arthralgia	£176	(A) NCL: WF02B; service code: 191
Back pain	£467	(A) Non-elective short stay: HC32D-F
Bone pain	£606	(A) Non-elective short stay: HD40D-F
Deterioration	£12	Assumed equal to fatigue
Dyspnoea	£0	(B) table 24, p. 64
Fatigue	£12	(B) table 24, p. 64
Feb. neutropenia	£4,519	(A) Non-elective long stay: PA45Z
Hypertension	£432	(A) Non-elective short stay: EB04Z
Hypokalaemia	£348	(A) Outpatient HCD: XD26Z
Neutropenia	£161	(A) Admitted patient care: HCD: XD25Z
Fluid retention	£914	(B) table 24, p. 64

This result in the following adverse event costs for each treatment, per cycle and on an annualised basis.

Table 42 Serious adverse event costs by treatment

	Mean per event	Prob per cycle	Mean per cycle	Annualised
1st line enzalutamide	£678	0.0023	£1.55	£80
1st line abiraterone	£499	0.0021	£1.04	£54
1st line BSC	£774	0.0035	£2.72	£141
2nd line docetaxel	£618	0.0158	£9.76	£507
3rd line enzalutamide	£678	0.0023	£1.55	£80
3rd line abiraterone	£499	0.0021	£1.04	£54
Palliative care	£774	0.0035	£2.72	£141

Costs: concomitant medications

Concomitant medication rates were taken from PREVAIL for 1st line enzalutamide and 1st line BSC. Concomitant medication for 1st line abiraterone was assumed to be the same as that for 1st line enzalutamide with the exception of all requiring prednisolone. The submission states that concomitant medication was not reported for docetaxel in TAX327, so was assumed to be equal to cabazitaxel. The source of the estimates for cabazitaxel does not appear to be given.

Drug costs were source from the CMU EMIT data base as per NICE guidelines, with the exception of the G-CSF filgrastim which was taken from the BNF 68 due to there being no entry for it within the CMU EMIT database.

Table 43 Concomitant medication use and costs

		Per cycle	Enza.	Abir.	BSC	Doc.
Biphosphonates	Zoledronate	£19.29	35%	35%	35%	47%
Antihistamine	Chlorpenamine	£0.08	0%	0%	0%	100%
H2-antagonist	Ranitidine	£0.03	42%	42%	38%	100%
Anti-emetic	Ondansetrone	£0.39	8%	8%	8%	100%
Corticosteroid	Prednisolone	£0.40	27%	100%	30%	100%
GSCF	Neupogen	£246.61	0%	0%	0%	25%
Costs per cycle			£6.86	£7.15	£6.93	£71.65
Annual			£357	£372	£360	£3,726

Costs: palliative care

Annual palliative care costs of £3,765 in 2001 prices were drawn from Guest et al[40] and uprated for inflation to result in an annual cost for palliative care of £5,398, or £104 per cycle.

Costs: terminal care

Terminal care costs of £3,598 were taken from the abiraterone pre-chemotherapy submission [ID503].[11]

5.2.9 Cost effectiveness results

The model suggests the following undiscounted year's survival in each of the model health states.

Table 44 Mean years survival by health state by arm

	1st line	2nd line	3rd line	Palliative	Total
Enzalutamide	2.001	0.340	0.000	0.896	3.238
BSC	0.606	0.603	0.464	1.072	2.745
Abiraterone	1.854	0.320	0.000	0.829	3.003

It is anticipated the enzalutamide will result in an overall survival gain of 0.493 years compared to BSC and of 0.235 years compared to abiraterone. 2.001 years is

anticipated to be spent progression free and on 1st line enzalutamide treatment, compared to 0.606 years in the BSC arm and 1.149 in the abiraterone arm.

This means that enzalutamide is also anticipated to reduce the amount of time spent in the post-progression health state with only 1.236 years being spent in survival after having ceased 1st line therapy compared to 2,139 years in the BSC arm. This is mainly due to it being modelled that patients in the BSC will spend longer receiving 2nd line docetaxel and 3rd line treatment, net increases of 0.262 and 0.464 years respectively. The amount of time spent in palliative care shows less of a difference, with a net increase of only 0.176 years.

The model outputs and cost effectiveness estimates of the company model, excluding both the enzalutamide PAS and the abiraterone PAS are as below.

Table 45 Company deterministic base case results exclusive of PASs

	Enzalutamide	BSC	net	Abiraterone	net
Direct drug and admin					
1st line	£68,213	£0	£68,213	£63,203	£5,010
2nd line	£1,949	£3,525	-£1,577	£1,858	£91
3rd line	£0	£15,618	-£15,618	£0	£0
Health state costs					
1st line	£2,240	£1,139	£1,101	£3,693	-£1,454
2nd line	£1,244	£2,250	-£1,006	£1,186	£58
3rd line	£0	£565	-£565	£0	£0
Concomitant medication					
1st line	£683	£213	£470	£659	£23
2nd line	£1,207	£2,183	-£976	£1,151	£56
3rd line	£0	£156	-£156	£0	£0
SREs	£1,294	£1,562	-£268	£1,210	£84
AEs	£319	£417	-£99	£253	£66
Palliative	£4,414	£5,334	-£920	£4,154	£261
Terminal	£3,277	£3,332	-£55	£3,306	-£29
Total costs	£84,840	£36,296	£48,543	£80,672	£4,168
LY (undiscounted)	3.238	2.745	0.493	3.003	0.235
QALYs (discounted)	2.274	1.657	0.618	2.120	0.154
ICERs			£78,587		£27,076

For the comparison with BSC the high 1st line treatment costs for enzalutamide are offset to quite a large degree by the additional costs of 3rd line enzalutamide in the BSC arm. There are also reasonable cost offsets due to patients in the enzalutamide arm being estimated to spend less time receiving 2nd line docetaxel, and also to spend less time in palliative care. These cost offsets to the £68,213 1st line costs in part account for the total net costs being only £48,543. The overall undiscounted survival gain of 0.493 years translates into a gain of 0.618 QALYs, which given the net costs results in a cost effectiveness estimate of £78,587 per QALY.

For the comparison with abiraterone 1st line treatment costs are slightly higher in the enzalutamide arm due to its superior time to treatment discontinuation curve, with a net cost of £5,010. But these are in part offset by the somewhat higher health state costs for 1st line abiraterone treatment, resulting in a net total cost of £4,168. A reasonably large gain in undiscounted survival of 0.235 years is estimated for enzalutamide, which translates into a 0.154 QALY gain. These result in a cost effectiveness estimate for enzalutamide compared to abiraterone of £27,076 per QALY.

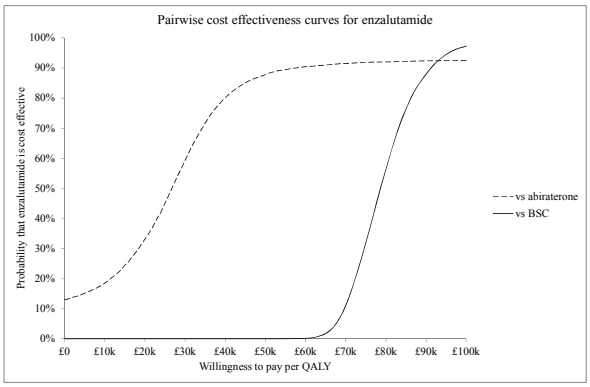


Figure 9 Pairwise CEACs for company base case excluding PAS

Over 10,000 iterations the central estimates for enzalutamide, abiraterone and BSC are total costs of £84,839, £80,822 and £36,298 and total QALYs of 2.275, 2.124 and 1.659. These result in central cost effectiveness estimates of £78,767 per QALY for the comparison with BSC and £26,658 per QALY for the comparison with abiraterone. These estimates are in line with those of the deterministic modelling. The company notes that the IPCW method will have resulted in standard errors for the

effectiveness estimates that are too small, and that as a consequence the above probably understates the amount of uncertainty there is around the estimates.

5.2.10 Sensitivity analyses

A large range of univariate sensitivity analyses are conducted, with the electronic model that underlies the company submission presenting the fifteen parameters that have the largest impact given the range of values inputted for them. These are presented below.

Table 46 Univariate sensitivity analyses vs BSC: base case ICER £78,587 per QALY

	Base	Low		High	
Parameter	Value	Value	ICER	Value	ICER
Enzalutamide cost	£97.67	£73.25	£57,300	£122.08	£99,874
Enzalutamide OS Weibull intercept	[redacted]	[redacted]	£91,081	[redacted]	£69,227
BSC % patients receiving 3rd line	81%	0%	£92,221	100%	£74,924
BSC OS Weibull intercept	[redacted]	[redacted]	£71,873	[redacted]	£87,888
BSC % receiving 2nd line docetaxel	84%	0%	£89,069	100%	£76,059
Enzalutamide QoL treatment gain	0.022	0.003	£83,527	0.041	£74,199
Discount rate for benefits	3.5%	0.0%	£73,398	5.0%	£80,791
Palliative care QoL	0.500	0.344	£75,348	0.656	£82,117
BSC TTD gamma intercept	[redacted]	[redacted]	£75,893	[redacted]	£81,672
3rd line treatment QoL	0.612	0.564	£75,999	0.659	£81,294
BSC TTD gamma shape	[redacted]	[redacted]	£81,438	[redacted]	£76,270
Discount rate for costs	3.5%	0.0%	£81,734	5.0%	£77,370
2nd line docetaxel median duration	6.577	4.933	£76,796	8.221	£80,521
Time horizon	10.0	5.0	£81,381	15.0	£78,589
Baseline QoL	0.844	0.836	£79,903	0.852	£77,338

Table 47 Univariate sensitivity analyses vs abiraterone: base case ICER £27,076 per QALY

	Base	Low		High	
Parameter	Value	Value	ICER	Value	ICER
Enzalutamide cost	£97.67	£73.25	Dominant	£122.08	£137,858
Abiraterone cost	£97.67	£73.25	£129,721	£122.08	Dominant
Abiraterone OS weibull intercept	[redacted]	[redacted]	£25,706	[redacted]	£159,078
Abiraterone TTD gamma intercept	[redacted]	[redacted]	£49,170	[redacted]	Dominant
Abiraterone TTD gamma shape	[redacted]	[redacted]	Dominant	[redacted]	£47,922
Enzalutamide TTD gamma intercept	[redacted]	[redacted]	Dominant	[redacted]	£43,921
Enzalutamide TTD gamma shape	[redacted]	[redacted]	£41,601	[redacted]	Dominant
Enzalutamide OS Weibull intercept	[redacted]	[redacted]	£47,881	[redacted]	£22,406
Enzalutamide % receiving 2nd line docetaxel	84%	0%	£9,191	100%	£29,183
Enzalutamide QoL treatment gain	0.022	0.003	£35,500	0.041	£21,883
Abiraterone QoL treatment gain	0.022	0.003	£22,194	0.041	£34,711
Abiraterone OS weibull scale	[redacted]	[redacted]	£32,777	[redacted]	£20,472
Abiraterone % receiving 2nd line docetaxel	84%	0%	£35,943	100%	£24,822
Abiraterone health state cost mth4+	£36.26	£29.51	£30,628	£43.71	£23,163
Enzalutamide TTD gamma scale	[redacted]	[redacted]	£22,242	[redacted]	£29,698

As would be expected, the main sensitivities are to the cost of enzalutamide, the cost of abiraterone, the parameterisations of the overall survival curves, the parameterisations of the TTD curves, the proportions receiving subsequent line of treatment and the quality of life values.

A wide range of scenario analyses are also presented as summarised below.

Table 48 Company scenario analyses

	ICER vs BSC	ICER vs Abiraterone
Base case	£78,587	£27,076
Data cut-off date		
Data cut-off September 2013	£98,751	£47,213
Survival modelling		
Two stage OS adjustment method	£87,677	£39,399
Unadjusted survival data	£97,185	£33,291
Gamma distribution for OS	£90,019	£34,499 SW
Proportional hazards	£69,377	£40,187
Adjusted indirect comparison for abiraterone OS	..	Dominant
TTD modelling		
rPFS Sept 2013 instead of TTD 2014	£86,696	£28,894
TTD Sept 2013 instead of TTD Sep 2014	£81,449	£28,642
Weibull distribution for TTD	£78,317	£30,404
Costs		
BNF price for docetaxel	£71,908	£28,623
Including unscheduled costs as per abiraterone submission	£75,159	£29,006
Applying the PPRS payment percentage for 2015 (10.36%)	[redacted]	[redacted]
Increase costs for spinal cord compression	£78,210	£27,314
Treatment pathway		
Abiraterone is given after docetaxel in the BSC arm	£79,535	£27,076
SREs		
Increase duration of SREs	£77,044	£27,690
Utilities		
Baseline utility from AFFIRM is used for 3rd line	£83,042	£27,076
AEs		
No AEs	£78,835	£26,432

Using the September 2013 data cut rather than the June 2014 data has a major detrimental effect upon the cost effectiveness estimates.

The scenario analyses that alter the functional forms for overall survival modelling all worsen the cost effectiveness estimates for enzalutamide compared to BSC with the exception of applying the hazard ratio.

The cost effectiveness of enzalutamide compared to abiraterone is also worsened by the scenario analyses that alter the functional forms for overall survival modelling, with the exception of using the gamma extrapolations. The latter results in a point in the SW quadrant of the cost effectiveness plane hence the £34,499 per QALY is the cost effectiveness of abiraterone compared to enzalutamide. At a willingness to pay of £20,000 per QALY the net health benefits of the base case are around a loss of £1,088 whereas the sensitivity analysis that applies the gamma extrapolations causes this to change to a gain of £1,535. Increasing the willingness to pay to £30,000 causes the net health benefits to change only a little from around a gain of £452 to a gain of £485.

Changes to the modelling of the time to treatment discontinuation tend to worsen the cost effectiveness estimates, though the impacts are not as large as the revisions to the overall survival modelling.

Increasing the cost of 2nd line docetaxel treatment improves the cost effectiveness estimate compared to BSC, though worsens it slightly for the comparison with abiraterone. Applying the PPRS payment percentage improves the cost effectiveness estimates by a reasonable amount. Note that this scenario analysis also applies this discount to the cost of abiraterone, though not to the costs of any other drugs within the modelling.

Applying the AFFIRM baseline utility for 3rd line enzalutamide treatment, as was used in the company submission for the post-chemotherapy enzalutamide STA [TA316],[41] worsens the cost effectiveness estimate compared to BSC by a reasonably large amount.

5.2.11 Model validation and face validity check

The ERG has rebuilt the company model structure, and given the company modelling assumptions there is a very good correspondence between the two models.

Table 49 ERG cross check model rebuild results compared to company model results

	ERG cross check rebuild			Company model		
	QALY	Cost	ICER	QALY	Cost	ICER
Enzalutamide	2.273	£84,843		2.274	£84,840	
Abiraterone	2.119	£80,648	£27,260	2.120	£80,672	£27,076
BSC	1.657	£36,299	£78,825	1.657	£36,296	£78,587

In terms of face validity the main check that can be made is the proportions of patients modelled as surviving at 3 years, at 5 years and at 10 years.

Table 50 Proportions modelled as surviving at 3 years, 5 years and 10 years

	Enzalutamide	Abiraterone	BSC
3 year	[redacted]	[redacted]	[redacted]
5 year	[redacted]	[redacted]	[redacted]
10 year	[redacted]	[redacted]	[redacted]

ERG expert opinion suggests that 10% survival at 5 years for BSC may be towards the high side, and that 10% to 15% survival at five years for enzalutamide may be reasonable. But these figures are indications rather than formal estimates, and given the sequences of treatments being modelled arriving at a reasonable figure for survival at five years is more complicated than for the later treatments such as for the use of abiraterone after docetaxel.

While there is a survival gain from abiraterone over BSC at year 3, this has disappeared by year 5. This seems questionable and may suggest that the model tends to overestimate the survival gain from enzalutamide over abiraterone.

Table 51 Median survival in months: enzalutamide vs BSC

	PREVAIL		June 2014 Weibulls	
	Sep 2013	Jun 2014	Unadj.	IPCW
Enzalutamide	32.40	[redacted]	[redacted]	[redacted]
BSC	30.20	[redacted]	[redacted]	[redacted]
net	2.20	[redacted]	[redacted]	[redacted]

The PREVAIL trial data suggests considerably smaller differences in the median overall survivals than the unadjusted Weibulls of the model. The impact of the IPCW adjustment upon the differences in the median overall survivals Weibulls of the model is marked. The face validity of this modelling should perhaps also be judged through an examination of the IPCW adjusted Kaplan Meier curves and adjusted Weibull curves as presented in Figure 11 in section 5.3.4 below.

The validity of the model structure for the comparison with abiraterone can also be investigated by comparing the estimated survival for the abiraterone arm compared to BSC arm with that estimated during the STA of abiraterone for the same indication [ID503].[11] The ERG report for this assessment reports the median survival estimates of the model and of the trial[f], and the estimates of the current modelling can be presented alongside these.[42]

Table 52 Median survival in months: abiraterone vs BSC [ID503]

	STA ID503		Current
	Model	Trial	model
Abiraterone	31.11	35.29	33.69
BSC	29.68	30.13	[redacted]
net	1.43	5.16	[redacted]

The ERG report of the abiraterone STA criticised the model for being an overly complicated discrete event simulation. When examined solely by the median survival estimates it also appears to have performed relatively poorly. The current modelling approach appears to perform more satisfactorily, though may also tend to underestimate the benefits of abiraterone compared to BSC.

It should also be borne in mind that the above comparison of median survivals is only a cross check of the model outputs to the end of year 3, and is not a cross check of the face validity of the model outputs for the remaining 7 years of the model.

[f] http://www.nice.org.uk/guidance/gid-tag434/documents/prostate-cancer-metastatic-hormone-relapsed-not-treated-with-chemotherapy-abiraterone-acetate-with-prednisolone-id503-evaluation-report2 table 5.4 of the ERG report

The mean duration of 2nd line docetaxel within the model is 9.6 months, and the mean duration of 3rd line enzalutamide within the model is 12.1 months[g]. The company response to ERG clarification question B8 states that the mean undiscounted time to treatment discontinuation modelled for enzalutamide post-chemotherapy [TA316][41] was [redacted] years of around [redacted] to [redacted] months which is broadly in line with that of the current model.

5.3 ERG cross check and critique

5.3.1 Base case results

The base case results of the model cross check with those reported in the submission.

5.3.2 Data inputs: correspondence between written submission and sources cited

Quality of life: 1st line treatments

The company PRO report undertakes a mixed model repeated measures (MMRM) analysis and a pattern mixed model (PMM) analysis. Only the MMRM analysis quality of life values appear to have been reported.

Quality of life: 2nd line docetaxel

The submission references Wolff et al[28] and Diels et al[27] as the sources underlying the 0.658 quality of life value used for 2nd line docetaxel. The supplied references are both abstracts rather than full articles and as outlined in the brief summary of the company literature review of section 5.1.4 above the derivation of the 0.658 value is unclear.

But in the light of the baseline EQ-5D value of PREVAIL of 0.844 minus 0.064 for 1st line BSC and the baseline EQ-5D value of AFFIRM of [redacted] for 3rd line treatment, these would seem to suggest that a value somewhere between these two values might be reasonable unless docetaxel is particularly unpleasant and toxic. A simple average would be [redacted].

[g] Note that these calculations are based solely upon the monthly discontinuation rates of 2.4% and 1.9% and do not take into account the situation in which the probability of death exceeds these.

The full paper of Diels et al[2] provides more detail and mean EQ-5D values of 0.70 for chemotherapy naïve patients (n=236), 0.66 for those undergoing chemotherapy (n=223) and 0.60 for post-chemotherapy (n=143). Despite these values being quite different from the baseline values of PREVAIL and AFFIRM, this provides some further justification for the quality of life for those on 2nd line docetaxel being the mid-point of the values for those pre and post-chemotherapy, though it has to be acknowledged that the post-chemotherapy quality of life value of Diels et al[2] may include values for those who have moved into palliative care.

Quality of life: 3rd line enzalutamide

The submission estimates a mean quality of life value from Wolff et al[28] and Diels et al[2] of 0.612 for 3rd line treatment, and couples this with a 0.04 gain from treatment with enzalutamide the source of which is given as the FAD for the STA of enzalutamide post-chemotherapy [TA316].[2,41] As outlined in the brief summary of the company literature review of section 5.1.4 above the derivation of the 0.612 value is unclear.

As for the quality of life for 2nd line docetaxel, the ERG cannot arrive at the estimate of 0.612 for 3rd line treatment given the company stated values drawn from Wolff et al[28] and Diels et al.[2] The EQ-5D data from the AFFIRM trial suggested a baseline value of [redacted] which is what appears to have been used in TA316.[2,41] The TA316 FAD[h] appears to have accepted this baseline value as reasonable though subject to some uncertainty due to small sample size.

The 0.04 gain from treatment with enzalutamide arises within the FAD due to the assessment committee considering it unreasonable to differentiate the treatment gain of enzalutamide from abiraterone. It seems likely that the 0.04 increment arising from treatment is an average of the EQ-5D [redacted] quality of life gain estimated for enzalutamide and some lower value for abiraterone.

[h] http://www.nice.org.uk/guidance/ta316/documents/prostate-cancer-hormone-relapsed-metastatic-enzalutamide-after-docetaxel-fad-document2

Quality of life: Palliative care

The value of 0.500 does not appear to correspond to anything stated explicitly in Sandblom et al[1] but it does appear to correspond with the value implied within Sandblom et al[1] for the last eight months of life. It is the same value that was used for the STA of enzalutamide post-chemotherapy [TA316].[41] Sandblom et al[1] reported an average of 0.538 among the subset that died of prostate cancer during the study period, which appears to be 16 months.

It can also be noted that the EQ-5D data of the AFFIRM study suggested a disutility at progression of -0.085 which given the value for stable disease of [redacted] suggests a quality of life of [redacted] upon progression from 3rd line enzalutamide to palliative care. The 0.500 from Sandblom et al may consequently be an underestimate for those entering palliative care, though it also has to be recognised that quality of life will deteriorate further thereafter as identified in Sandblom et al.[1]

5.3.3 Data inputs: correspondence between written submission and electronic model

The summary of the company model presented above and the associated tables has taken its values from the electronic model. Where these are presented within the written submission the values correspond between the two sources.

Overall survival and TTD: company model compared to extrapolation report: Enzalutamide and BSC

The model simulates the percentage of patients surviving and the percentage of patients surviving and remaining on 1st line treatment through the repeated application of per cycle hazards and per cycle probabilities. The ERG has cross checked these by calculating the percentage of patients surviving and the percentage of patients surviving and remaining through the use of a direct survival function. These have been further cross checked with the values presented in table 8 and table 19 of the company extrapolation report.

Table 53 Modelled OS and TTD for the company base case

	OS Weibulls		TTD gammas	
	Enzalutamide	BSC	Enzalutamide	BSC
3 year	[redacted]	[redacted]	[redacted]	[redacted]
5 year	[redacted]	[redacted]	[redacted]	[redacted]
10 year	[redacted]	[redacted]	[redacted]	[redacted]

Table 54 ERG cross check of the OS and TTD for the company base case

	OS Weibulls		TTD gammas	
	Enzalutamide	BSC	Enzalutamide	BSC
3 year	[redacted]	[redacted]	[redacted]	[redacted]
5 year	[redacted]	[redacted]	[redacted]	[redacted]
10 year	[redacted]	[redacted]	[redacted]	[redacted]

Table 55 Extrapolation report values of the OS and TTD for company the base case

	OS Weibulls		TTD gammas	
	Enzalutamide	BSC	Enzalutamide	BSC
3 year	[redacted]	[redacted]	[redacted]	[redacted]
5 year	[redacted]	[redacted]	[redacted]	[redacted]
10 year	[redacted]	[redacted]	[redacted]	[redacted]

For overall survival, the company model and the ERG cross check correspond. But there is a discrepancy with the extrapolation report. For the percentage modelled as surviving at 5 years in the BSC arm the company and ERG modelling suggests [redacted] while the extrapolation report suggests [redacted] The reason for this discrepancy is unclear, and there is no means of further examining the values given in the extrapolation report.

The time to treatment discontinuation curves broadly correspond between the three sources. The company model suggests a slightly lower proportion remaining on enzalutamide at year 5. While not major, this discrepancy appears to arise due to the model structure as discussed in more detail in the ERG review of the model structure and implementation below. This concern about the model structure has a more dramatic effect upon the modelled time to treatment discontinuation curve for abiraterone.

Quality of life: 2nd and 3rd line treatment

The electronic model does have base values of 0.658 for 2nd line docetaxel and 0.612 for 3rd line as per the written submission. The 0.612 for 3rd line is also augmented with 0.040 treatment effect as drawn from the STA of enzalutamide post-chemotherapy [TA316].[41]

Adverse event rates: enzalutamide and BSC

The values of Table B37 of the clinical effectiveness in general do not cross check with the values of Table B62 of the economics and the electronic model. For instance, while the values of back pain and bone pain do cross check, the economics suggests no arthralgia or fatigue while there are rates for these in Table B37.

Averse event rates: abiraterone

Table B62 of the submission suggests that the adverse events rates are taken as the net impact for abiraterone over BSC of COU-AA-302. It appears that the rates applied within the model are those from the ITC.

Docetaxel cost and administration cost

The cost per 160mg 8ml vial in the company supplied CMU EMIT data base end June 2014, which is as per the on line version, is £29.78 rather than the £47.30 of the electronic model. However, the 2013-14 reference costs schedule 3a also suggests a higher administration cost of £314 compared to the £302 of the electronic model.

Monitoring visit costs

The PSSRU costs cited of £139 per consultant led outpatient appointment and £42 per nurse led outpatient appointment are actually the cost per contract hour and the cost per hour respectively. It would be more reasonable to apply the 2013-14 NHS reference costs 3a schedule of WF01A non-admitted face to face follow up outpatient appointment for 370: Medical oncology of £143 for consultant led and £90 for non-consultant led[i].

[i] Note that the ERG is not clear whether nurse appointments would still in some sense be consultant led within the reference costs coding.

The ERG has also not been able to source all the other visit costs from the 2012-13 reference costs, but the 2013-14 NHS reference costs 3a schedule suggests £124 per RA10Z CT scan, £212 per RA03Z MRI scan, £215 per medical oncology EA47Z ECG, £52 per RA23Z ultrasound scan and £204 per RA36Z bone scan.

5.3.4 ERG commentary on model structure, assumptions and data inputs

Quality of life and costs by treatment arm and by line of treatment

For much of the discussion that follows it will be useful to have a summary of the quality of life values and the costs associated with each line of treatment in each of the arms.

The discussion will highlight issues around the possible impact of allowing for the gap between the cessation of 1st line treatment and the start of 2nd line docetaxel; i.e. introducing an additional post-progression treatment free (PPTF) state between the 1st line treatment and the 2nd line docetaxel. The submitted electronic model has the facility for this and applies a [redacted] week interval for this as drawn from PREVAIL, though the company submission does not make use of it. The summary of quality of life and costs presented below includes these elements, but it should be borne in mind that none of the company modelling includes these elements.

The discussion will also highlight the impact of the inclusion of a 3rd line active treatment in the enzalutamide and the abiraterone arms. The submitted electronic model has the facility for this, though the company submission does not make use of it. The ERG assumption in what follows is that if there is an active 3rd line treatment following 1st line enzalutamide and 2nd line docetaxel, it will be 3rd line abiraterone. Similarly, the ERG assumption in what follows is that if there is an active 3rd line treatment following 1st line abiraterone and 2nd line docetaxel, it will be 3rd line enzalutamide. The summary of quality of life and costs presented below includes these elements, but it should be borne in mind that none of the company modelling includes these elements.

In what follows the health state costs are those that apply after the first quarter for ease of presentation. The quality of life values for 3rd line treatments in the

enzalutamide and abiraterone arms also assume the same treatment gain as is applied in the BSC arm.

Table 56 Quality of life and costs in the BSC arm

	Quality of life				Costs per cycle and annualised							
	Main	AEs	SREs	Total	Tx	Admin	State	C.Med.	AEs	SREs	Total	Annual
1st	[redacted]											
PPTF												
2nd												
3rd												
Pall.												

Table 57 Quality of life and costs in the enzalutamide arm

	Quality of life				Costs per cycle and annualised							
	Main	AEs	SREs	Total	Tx	Admin	State	C.Med.	AEs	SREs	Total	Annual
1st	[redacted]											
PPTF												
2nd												
3rd												
Pall.												

Table 58 Quality of life and costs in the abiraterone arm

	Quality of life				Costs per cycle and annualised							
	Main	AEs	SREs	Total	Tx	Admin	State	C.Med.	AEs	SREs	Total	Annual
1st	[redacted]											
PPTF												
2nd												
3rd												
Pall.												

The reason for presenting the tables above is that the model has two main aspects:

- Modelling overall survival
- Modelling what happens within that survival

The key point is that modelling overall survival is determined by the overall survival curve that is applied, and so is entirely independent of the modelling of what happens

during that survival. Because of this, the modelling of what happens during that survival can have what may initially appear to be perverse effects.

For instance, suppose that the TTD curve for the enzalutamide arm is worse than that of the base case and patients discontinue 1st line enzalutamide more quickly. The implied cost effectiveness of 1st line enzalutamide compared to PPTF is [redacted] = £233k per QALY. Clearly this is not cost effective. As a consequence, causing patients to discontinue 1st line enzalutamide more quickly when this does not affect overall survival can improve the overall cost effectiveness of the enzalutamide arm.

Table 59 Implied cost effectiveness of subsequent lines of therapy compared to 1st line

	BSC			Enzalutamide			Abiraterone		
	ΔCost	ΔQALY	ICER	ΔCost	ΔQALY	ICER	ΔCost	ΔQALY	ICER
PPTF	[redacted]	[redacted]	Dom.	[redacted]	[redacted]	£233k	[redacted]	[redacted]	£238k
2nd	[redacted]	[redacted]	Dom.	[redacted]	[redacted]	£107k	[redacted]	[redacted]	£111k
3rd	[redacted]	[redacted]	Dom.	[redacted]	[redacted]	Dom.	[redacted]	[redacted]	Dom.
Pall.	[redacted]	[redacted]	Dom.	[redacted]	[redacted]	£84,783	[redacted]	[redacted]	£86,930

For the BSC arm, due to the low cost and high quality of life of 1st line treatment anything that increases the rate of discontinuations from 1st line therapy will worsen the cost effectiveness of the BSC arm. PPTF is dominated by 1st line BSC, as are all the other treatment lines. But this is only part of the story in terms of introducing the option of PPTF. PPTF in turn dominates 2nd line, 3rd line and palliative care, so if the time on 1st line treatment is unchanged, introducing PPTF within the BSC arm will tend to improve its cost effectiveness.

For the enzalutamide arm, as already noted the cost effectiveness of 1st line enzalutamide compared to PPTF is poor, and if the TTD curve for 1st line enzalutamide is worsened this may improve the cost effectiveness of the enzalutamide arm if patients tend to remain in the PPTF health state. And as for the BSC arm, if the time on 1st line treatment is unchanged, introducing PPTF within the enzalutamide arm will tend to improve its cost effectiveness.

By definition the PPTF health state only lasts six weeks. While the mean overall survival in the BSC arm is 2.74 years, the mean post-progression survival is 2.14 years. If the PPTF health state is introduced 0.13 years is modelled as being spent within it. The mean overall survival in the enzalutamide arm is 3.24 years, with a mean post-progression survival of only 1.24 years. If the PPTF health state is introduced only 0.08 years is modelled as being spent within it. The net effect tends to favour the BSC arm more, and as a consequence the cost effectiveness of enzalutamide compared to BSC will worsen if the PPTF health state is introduced.

2nd line docetaxel dominates 3rd line treatment so anything that reduced the amount of time that patients spend in 2nd line treatment and increase it for 3rd line treatment will tend to worsen the cost effectiveness of the arm concerned. But the picture is more complicated since those on 3rd line treatment move onto palliative care. The cost effectiveness of docetaxel compared to palliative care is £55,194 per QALY. Provided that overall survival is not affected, the modelled cost effectiveness of an arm may increase if less time is spent on 2nd line docetaxel and more time is spent in palliative care.

The implied cost effectiveness of 3rd line treatment relative to palliative care is £210k per QALY in the BSC arm and £214k per QALY in the enzalutamide arm. Increasing the proportion of patients that receive 3rd line treatment or slowing the rate at which those on 3rd line treatment move onto palliative care will tend to worsen the cost effectiveness of the arm in which this is occurring. As a consequence, removing the possibility of 3rd line treatment in the enzalutamide arm and in the abiraterone arm will tend to improve their cost effectiveness compared to the BSC arm.

Treatment sequences modelled

The company references Mottet et al[14] and various NICE guidelines in constructing Figure A2 on page 32 of the submission. This suggests that asymptomatic or mildly symptomatic patients may receive either abiraterone or BSC. Once patients become symptomatic they move on to receive 2nd line docetaxel, and subsequent to this may receive a 3rd line of one of abiraterone, enzalutamide, cabazitaxel or radium-223. Within Figure A2 of the submission, the likelihood of receiving a 3rd line treatment is not differentiated by whether a patient received 1st line abiraterone or 1st line BSC.

Figure A2 appears to suggest that both 1st line abiraterone patients and 1st line BSC patients can progress to 2nd line docetaxel, and then on to a 3rd line treatment. This would seem to apply equally to 1st line enzalutamide patients.

ERG expert opinion suggests that patients who receive 1st line enzalutamide would in all probability be treated with 3rd line abiraterone, that patients who receive 1st line abiraterone would in all probability be treated with 3rd line enzalutamide, and that 1st line BSC may tend to currently receive enzalutamide as their 3rd line treatment. To the ERG this suggests that the base case should model the following treatment sequences.

- 1st enzalutamide 2nd docetaxel → 3rd abiraterone → 4th palliative,
- 1st abiraterone 2nd docetaxel → 3rd enzalutamide → 4th palliative,
- 1st BSC 2nd docetaxel → 3rd enzalutamide → 4th palliative

With a possible scenario analysis for the BSC arm of:

- 1st BSC 2nd docetaxel → 3rd abiraterone → 4th palliative

The company submission states that treatment with 3rd line enzalutamide and 3rd line abiraterone is not recommended, referencing the enzalutamide post-chemotherapy STA FAD [TA316] as justification for this. The TA316 guidance recommends enzalutamide post-chemotherapy and also states that:

> *The use of enzalutamide for treating metastatic hormone-relapsed prostate cancer previously treated with abiraterone is not covered by this guidance.*

The parallel guidance for abiraterone [TA259][34] also recommends its use, but does not mention any prior treatment other than docetaxel. In the light of this it is not clear that NICE guidelines prohibit the use of 3rd line abiraterone, hence the sequence of 1st line enzalutamide followed by 2nd line docetaxel followed by 3rd line abiraterone appears to be acceptable. The guidance for TA316 could be read as suggesting that the sequence of 1st line abiraterone followed by 2nd line docetaxel followed by 3rd line enzalutamide is not recommended, but the ERG reading is simply that the guidance does not cover this.

The key ERG criticism is that it seems unreasonable to have a 3rd line active treatment in the BSC arm but to not have explored this in the enzalutamide arm or in the abiraterone arm. Within the company modelling this tends to improve the cost effectiveness estimate for enzalutamide compared to BSC. ERG expert opinion suggests that the base case should model all arms as having the possibility of a 3rd line treatment.

The modelling of 3rd line treatment for BSC and its exclusion for enzalutamide

Not applying 3rd line enzalutamide for BSC worsens the cost effectiveness estimate for enzalutamide compared to BSC from £78,587 per QALY to £92,221 per QALY. The poor cost effectiveness of enzalutamide post-chemotherapy compared to palliative care of the current company model of £210k per QALY means that including it as an option after BSC and chemotherapy improves the estimated cost effectiveness of enzalutamide prior to chemotherapy.

The FAD for enzalutamide for those previously treated with chemotherapy [TA316][41] suggests in section 3.31 a company estimate of £43,587 per QALY and in 3.47 an ERG estimate of £51,014 per QALY. While these estimates are inclusive of the enzalutamide PAS, the ERG is confident that the parallel cost effectiveness estimates that exclude the enzalutamide PAS would still be somewhat lower than that implied within the current modelling. If the current company model had been consistent with that which it supplied for TA316, the cost effectiveness estimate for enzalutamide compared to BSC of the current submission would be worse.

Overall survival and extrapolation

The September 2013 and the June 2014 OS Kaplan Meier curves and IPCW adjusted Kaplan Meier curves are presented alongside one another in Figure 8 of the company extrapolation report, as reproduced below. The placebo curves lie below those of enzalutamide, with the dashed curves being the IPCW adjusted Kaplan Meier curves.

Sep 2013 data cut Jun 2014 data cut

Figure 10 OS KM curves and IPCW adjusted KM curves

The IPCW adjustment tends to push the tail of the BSC Kaplan Meier OS curve slightly below that of the original, while it tends to push the tail of the enzalutamide Kaplan Meier curve above that of the original. This effect is not noticeable until around month 24, and affects the enzalutamide OS Kaplan Meier curve to a greater degree than the BSC OS Kaplan Meier curve. It also appears to have a greater impact for the June 2014 data cut than for the September 2013 data cut.

The approximate percentages can be read from the above figure for the June 2014 data cut. These percentages will not be exactly correct, but are accurate to within a few percentage points. They are only used for illustrative purposes, so in the opinion of the ERG this degree of inaccuracy is acceptable. They can be presented alongside the numbers at risk that underlie the unadjusted OS Kaplan Meier curve (KM1)[j], and the proportion modelled as surviving within the Weibull overall survival curves that were fitted to the IPCW adjusted KM curves (KM2) as below.

[j] Taken from Figure 1 of the company extrapolation report.

Table 60 N at risk, June 2014 OS and IPCW OS KM curves and fitted Weibulls

	BSC					Enzalutamide				
Mth	n	%N	KM1	KM2	Weib.	n	%N	KM1	KM2	Weib.
0	[redacted]	[redacted]	100%	100%	[redacted]	[redacted]	[redacted]	100%	100%	[redacted]
3	[redacted]	[redacted]	99%	99%	[redacted]	[redacted]	[redacted]	99%	99%	[redacted]
6	[redacted]	[redacted]	93%	93%	[redacted]	[redacted]	[redacted]	98%	98%	[redacted]
9	[redacted]	[redacted]	89%	89%	[redacted]	[redacted]	[redacted]	94%	94%	[redacted]
12	[redacted]	[redacted]	84%	84%	[redacted]	[redacted]	[redacted]	92%	92%	[redacted]
15	[redacted]	[redacted]	78%	78%	[redacted]	[redacted]	[redacted]	88%	88%	[redacted]
18	[redacted]	[redacted]	73%	73%	[redacted]	[redacted]	[redacted]	82%	82%	[redacted]
21	[redacted]	[redacted]	65%	66%	[redacted]	[redacted]	[redacted]	77%	77%	[redacted]
24	[redacted]	[redacted]	61%	62%	[redacted]	[redacted]	[redacted]	71%	72%	[redacted]
27	[redacted]	[redacted]	54%	56%	[redacted]	[redacted]	[redacted]	66%	67%	[redacted]
30	[redacted]	[redacted]	50%	52%	[redacted]	[redacted]	[redacted]	59%	63%	[redacted]
33	[redacted]	[redacted]	44%	46%	[redacted]	[redacted]	[redacted]	51%	57%	[redacted]
36	[redacted]	[redacted]	41%	41%	[redacted]	[redacted]	[redacted]	48%	56%	[redacted]
39	[redacted]	[redacted]	39%		[redacted]	[redacted]	[redacted]	41%		[redacted]
42	[redacted]	[redacted]	39%		[redacted]	[redacted]	[redacted]	41%		[redacted]
60					[redacted]					[redacted]
120					[redacted]					[redacted]

From the above, the OS Kaplan Meier curves are far from being complete. Even at the very tail of the OS Kaplan Meier curves when few remain at risk the percentages remaining alive in the adjusted Kaplan Meier curves at month 36 are roughly 56% for enzalutamide and 41% for placebo, compared to around 40% for both arms in the original Kaplan Meier curves.

The above curves can be graphed over the time horizon of the model as below.

Figure 11 OS: adjusted Kaplan Meier curves, N at risk and Weibull extrapolations

The numbers at risk are reasonably in line with the OS Kaplan Meier curves up to around 24 months, but then begin to drop quite rapidly below them and tail off to close to zero between month 24 and month 36. At 24 months the proportions remaining alive within the OS Kaplan Meier curves are well above 50% in both arms. The modelled survival gain from enzalutamide over BSC is the area between the two Weibulls. As can be seen from the above, the majority of this gain occurs after the numbers at risk has tailed off. There is also quite a considerable tail to both the Weibulls which is not obviously justified by a visual inspection of the IPCW adjusted Kaplan Meier curves. There is as a consequence considerable structural uncertainty about the gains in survival which have been extrapolated from the IPCW adjusted PREVAIL trial data.

The company submission states that:

> *The lack of long-term registry data on the survival of mHRPC patients is a limitation for the validation of the OS extrapolation. As no registry data was available, the extrapolation had to rely on the estimates of clinical experts.*

Section 5.7.7 of the NICE methods guide states that:

> *Alternative scenarios should also be routinely considered to compare the implications of different methods for extrapolation of the results. For example, for duration of treatment effects, scenarios might include when the treatment*

benefit in the extrapolated phase is: (i) nil; (ii) the same as during the treatment phase and continues at the same level; or (iii) diminishes in the long term.

Given the current modelling approach, it might be reasonable to explore the impact of the survival curves converging at points other than the time horizon of the model.

TTD and extrapolation

A similar exercise to the above can be conducted for the TTD curves, though for these only the raw Kaplan Meier curves are available. The company submission relies upon the post-unblinding June 2014 TTD curves. As for the OS analysis presented above, the Kaplan Meier proportions are taken from a figure in the extrapolation report[k] so are approximate, but are sufficient for the current illustrative purposes.

Table 61 N at risk, June 2014 TTD curves and fitted gammas

	BSC				Enzalutamide			
Mth	n	%N	KM	Gamma	n	%N	KM	Gamma
0	[redacted]	[redacted]	100%	[redacted]	[redacted]	[redacted]	100%	[redacted]
3	[redacted]	[redacted]	72%	[redacted]	[redacted]	[redacted]	96%	[redacted]
6	[redacted]	[redacted]	37%	[redacted]	[redacted]	[redacted]	87%	[redacted]
9	[redacted]	[redacted]	27%	[redacted]	[redacted]	[redacted]	78%	[redacted]
12	[redacted]	[redacted]	18%	[redacted]	[redacted]	[redacted]	68%	[redacted]
15	[redacted]	[redacted]	12%	[redacted]	[redacted]	[redacted]	57%	[redacted]
18	[redacted]	[redacted]	10%	[redacted]	[redacted]	[redacted]	50%	[redacted]
21	[redacted]	[redacted]	6%	[redacted]	[redacted]	[redacted]	43%	[redacted]
24	[redacted]	[redacted]	3%	[redacted]	[redacted]	[redacted]	38%	[redacted]
27	[redacted]	[redacted]	2%	[redacted]	[redacted]	[redacted]	34%	[redacted]
30	[redacted]	[redacted]	1%	[redacted]	[redacted]	[redacted]	30%	[redacted]
33	[redacted]	[redacted]	0%	[redacted]	[redacted]	[redacted]	26%	[redacted]
36	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	22%	[redacted]
39				[redacted]	[redacted]	[redacted]	21%	[redacted]
42				[redacted]	[redacted]	[redacted]	13%	[redacted]
60				[redacted]				[redacted]
120				[redacted]				[redacted]

[k] Figure 3 B

With this resulting in the parallel set of curves for TTD.

Figure 12 TTD: Kaplan Meier curves, N at risk and gamma extrapolations

The TTD Kaplan Meier curves are much more complete than the OS curves, though again at about month 30 the number at risk for the enzalutamide curve begins to drop away from the Kaplan Meier curve. The gamma extrapolation for TTD has quite a long tail after the end of the PREVAIL trial data which may be questionable. Given the near completeness of the BSC Kaplan Meier curve, the long tail to its gamma extrapolation seems implausible. But as this asymptotes from month 24 to the horizontal axis starting with only 3% remaining it seems likely to have only a limited impact upon the model output.

Palliative care

Discontinuing from 2nd line docetaxel without moving onto a 3rd line treatment and discontinuing from a 3rd line treatment is taken to be synonymous with being in palliative care. This is not obviously necessarily the case. Palliative care within Guest et al[40] was also defined as being from the initiation of strong opioid treatment.

If patients might discontinue from 2nd line docetaxel without moving onto a 3rd line treatment or discontinue from a 3rd line treatment without immediately moving on to a strong opioid treatment the costs of palliative care within the model are likely to have been overstated. However, Guest et al[40] report a mean duration of strong opioid treatment among prostate cancer patients of 360 days.

Use of June 2014 data cut rather than the September 2013 data cut

PREVAIL was unblinded in December 2013.

The IPCW analyses correct the data as needed for treatments subsequent to the study drug which would not be usual UK practice and for cross-over. The ERG accepts that the IPCW analyses are to be preferred over both the two stage adjustment analyses and the analyses that use the unadjusted PREVAIL data.

There are two sets of IPCW analyses. One relates to the pre-unblinding September 2013 data cut, the other to the post-unblinding June 2014 data cut. The company argument is that "*As extrapolation is associated with uncertainty, the most mature OS data is preferred for economic modelling*", with it choosing the post-unblinding June 2014 IPCW analysis over the pre-unblinding September 2013 IPCW analysis as a consequence. As outlined below, the numbers at risk since randomisation is considerably fuller from the 18 month point for the June 2014 data cut than for the Sep 2013 data cut.

Table 62 Numbers at risk: Sep 2013 data cut versus Jun 2014 data cut

	Sep 2013 cut		Jun 2014 cut	
Mth	BSC	ENZA	BSC	ENZA
0				
3				
6				
9				
12				
15				
18				
21				
24				
27				
30				
33				
36				
39				
42				

The choice of data cut has quite a large impact upon the cost effectiveness estimates. Changing the source of overall survival estimates from the June 2014 IPCW adjusted

Weibulls to the Sep 2013 IPCW adjusted Weibulls worsens the cost effectiveness estimate for enzalutamide compared to BSC from £78,587 per QALY to £94,730 per QALY. It also worsens the cost effectiveness estimate for enzalutamide compared to abiraterone from £27,076 per QALY to £43,932 per QALY.

The company base case also uses the June 2014 data for the TTD curves. This seems less appropriate since unblinding the trial will more directly affect the likelihood of continuing treatment. In the opinion of the ERG, the base case should apply the September 2013 TTD curves. Changing the source of the TTD curve from the June 2014 gammas to the Sep 2013 gammas worsens cost effectiveness estimate for enzalutamide compared to BSC from £78,587 per QALY to £81,449 per QALY. It also worsens the cost effectiveness estimate for enzalutamide compared to abiraterone from £27,076 per QALY to £28,642 per QALY.

There is an argument that if unblinding will affect the likelihood of discontinuation and that as a consequence the Sep 2013 TTD curves are to be preferred, changing the rate of discontinuation might in turn affect overall survival and as a consequence the pre-unblinding Sep 2013 IPCW overall survival analysis might be preferred. Applying the Sep 2013 IPCW adjusted Weibulls for overall survival and the Sep 2013 TTD curves worsens the cost effectiveness estimate for enzalutamide compared to BSC from £78,587 per QALY to £98,751 per QALY. It also worsens the cost effectiveness estimate for enzalutamide compared to abiraterone from £27,076 per QALY to £47,213 per QALY.

In the opinion of the ERG the Sep 2013 data cut is preferable for the TTD curves and, due to the fuller data and despite the possible risks from it being post-unblinding, the June 2014 data cut with IPCW adjustment is preferable for the OS curves.

Equal probability of death across model health states

The company model calculates the proportion of patients transferring from being on first line treatment to ceasing first line treatment as max(P(discontinue)-P(death),0). The company has also confirmed that the Kaplan Meier TTD curves treat death as an event. Within a model that only considers cessation of first line treatment and death this would result in the correct TTD and OS curves. But the current modelling

approach attempts to model a range of additional health states subsequent to the discontinuation of 1st line treatment.

The OS curves are used to estimate a probability of death for a given model cycle. But this probability is applied equally across the health states. A patient has the same weekly probability of death when in stable asymptomatic or mildly symptomatic disease on 1st line treatment as when in progressive disease on palliative care after failure on up to three lines of active treatment. In other words, the same life expectancy is modelled for a patient on 1st line treatment as for a patient in palliative care[l]. The ERG thinks this assumption of same life expectancy is questionable.

An alternative model structure could have been to assume that as the patients progress through the health states of the model, the probability of death rises in the worse health states. The required number of deaths in each cycle could then have been modelled sequentially starting with the worst health state, and working backwards up the chain of health states from this. For instance, if the model suggests that 5% of patients would die in a given cycle and 10% of patients were in the palliative health state at the start of the cycle it could be assumed that the 5% of deaths would all occur among those in palliative care. But if only 3% of patients were in the palliative health state at the start of the cycle it could be assumed that all 3% would die, with the remaining 2% of deaths being among those receiving 2nd line docetaxel, or 3rd line enzalutamide if in the BSC arm.

In short, applying an equal probability of death across the health states in the model appears likely to have tended to reduce the proportion of patients receiving 2nd line docetaxel, to a lesser degree reduce the proportion of patients receiving 3rd line treatment within the BSC arm, and to increase the proportion of patients remaining in palliative care compared to the alternative model structure.

The degree and direction of any possible bias from assuming the same probability of death applies to all health states cannot be determined a priori. It may also vary

[l] This is most easily seen by revising the baseline patient distribution from all being on stable disease and 1st line treatment to all being on palliative care. This can be achieved within the *Calculations_* worksheets by setting cell E9=0 and cell I9=1. This appears to have no impact upon the mean life expectancies of the model.

depending upon whether 3rd line treatment is or is not an option within the enzalutamide arm.

The possible alternative modelling of death outlined above would also probably be to lean too far in the opposite direction; e.g. there being no deaths from 2nd line docetaxel if the model could account for these deaths within palliative care. The most reasonable cost effectiveness estimates might as a consequence lie somewhere between these two approaches.

TTD: company model compared to inputted curves

While some minor disparities have been previously noted between overall survivals estimated in the company model and the extrapolation report, a more serious disparity appears to apply in terms of the time to discontinuation curves that are inputted to the model and the model outputs.

Table 63 Modelled TTD for the base case: all comparators

	TTD gammas		
	Enzalutamide	Abiraterone	BSC
3 year	[redacted]	[redacted]	[redacted]
5 year	[redacted]	[redacted]	[redacted]
10 year	[redacted]	[redacted]	[redacted]

Table 64 ERG TTD for the base case: all comparators

	TTD gammas		
	Enzalutamide	Abiraterone	BSC
3 year	[redacted]	[redacted]	[redacted]
5 year	[redacted]	[redacted]	[redacted]
10 year	[redacted]	[redacted]	[redacted]

The most obvious disparity is in the modelling of the TTD gamma for abiraterone. The company model and the ERG cross check correspond at the 3 year point, but thereafter they diverge. The reason for this is that after the 122nd cycle, or at about 28 months, the probability of death in the abiraterone arm exceeds the probability of progression. At this point the proportion remaining on 1st line abiraterone treatment is still quite high at 30% and as a consequence the impact is quite large.

Figure 13 Modelled probability of death and ceasing 1st line treatment for abiraterone

The model applies the probability of ceasing 1st line treatment minus the probability of death to estimate the proportion of patients on 1st line treatment who progress to 2nd line treatment. The probability of death is then used to estimate the proportion of patients on 1st line treatment who die. The sum of these is the proportion who move out of progression free survival.

But within the model if the probability of death is estimated to be higher than the probability of ceasing 1st line treatment the model only applies the probability of death. As a consequence, the higher probability of death comes to solely determine the probability of ceasing 1st line treatment and the TTD curve becomes irrelevant. This is the reason for the discrepancy between the company model and the ERG cross check. It also throws into question the reasonableness of the OS and TTD curves that have been estimated for abiraterone, and their general alignment with one another.

The effect of this model structure when the probability of death exceeds the probability of progression is in effect to hold all the patients remaining on 1st line abiraterone on 1st line abiraterone and prevent them progressing through to the other health states of the model. As noted above, the impact of this is likely to be quite detrimental to the abiraterone arm, provided that the overall survival estimate is not affected.

This can be confirmed by comparing the gamma TTD curve and the weibull TTD curve with the OS curve for abiraterone. The gamma TTD curve has a mean of 31

months while the weibull TTD curve has a mean of 29 months, compared to the weibull overall survival curve mean of 36 months. As a consequence, using the gamma TTD curve estimates a greater clinical effectiveness for abiraterone than using the weibull TTD curve. Applying the gamma TTD curve results in a cost effectiveness estimate for enzalutamide compared to abiraterone of £27,076 per QALY. Applying the weibull TTD curve results in a cost effectiveness estimate for enzalutamide compared to abiraterone of £36,458 per QALY.

Figure 14 OS weibull, TTD gamma and TTD weibull for 1st line abiraterone

Coincidentally, the Weibull TTD curve and the gamma TTD curve are quite similar up to 24 months and remain reasonably so up to 28 months. From 28 months the gamma TTD curve is essentially irrelevant as noted above, due to the probability of ceasing treatment of the gamma TTD falling below the probability of dying of the weibull OS curve.

As a consequence, it seems reasonable to suggest that the cost effectiveness estimate of £27,076 per QALY is not due to the probabilities of the flatter section of the gamma TTD curve being applied, it is due to them not being applied. The weibull TTD probabilities of ceasing treatment do not exceed the weibull OS probabilities of dying until the 229th cycle or around 53 months when only 6.2% of patients are modelled as remaining on 1st line abiraterone treatment.

On this basis it may be more reasonable to apply the weibull TTD curve within the modelling of abiraterone, but without parallel changes in the other arms this would go against the recommendations of the DSU technical support document 14 which notes:

Where parametric models are fitted separately to individual treatment arms it is sensible to use the same 'type' of model, that is if a Weibull model is fitted to one treatment arm a Weibull should also be fitted to the other treatment arm. This allows a two dimensional treatment effect in that the shape and scale parameters can both differ between treatment arms, but does not allow the modelled survival for each treatment arm to follow drastically different distributions.

The probability of ceasing treatment from the June 2014 weibull TTD curve for enzalutamide does not exceed the probability of dying from the June 2014 IPCW OS curve until cycle 401 when only [redacted] of patients are modelled as remaining on 1st line enzalutamide treatment. Similarly, if the Sep 2013 weibull TTD is preferred, its probability does not exceed the probability of dying from the June 2014 IPCW OS curve until cycle 495 when less than 1.0% of patients are modelled as remaining on 1st line enzalutamide treatment.

Since these concerns appear to mainly apply within the abiraterone arm, the model structure may be biased against abiraterone and the estimated cost effectiveness of enzalutamide compared to abiraterone may be too favourable to enzalutamide.

There may also be some bias against enzalutamide in the comparison with BSC arising from this source. The same considerations apply within both the enzalutamide arm and the BSC arm, but with rather less impact:

- For enzalutamide the probability of death does not exceed the probability of discontinuing 1st line treatment until cycle 219 at which point only [redacted] are modelled as still being on 1st line treatment. The disparity between the cycle probability of death and the cycle probability of discontinuing 1st line treatment is also reasonably small with the former being around 1.4% compared to 1.1% for the latter. As a consequence, the disparities between the company model and the ERG cross check are relatively minor at the 5 year point: 6.47% compared to 6.72%.
- For placebo the probability of death does not exceed the probability of discontinuing 1st line treatment until cycle 290 at which point less than 1% are

modelled as still being on 1st line treatment. The disparity between the cycle probability of death and the cycle probability of discontinuing 1st line treatment is also reasonably small with the former being around 1.5% compared to 1.3% for the latter.

While a minor consideration, if the probability of death exceeds the probability of discontinuation for subsequent lines of treatment the probability of discontinuation becomes irrelevant and is not applied. But due to the per cycle discontinuation probability for 2nd line docetaxel being 2.40% this only applies within the modelling of the enzalutamide arm from the 388th cycle or around 7.46 years when less than 1% of patients are modelled as receiving 2nd line docetaxel. Similarly, due to the per cycle discontinuation probabilities for 3rd line enzalutamide and 3rd line abiraterone being 2.14% and 1.91% respectively the probability of death exceeding these only occurs to all intents and purposes if within the abiraterone arm the use of 3rd line enzalutamide is modelled. If this option is selected, the probability of death exceeds the enzalutamide discontinuation probability from the 306th cycle or around 5.88 years when only around 2% of patients are modelled as receiving 3rd line enzalutamide.

Note that the company submission has not presented the comparators together in a comprehensive table, but has rather presented pairwise comparisons of enzalutamide with BSC and enzalutamide with abiraterone. In the light of this, provided that the curves selected for a given function are of the same type within a pairwise comparison it may be reasonable for the functional forms to differ between the pairwise comparisons.

Implementation of gamma overall survival functions

Within the calculation of the gamma distributions for overall survival the calculations for:

- Enzalutamide IPCW final data cut; and,
- Abiraterone COU-AA-302;

appear to be correct. But there is some incorrect referencing of the third parameter of the overall survival gamma function for enzalutamide based upon the IPCW final data cut within the calculations for:

- BSC IPCW final data cut;

- BSC 2 stage final data cut;
- BSC 2 stage interim data cut;
- Enzalutamide 2 stage final data cut; and,
- Enzalutamide 2 stage interim data cut.

which renders the modelled curves for these incorrect. This does not affect the company base case.

Proportion of patients receiving 2nd line treatment

The estimate of 84.5% of patients receiving 2nd line treatment is based upon data from the BSC of PREVAIL. For the June 2014 data cut, 713 of the 844 who had discontinued had been recorded as having started a 2nd line antineoplastic treatment. This compares with only [redacted] of the [redacted] or [redacted] who had discontinued in the enzalutamide arm.

But the electronic model also notes that the average time between discontinuation and starting chemotherapy in PREVAIL was around [redacted] weeks. This might account for some of the differences in 2nd line treatment rates between the BSC arm and the enzalutamide arm. Since those in the enzalutamide arm would have tended to discontinue at a later date, more of them might have been between ceasing 1st line enzalutamide and starting a 2nd line treatment.

This provides support for the company model applying the estimate of 84.5% equally across the arms. But it might also suggest that even within the BSC arm this estimate is a lower bound due to some patients having been between ceasing 1st line enzalutamide and starting a 2nd line treatment at the June 2014 data cut. A sensitivity analysis increasing this proportion would seem justified.

Introducing a 6 week interval between end of 1st line treatment and start of 2nd line docetaxel

The electronic model has the facility to introduce a [redacted] week period between the end of 1st line treatment and the start of 2nd line docetaxel. Apparently this was the average interval within PREVAIL. The company submission does not apply this in the base case or as a scenario analysis. Those in this health state experience a reduced quality

of life of 0.720, the source of which the electronic model gives as the "York SLR". It also appears that the per cycle health state costs and concomitant medication costs for this are £43.40, which annualises to £2,257.

The ERG has not parsed this aspect of the company model due to it not having been used for the company submission. But applying it worsens the cost effectiveness estimate for enzalutamide compared to BSC from £78,587 per QALY to £81,438 per QALY. It slightly improves the cost effectiveness estimate for enzalutamide compared to abiraterone from £27,076 per QALY to £26,811 per QALY.

Quality of life for 1st line treatments

The number of patients reporting data can be presented by reporting week for weeks 1 to 121, alongside the raw mean EQ-5D data by reporting week. This can similarly be reported for the change from raw mean change from week 1 value for weeks 13 to 121. The number of patients reporting is presented on the left vertical axis, while the mean EQ-5D and mean change in EQ-5D from week 1 are reported against the right vertical axis.

Figure 15 Raw EQ-5D mean and mean changes from week 1 data

The main aim of the MMRM model was to estimate the changes from baseline among those remaining on treatment, and from this to estimate a treatment effect. Prior to data analysis a statistical analysis plan specified what form the model would take. It also specified that data would be disregarded from the point at which fewer than 10% remained in either arm, so only week 1 to week 61 data was analysed within the treatment effect MMRM model.

An immediate question is whether the MMRM should aim to estimate the mean treatment effect, or should aim to estimate the mean change from baseline among those remaining on treatment in each arm. If the aim should be to estimate the mean treatment effect, while the 10% cut-off point in the BSC is arbitrary there is some intuition behind it though it is still not obviously justified.

But if the aim should be to estimate the mean change from baseline among those remaining on treatment by arm, it is less obvious why the data of the enzalutamide arm should be arbitrarily curtailed at week 61. At week 73, 50% of patients in the enzalutamide arm are still reporting EQ-5D values. If the EQ-5D values in the enzalutamide arm are worse for week 73 and beyond when compared to the baseline or week 61 values, there is a concern that the estimate of the mean change from baseline among those remaining on treatment may be biased. However, the simple weighted means of the raw EQ-5D data in the enzalutamide arm are 0.827 for week 1 to week 61 and 0.825 for all time points.

The BSC arm saw an immediate, quite rapid fall in the mean EQ-5D quality of life between week 1 and week 13. Thereafter, the quality of life in the BSC remains reasonably steady and shows some sign of recovery between weeks 13 and 61. In contrast, there is no immediate rapid fall within the enzalutamide arm and the drift downwards in quality of life is steadier. This causes a gap in the mean EQ-5D values during weeks 1, 13, 25 and 37, though it tends to narrow as time progresses. By weeks 49 and 61 the quality of life values in the BSC arm and in the enzalutamide arm appear to have largely converged.

But the above does not take into account the various other covariates that might affect results. The MMRM took the following into account, with the p values of the fixed effects model being reported in brackets:

- Treatment : 2 levels (p=[redacted])
- Time as in treatment visit : 8 levels (p=[redacted])
- Baseline quality of life : continuous (p<[redacted])
- Investigation site : 80 levels (p=[redacted])
- ECOG at baseline : 2 levels (p=[redacted])

- Fatigue at baseline : 2 levels (p=[redacted])
- Pain at baseline : 2 levels (p=[redacted])
- Age : 2 levels (p=[redacted])
- Time by treatment arm interaction (p=[redacted])
- Time by baseline quality of life interaction (p=[redacted])

As already noted, the variables were specified prior to data analysis in the statistical analysis plan. It appears that this is the reason for there being no subsequent refinement of the statistical model through rejection of non-statistically significant parameters or groups of parameters.

The coefficients relating to treatment effect changes from baseline that resulted were as below.

Table 65 MMRM treatment effect coefficients

	Coefficient	S.E.	P Value
Enzalutamide	-0.042	0.010	<0.001
BSC	-0.064	0.012	<0.001
Net effect	-0.022	0.009	0.021

Within the above, the net effect is an estimate for the period spanning weeks 1, 13, 25, 37, 49 and 61. As noted above, there was an initial large fall in the BSC arm which led to a noticeable difference in values between the arms for weeks 1, 13, 25 and 37. But the more gradual decline in the quality of life in the enzalutamide arm over this period still resulted in the raw data appearing to largely converge by weeks 49 and 61. This is to some extent mirrored in the adjusted mean changes from baseline and the adjusted net difference between the arms of the MMRM as graphed and reported below.

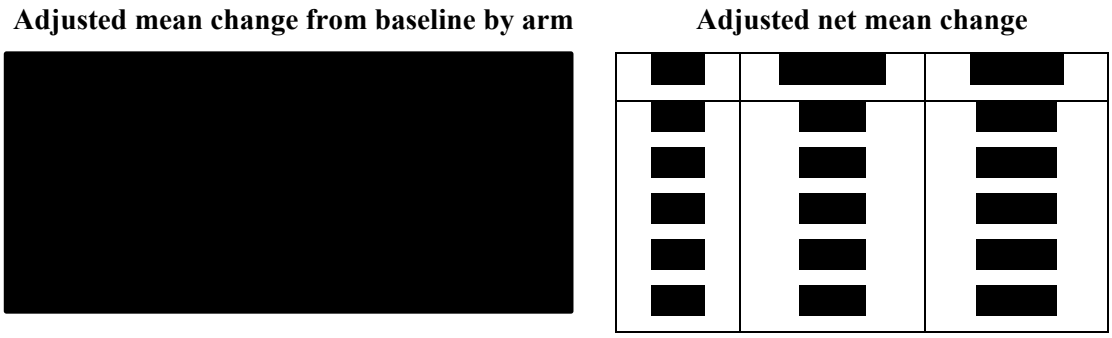


Figure 16 MMRM adjusted estimates by reporting week

The adjusted mean changes by arm tend to converge over the period from week 13 to week 49, though do then diverge at week 61. The estimated net impact of enzalutamide is largest in the earlier weeks, is statistically significant for the changes from week 1 to week 13, 25 and 37, but is not thereafter for weeks 49 and 61.

The model assumes that those in the BSC arm who remain on 1st line treatment have the PREVAIL baseline quality of life value of 0.844. The quality of life for those in the enzalutamide arm who remain on 1st line treatment is assumed to be 0.022 better than that of those remaining on 1st line treatment in the BSC arm, resulting in a quality of life value of 0.864. The enzalutamide quality of life value is also applied in the abiraterone arm.

But the 0.022 increment for enzalutamide compared to BSC is based upon least square mean estimates of quality of life losses relative to baseline of 0.042 for enzalutamide compared to 0.064 for BSC. This suggests that the quality of life losses relative to baseline should be applied to the mean baseline quality of life value of 0.864 for those who remain on 1st line treatment, resulting in quality of life values of 0.780 in the BSC arm and 0.802 in the enzalutamide arm.

The central parameter estimate of a treatment effect of 0.022 from enzalutamide over BSC applies to the data of the first 61 weeks of PREVAIL. In the light of the above, it seems reasonable to undertake a sensitivity analysis which only applies this parameter to the first 61 weeks of the model and sets it to zero thereafter; i.e. after week 61 there is a common 0.780 quality of life for those remaining on 1st line treatment.

Quality of life for active 3rd line treatment

The QALY calculation for 3rd line treatment for the BSC arm applies a base quality of life value of 0.612 and adds a further 0.040 to this as the treatment gain from enzalutamide when used after 2nd line docetaxel. The QALY calculations for 3rd line treatment for the enzalutamide arm and the abiraterone arm only apply the base quality of life value of 0.612. This does not affect the company base case since it is assumed that only those in the BSC receive an active 3rd line treatment after 2nd line docetaxel. But it would affect any scenario analyses which assume that a proportion of patients in either the enzalutamide arm or the abiraterone arm will receive an active 3rd line treatment after being treated with 2nd line docetaxel, probably biasing the analysis in favour of BSC. That said, it is not clear that the same quality of life increment of 0.040 that is applied for 3rd line enzalutamide treatment should be applied to other 3rd line therapies.

SREs: possible exaggeration of impacts

The main quality of life analysis applies a treatment effect. The SRE quality of life analysis is entirely separate to this and is pooled across treatments. This suggests that the main quality of life analysis treatment effect may already incorporate the net gain from any reduction in rates of SREs from 1st line enzalutamide compared to BSC.

The model also assumes a constant rate per cycle as derived from PREVAIL data during the TTD period for those on 1st line enzalutamide and those on 1st line BSC. Given the definition of TTD and the likelihood that an SRE may be the event that causes a treatment change, it may have been more appropriate to model SREs occurring at treatment change rather than as a constant rate per cycle while on treatment. But this seems likely to have minimal impact upon results.

SREs: general cross check

Due to time constraints the ERG has not cross checked the cost impacts of SREs beyond checking that the values within the model cross check with those of Table B62 of the economic section of the submission. There is no ready cross check with the clinical effectiveness section of the submission due to Table B17 reporting the number of patients experiencing an event rather than the number of events.

Data supplied at clarification summarises the SRE disutilities used by the company for enzalutamide post-chemotherapy [TA316].[41] A similar approach was used to analyse the EQ-5D data of the AFFIRM trial in TA316.[41]

Table 66 SRE disutilities comparison with TA316

	Submission	TA316
Spinal cord compression	-0.24	
Pathological fracture	-0.20	
Radiation to the bone	-0.06	
Surgery to the bone	-0.06	

The quality of life decrements applied in TA316 are somewhat lower than those of the current submission. But there is no particular reason for assuming these the values would necessarily be the same. Applying the TA316 decrements is inconsequential[m], worsening the cost effectiveness estimate for enzalutamide compared to BSC from £78,587 per QALY to £78,674 per QALY and improving the cost effectiveness estimate for enzalutamide compared to abiraterone from £27,076 per QALY to £27,035 per QALY.

The company submission only presents the disutilities from the 1st SRE analysis of the PRO report. Applying the disutilities of the most severe SRE analysis has virtually no impact upon the cost effectiveness estimates.

A cross check of the costs that have been applied can be made by comparing the values of the current submission with those applied in the MTA of denosumab for the prevention of SREs[n] [TA265] which included various outpatient appointments and other resource use. The costs from the denosumab MTA have been uprated by 8% for inflation using the HSCS index.

Table 67 SRE costs comparison with denosumab MTA

	Submission	TA265
Spinal cord compression	£4,688	£7,869
Pathological fracture	£5,351	£1,009

[m] Implemented within the *AEs* worksheet by setting cells C102:C104 equal to the relevant values.
[n] http://www.journalslibrary.nihr.ac.uk/__data/assets/pdf_file/0020/76016/FullReport-hta17290.pdf

Radiation to the bone	£683	£713
Surgery to the bone	£3,568	£7,823
Vertebral fracture	£3,568	£317
Non-vertebral fracture	£7,135	£1,702

While the values differ from those of the company, the impact of applying the denosumab MTA costs is relatively minor[o], improving the cost effectiveness estimate for enzalutamide compared to BSC from £78,587 per QALY to £78,309 per QALY and the worsening cost effectiveness estimate for enzalutamide compared to abiraterone from £27,076 per QALY to £27,103 per QALY.

Adverse events

Due to time constraints the ERG has not cross checked the quality of life or cost impacts of adverse events beyond checking that the rates applied within the electronic model correspond with those of the written submission Tables B62 and B37. Adverse events have minimal impact upon the model outputs.

Health state costs and monitoring frequency

The company submission cites the abiraterone SmPC when stating that "*enzalutamide does not require the additional monitoring for abiraterone*". This is the justification given for an assumption of 8 weekly monitoring for enzalutamide compared to 4 weekly monitoring for abiraterone, with these visits alternating between a consultant outpatient appointment and a nurse outpatient appointment.

The SmPC for abiraterone does state that:

> *Serum transaminases should be measured prior to starting treatment, every two weeks for the first three months of treatment and monthly thereafter. Blood pressure, serum potassium and fluid retention should be monitored monthly. However, patients with a significant risk for congestive heart failure should be monitored every 2 weeks for the first three months of treatment and monthly thereafter*

[o] Implemented within the *AEs* worksheet by setting cells G102:G105 equal to the relevant values.

But the SmPC for enzalutamide does not appear to specify any particular monitoring frequency.

The reasons for assuming a less frequent CT scanning for enzalutamide than for abiraterone are not clear. Similarly the reason for assuming a much more frequent CT scan for BSC with these only being 7 weeks apart is not clear, though this may be related to the higher rate of progression under BSC requiring more frequent monitoring with CT scans.

ERG expert opinion suggests that the most reasonable assumption is to assume the same frequency of monitoring across the 1st line therapies.

Drug wastage

The company states that drug waste has been addressed by not conditioning drug use by half cycle correction. But the error now tends to the opposite direction, with the end of cycle patient number rather than the start of cycle patient number being used for the drug cost calculation.

Drug usage is still conditioned by the proportion remaining on treatment during each weekly cycle. Both enzalutamide and abiraterone are administered in packs sufficient for four weeks use. The ERG assumption is that none of this four weekly administration is recycled, and that as a consequence the drug use should be based upon the proportion of patients who are on treatment at the start of each four weekly period within the model.

Pharmacy and administration costs for enzalutamide and abiraterone

During the ongoing STA of radium-223 for prostate cancer [ID576][16] the company concerned has argued that abiraterone should be associated with a specific cost of administration of £161.33[p] based upon the NHS reference cost SB11Z: deliver exclusively oral chemotherapy. This cost was in addition to the ongoing outpatient monitoring costs concerned. The ERG for this assessment was also the Aberdeen HTA group and was of the opposite opinion. The matter was not fully resolved.

[p] http://www.nice.org.uk/guidance/gid-tag345/resources/prostate-cancer-hormone-relapsed-bone-metastases-radium223-dichloride-id576-committee-papers2

The NHS data dictionary[q] defines chemotherapy as "*a treatment for cancer. It uses medication to kill cancerous cells*". Since enzalutamide and abiraterone work via testosterone to prevent cancer growth it appears that they are not chemotherapy for NHS reference cost coding purposes and are rather hormone therapies.

To the ERG it remains unclear whether some additional costs for prescribing and administration should be applied to the outpatient visit costs, or whether these outpatient visit costs include these costs. The 2013-14 reference costs collection guidance[r] notes that chemotherapy is unbundled, with this being further split into procurement costs, which include the pharmacy cost, and delivery or administration costs. But section 183 states that:

> *We are aware that some supportive drugs may have a disproportionately high cost compared to the other expected costs of care within the unbundled chemotherapy procurement HRG, and that some hormonal drugs may similarly have a disproportionately high cost within the core HRG. We are working towards implementing a solution to these issues. Currently the treatment of such drugs should be as per Table 11.*

Method of delivery	*Hormone treatments*	*Supportive drugs*
Intrinsic part of a regimen	*If included within a regimen then ignore, because the costs are already included within the chemotherapy procurement HRGs.*	*If included within a regimen then ignore, because the costs are already included within the chemotherapy procurement HRGs.*
By itself	*Code to the relevant admitted patient or outpatient core HRG generated (not chemotherapy specific)*	*Apportion over procurement bands, potentially extra delivery time and costs*
As part of supportive drug	*Include costs within supportive drug costs*	*N/A*

[q]http://www.datadictionary.nhs.uk/data_dictionary/nhs_business_definitions/c/chemotherapy_de.asp?shownav=1

[r]https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/289224/reference_costs_collection_2013-14_2.pdf

To the ERG this suggests that additional administration costs should not be attributed to abiraterone and enzalutamide if a dedicated outpatient review appointment has been included, though this is not definitive and has admittedly been taken from the chemotherapy section of the guidance.

Concomitant medication costs

Due to the very limited differences between the first line treatments and time constraints the ERG has not cross checked all elements of the concomitant medication costs. The costs of GSCF are the main concomitant cost element within 2nd line docetaxel and the applied cost of £246.61 broadly cross checks with the current eMIMS cost of £263.52.

Perhaps of more interest is that concomitant medication costs do not appear to include an LHRH-analogue which ERG expert opinion suggests would be used for all patients throughout. The cheapest is apparently triptorelin which is available in 1, 3 and 6 monthly formulations at a cost of £69, £207 and £414 respectively. These require an intramuscular injection so it could be argued that some additional administration cost should be allowed for this. Including a weekly cost of £16 for the direct drug cost[s] has a limited impact upon results, worsening the cost effectiveness estimate for enzalutamide compared to BSC from £78,587 per QALY to £79,359 per QALY and worsening the cost effectiveness estimate for enzalutamide compared to abiraterone from £27,076 per QALY to £27,956 per QALY.

5.4 Exploratory and sensitivity analyses undertaken by the ERG

The ERG has revised the company model to:

- Assume that 1st line enzalutamide patients can receive 3rd line abiraterone and that 1st line abiraterone patients can receive 3rd line enzalutamide.
- Apply the Sep 2013 gamma TTD curves.
- Apply the start of cycle patient numbers when calculating the 1st line drug cost[t].
- Apply 4 weekly dosing for 1st line therapies[u].

[s] Implemented within the *Input_Parameters* worksheet by adding £16 to cells F49:F58

[t] Implemented within the three *Calculations_* worksheets by having cell AU10 refer to cell E9 rather than E10 and likewise down column AU, with the parallel changes being made to columns AV:AY.

- Apply the quality of life estimates for those remaining on 1st line treatment of 0.780 for BSC and 0.802 for enzalutamide and abiraterone[v].
- Apply the baseline quality of life estimate for those on 3rd line treatment of [redacted] as within the modelling of the cost effectiveness of enzalutamide in TA316[w].
- Remove the SRE QoL decrement from 1st line treatments due to probable double counting[x].
- Apply the quality of life gain from 3rd line treatment for all treatments[y].
- Assume the same health state costs across the 1st line treatments[z].
- Apply the 2013-14 reference costs schedule 3a WF01A for medical oncology of £143 for a consultant led outpatient appointment and £90 for a nurse led outpatient appointment, £124 per RA10Z CT scan, £212 per RA03Z MRI scan, £215 per medical oncology EA47Z ECG, £52 per RA23Z ultrasound scan and £204 per RA36Z bone scan[aa].
- Include a weekly cost of £16 for LHRH analogues[bb].
- Apply the CMU EMIT cost per docetaxel vial of £29.78 and the 2013-14 reference costs schedule 3a SB15Z cost of £314 for docetaxel administration[cc].
- Correct the referencing within the gamma overall survival curves[dd].

The ERG has also undertaken a number of sensitivity analyses:

- Apply the September 2013 IPCW Weibulls for overall survival.
- Apply the June 2014 gammas for TTD.
- Apply the two stage June 2014 Weibulls for overall survival for enzalutamide and BSC.

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[u] Implemented within the three *Calculations_* worksheets by multiplying cell AU10 by 4, cells AU11:AU13 by 0 and continuing this 4 weekly pattern down through column AU.
[v] Implemented within the *Utilities* worksheet by subtracting 0.064 from cell E6.
[w] Implemented within the *Utilities* worksheet by setting cell E9=[redacted]
[x] Implemented within the *Input_Parameters* worksheet by setting F269:F271 equal to zero.
[y] Implemented within the *Calculations_Enzalutamide* and *Calculations_Abiraterone* worksheets by qualifying cells AK10:AK828 by (u_Post_Progression2+u_TreatmentGain_Enza_post_chemo) as in the *Calculations_BSC* worksheet.
[z] Implemented within the *Input_Parameters* worksheet by setting cells F33, F34, F36 and F37 equal to F42.
[aa] Implemented within the Unit_costs worksheet by setting cell E39=£143, E40=£90, E42=£124, E43=£212, E44=£215, E45=£52 and E47=£204.
[bb] Implemented within the *Input_Parameters* worksheet by adding £16 to cells F49:F58
[cc] Implemented within the *Unit_Costs* worksheet by setting I11=£29.78 and F34=£314.
[dd] Implemented within the *Overall_survival* worksheet by revising the referencing to cell BX96 within columns CD, CI, CN, CS and CX to refer to cells CC96, CH96, CM96, CR96 and CW96 respectively.

- Apply the PFS TTD Weibull within the enzalutamide arm and the Weibull TTD within the abiraterone arm.
- Apply the September 2013 Weibull for enzalutamide and the Weibull for abiraterone for TTD.
- Assuming the 100% receive 2nd line docetaxel[ee].
- Varying the 2nd line docetaxel discontinuation rate by ±20%[ff].
- Assume that 1st line enzalutamide patients cannot receive 3rd line abiraterone and that 1st line abiraterone patients cannot receive 3rd line enzalutamide as per the company base case.
- Apply the quality of life estimates for those remaining on 1st line treatment of 0.780 for all treatments from week 62 onwards[gg].
- Revert to the company estimate for the baseline quality of life for 3rd line treatment of 0.612.
- Apply the Sandblom et al[1] 0.538 quality of life estimate for prostate cancer patients within 16 months of death to palliative care[hh].
- Assume that the quality of life for docetaxel is the mid-point of the 1st line and 3rd line quality of life values[ii].
- Applying the EQ-5D quality of life values of Diels et al[2] of 0.70 for pre-chemotherapy, 0.66 for chemotherapy and 0.60 for post-chemotherapy[jj]. Note that sensitivity analysis this still retains the 0.500 quality of life value for palliative care.
- Retain the company estimates of health state resource use differing between 1st line treatments.
- Apply the PPRS rebate of 10.36% to the cost of enzalutamide and abiraterone[kk].

[ee] Implemented within the *Second_line_treatment* worksheet by setting cell D25=100%
[ff] Implemented within the *Sequencing_probabilities* worksheet by multiplying cell G8 by 120% or 80%.
[gg] Implemented within the *Calculations_Enzalutamide* and *Calculations_Abiraterone* worksheets by setting AH71=X71*cycle_length*u_Stable_Disease and copying this formula into the cells below.
[hh] Implemented within the *Utilities* worksheet by setting cell E10=0.538
[ii] Implemented within the *Utilities* worksheet by setting cell E8=(E6+E9)/2
[jj] Implemented within the *Utilities* worksheet by setting cells E6=0.70, E8=0.66 and E9=0.60.
[kk] Implemented within the *Unit_Costs* worksheet by multiplying cells I9:I10 by 89.64%.

Table 68 Exploratory ERG revised base case: exclusive of PAS

	Enzalutamide	BSC	net	Abiraterone	net
Direct drug costs					
1st line	£70,273	£0	£70,273	£64,840	£5,434
2nd line	£156	£278	-£122	£151	£5
3rd line	£7,734	£15,207	-£7,473	£8,535	-£801
Health state costs[ll]					
1st line	£4,362	£1,467	£2,895	£4,018	£344
2nd line	£3,034	£5,403	-£2,369	£2,928	£106
3rd line	£489	£571	-£81	£320	£169
Concomitant medication					
1st line	£2,289	£765	£1,525	£2,135	£155
2nd line	£1,725	£2,597	-£872	£1,664	£60
3rd line	£442	£863	-£421	£484	-£42
SREs	£1,557	£1,555	£2	£1,499	£58
AEs	£330	£415	-£86	£272	£57
Palliative	£3,199	£5,211	-£2,013	£2,861	£338
Terminal	£3,277	£3,332	-£55	£3,306	-£29
Total costs	£98,867	£37,665	£61,202	£93,012	£5,855
LY (undiscounted)	3.238	2.745	0.493	3.003	0.235
QALYs (discounted)	2.213	1.672	0.541	2.069	0.144
ICERs			£113,047		£40,776

The ERG revised base case quite considerably worsens the cost effectiveness estimates. For the comparison of enzalutamide with BSC the company estimate of £78,587 per QALY worsen to £113k per QALY. This is due in part to the additional costs of 3rd line treatment in the enzalutamide arm resulting in a smaller cost offset from this source. For the comparison of enzalutamide with abiraterone the cost effectiveness estimate worsens from £27,076 per QALY to £40,776 per QALY.

[ll] Includes chemotherapy administration costs.

Table 69 Exploratory ERG sensitivity analyses: exclusive of PAS

	vs BSC			vs Abiraterone		
	net Cost	net QALY	ICER	net Cost	net QALY	ICER
Base case	£61,202	0.541	£113k	£5,855	0.144	£40,776
Sep 2013 IPCW Weib OS	£57,698	0.404	£143k	£2,712	0.029	£92,092
Jun 2014 gamma TTD	£60,288	0.548	£110k	£5,573	0.141	£39,503
2 stage June 2014 Weib OS	£59,017	0.458	£129k	£3,443	0.051	£67,238
PFS TTD Weibull	£62,219	0.524	£119k	£7,601	0.159	£47,856
Sep 2013 Weibull TTD	£60,726	0.546	£111k	£7,475	0.157	£47,518
100% 2nd line	£59,445	0.526	£113k	£5,771	0.143	£40,360
2nd line disc +20%	£61,450	0.538	£114k	£5,957	0.145	£41,199
2nd line disc -20%	£61,070	0.544	£112k	£5,803	0.143	£40,574
No 3rd line Enza & Abir arms	£53,434	0.492	£109k	£6,442	0.149	£43,363
Same 1st line QoL wk 62+	£61,202	0.520	£118k	£5,855	0.142	£41,292
Company 3rd line QoL	£61,202	0.557	£110k	£5,855	0.145	£40,299
Sandblom palliative 0.538 QoL	£61,202	0.527	£116k	£5,855	0.146	£40,111
2nd line QoL midpoint	£61,202	0.522	£117k	£5,855	0.144	£40,535
Diels QoL	£61,202	0.457	£134k	£5,855	0.133	£43,896
Diff 1st line health state costs	£59,543	0.541	£110k	£3,753	0.144	£26,135
PPRS 10.36% rebate	[redacted]					

5.5 Conclusions of the cost effectiveness section

In the opinion of the ERG the company submission cost effectiveness estimates may be too optimistic for the following reasons:

- Not including the costs of any post-docetaxel treatment in the enzalutamide arm and the abiraterone arm, but including the costs of post-docetaxel enzalutamide in the BSC arm. The implied cost effectiveness of the post-docetaxel enzalutamide treatment in the BSC is extremely poor and very much worse than the estimate submitted by the company for TA316. This tends to improve the cost effectiveness estimate for enzalutamide within the current submission.
- The implementation of the PREVAIL quality of life estimates adds the net treatment effect to the baseline value, instead of applying each arm's change from baseline to the baseline value.
- The quality of life values are drawn from disparate sources and may exaggerate the quality of life differences between those on 1st line treatment, those on 2nd line treatment and those on 3rd line treatment.

- Routine monitoring for the 1st line treatments is differentiated by arm. This is particularly marked for the comparison with 1st line abiraterone, which is assumed to require twice the routine monitoring frequency of 1st line enzalutamide.
- There may be some bias within the model structure against abiraterone as after a certain point patients on 1st line abiraterone do not progress through the model health states but remain on 1st line abiraterone for their remaining survival.
- Dosing for enzalutamide and abiraterone is based upon the end of cycle patient numbers rather than the start of cycle patient numbers. It also assumes weekly prescribing of enzalutamide and abiraterone, rather than the monthly dosing that is implied by the pack size.

There are also some less significant input values and model structure elements that the ERG disagrees with and has attempted to correct in the exploratory analyses of section 5.4 above.

The main uncertainties that remain relate to the reasonableness of the extrapolated overall survival curves. The PREVAIL Kaplan Meier overall survival curves are far from complete due to a high proportion patients still surviving, and it is uncertain to what extent the extrapolated curves and their tails will apply in practice.

Results are also sensitive to whether the Sep 2013 data cut is used instead of the Jun 2014 data cut. While the ERG accepts the argument that the Jun 2014 data cut has a much fuller overall survival curve from randomisation, some concerns remain around the Jun 2014 data cut being post-unblinding of PREVAIL. The sensitivity of results to the choice of data cut remains a concern.

There is an oddity within the model structure, in that at any time point in the model patients have the same life expectancy regardless of their health state. This seems unrealistic, but the impact of addressing this is uncertain.

The company submission addresses the analyses specified in the scope. The company model incorporates a benefit of delaying chemotherapy through the time to treatment

discontinuation curves resulting in a longer period being spent pre-chemotherapy in the enzalutamide arm than in the BSC arm, and to some extent than in the abiraterone arm. A quality of life gain applies to this period.

The company model has the additional facility for incorporating a delay between cessation of 1st line treatment and starting chemotherapy, but this was not used in the company submission and the structure of this has not been rebuilt by the ERG.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

The full details of the impact of the ERG revisions to the company base case are tabulated in section 5.4. These revisions worsen the cost effectiveness estimates. For the comparison of enzalutamide with BSC the cost effectiveness estimate worsens from £78,587 per QALY to £113k per QALY. For the comparison of enzalutamide with abiraterone the cost effectiveness estimate worsens from £27,076 per QALY to £40,776 per QALY.

Applying the Sep 2013 IPCW Weibull overall survival curve rather than the Jun 2013 IPCW Weibull overall survival curve reduces the net costs but reduces the net QALY gain more, so worsens the cost effectiveness estimate compared to BSC to £143k per QALY and compared to abiraterone to £92,092 per QALY. The 2 stage June 2014 Weibull shows a similar pattern, worsening the cost effectiveness estimate compared to BSC to £129k per QALY and compared to abiraterone to £67,238 per QALY.

Applying the PFS TTD Weibull and the COU-AA-302 PFS Weibull, given that the COU-AA-302 curves are based upon PFS, worsens the cost effectiveness estimate compared to abiraterone to £47,856 per QALY.

Assuming that those in the enzalutamide arm and the abiraterone arm cannot receive 3rd line treatment after 2nd line docetaxel improves the cost effectiveness estimate compared to BSC to £109k per QALY, but worsens it compared to abiraterone to £43,363 per QALY.

Applying the same quality of life for those remaining on 1st line treatment from week 62 has only a limited impact upon results. The cost effectiveness estimate compared to BSC worsens to £118k per QALY, while the cost effectiveness estimate compared to abiraterone only worsens to £41,292 per QALY. The impact of applying the company preferred quality of life estimate for those on 3rd line treatment is similarly muted, improving the cost effectiveness estimate compared to BSC to £110k per QALY and the cost effectiveness estimate compared to abiraterone to £40,299 per QALY.

The quality of life estimates of Diels et al[2] have a larger impact, worsening the cost effectiveness estimate compared to BSC to £134k per QALY and the cost effectiveness estimate compared to abiraterone to £43,896 per QALY.

Retaining the company 1st line resource use improves the cost effectiveness compared to BSC to £110k per QALY, and improves it compared to abiraterone quite dramatically to £26,135 per QALY. Applying the PPRS 2015 rebate also improves the cost effectiveness estimates, to [redacted] per QALY compared to BSC and to [redacted] per QALY compared to abiraterone.

7 END OF LIFE

The interim FAD for the STA of abiraterone for the same indication, ID503, states that:

> *The Committee concluded that current mean life expectancy for people with metastatic hormone-relapsed prostate cancer for whom chemotherapy is not yet indicated was unlikely to be less than 24 months, and abiraterone at this stage in the treatment pathway did not meet the end-of-life criterion for short life expectancy.*

The company base case results are in line with this, suggesting an undiscounted overall survival in the BSC arm of 2.74 undiscounted life years.

8 OVERALL CONCLUSIONS

The main differences of opinion between the company and the ERG are:

- Whether those in the enzalutamide arm and the abiraterone arm would receive a 3rd line treatment after 2nd line docetaxel or would proceed straight to palliative care. The company assumes not, while the ERG assumes that all the treatment arms and not just the BSC arm would receive a 3rd line treatment after 2nd line docetaxel.
- What the modelling should imply for the cost effectiveness of 3rd line enzalutamide compared to palliative care. The company cost per QALY estimates for this are very large and well in excess of those it submitted for the evaluation of enzalutamide post-chemotherapy [TA316].[41] This tends to improve the cost effectiveness estimate for 1st line enzalutamide pre-chemotherapy compared to BSC. This effect of this is more marked in the company base case due to only the BSC arm incorporating a 3rd line of treatment.
- Whether it is more reasonable to apply the pre-unblinding Sep 2013 time to treatment discontinuation curves or the post-unblinding June 2014 time to treatment discontinuation curves. The ERG prefers the former as it seems possible that unblinding may have a direct effect upon treatment discontinuation rates.
- What quality of life values should be applied. The company adds the net treatment effect to the PREVAIL baseline value, while the ERG subtracts the changes from baseline for each arm from the PREVAIL baseline value. The company also draws a variety of values from disparate sources, the company literature review of which is in the opinion of the ERG incomplete. The ERG applies values that suggest a smaller difference in quality of life between 1st line and 3rd line, drawing supporting evidence for this from the company PREVAIL and AFFIRM baseline EQ-5D values and from the Diels et al paper.[2]
- Whether the resource use for 1st line treatments should be differentiated by arm to the extent suggested by the company. This has a particularly marked

effect upon the comparison with abiraterone where routine monitoring visits are assumed to be twice as frequent as for enzalutamide.

There is considerable uncertainty around the modelled survival gains due to the PREVAIL Kaplan Meier overall survival curves being quite incomplete. Whether the extrapolated curves and their tails are realistic representations of what will happen in practice is unclear. The company could have supplied sensitivity analyses around this limiting the anticipated gains, as suggested in the NICE methods guide.

The choice of data cut for the estimates of overall survival also has a large impact upon the cost effectiveness results, with the pre-unblinding Sep 2013 data cut worsening them considerable.

The naïve comparison with abiraterone also increases the uncertainty around the cost effectiveness estimates for this comparison.

The model structure may be biased against abiraterone due to the probability of death rising above the probability of treatment discontinuation, so holding the remaining abiraterone patients on 1st line therapy for their remaining survival.

The model structure also applies the same probability of death to all health states for a given cycle. This means that a patient in the asymptomatic 1st line health state has the same life expectancy as a patient on palliative care. This seems unrealistic, but the impact of this upon the cost effectiveness estimates cannot be determined.

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