NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

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

This premeeting briefing presents:

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

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

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

Key issues for consideration

Treatment pathway and clinical effectiveness

- Are there any subgroups of people for whom abiraterone is not suitable but who would receive enzalutamide in clinical practice?
- Are there any groups of people for whom enzalutamide and abiraterone taken before chemotherapy are unsuitable?
- The company's model compares three treatment sequences
    - 1st enzalutamide, 2nd docetaxel 3rd palliative
    - 1st abiraterone 2nd docetaxel 3rd palliative

- o 1st best supportive care 2nd docetaxel 3rd enzalutamide 4th palliative

  - Would people who had enzalutamide before chemotherapy be eligible to have abiraterone after chemotherapy and vice versa?
  - Is there evidence for the clinical effectiveness of treatment sequences in which people who have enzalutamide before chemotherapy have abiraterone after chemotherapy and vice versa?
  - Would people whose cancer progresses on chemotherapy receive best supportive care before palliative care?
  - Were the relevant treatment pathways modelled by the company?

- How would progression be assessed in clinical practice in England?

  - Does time to discontinuation data reflect rates of progression in clinical practice in England?
  - Is it reasonable to assume that rPFS with abiraterone in COU-AA-302 is the same as time to discontinuation from abiraterone in clinical practice?

- The company presented data from a number of data-cuts in its submission including event-driven pre-planned analyses of the primary outcomes for radiographic progression free survival (rPFS, May 2012 when 410 people had progressed) and overall survival (OS, Sept 2013 when 516 people had died) and also from a cut off (June 2014) after study unblinding in December 2013.

  - Which data cut is better for estimating OS, rPFS and time to treatment discontinuation?
  - To what extent would the results for these outcomes from the June 2014 cut be biased by the unblinding of the study in December 2013?

- Some patients in PREVAIL received 3rd line life-extending treatments not offered in the UK. The company tried to control for this. Did it do so correctly, and what does this imply?
- The company felt that a naïve comparison of enzalutamide with abiraterone was more appropriate than an indirect treatment comparison because a different

proportion of people received corticosteroids in the placebo arms of the PREVAIL trial of enzalutamide (30%) to the COU-AA-302 trial of abiraterone (100%- all received prednisone/prednisolone in abiraterone and placebo arms).

  - What is the treatment effect of corticosteroids?
  - Is the naïve comparison robust and appropriate for use in the economic model?

- The company assumed that people taking abiraterone would have double the monitoring visits compared with people taking enzalutamide.

  - What level of monitoring is required for enzalutamide?
  - Is it expected to be different to abiraterone?

Cost effectiveness

- The company extrapolated overall survival data and time to treatment discontinuation data from the trials. The ERG commented that most of the survival gain was in the extrapolated period of the model and that the time to treatment continuation and overall survival curves crossed in the extrapolated period. Are the extrapolated data used by the company to derive its base case estimates robust?

- Even with the later cut-off date, a large number of patients remain alive, requiring further extrapolation to the time when all patients would have died. However, the company has not presented sensitivity analyses around this.

- In PREVAIL quality of life decreased from baseline in both the enzalutamide and placebo arms. In the stable disease state the company applied an on-treatment utility increment for enzalutamide (which was based on the difference in the amount quality of life decreased with enzalutamide relative to placebo) to the baseline utility value. The ERG applied the decrease in utility based on the decrease in quality of life observed in PREVAIL in each arm to the baseline utility value. Which approach to using quality of life data from PREVAIL is appropriate, the company's or ERGs?

	Enzalutamide	Best supportive care	abiraterone
Stable disease company	0.866 (baseline 0.844 + 0.022)	0.844	0.866 (same as enzalutamide)
Stable disease ERG	0.802 (baseline 0.844- 0.042)	0.780 (baseline 0.844- 0.064)	0.802

- .The company used sources from the literature for utility values on subsequent treatments. The company chose a utility value of 0.612 for people starting enzalutamide post-chemotherapy rather than [redacted] based on data from the AFFIRM trial of enzalutamide taken post-chemotherapy. Which source of utility value is appropriate?
- The company assumed the death rate would be the same on all lines of treatment. Is this plausible?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of enzalutamide within its licensed indication for treating metastatic, hormone-relapsed prostate cancer for people in whom chemotherapy is not yet clinically indicated.

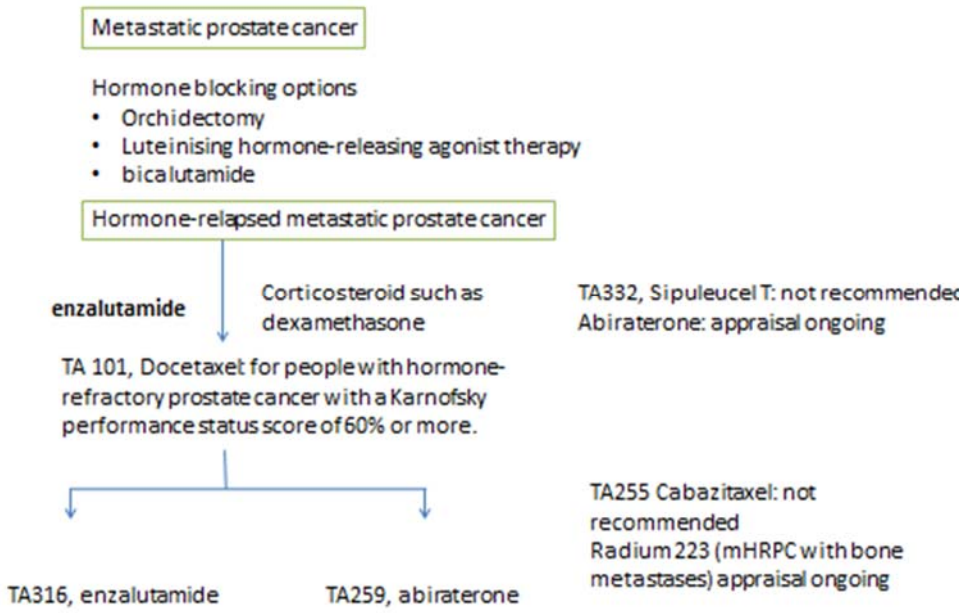
Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Pop.	Adults with asymptomatic or mildly symptomatic metastatic hormone-relapsed prostate cancer in whom chemotherapy is not yet clinically indicated.		None	None (as scope)
Int.	Enzalutamide		Enzalutamide once daily 160 mg (4 x 40 mg) capsules	None (as scope)
Com.	• Best supportive care • Abiraterone in combination with prednisone or prednisolone		Best supportive care may include radiotherapy, radiopharmaceuticals, analgesics, bisphosphonates, further hormonal therapies, and corticosteroids).	None (as scope)
Out.	The outcome measures to be considered include: • Overall survival • Progression-free survival (radiographic and prostate specific antigen response) • Time to initiation of cytotoxic chemotherapy • Response rate • Adverse effects of treatment • Health-related quality of life	As final scope with additional outcome: • Time to treatment discontinuation	Time to treatment discontinuation is a more accurate reflection of what happens to mHRPC patients in clinical practice than rPFS. This end point has previously been accepted by NICE.	Clinical advice to the ERG is that it is standard practice to stop treatment once progression is diagnosed. Additional outcomes presented by company • Time to first skeletal-related event (SRE) • Time to first post-baseline antineoplastic therapy

2 The technology and the treatment pathway

2.1 Enzalutamide (Xtandi, Astellas Pharma) is an androgen receptor antagonist that acts on the androgen receptor signalling pathway to decrease proliferation of cancer cells and induce cancer cell death leading to tumour regression. Enzalutamide is administered orally.

Figure 1: treatment pathway for prostate cancer



2.2 NICE clinical guideline 175 ('prostate cancer') states that once prostate cancer metastasises, the objective of treatment is to delay progression of the cancer. Stopping the body making testosterone using hormonal therapies can slow the growth of the cancer, or shrink it. Standard hormonal treatments for metastatic disease include orchidectomy (surgical removal of the testes, also known as surgical castration) or therapy with luteinising hormone-releasing agonists (known as medical castration). If the condition becomes refractory to hormone treatment, people may be offered a corticosteroid. NICE technology appraisal 101 recommends intravenous docetaxel (a form of cytotoxic chemotherapy) as

a treatment option for hormone-refractory prostate cancer for people with a Karnofsky performance-status score of 60% or more. Abiraterone (in combination with prednisolone or prednisone) or enzalutamide are recommended as treatment options for people whose disease has progressed on or after one docetaxel-containing chemotherapy regimen (technology appraisal guidance nos. 259 and 316 for abiraterone and enzalutamide respectively). NICE does not recommend cabazitaxel in combination with prednisone or prednisolone as a treatment option after a docetaxel containing regimen (technology appraisal guidance no. 255). In This appraisal considers enzalutamide for use before docetaxel chemotherapy. There is an ongoing appraisal of abiraterone acetate at the same position in the treatment pathway; however this appraisal was suspended while the company submitted a new patient access scheme to the Department of Health. NICE does not recommend Sipuleucel T as a treatment for people with metastatic non-visceral hormone-relapsed prostate cancer at the same point in the pathway.

Table 2 Technology

	Enzalutamide	**Abiraterone (with prednisone or prednisolone)**
Marketing authorisation	The treatment of adult men with metastatic castration-resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated. MA also covers the treatment of adult men with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel therapy.	Treatment of metastatic castration-resistant prostate cancer in adult men who are asymptomatic or mildly symptomatic after failure of androgen-deprivation therapy in whom chemotherapy is not yet clinically indicated. MA also covers the treatment of metastatic castration-resistant prostate cancer in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.
Administration method	160 mg enzalutamide (4 x 40 mg capsules) as a single oral daily dose. Dose can be reduced to 120 mg or 80 mg if a person	1,000 mg abiraterone (4 x 250 mg tablets) as a single daily dose that must not be taken with food and must be taken with steroids (prednisone/prednisolone) to reduce the effects of mineralcorticoid excess

	experiences grade 3 or more toxicity or an intolerable side effect.	10 mg prednisone or prednisolone daily
Cost	112 capsules (28 days of treatment) £2,734.67. [redacted]	Abiraterone 250 mg, 120-tablet pack (30 days of treatment) =£2,930. [redacted] Prednisone or prednisolone

See summary of product characteristics for details on adverse reactions and contraindications.

3 Comments from consultees

3.1 The professional groups commented on the treatment options available for people with hormone-relapsed prostate cancer in whom chemotherapy is not yet indicated. They stated that the 3 current treatment options include: docetaxel or abiraterone/prednisolone or enzalutamide (currently obtained through the Cancer Drugs Fund). If these treatments are not suitable, patients continue androgen blockade and add dexamethasone or diethylstilboestrol. A professional group further commented clinician offer that older therapies such as ketoconazole, diethylstilboestrol or “watchful waiting” less often because they have not been proven to prolong survival, and that abiraterone and enzalutamide are widely used before chemotherapy through the Cancer Drugs Fund. A professional group also commented that there are no criteria to determine which patients may benefit from a particular agent.

3.2 A patient group noted that abiraterone is not available to people with metastatic visceral disease because they were excluded from the abiraterone regulatory trial. However, enzalutamide is available to all people with metastatic disease who have not had prior chemotherapy.

3.3 A patient group commented that NICE technology appraisal guidance 316, ‘Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen’ does not cover enzalutamide taken after abiraterone. Similarly, enzalutamide is not

available on the Cancer Drugs Fund for men who have previously been treated with abiraterone, unless abiraterone had to be stopped within 3 months. The patient group acknowledged that the evidence for sequential use of abiraterone and enzalutamide was limited, but that there should be provision for people who are unable to tolerate enzalutamide. A professional group commented that abiraterone and enzalutamide should be continued for a minimum of 3 months to assess therapeutic response (provided the side effect profile is acceptable).

3.4 The professional groups commented that enzalutamide is well tolerated. Patients do not need to take corticosteroids with enzalutamide (unlike abiraterone) and enzalutamide has fewer side effects than corticosteroids or chemotherapy. They noted that it may benefit people who are not fit enough to tolerate chemotherapy. They noted that the main side effect of enzalutamide is hypertension, which is managed easily with medication, and that the only contra-indication is a history of seizures. The professional groups noted the adverse effects of abiraterone/prednisolone including cardiac failure, liver dysfunction/hypertension and electrolyte disturbances, and of diethylstilboestrol including venous embolism. Patient groups stated that that delaying chemotherapy and having treatment options when chemotherapy is unsuitable were benefits of enzalutamide important to patients.

3.5 The professional groups noted that currently oncologists initiate and monitor treatment for prostate cancer. A professional group representing urologists noted that patients on androgen deprivation therapy often remain under the care of an urologist, and that urologist could easily start enzalutamide because it is administered orally and is generally safe. They further noted that this would obviate the need to wait for an appointment with an oncologist to start treatment.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 PREVAIL was a randomised, double-blind placebo controlled trial comparing enzalutamide 160 mg once daily with placebo in adults with asymptomatic or mildly symptomatic metastatic hormone refractory prostate cancer in whom immediate chemotherapy was not yet clinically indicated. In total, 1717 people were randomised (intention to treat population [ITT]); 872 to enzalutamide and 845 to placebo, 1715 received at least one dose of the study drug (safety population); 871 received enzalutamide and 844 received placebo. The study was carried out at 207 sites in 22 countries and 153 participants were from the UK. People were eligible to participate if they were asymptomatic or mildly symptomatic (that is, had a score of less than 4 on the brief pain inventory (BPI) question 3), had an ECOG performance status of 0-1, and had an estimated life expectancy of 6 months or more (the full list of eligibility criteria in PREVAIL are listed in table B7 on page 53 of the company's submission). The mean age of the study population was 71 years (range 42 to 93). The majority of people in both arms had an ECOG status of 0 (enzalutamide 67.0%; placebo 69.2%). The characteristics of patients are listed in table B8 on page 55 of the company's submission.

4.2 The co-primary endpoints in PREVAIL were overall survival (OS) and radiographic progression free survival (rPFS). rPFS was defined as time from randomisation to the first objective evidence of radiographic disease progression [based on imaging review by a central (trial) radiologists] or death due to any cause within 168 days after discontinuing treatment, whichever was first. It was planned that to demonstrate a statistically significant treatment effect the p value for OS should be less than 0.049 and the p value for rPFS should be less than 0.001 at the final analysis. The study was powered on a target hazard ratio of 0.83 for overall survival (80% power, would require 765 deaths), and 0.57 for progression free

survival (>99% power). The company planned one (final) analysis for progression free survival and two (one interim at 516 deaths (2/3 of deaths used in sample size calculations)) and one final analysis (at 765 deaths). Because patients generally progress before dying, the 'final analysis' for rPFS was planned when 410 patients had progressed, This was carried out on 6th May 2012, at which point 439 people had progressed. The interim analysis for overall survival was carried out on 16th September 2013 at which point 540 deaths had occurred. To account for the increased risk of false positive results at an interim analysis for overall survival, the statistical plan stipulated that the p value could not exceed 0.012 to be considered statistically significant at this analysis. At the same time as the interim OS analyses the company performed another (post-'final', post hoc) analyses of rPFS. Following the planned interim OS analyses the Independent Data Monitoring Committee recommended unblinding the study and allowing people in the placebo arm to switch to enzalutamide. The study was unblinded on 3rd December 2013. However, the company continued to follow the participants and presented an analysis of OS carried out on 30th June 2014. Table 3 shows the planned and-post unblinding analyses carried out by the company.

Table 3: key dates in the PREVAIL trial (data from company's submission pages 12 and 13)

Pre-planned in protocol	Outcome and planned number of events	Date	Actual event no.
Yes for primary rPFS outcome	rPFS when 410 centrally confirmed events occurred	6th May 2012	439 progressed
Yes for primary OS outcome	OS 516 events	16th Sept 2013	540 died
No	rPFS	16th Sept 2013	889 progressed
IDMC meeting		21st Oct 2013	
Study unblinded		3rd Dec 2013	
Yes (Had study not stopped early, this would have	OS	30th June 2014	775 died

been the pre-planned final analysis)			

4.3 Patients remained on the study drug until they experienced (confirmed) radiographic disease progression or a skeletal related event (SRE), **and** either started cytotoxic chemotherapy or an investigational agent for prostate cancer. After stopping the study drug, people could receive docetaxel, hormonal treatments, abiraterone, enzalutamide, cabazitaxel and sipuleucel-T. Table 4 shows the treatments that people switched to in PREVAIL. The company noted that at this stage in current practice, clinicians would offer chemotherapy to patients and that [redacted] in the placebo arm and [redacted] in the enzalutamide arm received treatments which would **not** be given to patients at this stage of the treatment pathway in the UK. Nine people in the enzalutamide arm received enzalutamide (again) after docetaxel.

Table 4: Treatments received 2nd line after 1st line study treatment in PREVAIL (company submission table B23, page 94). The treatments in bold text are those which the company adjusted for in its overall survival estimates see section 4.6 of this briefing document)

Treatments received 2nd line (after study drug treatment) 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]

ERG comments

4.4 The ERG considered the clinical trial population represented the population which would receive enzalutamide before chemotherapy in clinical practice in the UK. Clinical advisers to the ERG stated that there were no subgroups of patients in PREVAIL that would have been eligible to start docetaxel at the point at which they entered the trial. The ERG stated that both arms of the trial were balanced in terms of demographics, baseline disease characteristics and medical history.

Clinical trial results

4.5 In the 1st pre-planned analysis for overall survival in September 2013, 241 (26.4%) people in the enzalutamide arm and 299 (35.4%) people in the placebo arm had died. Overall survival with enzalutamide was longer than with placebo (32.4 months and 30.2 months respectively, HR 0.706, 95% CI (0.596 to 0.837), log-rank test p<0.001). The Kaplan Meier curve for OS for the September 2013 data cut is shown in Figure B3, page 72 of the company's submission. Overall survival was also longer with enzalutamide compared with placebo in the data analysis carried out in June 2014 after study unblinding ([redacted] (see table 5). Median overall survival was longer with enzalutamide than placebo in all of the pre-specified subgroups (Figure B4 company's submission, page 75).

4.6 By September 2013, [redacted] people in the enzalutamide arm and [redacted] of people in the placebo arm had switched from their initial study treatment to a subsequent 2nd line treatment. By June 2014 [redacted] people in the enzalutamide arm and [redacted] people in the placebo arm had switched from their initially assigned treatment to a 2nd line treatment. The company applied 2 statistical methods to adjust the overall survival estimates for people switching to an active drug after their study drug which would not be given at this position in the treatment pathway in clinical practice in the UK (see table 4). These were the

Inverse Probability of Censoring Weights (IPCW) and a 'two stage method'. Applying these adjustments resulted in the treatment effect of enzalutamide relative to placebo on overall survival being greater than the unadjusted estimates. The ERG has provided a detailed explanation of the statistical techniques used by the company on pages 38 and 39 of its report.

Table 5: overall survival results (company submission table B13 and main text page 72 and table B24 page 94).

	16th Sept 2013		**30th June 2014**	
	Enzalutamide (N=845)	**Placebo (N=872)**	**Enzalutamide (N=845)**	**Placebo (N=872)**
Event (death)	241	299	[redacted]	[redacted]
Censored	631 (72%)	546 (65%)	[redacted]	[redacted]
Median (95% CI)	32.4 (30.1; not yet reached)	30.2 (not yet reached)	[redacted]	[redacted]
Hazard ratio (95% CI) (enzalutamide vs. placebo)	0.706 (0.596; 0.837)		[redacted]	
P value	P<0.0001 (P value to claim statistical significance was P<0.012†)		[redacted]	
Adjusted OS HR (95% CI IPCW	[redacted]		[redacted]	
Adjusted OS HR (95% CI) Two stage method	[redacted]		[redacted]	

† From trial protocol

4.7 In the pre-planned 'final' analysis for rPFS (6th May 2012), 118 (14.2%) people randomised to enzalutamide and 321 (40.1%) people randomised to placebo experienced radiographic progression determined by a central review team (HR 0.186; 95% CI 0.149 to 0.231, log-rank p<0.0001). The Kaplan Meier curve for rPFS is shown in figure B5 page 76 company's submission. Median rPFS was longer in all pre-specified subgroups for enzalutamide compared with placebo at the May 2012 cut (Figure B6, page 77 company's submission). Progression continued to be measured

after May 2012 but this was carried out by a study investigator rather than the central review team. The company carried out an additional analysis on 16th September 2013, by this time 387 (44.4%) people in the enzalutamide arm and 502 (59.4%) people in the placebo arm had a rPFS event (HR 0.307 95% CI 0.267 to 0.353, log-rank p<0.0001).

Table 6: radiographic progression free survival (tables B15 and B16 [analysis 6] company's submission pages 76 and 80)

	6th May 2012		**16th September 2013**	
	ENZA (N=832)	**PLA (N=801)**	**Enzalutamide (N=872)**	**Placebo (N=845)**
Status of rPFS Survival Follow up	Central review		Investigator assessed	
Events[a]	118 (14.2%)	321 (40.1%)	387 (44.4%)	502 (59.4%)
Radiographic progression	105 (12.6%)	295 (36.8%)	Not reported in submission	
Death without documented radiographic progression	13 (1.6%)	26 (3.2%)		
Censored[b]	714 (85.8%)	480 (59.9%)		
Duration of rPFS (months)[b,c]				
Censored	714 (85.8%)	480 (59.9%)		
25% percentile	9.5	1.9		
Median (95% CI)	NYR (13.8, NYR)	3.9 (3.7, 5.4)	19 (18.1, 22.3)	5.4 (4.2, 5.6)
75% percentile	NYR	8.3		
Unstratified Analysis				
Hazard ratio (95% CI)[d]	0.186 [0.149, 0.231]		0.307 [0.267,0.353]	
P-value (log-rank)	p<0.0001		P<0.0001	

4.8 In PREVAIL, patients continued treatment with the study drug until two things happened: one, their disease progressed as confirmed by radiologists or they experienced a skeletal rated event, and, two, they had started on cytotoxic chemotherapy or an investigational drug for treating prostate cancer. The company commented that it considered whether a patient had stopped treatment ("treatment discontinuation") in PREVAIL to be the best proxy for disease progression in clinical practice in the UK because its clinical experts had advised that the decision to discontinue

treatment is not made on a single measure of progression alone (such as rPFS). It carried out a post-hoc analysis of time to treatment discontinuation (TTD) in PREVAIL. In PREVAIL by September 2013, 57.8%, randomised to enzalutamide and 92.7% randomised to placebo had discontinued treatment. The median time to TTD was 17.71 (95% CI, 16.59 to 19.38) and 4.55 (95% CI, 4.11 to 5.13) months for the enzalutamide and placebo arms respectively. Please see table B11 page 68 of the company's submission for a breakdown of the reasons for study drug discontinuation the September 2013 data cut.

Figure 2: Kaplan Meier curve for time to treatment discontinuation (B15 page 93 company submission). The number of patients censored (were still on treatment) for this analysis was 367 in the enzalutamide arm and 61 in the placebo arm

4.9 In PREVAIL 31.9% of patients in the enzalutamide arm and 36.6% in the placebo arm experienced a skeletal related event during the study. The most commonly reported type of skeletal related event was an event requiring radiation therapy to bone (enzalutamide: n= 181/278, 65.1% of people with SREs; placebo: n=208/309, 67.3%), followed by spinal cord

compression (enzalutamide n=39/278, 14.0%; placebo n=40/309, 12.9%) and pathological fractures (enzalutamide n=39/278, 14.0%; placebo: n=31/309, 10%). Treatment with enzalutamide reduced the risk of experiencing a first skeletal related event (HR 0.718, 95% CI; 0.610, 0.844) p<0.0001).

4.10 The results of other secondary outcomes (pre-specified in protocol) and exploratory outcomes (not pre-specified in protocol) are summarised in table 7. The data were from the September 2013 cut.

Table 7: secondary and exploratory outcomes PREVAIL (results reported on pages 82, 83 and 86 of the company's submission)

Exploratory/secondary	outcome	Enzalutamide n (%)	Placebo n (%)	HR (95% CI)	P value
Secondary	Time to initiation of cytotoxic chemotherapy	308 (35.3%) [median 28.0 months, 95% CI 25.8, NYR]	515 (60.9%) [median 10.8 months, 95% CI 9.7, 12.2]]	0.349 (0.303, 0.403)	<0.0001
Secondary	Time to PSA progression	532 (61.0%) [median 11.2 months, 95% CI 11.1, 13.7]	548 (64.9%) [median 2.8 months, 95% CI 2.8, 2.9]	0.169 (0.147, 0.195	<0.0001
Exploratory	Time to 1st antineoplastic therapy after study treatment	382 (43.8%) [median 22.8 months 95% CI not reported]	642 (76.0%) [median 7.4 months, 95% CI not reported]	0.273 (0.240, 0.311)	<0.0001

4.11 The company measured quality of life using the Functional Assessment of Cancer Therapy- Prostate (FACT-P) and European quality of life five-domain scale (EQ-5D) questionnaires at baseline, weeks 5, 13 and every 12 weeks until disease progression. The company also assessed pain using item 3 on the Brief Pain Inventory, relating to pain severity. These

outcomes were exploratory because they had not been pre-specified in the study protocol. People in both the enzalutamide and placebo arms showed a decrease in FACT-P scores (worsening of quality of life) from baseline over time. However, the company stated that a "clinically meaningful deterioration", which it defined as a decrease in more than 6 points, was observed only in the placebo group. The median time to worst pain experienced was 5.65 months (95% CI 5.59 to 5.68) in the enzalutamide arm and 5.55 months (95% CI 5.36 to 5.55) in the placebo arm. The company found that time to deterioration in EQ-5D score (analysed as a utility value) was longer with enzalutamide than with placebo (19.19 months vs. 11.07 months). To estimate a treatment effect for enzalutamide relative to placebo, the company produced a mixed model with repeated measures model to estimate the change in baseline in utility value (derived from EQ-5D) among those people who remained on treatment. The results of these analyses are reported in section 5.13 of this briefing document.

Table 8: Pain progression in PREVAIL (results reported on page 89 company's submission)

Pain progression measure	enzalutamide	Placebo
BPI pain severity composite score	330/872 (41.0%	317/845 (50.5%)
BPI pain at its worst (item #3 of BPI)	330/872 (41.0%)	312/845 (49.4%)
Pain interference composite score	247/872 (31.3%)	255/845 (41.6%)

ERG comments

4.12 The ERG noted the company's assertion that time to treatment discontinuation (TTD) is the most appropriate endpoint to assess disease progression, with which it agreed as it is standard practice to stop treatment once progression is diagnosed. The ERG noted that at the September 2013 cut-off, median time to treatment discontinuation was comparable to median time to radiographic progression (rPFS). The ERG commented that in the PREVAIL study there were approximately 2

months between patients stopping treatment with enzalutamide or placebo and starting second line treatment. The ERG noted that the company used different data cut-off results for different variables in its model. The ERG commented that the company had used data up to June 2014 for TTD in its modelling but that the earlier unblinding of the data in December 2013 may have influenced the decision whether to continue or stop study treatment. The company did not present TTD data from the June 2014 data cut in its submission.

Indirect treatment comparison

4.13 Neither the company nor the ERG identified any head-to-head trials comparing enzalutamide with abiraterone. The company therefore compared enzalutamide and abiraterone indirectly using data from PREVAIL and COU-AA-302 as both had placebo arms. COU-AA-302 was a double blind randomised controlled trial of abiraterone 1000 mg once daily in combination with prednisone 10 mg once daily (N=546) compared with placebo in combination with prednisone 10 daily (N=542) in adult men with metastatic hormone relapsed prostate cancer who were asymptomatic or mildly symptomatic and in whom chemotherapy was not yet clinically indicated. COU-AA-302, like PREVAIL, also had a co-primary endpoint combining OS and rPFS (time from randomisation to the first evidence of radiographic disease progression, progression of soft tissue lesions measured by CT or MRI as defined in modified RECIST criteria or death from any cause, whichever was first).

4.14 Also like PREVAIL, COU-AA-302 had interim and final analyses, but unlike PREVAIL, it was stopped early without the criteria for a statistically significant difference in overall survival being met. The company used data from the September 2013 cut-off from PREVAIL (enzalutamide follow up 22.2 months, placebo 22.4 months) and from the 3rd analysis of COU-AA-302 (planned when 55% of events had been reached, follow up median 27.1 months) in an indirect treatment comparison using a fixed effect model. The company assumed that the treatment effect in the

control arm of COU-AA-302 was the same as that in the control arm of PREVAIL. However, the company noted that the proportion of people taking corticosteroids in the control arm of COU-AA-302 (100% taking prednisone) differed to that in PREVAIL (30% taking corticosteroids throughout the trial, 4% of people taking corticosteroids at baseline). The company considered that this may bias an indirect comparison of the two trials because of the potential effect of prednisone on the outcomes, but also the extent of prednisone's effect was unknown. The demographics and baseline characteristics in PREVAIL and COU-AA-32 are provided in table B29 on page 105 of the company's submission. The odds of best overall response (complete or partial) were higher for enzalutamide than abiraterone [redacted].

Table 9 Efficacy data included in the indirect treatment comparison enzalutamide and abiraterone for time to endpoints (table B30 page 108 company submission)

	Enzalutamide (ENZA) vs abiraterone (ABI) HR [95% CrI]
Overall Survival (OS)	
ENZA OS (unadjusted for treatment switching) vs ABI 3rd ínterim analysis	[redacted]
ENZA OS (unadjusted for treatment switching) vs ABI Final analysis	[redacted]
ENZA OS (adjusted for treatment switching using IPCW method) vs ABI 3rd ínterim analysis	[redacted]
ENZA OS (adjusted for tretament switching) vs ABI Final analysis	[redacted]
Radiographic progression free survival (rPFS)	[redacted]
Time to starting cytotoxic chemotherapy	[redacted]
Time to prostatic specific antigen (PSA) progression	[redacted]

IPCW : Inverse Probability of Censoring Weights (method of adjustment of OS estimate for treatment switching see section 4.6 of this briefing document)

4.15 The company also carried out a naïve treatment comparison (taking the active treatment arm in each trial and comparing the outcomes in the abiraterone arm of COU-AA-302 with the enzalutamide arm of PREVAIL without adjusting through a common comparator, in this case placebo). The company suggested that a naïve comparison was likely to be biased against enzalutamide (making it look worse than abiraterone) because PREVAIL was carried out after COU-AA-302 when more therapeutic options existed after stopping enzalutamide than were available after stopping of abiraterone in COU-AA-302. In addition, people with visceral disease were allowed to participate in PREVAIL (11.9%), but not in COU-AA-302 (0%).

Table 10: Results from PREVAIL and COU-AA-302 (adapted from table B30 page 108 company's submission)

Outcome	HR [95% CI]	Data cut-off	Reference
Enzalutamide vs placebo			
OS	[redacted]	June 2014 (unadjusted for treatment switching)	Company's OS adjustment report
	[redacted]	June 2014 (OS adjusted for treatment switching with IPCW method)	Company's OS adjustment report
rPFS	0.307 [0.267, 0.353]	September 2013 (investigator assessed)	PREVAIL CSR
Time to starting chemotherapy	0.349 [0.303, 0.403]	September 2013	Beer et al
Time to PSA progression	0.169 [0.147, 0.195]	September 2013	Beer et al
Abiraterone vs placebo			
OS	0.79 [0.66; 0.95]	3rd interim analysis cut-off	Rathkopf 2014
	0.80 [0.69; 0.93]	Final analysis	Ryan et al
rPFS	0.52 [0.45, 0.61]	3rd interim analysis cut-off	Rathkopf 2014
Time to starting chemotherapy	0.61[0.51, 0.72]	3rd interim analysis cut-off	Rathkopf 2014
Time to PSA progression	0.50 [0.43, 0.58]	3rd interim analysis cut-off	Rathkopf 2014

Abbreviations: ABI: abiraterone; ENZA: enzalutamide; HR: hazard ratio; IA3: third interim analysis; OR: odds ratio; OS: overall survival; PLA: placebo; rPFS: Radiographic Progression Free Survival.

IPCW : Inverse Probability of Censoring Weights (method of adjustment of OS estimate for treatment switching see section 4.7 of this briefing document)

ERG comments

4.16 The ERG commented that the company had not used the results from its indirect treatment comparison in its economic modelling because the control groups in PREVAIL and COU-AA-302 differed in terms of corticosteroid use. The ERG agreed that the control groups were different, but did not think that naïvely comparing the active arms of the 2 trials would give more accurate results. The ERG stated that there was a lack of transparency in the reporting of the methods the company used to carry out its indirect treatment comparison, however it checked the results using standard methods (Bucher) and produced similar results to the company.

Adverse effects of treatment

4.17 The overall incidence of adverse events with enzalutamide and placebo were similar (96.9% vs. 93.2%).across grades. The time on study treatment was longer in the enzalutamide arm than the placebo arm because patient randomised to enzalutamide took longer to progress (section 4.8). There were 279 people (32.0%) in the enzalutamide arm and 226 people (26.8%) in the placebo arm who had a serious adverse event. The overall incidence of adverse events grade 3 or over were 42.9% and 37.1% for the enzalutamide and placebo arms respectively. The incidence of grade 3 or over adverse events in the first year of treatment was 32.0% with enzalutamide and 35.1% with placebo. Statistically significantly higher rates of grade 3 or higher hypertension were observed with enzalutamide (6.8% compared with 2.3% for placebo, relative risk (RR) 3.01 95% CI 1.81 to 5.00) and cataract 1.3% compared with 0.1% (RR 10.66, 95% CI 1.38 to 82.38). Other grade 3 or higher adverse events that were observed in at least 0.5% more people with enzalutamide than placebo were: nausea 1.0% compared with 0.5%; general physical health deterioration 2.1% compared with 1.2%; pneumonia 1.3% compared with 0.8%; fall 1.4% compared with 0.7%; spinal cord compression 3.8% compared with 2.8% and syncope 1.6%

compared with 0.9%. Forty nine (5.6%) people taking enzalutamide arm and 51 (6.0%) taking placebo discontinued treatment because of an adverse event. Thirty seven people (4.2%) in the enzalutamide arm died because of an adverse event compared with 32 (3.8%) in the placebo arm (RR 1.12 95% CI 0.70 to 1.78).

ERG comments

4.18 The ERG commented that it considered that enzalutamide had a good safety profile relative to placebo.

5 Cost-effectiveness evidence

Model structure

5.1 The company produced a *de novo* Markov model to assess the cost effectiveness of enzalutamide compared with abiraterone or best supportive care in adults with metastatic hormone refractory prostate cancer who were asymptomatic or mildly symptomatic after androgen deprivation therapy failed and in whom chemotherapy was not yet indicated. The company assumed that the placebo arm of PREVAIL represented best supportive care because patients randomised to placebo could receive, when needed: LHRH analogues, corticosteroids, blood transfusions, bisphosphonates, radiotherapy, analgesics and palliative surgery to treat skeletal related events. The modelled population had the same characteristics as the PREVAIL population at baseline. The model ran over a lifetime horizon (10 years), and had a cycle length of 1 week with half-cycle correction. A 3.5% discount was applied for utility values and costs.

5.2 The model had 3 main health states: stable disease, progressed disease and death. People entered the model with stable disease having received prior androgen deprivation therapy. Within the progressed health state, there were 3 further health states to reflect that after progressing on

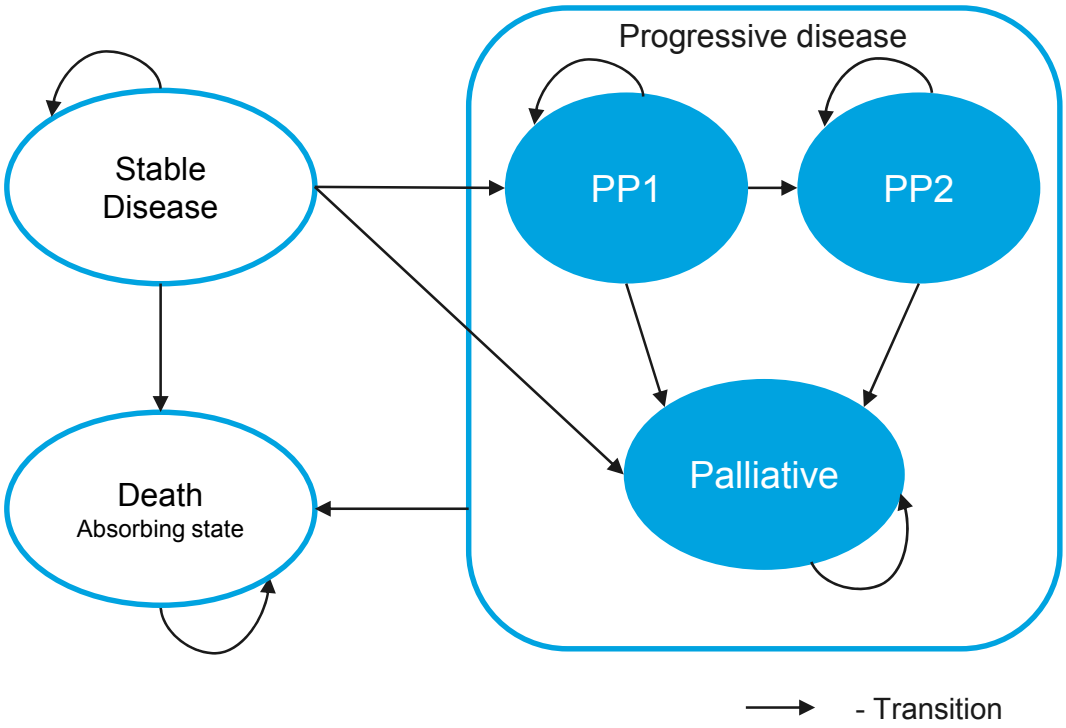
enzalutamide, abiraterone or best supportive care, people may progress on subsequent treatments. These health states were:

- Post-progression 1: this state included patients who initially received either enzalutamide, abiraterone or best supportive care and having progressed from stable disease, moved on to a 2nd line of treatment but had not yet further progressed. In this state all patients received docetaxel.
- Post-progression 2: this state included patients who initially received best supportive care before docetaxel, and having progressed on docetaxel had moved to a 3rd line of active treatment, but had not yet further progressed. In the base case, the company assumed that all patients received enzalutamide as an active treatment after docetaxel, having received best supportive care before docetaxel. In a scenario analysis it assumed all people received abiraterone rather than enzalutamide.
- Palliative care: this state included patients who had progressed (on docetaxel if their initial treatment was enzalutamide or abiraterone, or on enzalutamide taken after docetaxel if their initial treatment was best supportive care). In this state nobody received active treatment.

The model compared:

- 1st line enzalutamide --> 2nd line docetaxel-->3rd line palliative
- 1st line abiraterone --> 2nd line docetaxel--> 3rd line palliative
- 1st line BSC--> 2nd line docetaxel--> 3rd line enzalutamide--> 4th line palliative.

Figure 3: model structure (figure B17 page 139 company's submission)



Model details

5.3 The company took estimates of survival and time on treatment from PREVAIL for enzalutamide and best supportive care, and from COU-AA-302 for abiraterone. The company used time to treatment discontinuation (TTD) as a proxy for progression for first-line treatments because it said that this reflected clinical practice (see section 4.8). In its base case, the company used results from its naïve comparison rather than from its indirect treatment comparison to compare the effectiveness of enzalutamide and abiraterone. The company used data for time to treatment discontinuation and overall survival for enzalutamide and best supportive care from the 30th June 2014 cut-off (By this time, the study had been unblinded for 6 months) when [redacted]). For abiraterone, the company used estimates from the 3rd interim analysis from COU-AA-302 (55% deaths). As there were no published TTD from COU-AA-302 the company assumed that rPFS was equivalent to TTD for

abiraterone on the basis that rPFS and TTD were similar for enzalutamide in PREVAIL. The OS estimates for enzalutamide and best supportive were adjusted for treatment switching using the Inverse Probability of Censoring Weights (IPCW) adjustment resulting in an adjusted hazard ratio and weighted Kaplan Meier curves (see section 4.6). The company stated that it was not possible to adjust abiraterone OS data for treatment switching.

5.4 To extrapolate the likely rates of discontinuing the primary treatment or dying beyond the end of the trials, the company tested whether the hazard ratios were proportional, and determined they were not. This meant that the company needed to find which curve had the best fit to data for each treatment separately. The company therefore tested 5 parametric models (Exponential, Weibull, Log-logistic, Log-Normal and Generalised Gamma) on each of the enzalutamide and placebo arms from PREVAIL and on the abiraterone arm from COU-AA-302 to extrapolate the survival curves for OS and TTD. The Company considered that the exponential, log-normal and log-logistic curves gave implausible estimates for 5 and 10 year survival (see table 11). The Weibull and gamma extrapolation of enzalutamide and best supportive care resulted in curves that crossed (Gamma before [redacted] years and Weibull at approximately [redacted]). Because the Weibull curve crossed later than the gamma curve, the company selected the Weibull curve in its base case to extrapolate the enzalutamide and BSC OS trial data. The company also extrapolated the overall survival curve for abiraterone using a Weibull distribution. TTD curves for enzalutamide, best supportive care and abiraterone were extrapolated using a gamma distribution. The company replaced all the Kaplan Meier data from the trials with the parametric curves; it did not append the parametric projects onto the trial data.

Table 11: 5 year and 10 year survival estimates with different extrapolation curves applied (table B49 page 148 company's submission)

	PLA		ENZA	
Distribution	5-year	10-year	5-year	10-year
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

5.5 The company chose exponential curves to reflect time to discontinuation for second and third line treatments. The company estimated the time to discontinuation for people receiving docetaxel from Tannock et al 2004 (TAX 327 a trial of docetaxel with prednisone compared with mitoxantrone with prednisone for advanced hormone-refractory prostate cancer). In this trial, people received a median of 9.5 doses of docetaxel and a median treatment duration of docetaxel of 28.5 weeks. From this the company estimated that 2.04% of people receiving docetaxel in the model would discontinue it each cycle. The company estimated the time to discontinuation for people receiving enzalutamide or abiraterone third line using observations of median number of administrations of enzalutamide and abiraterone in AFFIRM and COU-AA-302 respectively. In AFFIRM, a placebo controlled trial of enzalutamide taken after docetaxel for metastatic hormone refractory prostate cancer, the median number of monthly administrations of enzalutamide was 8.3 suggesting a median duration of treatment of 36.0 weeks. The company assumed that 1.91% of people receiving enzalutamide 3rd line would discontinue it each cycle. In COU-AA-302, the median number of administrations of abiraterone was 7.4 suggesting a median treatment duration of 32.1 weeks. The company assumed that 2.14% of people receiving abiraterone 3rd line would discontinue it each cycle.

5.6 The company incorporated the rates of skeletal related events (SRE) observed in PREVAIL for people randomised to enzalutamide or placebo

(using data from the September 2013 data cut). The company assumed that the rate of SREs experienced by patient taking abiraterone before chemotherapy was the same as for enzalutamide before chemotherapy. The company assumed that the rates of SREs experienced by patient using second or subsequent-line treatments was the same as the rates observed in PREVAIL post-progression (across both treatment arms). The model included the rates of adverse events of grade 3 or higher from PREVAIL and COU-AA-302. Adverse events while on docetaxel came from Tannock et al. The company assumed that the rates of adverse event for 3rd line enzalutamide and abiraterone were the same as for 1st line treatment.

ERG comments

5.7 The ERG noted that people who received enzalutamide or abiraterone first line did not receive active treatment after docetaxel, whereas people who had best supportive care before docetaxel received enzalutamide after docetaxel (followed by palliative care). The ERG stated that advice from its clinical specialists was that people who receive enzalutamide before docetaxel would be likely to be treated with abiraterone after docetaxel and likewise, people who received abiraterone before docetaxel would be likely to be treated with enzalutamide after docetaxel. It considered that the cost effectiveness should be compared between the 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 for the BSC arm of :

- 1st BCS--> 2nd docetaxel--> 3rd abiraterone --> 4th palliative

The ERG noted the company's statement in its submission that it had not included 3rd line active treatments in the enzalutamide and abiraterone arms because NICE technology appraisal 316: enzalutamide for

metastatic hormone-relapsed prostate cancer previously treated with a docetaxel- containing regimen states that 'the use of enzalutamide for treating metastatic hormone-relapsed prostate cancer previously treated with abiraterone is not covered by this guidance'. This statement reflected that the Committee had not seen evidence for using enzalutamide and abiraterone sequentially, which also reflects the Cancer Drugs Fund's policies. The ERG was of the opinion that the statement in TA316 did not mean that enzalutamide could not be taken 3rd line if abiraterone had been taken 1st line before docetaxel. The ERG stated that the consequence of assuming that people do not take active treatments 3rd line active treatment (in the arms in which people receive enzalutamide or abiraterone first line) was that it was more likely that these drugs would be cost effective relative to best supportive care when used first line.

5.8 The ERG commented that adjusting overall survival for treatment switching using the Inverse Probability of Censoring Weights (IPCW) method resulted in estimates for overall survival after 24 months which were worse than the unadjusted results in the placebo arm but better in the enzalutamide arm. This effect was found when using either the September 2013 data cut or the June 2014 data cut, but the difference was greater when using the June 2014 data (as used by the company in its base case). The ERG considered that for overall survival, it preferred the June 2014 data cut with IPCW adjustment than the September 2013 cut because the later data provided more endpoints.

5.9 The ERG further commented that extrapolating the IPCW-adjusted Kaplan Meier overall survival curves using the Weibull distribution resulted in a 'long tail'. The ERG noted that the majority of the modelled survival gain with enzalutamide compared with BSC occurred in the period after the trials had ended. The ERG considered other survival curves in its exploratory analyses, including curves that converged before the time horizon of the model.

[redacted]

5.10 The ERG commented that the company had modelled TTD estimates for enzalutamide and best supportive care using PREVAIL data from the June 2014 cut-off, 6 months after unblinding the study. The ERG considered that unblinding the study may have influenced a clincian's or patients' decision to stop or continue with treatment. The ERG considered that the choice of curve (gamma) to extrapolate TTD was appropriate, but that the company should have used the data from the September 2013 cut for modelling.

Figure 5:

[redacted]

5.11 For abiraterone (but also for enzalutamide at a later time point), the ERG noted that in the model the TTD curve (extrapolated with a gamma distribution) crossed the OS curve for abiraterone (extrapolated with a Weibull distribution). The ERG noted that this implied that patients died before disease progression. To account for this, the company assumed that after the curves crossed, that the time of death reflected the time at which patients stop abiraterone. However, as a consequence, the company could not model subsequent treatments after abiraterone from the point at which the curves crossed. The ERG noted that using a Weibull distribution rather than a gamma distribution to extrapolate the abiraterone TTD curve meant that the curve did not cross over the OS curve. The ERG noted that although the enzalutamide TTD and OS curves also crossed, this occurred later and had less of an effect on the ICER estimates than did abiraterone's earlier-crossing curves.

Figure 4:

[redacted]

5.12 The ERG commented that in the model, a patient's probability of dying per cycle was the same in each health state. The ERG considered this to be implausible because it meant that people with stable, asymptomatic or mildly symptomatic, disease on their first treatment had the same risk of dying as people with progressive disease on palliative care after up to 3 lines of active treatment had failed.

Utility values used in the model

5.13 To estimate the changes from baseline EQ-5D score during the course of the trial among people remaining on their 1st line treatment in PREVAIL, the company developed a mixed model repeated measures (MMRM) model. It used this to estimate the effect on utility values of enzalutamide relative to BSC. In the statistical analysis plan, the company specified that it would include data only up to a timepoint when fewer than 10% completed the EQ-5D questionnaire in either arm. This meant the company included in the model data from week 1 to week 61 from PREVAIL. The company used the results from this model to determine a

utility value using UK tariffs for people in the stable disease health state receiving best supportive care (0.844 [95% CI: 0.836-0.852]). The company applied an additional 0.022 for people receiving enzalutamide, which it derived from its modelled estimate of a "treatment effect "of enzalutamide on quality of life in PREVAIL. The treatment effect was the difference between the degree that quality of life decreased over time with enzalutamide in PREVAIL relative to the degree quality of life decreased over time with placebo. The company assumed that abiraterone would have an equivalent on-treatment benefit as enzalutamide.

5.14 As the investigators in PREVAIL collected EQ-5D only from people on-treatment (enzalutamide or placebo pre-chemotherapy), the company estimated utility values in the progressed health states from the published literature. The company used a weighted average of 2 publications that had assessed the quality of life of people who were on chemotherapy, who had previously received chemotherapy, and who had metastatic hormone relapsed prostate cancer. The company used this to estimate a utility value of 0.658 post progression state 1 (when people had progressed on enzalutamide, abiraterone or best supportive care and were receiving r docetaxel) and 0.612 for post progression state 2 (when people had progressed on best supportive care and docetaxel and were receiving enzalutamide). In line with technology appraisal 316 Enzalutamide for metastatic hormone relapsed prostate cancer previously treated with a docetaxel containing regimen, the company applied an on treatment utility gain for patients treated with enzalutamide after docetaxel of 0.04 to people who had enzalutamide after docetaxel and best supportive care before docetaxel. The company estimated a utility values of 0.500 for people who received palliative care after progressing on active treatment (Sandblom et al).

5.15 To estimate the disutility associated with adverse events, the company sourced values from the published literature for adverse events of grade 3 or above. Because no data on the rates of adverse events were available

for the period people were taking abiraterone in COU-AA-302, the company assumed that these were the same as for enzalutamide. The disutility associated with a skeletal related event was derived from EQ-5D data from PREVAIL by modelling differences in pre- and post-SRE values. The company applied a disutility associated with a skeletal related event for 1 month.

Table 12: summary of quality-of life values for cost-effectiveness analysis (tables B67 and B68 page 180 company's submission; costs of adverse events from table B77 page 198 company's submission; costs of SREs from table B78 page 198 company's submission)

State	Utility value	CI / SE	Justification	
Stable disease	0.844	SE: 0.0039	The baseline utility (EQ-5D) values in PREVAIL represent patients in Stable Disease.	
PP1	0.658	SE: 0.0065	Literature value: weighted mean of Wolff (2012) and Diels (2014)	
PP2	0.612	SE: 0.0242	Literature value: weighted mean Wolff (2012)and Diels (2014)	
Palliative	0.500	SE: 0.08	Literature value: Sandblom	
On treatment benefit for enzalutamide	0.022	95% CI: [0.003; 0.041]	Enzalutamide showed a significant utility gain over placebo in PREVAIL	
On treatment benefit for abiraterone	0.022	95% CI: [0.003; 0.041]	Assumed equal to enzalutamide	
On treatment benefit for enzalutamide given after docetaxel	0.04	95% CI: [0.032; 0.048]	Enzalutamide and abiraterone showed a significant utility gain over placebo in AFFIRM and COU-AA-301 respectively	
SRE disutilities	**Disutility value**	**CI/SE**	**Justification**	**cost**
Spinal cord compression	-0.237	SE = 0.079	SREs in PREVAIL were associated with a decline in utility.	£4,688 NHS reference costs 2012-2013; NEI_L: Weighted average of HC28D
Pathological bone fracture	-0.201	SE = 0.080		£5,351 Average of HRG code HD39C, HD39B, HD39A weighted by the number of treatment in each HRG. Plus for patients with non-vertebral fractures (assumed 50%) the cost of outpatient care for long-bone fractures for 3 months (£5,073), assumed to be incurred by 61% of patients with non-vertebral fractures (total of £5,073 * 61% = £3,095) (based on Ross et al. set of assumptions)
Radiation to the bone	-0.056	SE = 0.021		£683 Average of HRG codes SC21Z, SC22Z, SC23Z, SC24Z, SC25Z, SC26Z, SC27Z, SC28Z weighted by the number of activity units in each HRG. NHS reference costs

				2012-2013, Radiotherapy (RAD). 5 fractions are given.
Surgery to the bone	-0.056	SE = 0.021		£3,568
Duration of disutility (days)	30.42	0-213		NHS reference costs 2012-2013; NEI_L: Weighted average of HD39E

AE disutilities

AE	Disutility	SE	Justification / Source	cost
Anaemia	-0.12 (7-14 days)	0.047	Swinburn (2010)	£1,779 (NHS reference costs 2012-13)
Arthralgia	-0.07 (7-14 days)	0.012	Doyle (2008)i	£176 (assumed to be equal to pain NHS reference costs 2012-13
Back pain	-0.07 (7-14 days)	0.012	Doyle (2008)i	£467 (NHS reference costs 2012-2013)
Bone pain	-0.07 (7-14 days)	0.012	Doyle (2008)i	£606 (NHS reference costs 2012-13)
Deterioration in general physical health	-0.13 (91.25 days)	0.030	Assumed equal to fatigue: Lloyd (2006), Nafees (2008), Swinburn (2010)	£12 assumed to be equal to fatigue in NICE ERG report abiraterone (post chemo)
Dyspnoea	-0.05 7-14 days)	0.012	Doyle (2008)i	£0 NICE ERG report abiraterone post chemo
Fatigue	-0.13 (91.25 days)	0.030	Lloyd (2006), Nafees (2008), Swinburn (2010)	£12 NICE ERG report abiraterone post chemo
Febrile neutropenia	-0.12 (7-14 days)	0.016	Lloyd (2006) and Nafees (2008)	£4,519 NHS reference costs 2012-13
Hypertension	-0.15 (7-14 days)	0.049	Swinburn (2010)	£432 NHS reference costs 2012-13
Hypokalaemia	0.00 (7-14 days)	0.000	No (dis-)utilities reported, assumed to have no detrimental impact on HRQL	£348 NHS reference costs 2012-2013
Neutropenia	-0.09 (7-14 days)	0.015	Nafees (2008)	£161 NHS reference costs 2012-13
Oedema Peripheral/Fluid retention	0.00 (7-14 days)	0.000	No (dis-)utilities reported, assumed to have no detrimental impact on HRQL	£914 NICE ERG report abiraterone post chemo

ERG comments

5.16 The ERG commented that for the utility value associated with stable disease before chemotherapy (stable disease health state), the values from the literature were lower than the company's estimate from PREVAIL data (0.844). These published estimates were 0.81 (Wolff et al 2012, EQ-5D n=33), 0.70 (Diels et al, EQ-5D n=236), 0.713 weighted average Wolff et al 2012 + Diels et al.) The ERG commented that the Wolff et al 2012 reference it found containing quality of life data differed from the Wolff reference cited by the company, which did not contain quality of life data.

5.17 The ERG discussed how the company had modelled the quality of life data from PREVAIL using the mixed model with repeated measures model. The ERG stated that the company had not explained why it used a cut off of 10% responding to the EQ-5D questionnaire in either arm, and the ERG could not identify a methodological reason for this approach. The ERG stated that the 0.022 increment for enzalutamide compared with BSC was based on quality of life decreasing by 0.042 from baseline with enzalutamide and decreasing even more (by 0.064) with BSC (i.e. 0.064 minus 0.042 equals 0.022). The ERG thought that it would have been more appropriate for the company to apply the decrease in quality of life from an average baseline utility of 0.844 (resulting in a utility value of 0.780 for BSC (0.844-0.064) and 0.802 for enzalutamide [0.844-0.042])

5.18 The ERG noted that while the company had modelled quality of life separately for enzalutamide and BSC, it had analysed the impact of having a skeletal related event by pooling both treatment arms. Therefore, the impact of SREs on quality of life may have already been captured in the analysis of quality of life by treatment arm and already reflect any reduction in the rates of SREs with enzalutamide compared with BSC.

5.19 The ERG commented that the company had reported different rates of adverse event rates in the clinical effectiveness section of it's submission from those it applied in its model.

Costs used in the model

5.20 Both enzalutamide and abiraterone have a confidential patient access scheme (price discount) established when NICE (Committee B) appraised both of the drugs for use after docetaxel. At the request of NICE, the company provided its base case results incorporating the list (non-discounted) prices for enzalutamide and abiraterone. The list price of enzalutamide is £2,734.67 for each 28 day pack (112 tablets of 40 mg). The list price of abiraterone is £2,930 for each 30 day pack (120 tablets of 250 mg). By contrast, NICE requested that the ERG provide the results of the company's base case, sensitivity analyses and its own exploratory analyses including both the list price and also the results with the discounts. The patient access scheme for enzalutamide is [redacted]). The patient access scheme for abiraterone is [redacted]. The company assumed that people receiving enzalutamide, best supportive care or abiraterone receive the same concomitant medications as did the patients in PREVAIL. These included H2 antagonists, anti-emetic drugs and bisphosphonates. The company assumed that the same proportion of people receiving enzalutamide or best supportive care would receive concomitant corticosteroids as in PREVAIL and that all people receiving abiraterone would also receive corticosteroids. The cost per week for concomitant drugs was £6.86 with enzalutamide, £6.93 with best supportive care and £7.15 with abiraterone. The company used the price of docetaxel listed in the database on pharmaceutical electronic market information from the Department of Health Commercial Medicines Unit (CMU EMIT, £47.30 per 160 mg/8 ml solution for infusion vial) rather than the price listed on the British National Formulary (£1008.54 per 160 mg/8ml). The company assumed that docetaxel costs £15 per week and concomitant medication costs £72 per week. The dosing regimen for docetaxel was once every 3 weeks and cost £301.56 to administer (NHS reference cost).

Table 13: drug, administration and monitoring costs (table B75 company's submission page 195)

Items	Enazalutamide (£)	Best supportive care (£)	Abiraterone (£)	Docetaxel (£)
Technology cost per 1 week cycle	684	0	684	15
Administration cost (weekly)	0	0	0	101
Monitoring cost	35* 21** 25***	36	65* 36** 45***	74
Concomitant medication	7	7	7	72
Total	719* 705** 709***	43	749& 720** 729***	262

Abbreviations: ABI: abiraterone; BSC: best supportive care; ENZA: enzalutamide; * First three months; ** Subsequent months, *** Post-docetaxel

5.21 The costs of adverse events are shown in table 12.

ERG comments on costs

5.22 The ERG noted that the cost of 160 mg 8ml vial of docetaxel listed on the (CMU EMIT on June 2014 was £29.78 rather than £47.30 as used in the company's model. The ERG noted that the 2013-14 reference costs (schedule 3a) are higher (£314) than those used in the model by the company.

5.23 The ERG noted that the concomitant medication costs did not include an LHRH analogue which the ERG expert suggests would be used for all patients throughout. The ERG were advised that the cheapest is triptorelin, available in 1, 3 and 6 month formulations at a cost of £69, £207 and £414 respectively. The ERG assumed in its exploratory base case that an LHRH analogue costs £16 per week.

5.24 The ERG noted that the company based drug costs on the number of people receiving the drug at the end rather than the start of the cycle. The

company assumed that clinicians prescribe enzalutamide and abiraterone weekly rather than monthly as implied by the package size.

5.25 The ERG noted that the company chose higher monitoring costs for abiraterone than for enzalutamide it had assumed a higher frequency of monitoring visits with abiraterone (every 4 weeks) than with enzalutamide (every 8 weeks). The ERG noted the summary of product characteristics for abiraterone stipulates the frequency of monitoring of patients taking abiraterone, but the summary of product characteristics does not state this for enzalutamide. The ERG stated that its clinical experts had advised that the frequency of monitoring of people taking enzalutamide and abiraterone would be expected to be the same.

Company's base-case results and sensitivity analysis

5.26 The company presented deterministic results using the list prices for enzalutamide and abiraterone. It presented pairwise comparisons against best supportive care, and also an incremental analysis. Enzalutamide compared with best supportive care resulted in an incremental cost effectiveness ratio of £78,587 per QALY gained (incremental costs £48,543, incremental QALYs 0.618). The ICER for abiraterone compared with best supportive care was £95,685 per QALY gained (incremental costs £44,375, incremental QALYs 0.464). In the incremental analysis abiraterone was extendedly dominated by best supportive care and enzalutamide, meaning that a combination of best supportive care and enzalutamide brought in more QALYs at a lower cost than abiraterone. The ERG re-ran the company's base case applying the confidential discounts for enzalutamide and abiraterone. In the best supportive care arm, the ERG applied the PAS to the costs of enzalutamide taken 3rd line, after docetaxel, see table 14.

Table 14: company's pair-wise base case (list price results table B90, company's submission page 214; PAS results ERG confidential appendix table 2 page 3; probabilistic ICER tables B94 and B95 company submission page 221) * back calculated by NICE

Company's base case results using list prices for enzalutamide and abiraterone									
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) (vs. BSC)	Incremental LYG (vs. BSC)	Incremental QALYs (vs. BSC)	ICER (vs. BSC)	ICER fully incremental analysis	ICER fully incremental analysis (probabilistic)
A: BSC	36,296	2.612	1.657	0	0	0	Not applicable	Not applicable	
B: ABI	80,672	2.860	2.120	44,375	0.248	0.464	£95,685	Extended dominance by ENZA	
C: ENZA	84,840	3.064	2.274	48,543	0.452	0.618	£78,587	£78,587 vs. BSC (£27,076 vs. ABI)	£78,631 vs. BSC (£26,705 vs. ABI)
Company's base case using PAS prices for enzalutamide and abiraterone									
Technologies	Total costs (£)	Total LYG (undiscounted)	Total QALYs (discounted)	Incremental costs (£) (vs. BSC)	Incremental LYG (undiscounted) (vs. BSC)	Incremental QALYs (vs. BSC)	ICER (vs. BSC)	ICER fully incremental analysis	
A: BSC	[redacted]	[redacted]	1.657	[redacted]	[redacted]	0	Not applicable	Not applicable	
B: ABI	[redacted]	[redacted]	2.120	[redacted]	[redacted]	0.464*	[redacted]*	[redacted]*	
C: ENZA	[redacted]	[redacted]	2.274	[redacted]	[redacted]	0.618	[redacted]	[redacted]	

Abbreviations: ABI: abiraterone; BSC: best supportive care; ENZA: enzalutamide; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted

5.27 The company presented univariate sensitivity analyses using the list prices for enzalutamide and abiraterone. The parameters most influencing cost effectiveness when comparing enzalutamide with abiraterone were the:

- costs of the 2 drugs,
- modelled extrapolation parameters for overall survival and time to discontinuing treatment,
- proportion of people receiving 2nd line chemotherapy in the enzalutamide arm, and
- utility gain associated with treatment with enzalutamide before docetaxel. The parameters most influencing cost effectiveness when comparing enzalutamide with best supportive care were:
- cost of enzalutamide,
- modelled extrapolation parameters for overall survival
- proportion of patients receiving enzalutamide as a 3rd line treatment after docetaxel,
- proportion of people receiving docetaxel in the best supportive care arm,
- on-treatment utility gain for patients treated with enzalutamide,
- discount rate for effect,
- utility value for the palliative care health state,
- time to treatment discontinuation extrapolation parameters
- and the utility vales in the post-progression 2 health state (Please see figures B26 and B27 on pages 215 and 216 and tables B91 and B92 on pages 215 and 217 of the company's submission for these results. The ERG re-ran the company's univariate sensitivity analyses while applying the PAS discounts for enzalutamide and abiraterone. The results including the PAS discounts are shown in tables 14 and 15

Table 14 Univariate sensitivity analyses vs. best supportive care including PAS (table 3 ERG confidential appendix page 5):

	Base	Low		High	
Parameter	Value	Value	ICER	Value	ICER
Enzalutamide cost	[redacted]				
BSC % receiving 2nd line docetaxel	84%	0%	[redacted]	100%	[redacted]
BSC % patients receiving 3rd line	81%	0%	[redacted]	100%	[redacted]
Enzalutamide OS Weibull intercept	[redacted]				
BSC OS Weibull intercept	[redacted]				
Enzalutamide QoL treatment gain	0.022	0.003	[redacted]	0.041	[redacted]
Enzalutamide % receiving 2nd line docetaxel	84%	0%	[redacted]	100%	[redacted]
Discount rate for benefits	3.5%	0.0%	[redacted]	5.0%	[redacted]
BSC TTD gamma intercept	[redacted]				
Palliative care QoL	0.500	0.344	[redacted]	0.656	[redacted]
BSC TTD gamma shape	[redacted]				
3rd line treatment QoL	0.612	0.564	[redacted]	0.659	[redacted]
Discount rate for costs	3.5%	0.0%	[redacted]	5.0%	[redacted]
Enzalutamide health state cost mth4+	£20.91	£17.01	[redacted]	£25.20	[redacted]
Cost chemotherapy administration	£302.39	£226.79	[redacted]	£377.98	[redacted]

Table 15 univariate sensitivity analyses vs. abiraterone inc. PAS (table 4 page 5 ERG confidential appendix)

	Base	Low		High	
Parameter	Value	Value	ICER	Value	ICER
Abiraterone OS weibull intercept	[redacted]				
Enzalutamide cost	[redacted]				
Abiraterone cost	[redacted]				
Abiraterone TTD gamma intercept	[redacted]				
Enzalutamide % receiving 2nd line docetaxel	84%	0%	[redacted]	100%	[redacted]
Abiraterone TTD gamma shape	[redacted]				
Enzalutamide TTD gamma intercept	[redacted]				
Abiraterone % receiving 2nd line docetaxel	84%	0%	[redacted]	100%	[redacted]
Enzalutamide TTD gamma shape	[redacted]				
Enzalutamide OS Weibull intercept	[redacted]				
Abiraterone health state cost mth4+	£36.26	£29.51	[redacted]	£43.71	[redacted]
Enzalutamide health state cost mth4+	£20.91	£17.01	[redacted]	£25.20	[redacted]
Enzalutamide QoL treatment gain	0.022	0.003	[redacted]	0.041	[redacted]
Abiraterone QoL treatment gain	0.022	0.003	[redacted]	0.041	[redacted]
Abiraterone OS weibull scale	[redacted]				

5.28 The company carried out a series of scenario analyses. The results are listed in table 16. The scenarios with the greatest effect on the ICER were

those surrounding the choice of data cut, whether the overall survival estimates were adjusted for switching and those testing the assumptions around extrapolation of the data.

Table 16: company's scenario analyses

Analysis	ICER vs. abiraterone (without PAS)	ICER vs. BSC (without PAS)	ICER vs. abiraterone (with PAS)	ICER vs. BSC (with PAS)
Base case	**£27,076**	**£78,587**	[redacted]	[redacted]
Data cut off				
Data cut for both OS (IPCW adjusted) and TTD Sept 2013 (rather than June 2014 for OS in base case).	£47,213	£98,751	[redacted]	[redacted]
Survival modelling				
OS adjustment for switching by 'two stage method' rather than IPCW method in base case	£39,399	£87,677	[redacted]	[redacted]
Unadjusted survival estimates from PREVAIL	£33,291	£97,185	[redacted]	[redacted]
OS extrapolation with gamma distribution rather than Weibull in base case.	£34,499 (Abiraterone vs. enzalutamide)	£90,019	[redacted]	[redacted]
Hazard rates for OS with enzalutamide and placebo assumed to be proportional and OS for enzalutamide was modelled by applying a hazard ratio to the best supportive care curve. In the base case each survival curve had been extrapolated separately.	£40,187	£69,377	[redacted]	[redacted]
Adjusted indirect comparison for abiraterone OS (using the estimates from the adjusted indirect comparison rather than the naïve comparison	dominant	£78,587	[redacted]	[redacted]
Progression modelling				
rPFS (sept 2013) rather than TTD (Jun 2014) to model progression.	£28,894	£86,696	[redacted]	[redacted]
(for comparison with scenario above using TTD Sept 2013 curve	£28,642	£81,449	[redacted]	[redacted]

Weibull distribution for extrapolating TTD rather than gamma	£30,404	£78,317	[redacted]	[redacted]
Costs				
BNF (£1008.54 per 160 mg/8ml) rather than eMIT cost for docetaxel (£47.30 per 160 mg/8ml)	£28,623	£71,908	[redacted]	[redacted]
Unscheduled costs included (these were not included in the base case). The company used the unscheduled costs that had been used in the abiraterone submission to NICE	£29,006	£75,159	[redacted]	[redacted]
Including a 10.36% price rebate as the PPRS agreement for 2015	£23,642	£69,911	[redacted]	[redacted]
Increased costs for spinal cord compression based on opinion of UK clinical experts and including the need for long-term care for 1/5 patients because of paraplegia (rather than NHS 2012-13 reference costs in base case)	£27,314	£78,210	[redacted]	[redacted]
Treatment pathway				
Abiraterone is given after docetaxel in the BSC arm (rather than assuming all of these patients would receive enzalutamide in the base case)	£27,076	£29,535	[redacted]	[redacted]
SREs				
Increased duration of SREs to 7 months from 30.42 days in the base case	£27,690	£77,044	[redacted]	[redacted]
Utility values				
Baseline utility from AFFIRM (trial of enzalutamide used post chemotherapy) [redacted]) used for PP2 health state rather than 0.612 in the base case	£27,076	£83,042	[redacted]	[redacted]
Adverse events				
No disutility values or costs applied for adverse events	£26,432	£78,835	[redacted]	[redacted]

5.29 The company stated that the key drivers of the ICER for enzalutamide compared with abiraterone were the:

- costs of enzalutamide and abiraterone and the
- on-treatment utility gain which it derived from PREVAIL.

It considered the key drivers of the cost-effectiveness results of enzalutamide compared with best supportive care were the:

- cost of enzalutamide,
- proportion of patients who receive second and third line treatments after best supportive care and the
- on-treatment utility gain

ERG exploratory analyses

5.30 The ERG used its preferred assumptions in the company's model to produce the 'ERG exploratory base case' including:

- Assuming that people who had enzalutamide 1st line could have abiraterone 3rd line and people who had abiraterone 1st line could have enzalutamide 3rd line (see section 5.7). In the company's base case people receiving enzalutamide or abiraterone 1st line received palliative treatment rather than active treatment 3rd line.
- Using the September 2013 cut time to discontinuation curves with a gamma extrapolation, rather than the June 2014 cut time to discontinuation curves with a gamma extrapolation, because the study was already unblinded at the June 2014 cut.
- Calculating drug costs using the number of patents at the start rather than at the end of a cycle.
- Assuming that dosing was 4 weekly for 1st line therapies
- Including values for quality of life for people on BSC before docetaxel of 0.780 and for people on enzalutamide or abiraterone 0.802, rather than 0.844 for people on BSC and 0.866 for people on enzalutamide and abiraterone as used by the company in its base case.

- Using a value for quality of life for people starting a 3rd line treatment of [redacted] based on the baseline utility value used in the company's submission for TA316, rather than 0.612 as used by the company in its base case
- Removing the utility decrement associated with SREs experienced while on 1st line treatments to avoid potential double counting
- Applying the quality of life gain from 3rd line treatment for all treatments (see bullet point 1)
- Assuming equal health state costs across the 1st line treatments (enzalutamide, abiraterone, BSC)
- Applying 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 RA03ZMRI scan, £215 per medical oncology EA47Z ECG, £52 per RA23Z ultrasound scan and £204 per RA36Z bone scan.
- Including weekly cost of £16 for LHRH analogues
- Applying the current Department of Health Commercial Medicines Unit cost per docetaxel vial of £29.78 and the 2013-14 reference costs schedule 3a SB15Z cost of £314 for docetaxel administration
- Correcting the referencing within the gamma overall survival curves.

5.31 The results of the ERG's exploratory base case are reported in table 18. For a breakdown of costs per health state please see table 68, ERG report page 134.

Table 18: ERG exploratory base case, pairwise and incremental results (summarised from table 68 ERG report page 134 and table 6 ERG confidential appendix page 7) * back calculated by NICE

Without PAS results								
	Total costs	Total LYs (undiscounted)	Total QALYs (discounted)	Incremental costs	Incremental Life years	Incremental QALYs	ICER vs. BSC (pairwise)	ICER incremental
BSC	£37,665	2.745	1.672	£0	0	0	-	
Abiraterone	£93,012	3.003	2.069	£55,347	0.258	0.397	£139,413	Extendedly dominated
Enzalutamide	£98,867	3.238	2.213	£5,855	0.235	0.144	£113,047	£113,047 vs BSC (vs abiraterone £40,776
With PAS results								
BSC	[redacted]	[redacted]	1.672	[redacted]	[redacted]			
Abiraterone	[redacted]	[redacted]	2.069*	[redacted]	[redacted]	0.397*	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]	2.213	[redacted]	[redacted]	0.144	[redacted]	[redacted])

5.32 The ERG carried out the sensitivity analyses outlined in table 19. The ERG based the sensitivity analyses on its own exploratory base case rather than the company's base case.

Table 19 ERG sensitivity analyses (table 69 ERG report page 135 and table 6 ERG confidential appendix page 7)

	Without PAS		[redacted]	
	ICER vs. BSC	ICER vs. abiraterone	[redacted]	[redacted]
ERG exploratory base case	£113k	£40,776	[redacted]	[redacted]
Data cut off at Sep 2013 rather than Jun 2104, adjusting using Inverse Probability of Censoring Weighted (IPCW), and extrapolating OS with Weibull	£143k	£92,092	[redacted]	[redacted]
Jun 2014 cut off rather than Sep 2013 and extrapolating TTD with gamma distribution	£110k	£39,503	[redacted]	[redacted]
Adjusting treatment switching with 2 stage adjustment rather than IPCW, using June 2014 cut off and extrapolating OS with Weibull	£129k	£67,238	[redacted]	[redacted]
Extrapolating rPFS curves (sept 2013) from PREVAIL with Weibull for enzalutamide and BSC and rPFS from COU-AA-302 with Weibull for abiraterone.	£119k	£47,856	[redacted]	[redacted]
Data cut off as of Sep 2013; extrapolating TTD with Weibull	£111k	£47,518	[redacted]	[redacted]
Assuming that 100% (rather than 84%) of people receive docetaxel 2nd line	£113k	£40,360	[redacted]	[redacted]
Increasing 2nd line docetaxel discontinuation rate by +20%	£114k	£41,199	[redacted]	[redacted]
Decreasing 2nd line docetaxel discontinuation rate by-20%	£112k	£40,574	[redacted]	[redacted]
Excluding possibility of enzalutamide or abiraterone 3rd line after docetaxel for people who received enzalutamide or abiraterone before docetaxel	£109k	£43,363	[redacted]	[redacted]
Same (0.780) 1st line QoL past week 62	£118k	£41,292	[redacted]	[redacted]
Using company assumptions for QoL while taking 3rd line active treatment (0.612) rather than ERGs preferred estimate of [redacted]	£110k	£40,299	[redacted]	[redacted]
Using value for quality of life for palliative care from Sandblom palliative of 0.538 and applying it for people in palliative treatment health state within 16 months of death	£116k	£40,111	[redacted]	[redacted]
Assuming that quality of life for docetaxel is the mid-point of the 1st line and 3rd	£117k	£40,535	[redacted]	[redacted]

line quality of life values				
Using alternative values for utility: Diels QoL estimates applied 0.70 pre-chemotherapy, 0.66 chemotherapy and 0.66 post chemotherapy (palliative care remains at 0.500)	£134k	£43,896	[redacted]	[redacted]
Different 1st line health state costs assumed dependent on whether person received enzalutamide, abiraterone or placebo (the company's cost assumptions)	£110k	£26,135	[redacted]	[redacted]
Assuming a Pharmaceutical Price Regulation Scheme 2014 (PPRS) rebate of 10.36% to cost of enzalutamide and abiraterone	£101k	£37,433	[redacted]	[redacted]

Innovation

5.33 The company considered enzalutamide to be innovative because enzalutamide:

- Is the first and only androgen receptor antagonist that bocks the androgen receptor signalling pathway at 3 distinct levels
    - Completely inhibits binding of androgens to androgen receptors in the cytosol
    - Inhibits the nuclear translocation of activated receptors
    - Inhibits the association of the activated androgen receptor with DNA
- Can be administered without corticosteroids (unlike abiraterone)
- Does not require regular hepatic, electrolyte or fluid balance monitoring, unlike abiraterone
- Enzalutamide can be administered with or without food in contrast to abiraterone where food modifies absorption.

6 End-of-life considerations [if relevant, otherwise delete this section]

6.1 The company did not make a case for enzalutamide fulfilling end of life criteria at this position of the treatment pathway.

7 Equality issues

7.1 The company did not consider there to be any equalities issues relevant to this appraisal

8 Authors

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Appendix A: Clinical efficacy section of the draft European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/002639/WC500180617.pdf