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

ERRATUM

This document contains the ERG report errata in response to the manufacturer's factual inaccuracy check.

The following are the pages to be replaced in the original document and the nature of the change:

Page 2

The hazard ratio of [redacted] with 95% CI ([redacted] *has been corrected to* [redacted] with 95% CI ([redacted] to match the 30th June 2014 data cut.

Page 6

The value for the net treatment benefit of 0.021 *has been corrected to* 0.022.

Page 40

The following sentence has been deleted:

"According to the trial protocol, this third line treatment should not be enzalutamide if they received it pre-docetaxel."

Page 44

The number of patients "5151" *has been corrected to* "515."

Page 46

"Pain preference composite score" *has been replaced with* "pain interference composite score"

Page 47

The heading in Table 12 "Adjusted LS mean (SE)" *has been replaced with* "Adjusted LS mean (95% CI)"

Page 52

The following sentence:

"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)."

Has been amended to:

"A lower proportion of patients died due to disease progression in the enzalutamide arm (21.0%) than the placebo arm (26.9%) with RR (95% CI) = 0.78 (0.66, 0.93)."

“Asthenia” *has been added* to *the list of adverse events and* “oedema peripheral” *has been removed from the following sentence*:

“There was a significantly higher incidence in the enzalutamide group compared to placebo for the following adverse events related to study medication: constipation, fatigue, asthenia, pain in extremity, dysgeusia, headache, psychiatric disorders, dyspnoea, dry skin, hot flush, hypertension and flushing (Table B38, company submission).”

Page 53

The following sentence:

“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).”

Has been amended to:

“The two trials were similar in terms of the patient population except for the proportion of patients on a corticosteroid in the control arm (100% in COU-AA-302, 30.2% in PREVAIL (but only 4% at baseline).”

Page 60

Data in Table 19 *are marked AIC*

Page 73

The five year survival rate of [redacted]% *has been corrected to* [redacted]%

Page 77

The following sentence:

"For 3rd line enzalutamide and abiraterone the median number of administrations of 8.3 and 7.4, as reported in Scher et al and Fizazi et al respectively, coupled with these being monthly or 4.3 weeks apart suggests median treatment durations of 36.0 weeks and 32.1 weeks. "

*has been replaced with***:**

"For 3rd line enzalutamide and abiraterone the median treatment duration of 8.3 and 7.4 months, as reported in Scher et al. and Fizazi et al. respectively suggests median treatment durations of 36.0 weeks and 32.1 weeks."

Page 81

The treatment effect estimate of 0.021 *has been corrected to* 0.022

Page 94

The following sentence has been deleted:

"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."

Page100

The following sentence:

“The reason for this discrepancy is unclear, and there is no means of further examining the values given in the extrapolation report.”

has been replaced with:

“A company erratum revised the [redacted] value to [redacted].”

Page 125

The quality of life value in the following sentence:

“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.”

has been corrected to:

“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 0.866.”

The baseline quality of life value in the following sentence:

“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.”

has been corrected to:

“This suggests that the quality of life losses relative to baseline should be applied to the mean baseline quality of life value of 0.844 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.”

Page 132

The following footnote 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."

has been amended to:

"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. Note that during the assessment the company also submitted a revised model that incorporated these changes".

Page 134

The ERG implementation of the weekly £16 cost of the LHRH agonist incorrectly added twice this amount to the lines of treatment that are subsequent to the 1st line treatments within the model. Correcting this has minimal impact upon results. *Table 68 of the ERG report has been revised*.

Page 135

The ERG implementation of the weekly £16 cost of the LHRH agonist incorrectly added twice this amount to the lines of treatment that are subsequent to the 1st line treatments within the model. Correcting this has minimal impact upon results. *Table 69 of the ERG report has been revised*.

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.

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 0.022 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.

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. 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.

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%)	515 (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

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 interference 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 (CI)			
	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.

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, asthenia, 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 (21.0%) than the placebo arm (26.9%) 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 for the proportion of patients on a corticosteroid in the control arm (100% in COU-AA-302, 30.2% in PREVAIL (but only 4% at baseline). The company argue that this use of

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)

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[1]	
	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

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

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 treatment duration of 8.3 and 7.4 months, as reported in Scher et al[17] and Fizazi et al[31] respectively 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.

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 0.022 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 0.500 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.

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.

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 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]

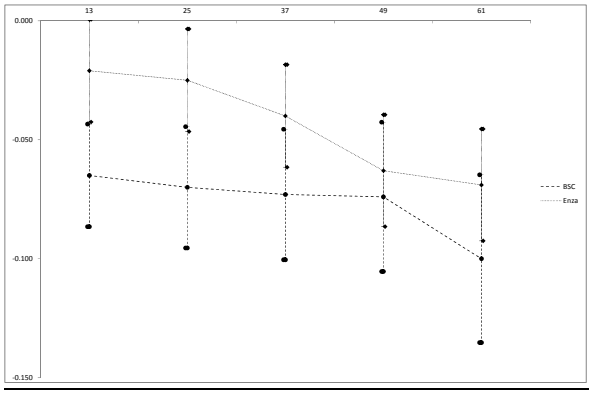
Table 55 Extrapolation report values of the OS and TTD for company the base case

	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] A company erratum revised the [redacted] value to [redacted].

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.

Adjusted mean change from baseline by arm



Adjusted net mean change

[redacted]

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 0.866. 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 0.866 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

- 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 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. Note that during the assessment the company also submitted a revised model that incorporated these changes.

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[11]					
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	£1,458	£2,597	-£1,139	£1,408	£51
3rd line	£261	£507	-£246	£285	-£23
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	£98,420	£37,309	£61,110	£92,556	£5,864
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			£112,878		£40,842

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.

[11] Includes chemotherapy administration costs.

Table 69 Exploratory ERG sensitivity analyses: exclusive of PAS[a]

	vs BSC			vs Abiraterone		
	net Cost	net QALY	ICER	net Cost	net QALY	ICER
Base case	£61,110	0.541	£113k	£5,864	0.144	£40,842
Sep 2013 IPCW Weib OS	£57,646	0.404	£143k	£2,759	0.029	£93,672
Jun 2014 gamma TTD	£60,201	0.548	£110k	£5,578	0.141	£39,532
2 stage June 2014 Weib OS	£58,960	0.458	£129k	£3,491	0.051	£68,169
Sep 2013 Weibull rPFS	£62,103	0.524	£119k	£7,657	0.159	£48,208
Sep 2013 Weibull TTD	£58,114	0.524	£111k	£5,013	0.136	£36,863
100% 2nd line	£59,337	0.526	£113k	£5,782	0.143	£40,438
2nd line disc +20%	£61,274	0.538	£114k	£5,962	0.145	£41,233
2nd line disc -20%	£61,035	0.544	£112k	£5,815	0.143	£40,658
No 3rd line Enza & Abir arms	£53,523	0.492	£109k	£6,433	0.149	£43,301
Same 1st line QoL wk 62+	£61,110	0.520	£118k	£5,864	0.142	£41,359
Company 3rd line QoL	£61,110	0.557	£110k	£5,864	0.145	£40,364
Sandblom palliative 0.538 QoL	£61,110	0.527	£116k	£5,864	0.146	£40,176
2nd line QoL midpoint	£61,110	0.522	£117k	£5,864	0.144	£40,601
Diels QoL	£61,110	0.457	£134k	£5,864	0.133	£43,966
Diff 1st line health state costs	£59,451	0.541	£110k	£3,762	0.144	£26,201
PPRS 10.36% rebate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[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.