Abiraterone acetate for the treatment of metastatic, castrate-resistant prostate cancer following previous cytotoxic chemotherapy

ERG commentary on Janssen's response to the Appraisal Consultation Document

Produced by: Warwick Evidence

Authors

Martin Connock, Senior Research Fellow, Warwick Evidence

Ewen Cummins, Health Economists, McMDC Ltd

Deepson Shyangdan, Research Fellow, Warwick Evidence

Kandala Ngianga-Bakwin, Principal Research Fellow, Warwick Evidence

Professor Aileen Clarke, Director for Warwick Evidence, Professor of Public Health & Health Services Research, Warwick Evidence

Address for correspondence: Dr Martin Connock, Warwick Evidence, Warwick Medical School, University of Warwick, Coventry, CV4 7AL; email:

Date completed: 20th March 2012

Table of Contents

List of Tables and Figures 3

Abbreviations 4

1. Summary 5

2. Abiraterone as end of life treatment for mCRPC (ACD 4.19) 7

3. Is the "one prior" population appropriate for determining the benefits delivered by abiraterone? (ACD 4.10) 9

4. Modelling of survival (ACD 4.11 & 4.13) 11

5. What is the ICER of abiraterone versus best supportive care under ERG inputs and a modified PAS? 16

References 23

Appendix 1 25

List of Tables and Figures

Tables

Table 1 Estimated number of patients that may receive abiraterone within its licensed indication in England and Wales 8
Table 2 Mean days gain from abiraterone according to model and observed data used (manufacturer's base case in bold and sensitivity analysis in italic). 15
Table 3. Sullivan paper average FACT-P subscale UK and All patients compared to trial averages .. 17
Table 4. Wu paper average FACT-P scores compared to trial averages 17
Table 5. Weibull central parameter estimates available to the ERG 20
Table 6. Revised models 21
Table 7. Sensitivity analyses utility values 22
Table 8. Sensitivity analyses results 22

Figures

Figure 1 Average hazard by cycle; calculated according to manufacturers method 12
Figure 2 Extrapolation using constant hazard and Weibull models with different cycle cut offs for fitted data. 13
Figure 3 Mean survival according to constant hazard and Weibull models with different cycle cut offs for fitted data. 14

Abbreviations

AAP	Abiraterone acetate plus prednisolone
ACD	Appraisal Consultation Document
AIC	Akaike Information Criterion
ASCO	American Society of Clinical Oncology
AUC	Area Under Curve
DSU	Decision Support Unit
EMA	European Medicines Agency
EoT	End of Therapy
EQ-5D	EuroQol 5-Dimension
ERG	Evidence Review Group
FACT-P	Functional Assessment of Cancer Therapy - Prostate
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
IPD	Individual Patient Data
ITT	Intention To Treat
KM	Kaplan-Meier
mCRPC	Metastatic Castration-Resistant Prostate Cancer
mHRPC	Metastatic Hormone-Resistant Prostate Cancer
mPC	Metastatic Prostate Cancer
OPC	One Prior Chemotherapy
OS	Overall Survival
PAS	Patient Access Scheme
PFS	Progression-Free Survival
PMB	Pre-Meeting Briefing
PP	Placebo plus prednisolone
PSA	Prostate-Specific Antigen
QALY	Quality Adjusted Life Years
RCT	Randomised Controlled Trial
SRE	Skeletal-Related Event

1. Summary

Janssen's new submission addresses the following issues material to the decision problem:

1] Does abiraterone qualify as an end of life treatment according to criteria set out by NICE?

- The ERG notes that Janssen's new estimate of 2,466 patients being eligible for second line abiraterone is based partly on clinical opinion and partly on the cabazitaxel submission to NICE, rather than "epidemiological figures" as suggested by the manufacturer.
- The ERG has checked the accuracy of Janssen's quoted estimates of the number patients eligible for various treatments considered by NICE to fulfill end of life criteria and finds them substantially correct.

2] Is the "one prior" population appropriate to determine the benefits delivered to mCRPC patients in England and Wales treated with abiraterone within its licensed indication?

- Contrary to Janssen's implication of strong statistical evidence for a superior response in the one prior population, the ERG notes that statistical significance was not attained. If the one prior population was considered an *a priori* sub-group then ERG would expect the sample would be powered to detect a significant difference in these subgroups, and hence the interaction test would not be considered to be underpowered.
- The ERG agrees with Janssen that statistical significance does not invariably determine clinical significance. Therefore, the use of broader evidence on clinical significance to justify their choice of the sub-group may represent an acceptable approach.
- ERG has checked and found correct Janssen's claim that a similar superiority of response by one prior chemotherapy subgroup populations has been observed in the TROPIC and AFFIRM studies of second line treatments for mCRPC.

3] What form or forms of modelling are appropriate to estimate survival and progression free survival (PFS) in the economic model?

- The ERG remain of the opinion that the more appropriate model for use as a base case is the Weibull model to extrapolate overall survival (OS) beyond the observed data. This is because the constant hazard model proposed by Janssen overestimates survival in the abiraterone arm. It depends on observed survival averaged for a single cycle and is therefore more susceptible to arbitrariness in the exact choice of which element of the observed data is used to model extrapolation.

4] Are the utility estimates presented in the original submission reliable?

- Janssen have presented pre-progression and post-progression utility estimates used in economic models of cost effectiveness of treatments for metastatic solid tumours previously considered by NICE. The ERG have checked these values and found they have been reproduced accurately.

5] What is the ICER of abiraterone versus best supportive care under ERG inputs and a modified PAS?

- ERG notes that in the new base economic analysis, Janssen have retained the following elements of their original modelling: use of 1-prior population; use of KM and constant hazard extrapolation for estimating survival; the same utility increments when passing from progression free to post progression states
- For the new base case economic analysis, Janssen have modified their PAS and have implemented some of the cost inputs suggested in the ERG assessment document.
- The calculated ICERs for abiraterone versus best supportive care under ERG inputs and as modified by the revised PAS are greater than the manufacturer's revised estimates.
- When sensitivity analyses are conducted, ICERs range from £53,529 to £87,276 taking into account the 1-prior population versus the ITT population, different utility mapping methods and different methods of modelling survival.

Below, the ERG briefly summarises and comments on the new information presented by the manufacturer that is relevant to each of these issues.

2. Abiraterone as end of life treatment for mCRPC (ACD 4.19)

The ACD considered abiraterone to have met two out of the three end-of-life criteria, but not to have met the third criterion stated in section 2.1.1 of NICE end of life consultation document[1] as follows:

2.1.1 The medicine is indicated, in its licence, for a patient population normally not exceeding 7000 new patients per annum,

Janssen present three pieces of evidence that it considers support the case that abiraterone is an end of life treatment. These are:

A] Janssen propose that since abiraterone and cabazitaxel are licensed for the same population and NICE have already accepted that cabazitaxel meets all three end of life criteria, it follows that consitency of approach would dictate that abiraterone should similarly be considered to fulfil end of life criteria.

Below the ERG presents the licensed indications for each drug taken from the EMA web site:

Abiraterone:
The approved indication is: "*Zytiga is indicated with prednisone or prednisolone for the treatment of metastatic castration resistant prostate cancer in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen*".[2]

Cabazitaxel:
The approved indication is: "*Jevtana in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen*".[3]

The ERG notes that if "castration resistant" and "hormone refractory" mPC are considered to be synonymous then the indicated populations appear to be identical.

B] Janssen presents a new estimate of the number of patients in England and Wales who would be eligible to receive second line treatment with abiraterone within its licensed indication. Relative to the original submission the manufacturer has made two modifications to their calculation: (a) the number of patients who receive docetaxel treatment has reduced to 3,523 (from 4,400), based on the assertion that the estimate provided in the cabazitaxel submission to NICE is likely to be the best estimate because both cabazitaxel and docetaxel are marketed by the same company. (b) the proportion of

docetaxel-treated patients who go on to receive abiraterone has been reduced from 75% to 70% based on responses to a survey of four UK oncologists.

The new estimate of the number of patients in England and Wales eligible to receive second line treatment with abiraterone within its licensed indication is 2,466 (rising to 3,124 in 2015); the original submission suggested 3,300 patients.

In Table 1 the ERG has summarised the various estimates of patient numbers presented in abiraterone and cabazitaxel submissions.

Table 1 Estimated number of patients that may receive abiraterone within its licensed indication in England and Wales

Categories of patients	Janssen submission 1	Janssen submission 2	Cabazitaxel submission	Cabazitaxel ERG
Incidence of prostate cancer in England and Wales in 2008	-	33,373	33,373	33,373
Estimate in 2011	-	-	36,105 (2.6% annual rate increase)	33,977 (0.6% annual rate increase)
Estimated number of mCRPC in England and Wales	10,856	10,856	7,047	6,632
mCRPC eligible for treatment with docetaxel	4,400 (40%)	3,523 (32%)	3,524 (50%)	3,316 (50%)
mCRPC eligible for 2nd line therapy	3,300 (75%)	2,466 (70%)	1,938 (55%)	1,823 (55%)

The ERG notes that given the proportions Janssen proposes for mCRPC proceeding to docetaxel and to eligibilty for abiraterone, the number of mCRPC patients in England and Wales would need to be >31,000 for those eligible to be treated with abiraterone to excede 7,000.

The ERG notes that Janssen described these estimates as "*epidemiological*" figures which the ERG considers to be unjustified since they might better be described as estimates.

C] Janssen have presented information on the number of patients treated within licensed indication for six drugs which in the last two years have been accepted by NICE as end of life treatments; these were: sunitinib, lenolidomide, lapatinib, trastuzumab, pazopanib and everolimus. The estimated number of patients was <4,000 in all instances other than trastuzumab for which the number was 7,000. The ERG has checked that these were considered to be end of life treatments and that the numbers of patients correspond to those in the manufacturer's submission. The only discrepancy identifed was that the estimate for sunitinib is 4,000 according to NICE (section 4.3.11)[4] but 2,438 in Janssen's appendix.

3. Is the "one prior" population appropriate for determining the benefits delivered by abiraterone? (ACD 4.10)

The ACD accepted that the one prior population reflected the patients in England and Wales that would be likely to receive abiraterone, however they did not consider that this subpopulation to be appropriate for determining benefit because it had not been identified *a priori* in the pivotal trial and the difference in effectiveness compared with the "two prior" population did not reach statistical significance. The manufacturer's original submission stated:[5]

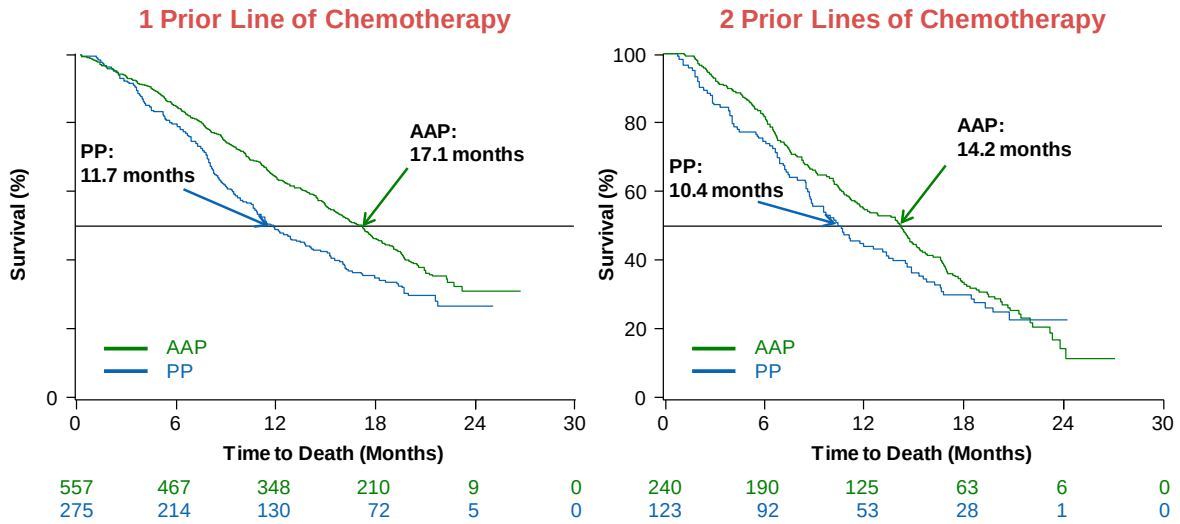
[redacted]

Janssen address this issue by proposing that the following considerations support the use of the one prior population in their economic model:

A] The number of prior chemotherapies was recognised as a likely important prognostic factor at inception of the RCT and was therefore used as a stratification factor for randomisation.

B] Although the interaction test of the greater benefit derived from abiraterone in the one prior group did not reach statistical significance ([redacted]) Janssen propose this may be attributable to lack of power in the statistical test. If the one prior population is to be considered an *a priori* sub-group then ERG would expect the sample would to be powered to detect a significant difference in these subgroups, and hence the interaction test should not be considered to be underpowered.

C] The manufacturer has presented new plots for OS for the two subgroups as shown below.



The manufacturer compared the two groups with respect to gain in mean survival derived from abiraterone determined using a Weibull fit (all observed data to life time horizon); this indicated a gain of 118 days for the one prior group and 26 days for the two prior group. (Because the cross-over of placebo and abiraterone plots in the "two prior" graph is associated with the greatest uncertainty this large difference should be viewed with caution).

D] A superior survival benefit experienced by the one prior group is biologically plausible since similar superiority can be observed for the following additional 5 outcomes: PFS (time to treatment discontinuation), modified PFS, skeletal related event (SRE) progression, and prostate specific antigen (PSA) progression. PFS a reached statistically significant difference between groups (p=0.0393) and PSA progression approached statistical significance for interaction terms (p=0.0613). These data appear to be new *post hoc* analyses not presented in the manufacturer's previous submission and not avaiable in the public domain, and the ERG has therefore been unable to check values.

E] That a superior survival benefit is experienced by the one prior group is supported by external data from two other RCTs of other second line treatments for mCRPC. The manufacturer stated that in the TROPIC study[6] (cabazitaxel versus mitoxantrone) the results for one prior and > one prior populations were: HR=0.67 (95% CI 0.55-0.83) vs. HR=0.75 (95% CI 0.55-1.02), and in the AFFIRM study of MDV3100 versus best supportive care the hazard ratios were 0.59 (95% CI 0.48-0.7) and 0.74 (95% CI 0.54-1.03) respectively.[7] Janssen did not supply references for the source of these values. The ERG has been able to confirm accuracy of the quoted results for the TROPIC study[6] and for the AFFIRM trial (available as video at http://www.gucasymposium.org/2012GenitourinaryCancersSymposium/GenitourinaryCancersSymposiumDailyNews/GULBA1.aspx)[7]

4. Modelling of survival (ACD 4.11 & 4.13)

The manufacturer asserts: "*Janssen believes that there is more than one appropriate approach to the fitting of survival functions, and that additional analysis conducted fails to indicate any one 'clear cut' approach*". Janssen note that:

1] The NICE DSU do not specify parametric fitting.

2] Extensive error analysis does not equivocally identify a superior model for the observed survival or identify an approach that is suited to observed OS in both arms of the trial, and further that this holds for other studies of survival in mCRPC

3] "*We note that the ERG did not provide any clear evidence to support their use of a parametric survival curve rather than the observed data in this case other than the DSU technical report by Latimer*"

The ERG concurs with points 1] and 2]. With regard to point 3] the ERG had no access to IPD (only data average across 21 day cycles). Also the ERG did not make or select the Weibull fit, this was done by the manufacturer who provided the Weibull parameters and selected the Weibull fit for their sensitivity analysis. ERG merely indicated that for extrapolation beyond the observed (Kaplan Meier) data the Weibull fit appeared more reasonable than the constant hazard model used by the manufacturer since the latter is informed by very little data, only by the hazard across a single and arbitrarily chosen cycle.

Below the ERG further explores the choice between constant hazard and Weibull models for extrapolation beyond the observed data.

To estimate the mean survival up to the end of the observed data, Janssen chose the KM observed survival plots in preference to parametric fits. Since all the parametric fits (other than exponential) follow the observed data well, the choice between the different alternatives has little effect on the mean survival over the period of observation (about 2 years). The key decision, as far as the estimation of mean survival is of course how to extrapolate beyond the observed data to the ten year time horizon.

To extrapolate beyond the observed data Janssen have used a constant hazard model where the hazard employed is based on that averaged across the cycle at which 10% of patients remain at risk. The average hazard for a cycle can be calculated in several ways (see Appendix 1). Figure 1 depicts the

hazard at each cycle calculated according to manufacturer's method for AAP and PP groups for the ITT and one prior population.

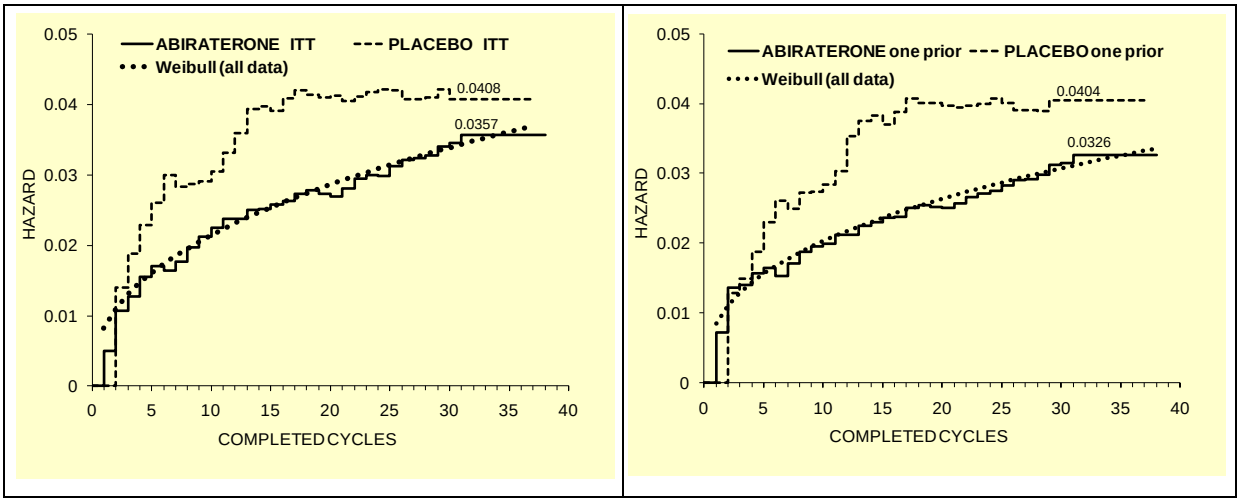


Figure 1 Average hazard by cycle; calculated according to manufacturers method

The trajectory of hazard for the abiraterone arm implies increasing hazard for time beyond the observed data and a hazard value for extrapolation greater than that used in Janssen's base case (i.e. for ITT population 0.0357; based on the average hazard at cycle 31). Thus the manufacturer's base case will overestimate mean survival in the abiraterone group. The manufacturer's base case has been chosen from a flat part of the plot which is inconsistent with the remaining observed hazard and where uncertainty is at its greatest. The observed hazard can be modelled using a Weibull distribution ($h = \lambda * \gamma * (t^{[\gamma - 1]})$), this implies a hazard of at least 0.037 for extrapolation beyond observed data. Hazard in the placebo group increases with cycle to a plateau that extends from about cycle 18 onwards; a constant hazard extrapolation appears consistent with the observed data.

A disadvantage of the constant hazard model is the arbitrariness of choice of cycle for estimation of the constant hazard to be used for extrapolation. Figure 2 (upper panel) illustrates the constant hazard extrapolation based on observed hazard from cycle 20 onwards. As shown in Figure 2 cycle choice has little influence on the estimate of mean survival (AUC to the 10 year time horizon) for the placebo group but a substantial influence on that for the abiraterone group.

An alternative approach for modelling extrapolation proposed by the manufacturer is to fit a Weibull distribution to the observed data. As with the constant hazard approach this may be influenced by the arbitrariness of choice in how much observed data should be used for fitting. The effect of this choice of cut-off is illustrated in Figure 2 which shows the extrapolations resulting from Weibull fits to the observed data up to cycle 20 and beyond. For the abiraterone group, the Weibull distribution explains

observed hazard well, the extrapolations overlap and the choice of observed data for fitting has little influence on the estimate of mean survival. For the placebo arm the choice of data does influence the extrapolation. Across both arms the constant hazard model appears more strongly dependent on choice of cut-off of observed data than the Weibull, however as indicated by the manufacturer neither model suits both arms equally well.

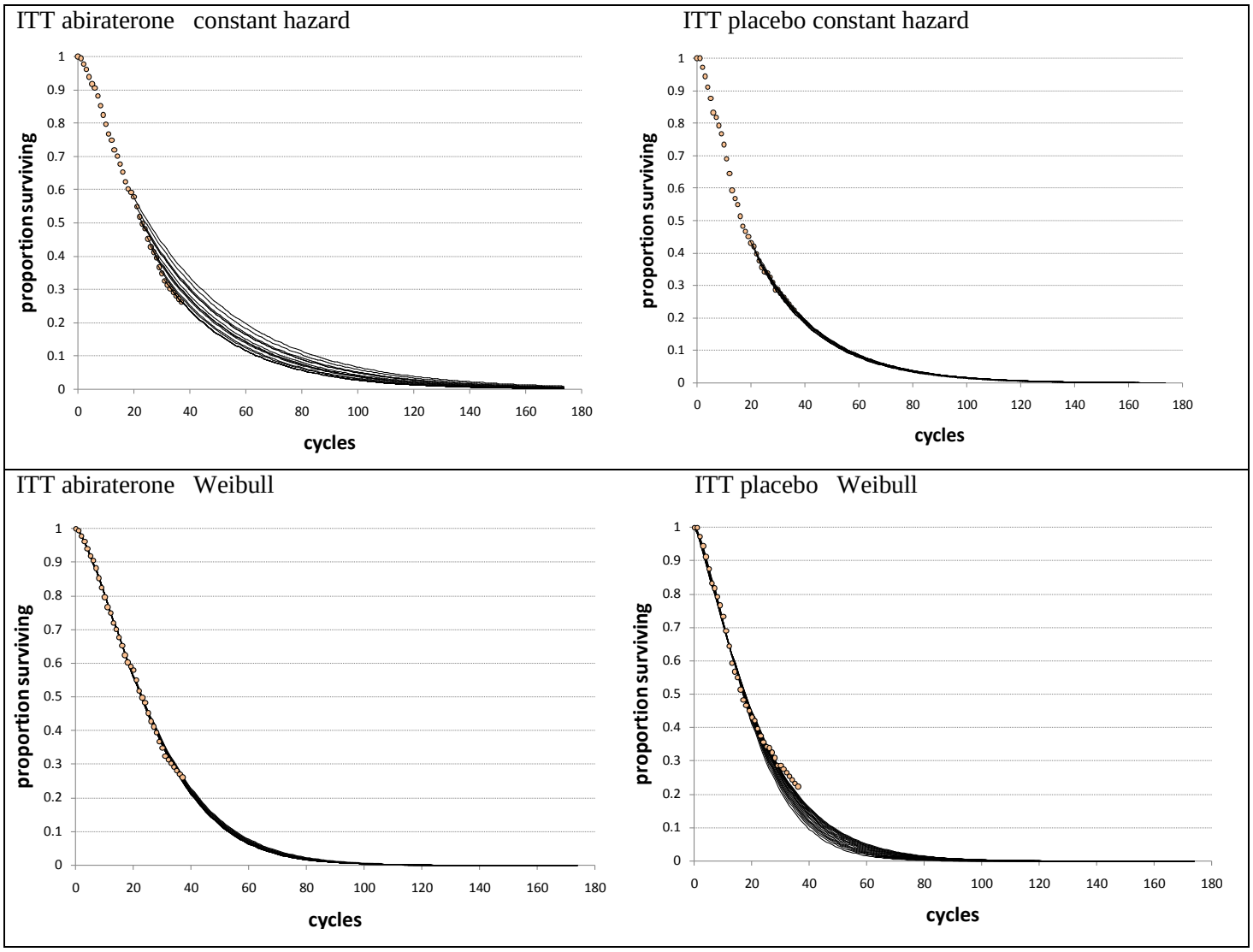


Figure 2 Extrapolation using constant hazard and Weibull models with different cycle cut offs for fitted data.

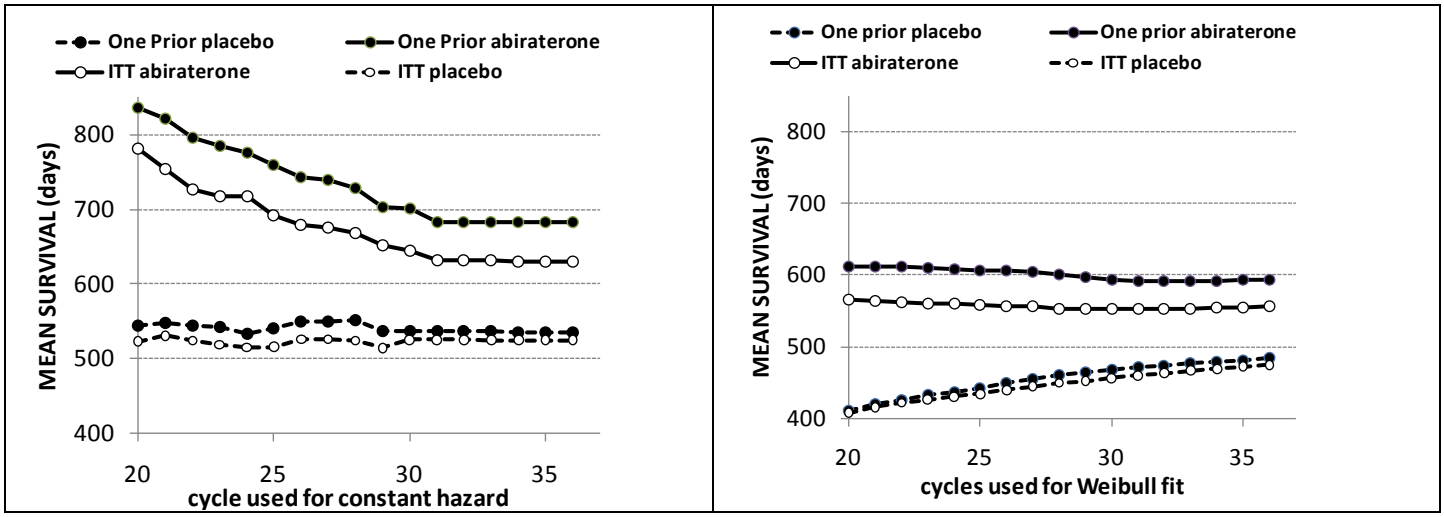


Figure 3 Mean survival according to constant hazard and Weibull models with different cycle cut offs for fitted data.

The mean survival predicted from constant hazard and Weibull models is summarised in Figure 3. In the constant hazard model, the gain from abiraterone over placebo remains constant from cycle 31 onward, at 106 days for the ITT population and 146 days for the one prior population. However, as explained above, these are overestimates because the abiraterone arm receives a lower hazard for extrapolation than is consistent with the observed data. Using the Weibull model the gain from abiraterone over placebo across cycles from 30 onward varies between 81 and 96 days for the ITT population and between 110 and 126 days for the one prior group. Figure 3 shows that the Weibull models generate less survival in the placebo arm than the constant hazard model. Ceteris paribus a low estimate for the placebo arm tends to favour benefit from abiraterone. As stated in the manufacturer's original submission: "*Data from other mCRPC studies support an assumption of a monotonically increasing hazard, such as a Weibull function*".[5]

As indicated in Figure 3 the model that is most stable to changes in cut off is different for the two arms. The gain from abiraterone remains remarkably similar across cut-offs if calculated from the Weibull models for the abiraterone arm and the constant hazard models for the placebo arm (varying from 31 to 41 days). This approach using different models is not consistent with NICE DSU recommended procedures.[8]

Table 2 summarises the gain in mean survival from abiraterone over placebo when the same model is applied to both arms and when the manufacturer's choice of cycle cut off is employed (the cycle when 10% patients remain at risk).

Table 2 Mean days gain from abiraterone according to model and observed data used (manufacturer's base case in bold and sensitivity analysis in italic).

ITT POPULATION				
MODEL FOR ABIRATERONE ARM	MODEL FOR PLACEBO ARM	MEAN DAYS GAINED		
		ABIRATERONE	PLACEBO	DIFFERENCE
CH (cycle 32)	**CH (cycle 30)**	**631**	**526**	**107**
W (cycle 32)	***W (cycle 30)***	***553***	***456***	***96***
CH (cycle 32)	W (cycle 30)	631	456	175
W (cycle 32)	CH (cycle 30)	553	526	27
ONE PRIOR POPULATION				
MODEL FOR ABIRATERONE ARM	MODEL FOR PLACEBO ARM	MEAN DAYS GAINED		
		ABIRATERONE	PLACEBO	DIFFERENCE
CH (cycle 32)	**CH (cycle 29)**	**683**	**537**	**146**
W (cycle 32)	***W (cycle 29)***	***592***	***465***	***127***
CH (cycle 32)	W (cycle 29)	683	465	218
W (cycle 32)	CH (cycle 29)	592	537	55

CH = constant hazard model. W = Weibull model.

The ERG consider the Weibull model more appropriate for the base case economic analysis because it is informed by more of the observed data, is somewhat less influenced by arbitrariness of choice of observed data, and because the constant hazard model clearly tends to overestimate survival in the abiraterone arm.

The clinical cut off for the updated analysis of OS was 20 September 2010. At this time nearly all censored patients had been observed for at least 17 months (24 cycles) and 63% of patients in the AAP arm had died. By December 2011 a further 21 cycles would have accumulated bringing the maximum time of observation to about 58 cycles. At this time the constant hazard model predicts about 13% patients alive in the abiraterone arm while the Weibull model predicts about half of this (~7%). A relatively modest investment of resources into follow up of the abiraterone treated patients might indicate which prediction is closer to reality.

5. What is the ICER of abiraterone versus best supportive care under ERG inputs and a modified PAS?

ERG commentary on Janssen response to ACD 4.14

The ERG agrees that the FACT-P mapping to EQ-5D has advanced the procedures that are available. But the mean FACT-P score at baseline in the abiraterone trials was 106 compared to [redacted] within the Adelphi data set. This might mean that the mapping function was extrapolating beyond its reliable range.

The manufacturer conducted a systematic review of the literature for the pre-progression utility values and updated a previous NICE HTA report.[9] Janssen then selected values that were considered most relevant. The manufacturer cites as alternative sources:

1. >16months from death in the Sandblom study with a utility of 0.77,[10]
2. the UK subgroup of the Sullivan study with a utility of 0.715,[11] and
3. the progression free utility values used in the NICE submission for cabazitaxel.[12]

For the first point it should be borne in mind that the manufacturer model simulates an average life expectancy in the AAP arm of 22 months and in the PP arm of 17 months. These are admittedly over the 16 months to death, the period from which Sandblom reports utility as a function of time to death and as summarised within the ERG report. The Sandblom study was undertaken specifically to estimate the HRQoL among men with prostate cancer in the year prior to death, the method being to estimate their HRQoL at a given time point then relate this to the date of death among those who had died over the period of the study: Sep 1999 to Jan 2001. All patients within an area of Sweden with any form of prostate cancer (n=1,442) were sent the questionnaire of whom 86% (n=1243) responded. Only 167 had died by the end of study (utility = 0.538). It seems reasonable to use the Sandblom estimates to characterise the progression of utility in the last 16 months of life. It seems less reasonable to assume that the baseline utility (0.77) of the 1,046 patients who had not died by study end were representative of mHRPC patients in the PFS phase with a life expectancy of 16 to 22 months.

As summarised within the ERG report[13] the UK subgroup of the mHRPC within the Sullivan paper do have a utility estimate of 0.715 (n=29) but this also has to be read in conjunction with an estimate across all patients of 0.635 (n=280), and with the FACT-P subscore in the manufacturer data being more in line with that across all patients in the Sullivan study than the UK subset.

Table 3. Sullivan paper average FACT-P subscale UK and All patients compared to trial averages

			Sullivan	
Average values	AAP	PP	UK	All
Fact P Subscale	[redacted]	[redacted]	30.7	29.8
Mean HRQoL			0.715	0.635

The PMB document[14] for the cabazitaxel STA reports decrements for moving from progression free utility to survival with progression of 0.070 for the base case and 0.085 as a sensitivity analysis. This compares with the manufacturer applied decrement of [redacted] in the PP arm. Admittedly those receiving cabazitaxel or mitoxantrone may be experiencing adverse events, but it seems likely that not all patients within either arm of the cabazitaxel STA will be being modelled as still being on chemotherapy at the point of progression. Also note that within the abiraterone submission the utility decrement from mitoxantrone is estimated as [redacted].

The manufacturer response also ignores the baseline estimates from the Wu reference[15] of utility estimates among mHRPC patients. This is a pity as these patients were at baseline of a similar average age of 72 years and very similar in terms of the average FACT-P scores for the various dimensions used within the manufacturer regression mapping function.

Table 4. Wu paper average FACT-P scores compared to trial averages

Average values	AAP	PP	Wu
Fact P Subscale	[redacted]	[redacted]	29.8
Emotional Well Being	[redacted]	[redacted]	17.2
Functional Well Being	[redacted]	[redacted]	16.6
Physical Well Being	[redacted]	[redacted]	20.9
Social Well Being	[redacted]	[redacted]	21.0
Mean HRQoL			0.635

While the mapping function of Wu has been misreported within the paper, there is no reason to believe that the baseline utility values calculated using the UK preference weights have been misrepresented. This provides a direct estimate of EQ-5D utility among mHRPC patients using the UK preference weights for the patient group with the above concurrent FACT-P values. As summarised within the ERG report, Wu reports a mean baseline EQ-5D utility among 276 mHRPC

patients based upon the UK social tariff of 0.635, though this is skewed with a median of 0.73 and a skewness of -1.53.

Applying the manufacturer mapping function to the Wu average FACT-P values results in a utility estimate of [redacted] which is, as would be anticipated given the similarity of FACT-P values, very similar to the estimated baseline utilities within the submission.

Also note that based upon a comparison of patient numbers the Sullivan paper[11] and the Wu Paper[15] appear to be based upon the same patient data set. There is the 0.635 average from all patients in the data set, who had very similar mean FACT-P values to the abiraterone trial baseline averages. And there is the 0.715 average from the UK patient subset among whom most FACT-P values are not reported and for whom the FACT-P specific subscale mean was around 1 point above that across all patients in the data set and the abiraterone trial baseline averages.

ERG commentary on Janssen response to ACD 4.15

The ERG has not undertaken a systematic review of quality of life values for pre and post progression health states within recent NICE assessments of treatments for metastatic and advanced solid tumour cancers.

The manufacturer notes that end of therapy (EoT) values were available for only a relatively small subset of patients. This is correct. But it has to be borne in mind that this is the only data set which is from the same source as the PFS utility values and aligned with them, and it seems incorrect to simply ignore these values.

The manufacturer also notes that quality of life will further decline after the point of progression as the patient condition worsens towards death. This is also correct but to the extent that all patients are modelled as progressing and that their average HRQoL changes in, say, the last three months of life follow a similar pattern regardless of the treatment arm the impact of this would be anticipated to largely cancel out between the arms

The base case of the manufacturer model anticipates an average survival post progression of 9.9 months in the AAP arm and 11.0 months in the PP arm. Barring minor effects due to discounting, it is really only the modelled different average duration of post progression survival that gives rise to the evolution of HRQoL in the end stages being a possible concern. These differences might suggest that the manufacturer argument for an adjustment to the EoT HRQoL values would apply with greater force in the AAP arm than the PP arm, since the decline in the AAP arm might tend to occur sooner after progression.

But it should also be borne in mind that the average reported EoT HRQoLs of [redacted] in the AAP arm and [redacted] in the PP arm retain a similar HRQoL increment from AAP over PP to that estimated for the PFS health states.

Section 2: Revised PAS and updated economic analysis

Summary of revised manufacturer modelling

The ACD concluded that:

1. Restricting the base case population 1-prior chemotherapy subgroup was not appropriate.
2. For OS the KM curves reflected the trial and population and a well-fitting parametric distribution would be more generalisable to all patients. For PFS the shape of the KM curve for treatment discontinuation in the prednisolone group was unusual. This was unlikely to represent actual disease progression and a well-fitting parametric distribution should have been used. Well-fitting parametric curve should have been used to extrapolate OS and PFS. The Weibull model should be applied for OS and PFS throughout the course of follow-up.
3. Utilities for pre and post progression should where possible be derived from the same source. The difference in the values used was unreasonably large and a lower baseline utility should be applied.
4. Resource use estimates should be corrected.

Taking these points in turn the revised cost effectiveness estimates presented by the manufacturer:

1. Retain the 1-prior chemotherapy subgroup for the base case. The ITT population is presented as a scenario analysis in Table 6 but without the full range of sensitivity analyses.
2. Retain the KM curve approach for both OS and PFS, with 10% and 5% cutoffs respectively and constant hazard extrapolation thereafter
3. Retain the utilities for pre and post progression of the original submission
4. Change: administration costs per oncology consultation to £101 for the pre-progression health states; mitoxantrone acquisition cost to £187 per dose; mitoxantrone administration costs to £212 per dose; and, the percentage of patients receiving bisphosphonates post-progression to the 37% assumed for pre-progression. These changes are in line with those of the ERG revised baseline. It would also have been appropriate to change the post progression monthly cost to reflect the oncology consultation cost of £101, though in itself this has only a limited impact upon results.

The revised cost effectiveness estimates also incorporate a revised PAS which further reduces the monthly cost of abiraterone from the £2,930 list price and the [redacted] with PAS price to a revised [redacted] with PAS price.

Note that the model has not been corrected to reflect the error introduced through half cycle correction being applied to the direct drug costs. As per the ERG report this would be anticipated to increase the direct drug costs by approximately half the monthly cost; i.e. by around [redacted] in the abiraterone arm.

In short, the revised base case changes the resource use to be in line with the ERG revised baseline and amends the PAS. But otherwise it is as per the original submission. This results in cost effectiveness estimates for abiraterone compared to prednisolone of £52,851 per QALY for the ITT population and £46,800 per QALY for the 1-prior patient population.

ERG additional analyses

During clarification the ERG asked for the parametric curves' central parameter estimates and goodness of fit comparison only for the 1-prior patient population. As a consequence the ERG does not have this data for the ITT patient population. For the ITT patient population, the electronic model contains the Weibull parameter values for the OS curves for the AAP and PP arms. It also contains the Weibull parameter values for the AAP PFS curve, but it does not contain those for the PP PFS curve.

Table 5. Weibull central parameter estimates available to the ERG

1-prior patient population	Intercept	Scale	Shape
AAP OS	3.4456	0.7155	1.3977
PP OS	3.2157	0.7551	1.3243
AAP PFS	2.8624	0.9079	1.1015
PP PFS	2.2931	0.8920	1.1211
ITT patient population	Intercept	Scale	Shape
AAP OS	3.3643	0.6868	1.4560
PP OS	3.1816	0.7714	1.2963
AAP PFS	2.7680	0.9241	1.0821
PP PFS	n.a.	n.a.	n.a.

As a consequence, for the ITT patient population the closest the ERG can approximate the analysis requested under the ACD is to apply

- the Weibull parameter estimates for the OS curves
- the KM curves for the PFS to the 5% cut-off
- the Weibull extrapolation for the AAP PFS curve thereafter
- an assumption that the PP PFS KM curve is complete, which it virtually is.

In the light of this, an additional structural sensitivity analysis is presented for the 1-prior patient population which adopts the same modelling approach.

This gives rise to three model implementations:

- The 1-prior patient population with Weibulls for both OS and PFS
- The 1-prior patient population with Weibulls for OS and KMs for PFS trial period
- The ITT patient population with Weibulls for OS and KMs for PFS trial period

These are all implemented for the revised [redacted] with PAS price.

Table 6. Revised models

Model	1-prior Weibulls	1-prior Weibulls/KM	ITT Weibulls/KM
Patient group	1-prior	1-prior	ITT
Trial period			
OS	Weibull	Weibull	Weibull
PFS	Weibull	KM	KM
Extrapolation			
OS	Weibull	Weibull	Weibull
PFS	Weibull	None	None

The main remaining uncertainties that can be addressed appear to relate to the utility values to employ.

The baseline PFS utility values differ between the 1-prior patient population and the ITT patient population due to them having specific regressions for the change from the baseline value of [redacted]. For the same reason the increment from AAP over PP for PFS is [redacted] for the 1-prior patient population and [redacted] for the ITT patient population. These PFS increments are retained throughout.

Table 7. Sensitivity analyses utility values

	HRQoL PP PFS		HRQoL PPS		Rationale
SA1 Baseline	[redacted]	1-prior ITT	0.500		For PFS manufacturer regressions For PPS manufacturer base case
SA2 Sandblom	0.770		0.500		For PFS Sandblom >16 mths to death
SA3 Sullivan UK	0.715		0.500		For PFS Sullivan UK patients
SA4 Wu	0.635		0.500		For PFS Sullivan All patients and Wu
SA5 Cabazitaxel (1)	0.570		0.500		Cabazitaxel decrement 0.070
SA6 Cabazitaxel (2)	[redacted]	1-prior ITT	0.689 0.686	1-prior ITT	Cabazitaxel decrement 0.070
SA7 Cabazitaxel (3)	0.585		0.500		Cabazitaxel decrement 0.085 SA
SA8 Cabazitaxel (4)	[redacted]	1-prior ITT	0.674 0.671	1-prior ITT	Cabazitaxel decrement 0.085 SA
SA9 EoT PP	[redacted]	1-prior ITT	[redacted]		Trial EoT HRQoL for PP arm

Table 8. Sensitivity analyses results

	1 prior Weibulls		1 prior Weibulls/KM		ITT Weibulls/KM	
SA1 Baseline	£53,140	[redacted]	£52,186	[redacted]	£60,038	[redacted]
SA2 Sandblom	£52,362	[redacted]	£51,395	[redacted]	£58,797	[redacted]
SA3 Sullivan UK	£56,498	[redacted]	£55,611	[redacted]	£63,993	[redacted]
SA4 Wu	£63,832	[redacted]	£63,143	[redacted]	£73,432	[redacted]
SA5 Cabazitaxel (1)	£71,358	[redacted]	£70,952	[redacted]	£83,431	[redacted]
SA6 Cabazitaxel (2)	£56,788	[redacted]	£56,572	[redacted]	£67,765	[redacted]
SA7 Cabazitaxel (3)	£69,468	[redacted]	£68,984	[redacted]	£80,889	[redacted]
SA8 Cabazitaxel (4)	£56,480	[redacted]	£56,197	[redacted]	£67,069	[redacted]
SA9 EoT PP	£55,935	[redacted]	£55,535	[redacted]	£65,985	[redacted]

The values in brackets are the ICERs which provide an approximate correction to the incorrect application of half cycle correction to the abiraterone drug costs by increasing the average treatment cost in the abiraterone arm by the cost of 15 days of abiraterone.

References

1. National Institute for Health and Clinical Excellence. Appraising end of life medicines. Consultation 2008: End of life care criteria. Available from http://www.nice.org.uk/newsroom/features/endoflifemedicinesconsultation.jsp 2012, February 2

2. European Medicines Agency. Assessment report for Zytiga (abiraterone) Procedure No: EMEA/H/C/002321. 2011.

3. European Medicines Agency. Assessment Report For Jevtana (cabazitaxel) Procedure No.: EMEA/H/C/002018. 2011.

4. National Institute for Health and Clinical Excellence. TA169 Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma. Available from http://publications.nice.org.uk/sunitinib-for-the-first-line-treatment-of-advanced-andor-metastatic-renal-cell-carcinoma-ta169/evidence-and-interpretation 2012, March 9

5. Janssen. Abiraterone Acetate (Zytiga®) for the treatment of metastatic castration resistant prostate cancer following previous cytotoxic therapy. 2011.

6. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I *et al*. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* 2010;376:1147-54.

7. Scher, H. I. MDV3100 Shows Unprecedented Efficacy, Safety in Post-Docetaxel CRPC. 2012 Genitourinary Symposium. 2012.

8. Latimer N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials- extrapolation with patient-level data. Available from http://www.nicedsu.org.uk 2011

9. Collins R, Fenwick E, Trowman R, Perard R, Norman G, Light K *et al*. A systematic review and economic model of the clinical effectiveness and cost-effectiveness of docetaxel in combination with prednisone or prednisolone for the treatment of hormone-refractory metastatic prostate cancer. *Health Technol Assess* 2007;11:iii-xviii, 1.

10. Sandblom G, Carlsson P, Sennfalt K, Varenhorst E. A population-based study of pain and quality of life during the year before death in men with prostate cancer. *Br J Cancer* 2004;90:1163-8.

11. Sullivan PW, Mulani PM, Fishman M, Sleep D. Quality of life findings from a multicenter, multinational, observational study of patients with metastatic hormone-refractory prostate cancer. *Qual Life Res* 2007;16:571-5.

12. Stevenson M, Lloyds Jones M, Kearns B, Littlewood C, Wong R. Cabazitaxel for the second-line treatment of hormone refractory, metastatic prostate cancer: A single Technology Appraisal. ScHARR, The University of Sheffield. 2011.

13. Connock M, Cummins E, Shyangdan D, Hall B, Grove A, Clarke A. Abiraterone acetate for the treatment of metastatic, castrate-resistant prostate cancer following previous cytotoxic chemotherapy: A Single Technology Appraisal. Warwick Evidence. 2011.

14. National Institute for Health and Clinical Excellence. Premeeting briefing. Cabazitaxel for the second-line treatment of metastatic hormone refractory prostate cancer. 2011 August.

15. Wu EQ, Mulani P, Farrell MH, Sleep D. Mapping FACT-P and EORTC QLQ-C30 to patient health status measured by EQ-5D in metastatic hormone-refractory prostate cancer patients. *Value Health* 2007;10:408-14.

Appendix 1

Several procedures may be used for estimating averaged hazard across a cycle:

(A) Janssen procedure:

$$h(t_i) = 1 - \left(\frac{s(t_i)}{s(t_{i-1})} \right)^{\frac{1}{(t_i - t_{i-1})}}$$ Because t_{i-1} was taken as zero, at which time S=1, this simplifies to:

$$h(t_i) = 1 - \left(\frac{s(t_i)}{1} \right)^{\frac{1}{t_i}}$$

Thus at cycle 33 $h(t_i) = 1 - \left(\frac{s_{(33)}}{1} \right)^{\frac{1}{33}}$ where $S_{(33)}$ is the observed survival at cycle 33.

The constant hazard employed in the model then depends on the survival at a single specified cycle.

(B) alternative procedure: $h(t_i) = -1 * (\ln S) / t_i$

(C) alternative procedure: *$h(t_i)$ = (events during cycle) / (average at risk during cycle)*

Methods A and B yield almost identical results (below). Method C generates considerable fluctuations form cycle to cycle.