NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated [ID503]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Janssen
   - Tackle Prostate Cancer
   - British Uro-Oncology Group
   - Royal College of Physicians
   - The Institute of Cancer Research

   The Department of Health stated that they had no comments

3. **Comments on the Appraisal Consultation Document received through the NICE website**

4. **ERG response to the Company's response to the 2nd ACD on 15 January 2016**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated

Response to consultee, commentator and public comments on the second Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Janssen	Janssen is extremely disappointed that the Appraisal Committee's preliminary decision is to not recommend abiraterone for patients with metastatic hormone-relapsed prostate cancer not previously treated with chemotherapy. We remain committed, however, to continue working with NICE in order to address the Committee's key concerns outlined in the ACD. This appraisal was scoped in by NICE in 2011, and Janssen has worked collaboratively with both NICE and NHS England to ensure funding for abiraterone has been maintained throughout this period, given the important clinical need in advanced prostate cancer. Abiraterone for use prior to chemotherapy is routinely available and funded in 61 countries around the world, including Scotland. It has been available on the Cancer Drugs Fund (CDF) since January 2013, and has been the second most requested drug on the fund . Thus, there is a clear clinical demand for the drug, and it has become the standard of care in many countries. Janssen urges the Committee to take this into account when reconsidering its recommendation at the forthcoming Appraisal Committee meeting. Our response addresses the following key issues: • Appraisal Committee's preferred assumptions in the economic model • Survival benefit associated with abiraterone • End of life criterion for life expectancy We believe this response document addresses the key concerns raised in the ACD, and provides the necessary information for the Committee to be able to reach a positive decision.	Comments noted. The final appraisal determination (FAD) recommends abiraterone within its marketing authorisation (see section 1 of the FAD).
Janssen	**2.1 Choice of covariates included in the prediction equations** *"…for each of the model's 17 equations predicting time to events, the Committee noted that the company made a large number of judgements when determining which covariates to include in the prediction equations and which parametric distributions to choose for extrapolation. The Committee concluded that the company had not fully justified the approach it used for choosing the different covariates to include in each prediction equation" [para. 4.8].* *"The ERG stated that its preferred base case would: […] derive prediction equations for time to*	These comments were considered carefully by the appraisal committee. Please see sections 4.8 and 4.16 of the FAD.

Consultee	Comment [sic]	Response
	stopping treatment, time to starting treatment and time to death from the full ITT population in COU-AA-302, accounting for treatment effect only, and not including other risk predictors based on baseline characteristics […]" [para. 3.27] Janssen contends that we did not make a large number of judgements when determining which covariates to include in the prediction equations. Rather, the economic model was powered by prediction equations that included all predictors that met significance criteria per a systematic and pre-specified analysis plan. The two exceptions were, however, clinically and statistically justified and had little impact on the ICER (see Appendix 1 for details). **Moreover, using treatment as the only predictor, as suggested by the ERG to better capture the ITT patients, is wholly inappropriate, as it does not reflect how clinical decisions are made.** Using treatment as the only predictor necessitates that different stages of disease are completely independent from each other, which not only lacks clinical and face validity but also results in a significant underestimate of the predicted OS associated with AAP treatment compared with the COU-AA-302 trial final data cut OS KM curve (see Figures 1 and 2). Predicted OS (Figure 2), where time to each event is dependent upon a unique set of patient characteristics, better replicates the trial dataset when compared to the ERG-proposed base case (see Figure 1). In particular, the AAP arm under the ERG-proposed base case deviates from the KM final data, whilst the company base case is a close fit. [Figures provided but not reproduced here.]	
Janssen	**2.2. Impact of cross-over and subsequent therapies on BSC arm** *" The Committee agreed that treatment switching and subsequent treatments that are not available in the NHS probably extended survival in both groups of COU-AA-302, but the effect was probably greater for the placebo group because more people took these treatments." [para. 4.7.]* In COU-AA-302, 93 (17%) patients in the PP arm were allowed to cross-over and receive abiraterone prior to docetaxel. Furthermore, seventy-nine percent of PP patients received active treatments including AAP (43%), sipuleucel-T (5.9%), cabazitaxel (19%) and enzalutamide (10%) post-docetaxel in the final dataset. Unlike the trial, the model pathways for the BSC (PP) arm do not allow use of abiraterone until after the post-docetaxel phase to reflect current treatment in the UK. Model predictions, therefore, must adjust for these cross-over differences. Figures 1 and 2 above also show the OS curve of the BSC arm adjusted for cross-over (0.74 as specified in the ACD versus 0.81 for the unadjusted HR), and demonstrates that our projection is reasonable and may even overestimate the BSC arm. The ERG-proposed base case also overestimates the BSC survival, since the OS KM data contains cross-over and subsequent treatments. This point is further addressed under Section 2.3.	Comments noted. Please see section 4.14 of the FAD.
Janssen	**2.3 Fit of the best supportive care arm to the final trial data**	Comments noted. Please see

Consultee	Comment [sic]	Response
	"For the best supportive care arm, the Committee was concerned that neither parametric distribution provided a good fit to the final trial data. It noted that both distributions overestimated the time that patients would remain on best supportive care" [para 4.12] Janssen strongly believes it is important to differentiate between uncertainty that can and can never be addressed. The modelled extrapolation associated with the best supportive care arm is an example of uncertainty that can never be fully addressed. Given that the COU-AA-302 trial studied patients with metastatic cancer, once a 'highly significant benefit' was observed, the Independent Data Monitoring Committee (IDMC) advised that the trial be unblinded to allow patients in the control arm to receive treatment with abiraterone. This is a common occurrence in oncology trials for ethical reasons. Given the subsequent cross-over and high number of subsequent treatments that patients were allowed to receive after their trial treatment, it is not a surprise that neither parametric distribution provides a good fit to the final trial data, and that both distributions overestimate the time on best supportive care, thus favouring the BSC arm of the model (conservative approach). Janssen urges the Committee to factor this into account, and consider that the modelled extrapolations do in fact provide a good fit to the abiraterone arm, which is the uncertainty that can be, and has been, addressed.	section 4.13 of the FAD.
Janssen	**2.4 Choice of parametric distribution** *"Having considered the evidence carefully, the Committee did not agree with the company's statement that the final data supported the company's choice of a log-logistic distribution for predicting time on first treatment. The Committee could not choose a preferred parametric distribution for predicting time on first treatment because no data were available to validate predictions beyond about 5 years. Accordingly, it considered both the log-logistic curve and the Weibull curve in its decision-making" [para. 4.12]* *"The Committee, noting NICE's Guide to the methods of technology appraisal 2013, concluded that it was appropriate to explore the impact of using different parametric distributions on the model results." [para. 4.12]* As the final dataset from the COU-AA-302 trial provides longer follow up and captures more death events than the 55% data cut, there is less uncertainty around the long-term projection associated with the final data cut. In this context, statistical analyses were performed on the COU-AA-302 trial 55% data cut to check the best fit distribution for predicting time to AAP/BSC (PP) treatment discontinuation. Standard procedures were employed to derive the prediction equation, and the log-logistic distribution had the best statistical fit based upon both AIC/BIC criteria and visual inspection. The best statistical fit for characterizing time to AAP/BSC (PP) treatment discontinuation was further verified using the COU-AA-302 trial final data cut. The 55% data cut was used to inform the analyses as it needed less adjustment for patients who crossed over from the placebo arm to AAP, and gives OS estimates in line	Comments noted. Please see sections 4.10 to 4.13 of the FAD.

Consultee	Comment [sic]	Response
	with the final trial data. Similarly, the log-based model provided the best fit for predicting time to treatment discontinuation (see Appendix 1 for details) and was therefore used in the model. This approach is further supported by several publications that advocate the use of log models in order to provide a better fit to data than a Weibull model in these cases . Figure 3 below compares the final KM data to predicted time to discontinuation informed by a log-logistic model showing a good fit of the modeled time to discontinuation curves to the KM curves for the AAP arm, and a slight over-estimation of trial KM curve for the BSC arm, therefore disadvantaging AAP (a conservative approach). Similarly, when OS is extrapolated using the log-logistic function, the modeled OS curve is also a close match to the observed KM trial curves, as shown in Figure 2 above. Notwithstanding the above, given the Committee's concerns surrounding the long-term plausibility of the log-logistic distribution as well as for the Weibull extrapolation (preferred by the ERG), additional sensitivity analyses have been conducted in which a combined two-part model (log-logistic+Weibull) is applied to inform treatment duration. Under this scenario, time is estimated based upon the best-fit log-logistic function up to the point of extrapolations (approximately 2.5 years) outside of the COU-AA-302 trial. After this point, time to AAP treatment end is estimated following a Weibull function. Patients on BSC (PP) are assumed to discontinue treatment after 2.5 years (approximately 1000 days), based upon observations from the COU-AA-302 final data cut. As shown in Figure 4 below, predicted AAP (using a log-logistic function to capture time on AAP until follow-up in the trial and then a Weibull function to capture the remaining treatment duration) and BSC (PP) (all patients discontinue by 2.5 years) treatment duration is a close match to the COU-AA-302 trial final KM data (see Figure 4 below). A slightly increased ICER of £32,849 is estimated under this scenario analysis compared to a base case ICER of £28,563 (see Table 1 below). [Figures, tables and references provided but not reproduced here.]	
Janssen	**2.5 Intention-to-treat (ITT) population** *"The Committee concluded that the ITT population represented all patients, was less likely to bias the results, and provided more data, and, for these reasons, preferred it" [para 4.15]* **<u>Use of COU-AA-302 Patient Level Data</u>** In order to clarify how the ITT population was employed in the model, we provide a complete explanation below. It appears that the Committee has concluded that only a subset of 902 patients are included in the model, as opposed to the entire trial population, and this is fundamentally not the case – data from all patients are utilised in the model at appropriate times.	Comments noted. Please see section 4.16 of the FAD.

Consultee	Comment [sic]	Response
	The COU-AA-302 patient level data are used to inform the model in two key ways: • To create the prediction equations that power the model. • To create the patient profiles that are then run through the prediction equations in the model to generate results. <u>Prediction equations</u> The COU-AA-302 trial enrolled 1088 patients (546 treated on AAP and 542 treated on BSC (PP)). Prediction equations for each treatment phase were derived using all patients with non-missing values for covariates that were statistically significant and included in the final multivariate equation. The number of patients contributing to each equation depended on which characteristics or predictors were retained in the final regression model and the patients with follow-up data to contribute to informing the time to event equation. At each phase of treatment, data on certain covariates was missing for a small number of patients. Ultimately, the prediction equations were derived based on all patients with non-missing data (i.e. for whom data on all significant covariates included in particular equation were available). In the first equation (i.e. equation for the time to first treatment discontinuation that included the largest most inclusive number of significant predictors), 902 of the 1088 had non-missing values for important predictors. However, it is not simply the data from these 902 patients that continues to only be used throughout the remaining phases of the model. The number of patients informing equations varied as time progressed, which would be the case even for a Markov approach (i.e. fewer patients experiences the more downstream events). Because the covariates that were found to be significant were slightly different at each stage of treatment, a patient who did not contribute data for one prediction equation due to missing data may contribute data to a later stage of treatment for which different covariates were required. For example, if baseline ECOG was missing for a patient, then this patient **wasn't** included for derivation of time to first treatment discontinuation, but **was** included for deriving the equation for the time to death after AA/Placebo treatment discontinuation, since ECOG at baseline was not predictor that was considered for the time to death after AA/Placebo treatment discontinuation equation. In other words, the inclusion of patient information did not function as a funnel, excluding more and more patients at each subsequent stage of treatment; rather, patient information from the entire ITT trial population was included at relevant phases of the model. Consequently, Janssen maintains that our base case assumption in which prediction equations are based on all patients with non-missing values better replicates trial OS for the ITT population compared to the ERG recommended base case (see Figure 2 vs Figure 1). <u>Patient Profiles</u> The 902 patients ("analysable") with non-missing data for the first equation are also used for the individual patient profiles used in the simulation model. Using actual patient profiles takes into account	

Consultee	Comment [sic]	Response
	the natural correlation between the various variables. To allow profiles to be sampled directly from actual patient data, a dataset was constructed including the necessary variables and transferred into a format usable by the simulation model. A total of 186 patients (87 for AAP and 99 for BSC (PP)) were excluded due to missing baseline data that were used as predictors (e.g. BPI). The 902 patient profiles were cloned and each run through the model which is equivalent to a perfect randomization. Notwithstanding this, given the Committee's concerns surrounding our approach to the analysable population, we have run an analysis using the entire ITT population at the start of the model, by filling in missing predictor variable values with the population mean. In the analysis, the company base case ICER of £28,563 becomes £28,240 (See Table 2 below), a minimal decrease. [Table provided but not reproduced here.]	
Janssen	<u>Comparison of the analysable versus the ITT population</u> As Table 3 below shows, the characteristics of the analysable dataset versus the ITT population are very similar. The p-values comparing the analysable population versus the ITT population demonstrate a lack of statistically significant difference. In addition, a logrank test was conducted to compare the time to treatment discontinuation (TTD) for the ITT population and analysed patients. The p-value is 0.7481 for the AAP group and 0.7745 for the BSC (PP) group, indicating that there is no statistically significant difference in terms of TTD between the ITT population and analysed patients. A similar analysis was conduct for OS and no statistically significant difference was identified (p-value of 0.3117 for the AAP group and 0.6328 for the BSC (PP) group). By visually inspecting these graphs, the OS KM curves are identical (See Figure 5 and Figure 7 below), and analysed patients who were treated with AAP had slightly longer TTD (but not statistically significant) as presented in Figure 6 and Figure 8 below, which implies that results of the model are conservative given that treatment duration is slightly longer. This contributes to a slightly higher drug cost for the modelled population vs the ITT population. Janssen therefore maintains that the 'analysable' population is the most appropriate population upon which to model, and suggests that there appears to be a fundamental misunderstanding in terms of how the model population compares to the ITT population. [Figures and table provided but not reproduced here.]	Comments noted. Please see section 4.16 of the FAD.
Janssen	**2.6 PAS administration costs** *"The Committee noted that the administration costs of administering the PAS, although low, had not been included in the modelling and considered that these costs should have been included" [para 4.18]* Janssen acknowledges that the cost of administering the PAS should have been included in the modelled evaluation, and admits that this was simply an omission error. Consequently, we have	Comments noted. Please see section 4.19 of the FAD.

Consultee	Comment [sic]	Response
	included this administration cost and its inclusion has a negligible impact on the ICER, see Table 4 below.	
Janssen	**2.7 Price of docetaxel** *"The Committee noted that generic versions of docetaxel have become available during the course of the appraisal…The Committee agreed that the cost of docetaxel may vary across the NHS, but it was likely to be closer to the eMIT cost than that modelled by the company" [para 4.18]* Janssen maintains that it is difficult to determine an accurate estimation of the national average price of docetaxel, and agrees with the Committee that the price is likely to vary across the UK. We also assert that it is most appropriate to use the British National Formulary (BNF) price in appraisals, and not tendered prices. Janssen believes the inclusion of tendered prices of genericised drugs, particularly when the prices change over the course of an appraisal, into NICE appraisals as a matter of course is not appropriate, as not only are these prices not agreed at a national level, but they also do not reflect the actual value that these drugs bring to the NHS. However, in response to the Committee's concerns, we have conducted a sensitivity analysis applying the significantly reduced, electronic market information tool (eMIT) price of docetaxel. The analysis shows that inclusion of the eMIT cost of docetaxel has a negligible impact on the ICER, see Table 4 below.	Comments noted. Please see section 4.19 of the FAD.
Janssen	**2.8 Compliance rate** *"…in the COU-AA-302 trial, patients took 98% of the licensed dose on average and so the company's base-case model used 98% of the cost of the licensed dose of abiraterone. The Committee considered that the cost of unused tablets was unlikely to be recovered by the NHS, so the full cost of the licensed dose of abiraterone should be included in the model" [para 4.18]* Janssen appreciates that the cost of unused tablets is unlikely to be recovered by the NHS, however, we note that the treatment effect observed in the COU-AA-302 trial and consequently modelled in the economic evaluation represents the treatment effect associated with a compliance rate of 98%, not 100%. Adjustment of only the drug cost, without a corresponding adjustment assuming a treatment effect associated with 100% compliance will likely bias against abiraterone. However, in order to address the Committee's concern, we have included 100% of the cost of the licensed dose of abiraterone, which has a minimal impact on the ICER, see Table 4 below.	Comments noted. Please see section 4.19 of the FAD.
Janssen	**2.9 Adjustment for cabazitaxel** *"The Committee noted that cabazitaxel is not recommended by NICE and is currently available on the Cancer Drugs Fund. The Committee accepted that it was appropriate to adjust for treatments that have a survival benefit and which are not available in the NHS…The Committee noted that adjusting for subsequent treatments had a modest impact on the ICER…the Committee concluded that*	Comments noted. Please see section 4.15 of the FAD.

Consultee	Comment [sic]	Response
	adjustment for subsequent treatments in the abiraterone arm should be included in the analyses used for decision-making" [para 4.14] Janssen notes that cabazitaxel is currently undergoing a NICE appraisal, and may receive a positive recommendation this year. If this is the case, then exclusion of cabazitaxel may not be appropriate. Consequently, we have conducted a sensitivity analysis which includes cabazitaxel as an acceptable post-docetaxel alternative. This results in a lower ICER, see Table 4 below.	
Janssen	**2.10 Results using Committee's preferred assumptions** Table 4 below displays the cost-effectiveness results using each of the Committee's preferred assumptions, discussed under Sections 2.1-2.9 above. Importantly, the ICER is not very sensitive to these assumptions. [Table provided but not reproduced here.]	Comments noted. Please see section 4.19 of the FAD.
Janssen	**3. Survival benefit associated with abiraterone** *"Overall, the Committee concluded that abiraterone delayed disease progression and improved overall survival compared with placebo, but that there was uncertainty about the extent of the survival benefit" [para 4.7]* *"For the abiraterone arm, for the time period (the trial period) for which data were available, the Committee agreed with the company that the log-logistic curve fitted the trial data better than the Weibull curve. However, it noted that the log-logistic curve predicted that some patients remained on abiraterone for a long time and about 4% took abiraterone for at least 8 years. The Committee heard from the company that there was anecdotal evidence that a few patients take abiraterone for several years. However, the Committee agreed that it had not seen data to support the extrapolation in the company's model because the maximum follow-up time in the trial was about 5 years" [para 4.12]* The COU-AA-302 trial is a well-designed, randomised controlled trial against the relevant comparator in the UK with over four years of follow-up. This trial has demonstrated a statistically significant survival benefit versus BSC and, therefore, Janssen strongly contends that there is little uncertainty surrounding the extent of the survival benefit associated with abiraterone. We fully maintain that those patients who respond very well to treatment with abiraterone can remain on treatment for extended periods of time and can provide supporting evidence, firstly in the form of data from several centres across the UK that have treated patients with abiraterone and secondly, data from the US, where abiraterone has been available for longer than in the UK (Appendix 2). Both sources of data demonstrate that there is in fact a proportion of patients that respond particularly well on abiraterone, and thus remain on the drug for several years in real life clinical practice. Janssen	Comments noted. Please see sections 4.7, 4.10–4.14 of the FAD.

Consultee	Comment [sic]	Response
	asserts that these data support our choice of extrapolation, and provide clinical plausibility to the modelled results. [Appendices provided but not reproduced here.]	
Janssen	**4. End of life (EoL) criteria** Whilst we recognise that the Committee has determined that abiraterone in the pre-chemotherapy setting does not meet the life expectancy criterion of the EoL criteria, we wish to refer to the following quote taken from the current ACD: "The Committee agreed that treatment switching and subsequent treatments that are not available in the NHS probably extended survival in both groups of COU-AA-302, but the effect was probably greater for the placebo group because more people took these treatments" [para 4.7]. This lends credence to our contention that the control arm of the trial does not in fact reflect the true life expectancy of patients in UK clinical practice and has been associated with better results than patients would normally experience in normal clinical practice (conservative approach). COU-AA-302 was an international study, and patients in the trial had significant exposure to other novel medications after the point of disease progression, which are not routinely available in the UK, and which would have the effect of extending survival over that which would be observed in usual practice (Table 5). Some of these medications, such as sipuleucel-T, cabazitaxel, ketoconazole and retreatment with abiraterone are not currently recommended by NICE and therefore do not align with current clinical practice in England and Wales. Of note, a higher proportion of patients received subsequent therapies in the control arm than in the abiraterone arm. [Table provided but not reproduced here.]	Comments noted. Please see section 4.23 to 4.26 of the FAD.
Janssen	**5. Conclusion** In this current appraisal in the pre-chemotherapy setting, the Committee made an initial decision to reject abiraterone, and Janssen has been responsive and offered a new PAS that increases the cost-effectiveness of the drug. Importantly, the new PAS is specifically designed to address the Committee's main identified area of uncertainty of long-term time on treatment and survival benefit. We strongly believe that the balance of evidence demonstrates that under the conditions of the PAS, abiraterone in the pre-chemotherapy setting is a cost-effective use of NHS resources. As demonstrated in Section 2.10, many of the Committee's key concerns and preferred assumptions have little impact the ICER. Moreover, the Committee's main concern regarding our choice of parametric extrapolation is significantly reduced by our supportive real-world data from the US and the UK, and hence Janssen believes that the Committee can be reassured that the ICER is below £30k. If the Committee grants a positive recommendation to abiraterone in the current appraisal, the question	Comments noted. The final appraisal determination (FAD) recommends abiraterone within its marketing authorisation (see section 1 of the FAD).

Consultee	Comment [sic]	Response
	regarding long term uncertainty in modelled treatment duration can in fact be answered. The Janssen portal associated with the complex PAS, which will become operational once positive NICE guidance is granted, will allow the NHS to track treatment duration, as it is based upon the Blueteq system already in place to monitor PbR excluded drugs. **Through this PAS portal, regular reports can be provided to NHS England and NICE to monitor the duration of treatment in real clinical practice, providing data for any future guidance review of abiraterone in this specific indication. This would allow the data to mature, and for the Committee to assess the accuracy of our modelled economic evaluation during the normal 3-year review associated with NICE guidance.** Janssen remain committed to finding a way forward that results in the routine commissioning of abiraterone in this earlier setting, as we have heard from the patient and clinical community that men with mCRPC would strongly benefit from delaying chemotherapy. This is particularly important given that enzalutamide has recently received a positive recommendation from NICE, and as sequential use of the two treatments is not permitted in the NHS, it is unlikely that patients will be offered abiraterone after chemotherapy if they have received enzalutamide in the pre-chemotherapy setting. From our extensive discussions with clinicians we note that they feel it is essential to have both treatments routinely available, as they recognise clear differences between the treatments due to their differing modes of action. Allowing both treatments to be available would permit clinicians to select the best option on an individual patient basis, depending upon individual patient characteristics. This need for choice can be observed by the continuing high numbers of requests for both agents through the CDF.	
Tackle Prostate Cancer	Tackle Prostate Cancer is dismayed and surprised that NICE has not recommended abiraterone for use in chemotherapy naive patients. This is despite the fact that the manufacturer has offered to pay for the treatment for anybody who is continuing to benefit from the medicine for longer than 10 months. Abiraterone has already proved to be an excellent treatment for metastatic hormone relapsed prostate cancer in the post chemotherapy setting and trials show it is even more effective when given pre-chemotherapy. It is important that clinicians and patients are given a choice of treatments when there are so few options available. We urge the Panel to look at this recommendation again, taking into account all of the relevant facts.	Comments noted. The FAD (section 1) recommends abiraterone within its marketing authorisation.
British Uro-oncology Group (BUG)	Men with metastatic Castration Resistant Prostate Cancer (mCRPC), whose disease is asymptomatic or mildly symptomatic, and for whom chemotherapy may not be immediately appropriate or necessary, have limited treatment options. The British Uro-oncology Group (BUG) fails to understand NICE's preliminary recommendation that: *1.1 Abiraterone is not recommended for treating metastatic hormone relapsed prostate cancer in people who have no or mild symptoms after androgen deprivation therapy has failed and in whom chemotherapy is not yet clinically indicated.*	Comments noted. The FAD (section 1) recommends abiraterone within its marketing authorisation.

Consultee	Comment [sic]	Response
	BUG strongly urges NICE to re-consider its ACD recommendation on the basis that abiraterone in the pre-chemotherapy setting has the potential to prolong survival, palliate symptoms, and improve quality of life for men suffering from prostate cancer. The importance of abiraterone in daily clinical practice has been demonstrated by the number of applications by oncologists to the Cancer Drugs Fund (CDF). As experts in their field, oncologists recognise that there are patients who will respond very well to either abiraterone or enzalutamide so it is important to have both these treatment options available for men with asymptomatic or minimally symptomatic mCRPC who are chemotherapy naïve. Some men with a history of seizures or neurological disorders would be unsuitable for treatment with enzalutamide and it would be vital for them to have the opportunity to benefit from abiraterone. Individual discussions with patients and their choices must be taken into account with regard to the different toxicities of therapy. These choices and discussions are apparent when prescribing from the CDF. Oncologists should be able to prescribe either enzalutamide or abiraterone having evaluated the individual's circumstances and co-morbidities. Prostate cancer treatment should be individualised to the patient with the best choice of treatment based on evidence, patient characteristics and specific tumour and cancer response data; there can be no one size fits all approach without patient harm. The treatment decision for each individual man needs to be made on the basis of both potential side-effects and existing co-morbidities. In summary, abiraterone demonstrates excellent efficacy and tolerability with meaningful endpoints and maintenance of QOL for men with mCRPC. The British Uro-oncology Group requests a positive NICE appraisal allowing the prescribing of abiraterone in chemotherapy naive patients. The addition of abiraterone as an option alongside enzaluatamide provides meaningful clinical benefit to men with metastatic castration resistant prostate cancer.	Comments noted. See section 4.1 of the FAD.
Royal College of Physicians (RCP)	Overall, we believe that all the relevant evidence has been taken into account, and the summaries seem reasonable interpretations of the evidence. However, our experts believe that the decision will likely have a detrimental impact on patients, most particularly those who would not normally receive docetaxel. It is thought that up to half of Castration Resistant Prostate Cancer (CRPC) patients in the UK never get docetaxel. Until now they have been able to access abiraterone via the CDF. We believe that to deny these patients access to abiraterone, unless they have docetaxel first, is most regrettable. Further to this, if a similar decision is made for enzalutamide it may have the unintended consequence of massively increasing the use of docetaxel (in order to get subsequent access to abiraterone or enzalutamide). This would place increased pressure on the capacity to deliver chemotherapy for all	Comments noted. See sections 4.1 and 4.4 of the FAD.

Consultee	Comment [sic]	Response
	cancers.	
Department of Health	No comments.	Comment noted.

No comments were received from clinical experts and patient experts.

Comments received from commentators

Commentator	Comment [sic]	Response
Institute of Cancer Research (ICR)	Abiraterone was discovered by the ICR, in what is now the Cancer Research UK Cancer Therapeutics Unit, and the ICR and The Royal Marsden carried out initial clinical development on the drug, as well as leading the UK arms of later-stage international clinical trials. ICR researchers have been treating patients with abiraterone for more than 10 years. Abiraterone is now used as standard treatment after chemotherapy and has extended the lives of thousands of men in the UK with advanced prostate cancer. We are very disappointed that NICE did not recommend use of abiraterone for men with prostate cancer who are yet to receive chemotherapy in draft recommendations in this second ACD. We understand that the manufacturer has discounted the costs of abiraterone, and we believe that it is crucial that the DH, NICE and the manufacturer continue to work together to ensure that this drug is made available and that more patients can benefit from it.	Comments noted. The FAD (section 1) recommends abiraterone within its marketing authorisation.

Commentator	Comment [sic]	Response
Institute of Cancer Research	**Cost-effectiveness** The Committee concluded that the incremental cost-effectiveness ratio (ICER) for use of abiraterone before chemotherapy was likely to be above the range normally considered a cost-effective use of NHS resources, calculated to lie between £35,500 and £59,600 per quality-adjusted life year (QALY) gained. The reason given for the large range in the potential cost-effectiveness was uncertainty in overall survival and how long people would receive abiraterone. We believe the evidence is clear that abiraterone is effective when given before chemotherapy and can give men many extra months free of disease. We felt it was important to respond to questions raised by the committee about overall survival and the length of time that patients receive abiraterone. The committee and the evidence review groups discussed the company's modelling, particularly the distributions used for extrapolating to long-term survival. The committee noted that the log-logistic curve used in the modelling predicted that some patients would remain on abiraterone for a long time, with some taking abiraterone for eight years. The committee felt that there wasn't data to support this extrapolation because the maximum follow-up time of the trial was about five years. It felt that the final data did not support use of this distribution for predicting time on treatment. At the ICR, we would not claim to be experts in economic modelling and we cannot comment on the appropriateness of the extrapolation methods used by the company. However, ICR staff have great experience of treating patients with abiraterone and have treated a patient with abiraterone for more than eight years.	Comments noted.
Institute of Cancer Research	**Innovation** The committee considered that abiraterone is innovative compared with best supportive care because it was the first active treatment available for this position in the treatment pathway. We think it is important to point out that abiraterone is also innovative in that it was a drug acting on a novel target with a completely new mechanism of action. It is very important that NICE recognises the degree of innovation in the drugs it assesses, and takes this into account in making its judgements. It is much riskier and more expensive to produce drugs with novel mechanisms of action than to produce improved versions of what has come before. If NICE does not give innovation due recognition, there will be no incentive for companies or research institutes to create genuinely new and innovative treatments.	Comments noted. Please see section 4.27 of the FAD.

Commentator	Comment [sic]	Response
Institute of Cancer Research	**Benefit in delaying chemotherapy** We are very disappointed that abiraterone was not recommended in the ACD for men with prostate cancer who are yet to receive chemotherapy. This decision would deny many thousands of men the opportunity to access this drug earlier in their course of treatment, as well as some men who may never qualify for treatment with abiraterone as they are not in the position to receive chemotherapy as they might not be fit enough or might be too old. We understand – although are disappointed by – the decision taken by NICE to not apply end-of-life criteria in this case, even though they were applied in assessing abiraterone post chemotherapy. However, we would ask NICE to consider whether end-of-life criteria could be applied in the specific subset of men who are too frail to receive chemotherapy and for whom treatment options are therefore currently limited. These men would be expected to have significantly shorter survival than men with equivalent disease who are able to go on to receive further treatment.	Comment noted. Please see section 4.4 of the FAD.
Institute of Cancer Research	**Inequality across the UK** Since the last draft recommendation from NICE, abiraterone has been made available on the NHS in Scotland for men with advanced prostate cancer before treatment with chemotherapy, following a decision from the Scottish Medicines Consortium. It is very disappointing that men in England and Wales will not be able to access the treatment – even though in Scotland it has been made available on the NHS. We want to see NICE follow the lead of Scotland so that this highly innovative drug can be made available for all men with prostate cancer in every part of the UK.	Comment noted. The FAD (section 1) recommends abiraterone within its marketing authorisation.

Comments received from members of the public

Role*	Section	Comment [sic]	Response
Patient	General	NICE is provisionally recommending that Abiraterone is not recommended for treating metastatic hormone relapsed prostate cancer in people who have no or mild symptoms after androgen deprivation therapy has failed and in whom chemotherapy is not yet clinically indicated. I would like to submit that NICE should change this recommendation, as many studies have shown that continued treatment with Abiraterone can	Comment noted. The FAD (section 1) recommends abiraterone within its marketing authorisation.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment [sic]	Response
		have significant benefits for men with prostate cancer in this situation. This is born out by several studies and is supported by medical practitioners in my area ([redacted]). The proposed cost saving measure will have a damaging impact on many men's quality of life.	
Carer	General	Please keep abiteraone pre-chemotherapy its a very important and necessary drug for treatment of prostate cancer (my father is a prostate cancer patient)	Comment noted. The FAD (section 1) recommends abiraterone within its marketing authorisation.
Patient	General	As a Prostate cancer patient I feel the need to give any man with the disease all and any treatments that may help them with their plight, regardless of cost. I therefore strongly feel that the proposal to attempt the use of the treatment in the future to be wrong.	Comment noted. The FAD (section 1) recommends abiraterone within its marketing authorisation.
Patient	General	"There are a number of issues which occur to me, having read the report about the proposal to limit if not remove abiraterone from the approved list of treatments for metastatic prostate cancer. 1, The report seems to confine itself to the late stages of cancer development before the issue of abiraterone to the patient rather than when there are other early indications of the presence of metastatic cancer. The accepted wisdom is that treatment of cancer is most effective if the treatment starts early yet I can't seem to find any suggestions that abiraterone should be used in this way. The only reference to long term use is 4% who were on it for eight years (paragraph 4.12)which to me shows its effectiveness in extending life."	The committee discussed the effectiveness of abiraterone within its licensed indication. That is, for treating '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'. The committee did not discuss the use of abiraterone at other stages of the treatment pathway, because that is beyond the remit of the appraisal.

Role*	Section	Comment [sic]	Response
		2. In proposing the withdrawal of abiraterone important matters are called into question. The human body as not a mechanical machine which responds in a predictable manner but can respond in unpredictable ways such as the patient suffering unacceptable side effects or not responding as anticipated. Allowing for that eventuality the clinicians must be allowed as many treatment options as possible which must include abiraterone The report acknowledges the effectiveness of abiraterone so why is there consideration to remove it from treatment options? As far as I can see, there is an unsubstantiated assumption that enzalutamide and abiraterone are equivalent. As noted above, the human body does not necessarily respond as hoped to a given treatment. I am sure that if medical records are examined there will be patients who are intolerant of one or the other making this assumption of equivalence a nonsense. As a person with metastatic prostate cancer I am aware from conversations with fellow sufferers that in some cases, this is true. At 546/542 patient numbers in some of the tables, I am curious as to the statistical significance of these numbers in terms of accuracy of interpretation of results. Considering the number of patients suffering from prostate cancer, I should have thought that there would be many more than this from which to obtain data to make the interpretation of that data more certain and believable(I am not saying that the report conclusions are inaccurate as such just that data from a larger population would give greater confidence).	The committee was aware that it is important to patients and clinicians to have a choice of treatments (please see section 4.1 of the FAD). The committee assessed abiraterone compared with best supportive care (section 4.2 of the FAD). Abiraterone was not compared with enzalutamide. Having considered the evidence carefully, the committee decided to recommend abiraterone within its marketing authorisation (section 1 of the FAD).

Role*	Section	Comment [sic]	Response
		3. Paragraphs 3.5 - 3.7 and other parts of the report indicate as far as I can see, the effectiveness of treatment with abiraterone which to me counters the decision in the introduction that abiraterone is not to be recommended for the treatment of metastatic hormone relapsed prostate cancer.	The committee agreed that abiraterone was clinically effective (see section 4.7 of the FAD).
		It seems to me as a patient that abiraterone should be given when symptoms of cancer are still mild, minimising the spreading(paragaph 4.6) and reducing the existing sites before chemotherapy is considered necessary. Perceived wisdom as noted above is to treat cancer early to ensure the best outcome of a longer life for the patient. Paragraph 4.26 hints at the benefit of abiraterone before a delayed treatment with chemotherapy but this had not been included in the modelling yet would not have lowered the ICER for abiraterone. If this had not been modelled and studied, how can the committee reach this sort of conclusion?	The economic model predicted that people treated with abiraterone would have more time with a higher quality of life before having chemotherapy than people treated with best supportive care. Thus, this benefit was at least partly captured by the model. However, the committee heard from patients that delaying chemotherapy was very important to them, and the committee agreed that the full benefit of delaying chemotherapy may not have been fully captured by the model. Please see section 4.7 of the FAD.
		The assessment process has not included this option of early administration of abiraterone. To me this is a serious weakness in the overall process and casts serious doubt on the conclusion not to support abiraterone.	
		I further suggest that this will probable reduce the dose of chemotherapy drugs(post abiraterone) with a resultant saving of cost to the NHS by offsetting the cost of abiraterone as well as reducing the severity of chemotherapy side effects for the patient.	The committee was not presented with evidence that treatment with abiraterone reduces the subsequent dose of chemotherapy.
		The benefit of chemotherapy before abiraterone is not explained so presumably has not been properly investigated.	NICE technology appraisal 259 recommends abiraterone as an option for treating prostate cancer that has progressed on or after chemotherapy.
		4. Section 4.3 'the Committee concluded that there is some uncertainty about the benefits or consequences of delaying chemotherapy but accepted the view of patients that delaying chemotherapy is of value to them' - why was this not thoroughly investigated and assessed before reaching a decision?	The committee was aware of differing views about the benefits and potential disadvantages of delaying chemotherapy (see FAD section 4.3). It was not presented with evidence from clinical trials about the advantages and disadvantages of having chemotherapy earlier or later in the treatment pathway.
		Section 4.7 last paragraph 'Overall the Committee concluded that abiraterone delayed disease progression and improved overall survival	There are often uncertainties about the clinical or cost effectiveness of treatments being appraised by

Role*	Section	Comment [sic]	Response
		compared with placebo but there was uncertainty about the extent of the survival benefit' - Would it not be wise to clarify the extent of the survival benefit before denying patients the use of abiraterone? I find aspects of this report confusing if not conflicting. In Section 4.13 test results are mentioned which refer to treatment switching to drugs not available on the NHS. Why is this data included it simply confuses the decision making process and contributes nothing? That the company amend the data in 4.14 is not helpful and begs the question why did they include it in the first place? Why do the committee accept that it is appropriate to include drugs which have a survival benefit but are not available on the NHS? Does this mean they will consider making them available on the NHS?	NICE. Nonetheless, the committee has to decide whether or not to recommend the treatment for routine use in the NHS, based on the current evidence. Often, in clinical trials, patients have treatments that are not part of established NHS care. Sometimes these treatments are known to prolong life. It is common to adjust the survival times in an economic model, to remove the benefit of those treatments that are not available in the NHS. See section 4.15 of the FAD. This appraisal looked at abiraterone only.

Response to the Appraisal Consultation Document (ACD)

Abiraterone for metastatic hormone-relapsed prostate cancer not previously treated with chemotherapy [ID503]

January 2016

Table of contents

1. Overview

Janssen is extremely disappointed that the Appraisal Committee's preliminary decision is to not recommend abiraterone for patients with metastatic hormone-relapsed prostate cancer not previously treated with chemotherapy. We remain committed, however, to continue working with NICE in order to address the Committee's key concerns outlined in the ACD. This appraisal was scoped in by NICE in 2011, and Janssen has worked collaboratively with both NICE and NHS England to ensure funding for abiraterone has been maintained throughout this period, given the important clinical need in advanced prostate cancer. Abiraterone for use prior to chemotherapy is routinely available and funded in 61 countries around the world, including Scotland. It has been available on the Cancer Drugs Fund (CDF) since January 2013, and has been the second most requested drug on the fund[1]. Thus, there is a clear clinical demand for the drug, and it has become the standard of care in many countries. Janssen urges the Committee to take this into account when reconsidering its recommendation at the forthcoming Appraisal Committee meeting.

Our response addresses the following key issues:

- **Appraisal Committee's preferred assumptions in the economic model**
- **Survival benefit associated with abiraterone**
- **End of life criterion for life expectancy**

We believe this response document addresses the key concerns raised in the ACD, and provides the necessary information for the Committee to be able to reach a positive decision.

[1] National Audit Office. Investigation into the Cancer Drug Fund. 17 September 2015. Available online: https://www.nao.org.uk/report/investigation-into-the-cancer-drugs-fund/#

2. Appraisal Committee preferred assumptions in the economic model

Janssen appreciates the Committee had concerns with the design of the economic model, and has expressed a preference for assumptions that differ to that included in our submission. We have addressed each key concern in turn, and have also presented the cost-effectiveness results using the Committee's preferred assumptions.

2.1 Choice of covariates included in the prediction equations

"…for each of the model's 17 equations predicting time to events, the Committee noted that the company made a large number of judgements when determining which covariates to include in the prediction equations and which parametric distributions to choose for extrapolation. The Committee concluded that the company had not fully justified the approach it used for choosing the different covariates to include in each prediction equation" [para. 4.8].

"The ERG stated that its preferred base case would: […] derive prediction equations for time to stopping treatment, time to starting treatment and time to death from the full ITT population in COU-AA-302, accounting for treatment effect only, and not including other risk predictors based on baseline characteristics […]" [para. 3.27]

Janssen contends that we did not make a large number of judgements when determining which covariates to include in the prediction equations. Rather, the economic model was powered by prediction equations that included all predictors that met significance criteria per a systematic and pre-specified analysis plan. The two exceptions were, however, clinically and statistically justified and had little impact on the ICER (see Appendix 1 for details).

Moreover, using treatment as the only predictor, as suggested by the ERG to better capture the ITT patients, is wholly inappropriate, as it does not reflect how clinical decisions are made. Using treatment as the only predictor necessitates that different stages of disease are completely independent from each other, which not only lacks clinical and face validity but also results in a significant underestimate of the predicted OS associated with AAP treatment compared with the COU-AA-302 trial final data cut OS KM curve (see Figures 1 and 2). Predicted OS (Figure 2), where time to each event is dependent upon a unique set of patient characteristics, better replicates the trial dataset when compared to the ERG-proposed base case (see Figure 1). In particular, the AAP arm under the ERG-proposed base case deviates from the KM final data, whilst the company base case is a close fit.

Figure 1. Comparison of Final ITT OS vs ERG Base Case Prediction Based on 55% Data Cut

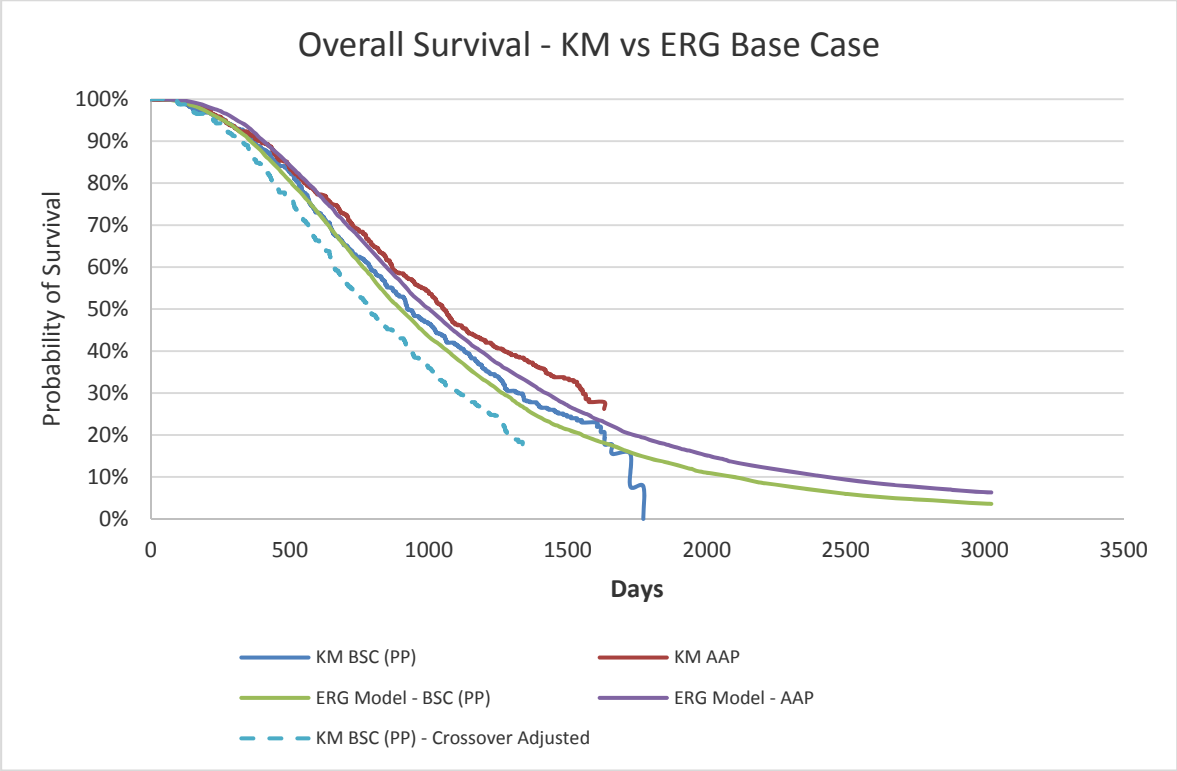
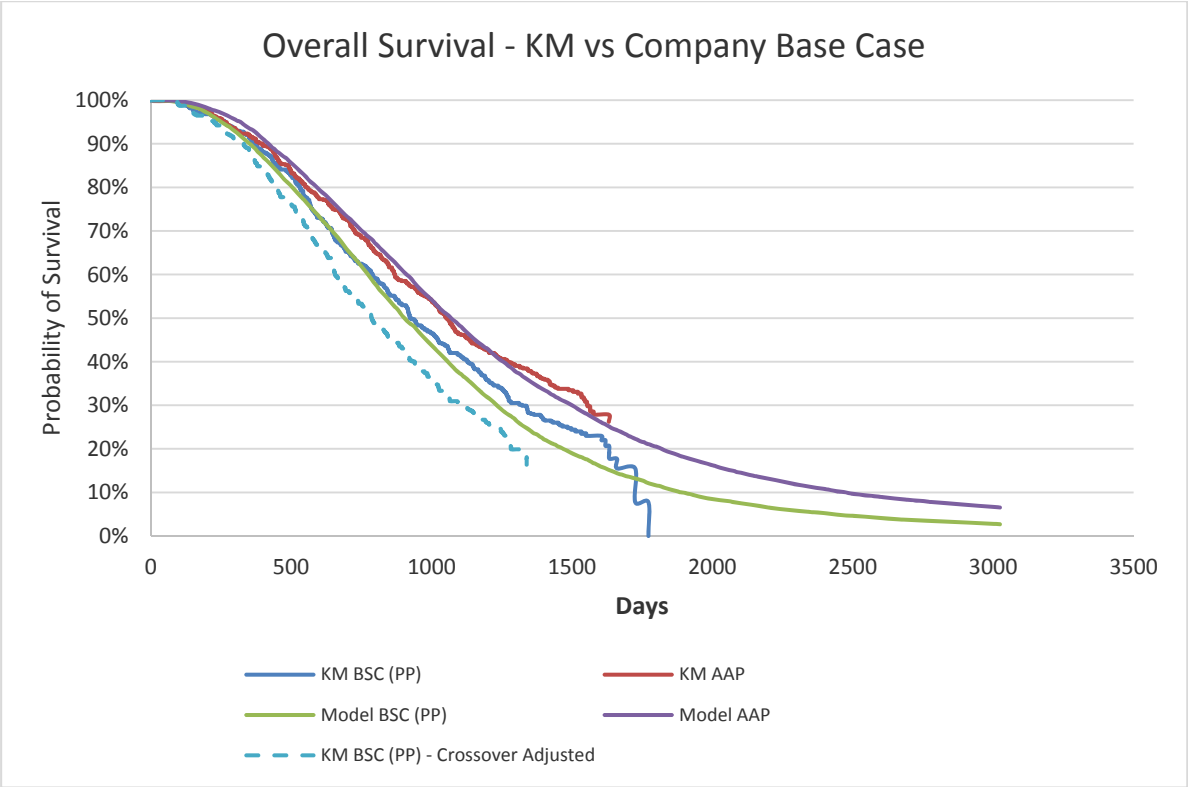


Figure 2. Comparison of Final ITT OS vs Company Base Case Prediction Based on 55% Data



2.2. Impact of cross-over and subsequent therapies on BSC arm

" The Committee agreed that treatment switching and subsequent treatments that are not available in the NHS probably extended survival in both groups of COU-AA-302, but the effect was probably greater for the placebo group because more people took these treatments." [para. 4.7.]

In COU-AA-302, 93 (17%) patients in the PP arm were allowed to cross-over and receive abiraterone prior to docetaxel. Furthermore, seventy-nine percent of PP patients received active treatments including AAP (43%), sipuleucel-T (5.9%), cabazitaxel (19%) and enzalutamide (10%) post-docetaxel in the final dataset. Unlike the trial, the model pathways for the BSC (PP) arm do not allow use of abiraterone until after the post-docetaxel phase to reflect current treatment in the UK. Model predictions, therefore, must adjust for these cross-over differences. Figures 1 and 2 above also show the OS curve of the BSC arm adjusted for cross-over (0.74 as specified in the ACD versus 0.81 for the unadjusted HR), and demonstrates that our projection is reasonable and may even overestimate the BSC arm. The ERG-proposed base case also overestimates the BSC survival, since the OS KM data contains cross-over and subsequent treatments. This point is further addressed under Section 2.3.

2.3 Fit of the best supportive care arm to the final trial data

"For the best supportive care arm, the Committee was concerned that neither parametric distribution provided a good fit to the final trial data. It noted that both distributions overestimated the time that patients would remain on best supportive care" [para 4.12]

Janssen strongly believes it is important to differentiate between uncertainty that can and can never be addressed. The modelled extrapolation associated with the best supportive care arm is an example of uncertainty that can never be fully addressed. Given that the COU-AA-302 trial studied patients with metastatic cancer, once a 'highly significant benefit' was observed, the Independent Data Monitoring Committee (IDMC) advised that the trial be unblinded to allow patients in the control arm to receive treatment with abiraterone. This is a common occurrence in oncology trials for ethical reasons. Given the subsequent cross-over and high number of subsequent treatments that patients were allowed to receive after their trial treatment, it is not a surprise that neither parametric distribution provides a good fit to the final trial data, and that both distributions overestimate the time on best supportive care, thus favouring the BSC arm of the model (conservative approach). Janssen urges the Committee to factor this into account, and consider that the modelled extrapolations do in fact provide a good fit to the abiraterone arm, which is the uncertainty that can be, and has been, addressed.

2.4 Choice of parametric distribution

"Having considered the evidence carefully, the Committee did not agree with the company's statement that the final data supported the company's choice of a log-logistic distribution for predicting time on first treatment. The Committee could not choose a preferred parametric distribution for predicting time on first treatment because no data were available to validate predictions beyond about 5 years. Accordingly, it considered both the log-logistic curve and the Weibull curve in its decision-making" [para. 4.12]

"The Committee, noting NICE's Guide to the methods of technology appraisal 2013, concluded that it was appropriate to explore the impact of using different parametric distributions on the model results." [para. 4.12]

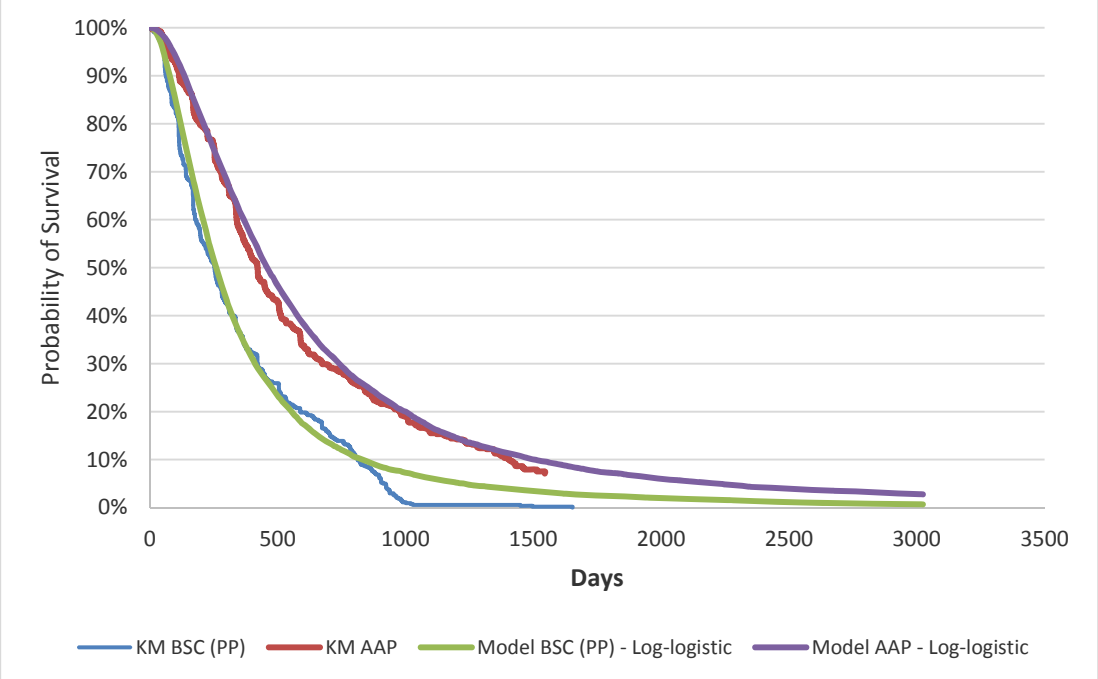
As the final dataset from the COU-AA-302 trial provides longer follow up and captures more death events than the 55% data cut, there is less uncertainty around the long-term projection associated

with the final data cut. In this context, statistical analyses were performed on the COU-AA-302 trial 55% data cut to check the best fit distribution for predicting time to AAP/BSC (PP) treatment discontinuation. Standard procedures were employed to derive the prediction equation, and the log-logistic distribution had the best statistical fit based upon both AIC/BIC criteria and visual inspection. The best statistical fit for characterizing time to AAP/BSC (PP) treatment discontinuation was further verified using the COU-AA-302 trial final data cut. The 55% data cut was used to inform the analyses as it needed less adjustment for patients who crossed over from the placebo arm to AAP, and gives OS estimates in line with the final trial data.

Similarly, the log-based model provided the best fit for predicting time to treatment discontinuation (see Appendix 1 for details) and was therefore used in the model. This approach is further supported by several publications that advocate the use of log models in order to provide a better fit to data than a Weibull model in these cases[2].

Figure 3 below compares the final KM data to predicted time to discontinuation informed by a log-logistic model showing a good fit of the modeled time to discontinuation curves to the KM curves for the AAP arm, and a slight over-estimation of trial KM curve for the BSC arm, therefore disadvantaging AAP (a conservative approach). Similarly, when OS is extrapolated using the log-logistic function, the modeled OS curve is also a close match to the observed KM trial curves, as shown in Figure 2 above.

Figure 3. Time to Discontinuation Informed by a Log-logistic Model



[2] Ishak KJ, Kreif N, Benedict A, Muszbek N. Overview of parametric survival analysis for health-economic applications. *PharmacoEconomics* (2013 Aug) 31(8): 663-675.

Muszbek N, Kreif N, Valderrama A, Agnes B, Ishak J, Ross P (2012) Modeling survival in hepatocellular carcinoma. Curr Med Res Opin 28(7): 1141-1153.

Joulain F, Proskorovsky I, Allegra C, Tabernero J, Hoyle M, Iqbal SU, Van Cutsem E. Mean overall survival gain with afibercept plus FOLFIRI vs placebo plus FOLFIRI in patients with previously treated metastatic colorectal cancer. British Journal of Cancer (2013) 109, 1735–1743.

Notwithstanding the above, given the Committee's concerns surrounding the long-term plausibility of the log-logistic distribution as well as for the Weibull extrapolation (preferred by the ERG), additional sensitivity analyses have been conducted in which a combined two-part model (log-logistic+Weibull) is applied to inform treatment duration. Under this scenario, time is estimated based upon the best-fit log-logistic function up to the point of extrapolations (approximately 2.5 years) outside of the COU-AA-302 trial. After this point, time to AAP treatment end is estimated following a Weibull function. Patients on BSC (PP) are assumed to discontinue treatment after 2.5 years (approximately 1000 days), based upon observations from the COU-AA-302 final data cut.

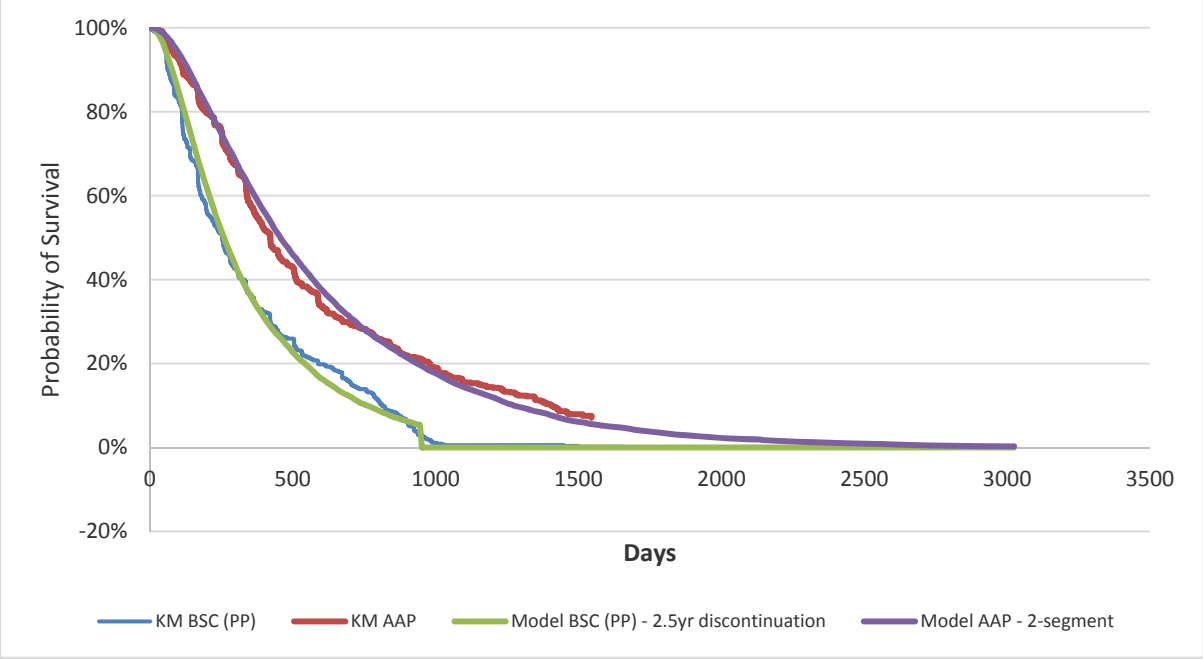
As shown in Figure 4 below, predicted AAP (using a log-logistic function to capture time on AAP until follow-up in the trial and then a Weibull function to capture the remaining treatment duration) and BSC (PP) (all patients discontinue by 2.5 years) treatment duration is a close match to the COU-AA-302 trial final KM data (see Figure 4 below). A slightly increased ICER of £32,849 is estimated under this scenario analysis compared to a base case ICER of £28,563 (see Table 1 below).

Table 1. Alternative Scenario: Time to Discontinuation Using 2-part Model (Log-logistic+Weibull)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	15,855	0.54	0.48	32,849

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

Figure 4. Treatment Duration – Final Data Cut KM vs. Model Predictions (using Log-logistic+Weibull)



2.5 Intention-to-treat (ITT) population

"The Committee concluded that the ITT population represented all patients, was less likely to bias the results, and provided more data, and, for these reasons, preferred it" [para 4.15]

Use of COU-AA-302 Patient Level Data

In order to clarify how the ITT population was employed in the model, we provide a complete explanation below. It appears that the Committee has concluded that only a subset of 902 patients are included in the model, as opposed to the entire trial population, and this is fundamentally not the case – data from all patients are utilised in the model at appropriate times.

The COU-AA-302 patient level data are used to inform the model in two key ways:

- To create the prediction equations that power the model.
- To create the patient profiles that are then run through the prediction equations in the model to generate results.

Prediction equations

The COU-AA-302 trial enrolled 1088 patients (546 treated on AAP and 542 treated on BSC (PP)). Prediction equations for each treatment phase were derived using all patients with non-missing values for covariates that were statistically significant and included in the final multivariate equation. The number of patients contributing to each equation depended on which characteristics or predictors were retained in the final regression model and the patients with follow-up data to contribute to informing the time to event equation. At each phase of treatment, data on certain covariates was missing for a small number of patients. Ultimately, the prediction equations were derived based on all patients with non-missing data (i.e. for whom data on all significant covariates included in particular equation were available). In the first equation (i.e. equation for the time to first treatment discontinuation that included the largest most inclusive number of significant predictors), 902 of the 1088 had non-missing values for important predictors. However, it is not simply the data from these 902 patients that continues to only be used throughout the remaining phases of the model. The number of patients informing equations varied as time progressed, which would be the case even for a Markov approach (i.e. fewer patients experiences the more downstream events). Because the covariates that were found to be significant were slightly different at each stage of treatment, a patient who did not contribute data for one prediction equation due to missing data may contribute data to a later stage of treatment for which different covariates were required. For example, if baseline ECOG was missing for a patient, then this patient **wasn't** included for derivation of time to first treatment discontinuation, but **was** included for deriving the equation for the time to death after AA/Placebo treatment discontinuation, since ECOG at baseline was not predictor that was considered for the time to death after AA/Placebo treatment discontinuation equation. In other words, the inclusion of patient information did not function as a funnel, excluding more and more patients at each subsequent stage of treatment; rather, patient information from the entire ITT trial population was included at relevant phases of the model.

Consequently, Janssen maintains that our base case assumption in which prediction equations are based on all patients with non-missing values better replicates trial OS for the ITT population compared to the ERG recommended base case (see Figure 2 vs Figure 1).

Patient Profiles

The 902 patients ("analysable") with non-missing data for the first equation are also used for the individual patient profiles used in the simulation model. Using actual patient profiles takes into account the natural correlation between the various variables. To allow profiles to be sampled directly from actual patient data, a dataset was constructed including the necessary variables and

transferred into a format usable by the simulation model. A total of 186 patients (87 for AAP and 99 for BSC (PP)) were excluded due to missing baseline data that were used as predictors (e.g. BPI). The 902 patient profiles were cloned and each run through the model which is equivalent to a perfect randomization.

Notwithstanding this, given the Committee's concerns surrounding our approach to the analysable population, we have run an analysis using the entire ITT population at the start of the model, by filling in missing predictor variable values with the population mean. In the analysis, the company base case ICER of £28,563 becomes £28,240 (See Table 2 below), a minimal decrease.

Table 2. Alternative Scenario: ITT population using mean population value to replace missing predictors

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	15,943	0.57	0.56	28,240

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Comparison of the analysable versus the ITT population

As Table 3 below shows, the characteristics of the analysable dataset versus the ITT population are very similar. The p-values comparing the analysable population versus the ITT population demonstrate a lack of statistically significant difference. In addition, a logrank test was conducted to compare the time to treatment discontinuation (TTD) for the ITT population and analysed patients. The p-value is 0.7481 for the AAP group and 0.7745 for the BSC (PP) group, indicating that there is no statistically significant difference in terms of TTD between the ITT population and analysed patients. A similar analysis was conduct for OS and no statistically significant difference was identified (p-value of 0.3117 for the AAP group and 0.6328 for the BSC (PP) group).

By visually inspecting these graphs, the OS KM curves are identical (See Figure 5 and Figure 7 below), and analysed patients who were treated with AAP had slightly longer TTD (but not statistically significant) as presented in Figure 6 and Figure 8 below, which implies that results of the model are conservative given that treatment duration is slightly longer. This contributes to a slightly higher drug cost for the modelled population vs the ITT population. Janssen therefore maintains that the 'analysable' population is the most appropriate population upon which to model, and suggests that there appears to be a fundamental misunderstanding in terms of how the model population compares to the ITT population.

Table 3. Patient Characteristics of Analysable Data vs. ITT Population

	ITT population		Analysed population		
Characteristic	AAP (N=546)	PP (N=542)	AAP (N=459)	PP (N=443)	p-value
Age, years, median	71	70	70	70	0.9298
<65	24.7%	28.6%	25.3%	26.9%	
65-69	20.5%	19.0%	21.4%	20.5%	
70-74	20.9%	22.0%	20.9%	21.3%	
≥75	33.9%	30.4%	32.5%	31.7%	
Male, %	100	100	100	100	
Race, %					
White	95.4	94.4	95.4	94.6	0.9963
Black	2.8	2.4	2.6	2.5	
Asian	0.7	1.7	0.9	1.6	
Native Hawaiian /	0	0.4	0.0	0.2	

Characteristic	ITT population		Analysed population		
	AAP (N=546)	PP (N=542)	AAP (N=459)	PP (N=443)	p-value
Other					
Pacific Islander					
Other	1.1	1.1	1.1	1.1	
Ethnicity, %					
Hispanic or Latino	4.6	4.5	3.7	4.8	0.7508
Not Hispanic or Latino	95.4	95.5	96.3	95.2	
Weight (kg), median	87.0	88.0	87.0	87.9	0.9612
Height (cm), median	175.0	175.3	175.0	176.0	0.6950
Mean time from diagnosis to first dose, years	6.7	6.5	6.79	6.5	0.7442
Alkaline phosphatase, IU/L, median	93	90	93	90	0.8768
Haemoglobin, g/dL, median)	13	13.1	13	13.1	0.7163
Lactate dehydrogenase, IU/L, median	187	184	187	183	0.9568
Baseline serum PSA, ng/mL					
Median	42	37.7	40.48	37.82	0.9804
Range	0 – 3,927	1 – 6,606	0.04 – 3927.43	.7 – 6606.44	
Baseline BPI score, %					
0–1	74.15	70.18	74.07	69.75	0.9127
2–3	25.85	29.82	25.93	30.25	
Bone-only metastasis, %	50.4	49.3	51.85	50.11	0.5716

Figure 5: Comparison of Analysed Patients vs. ITT Population: OS, AAP Arm

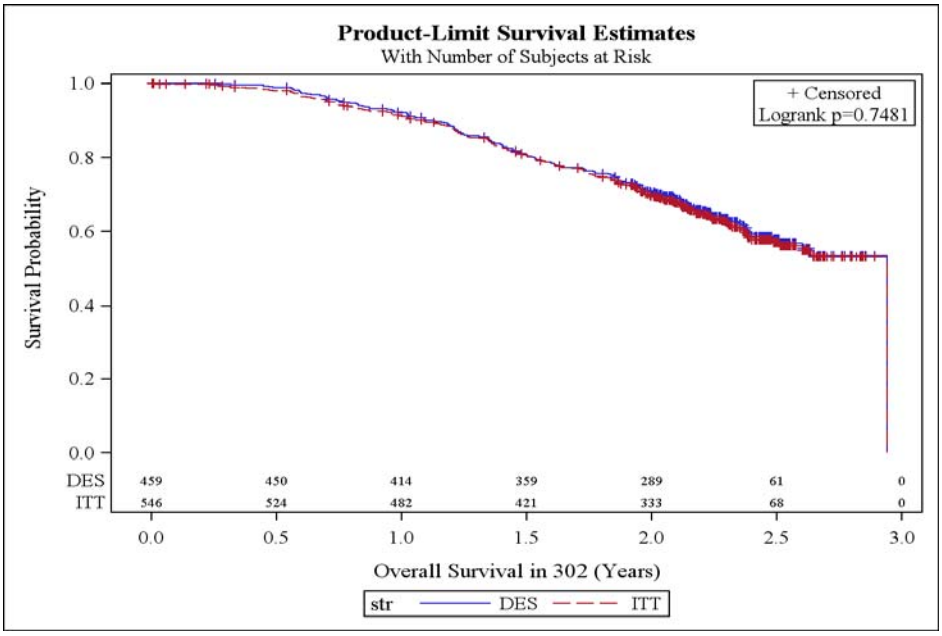


Figure 6: Comparison of Analysed patients vs. ITT Population: TTD, AAP Arm

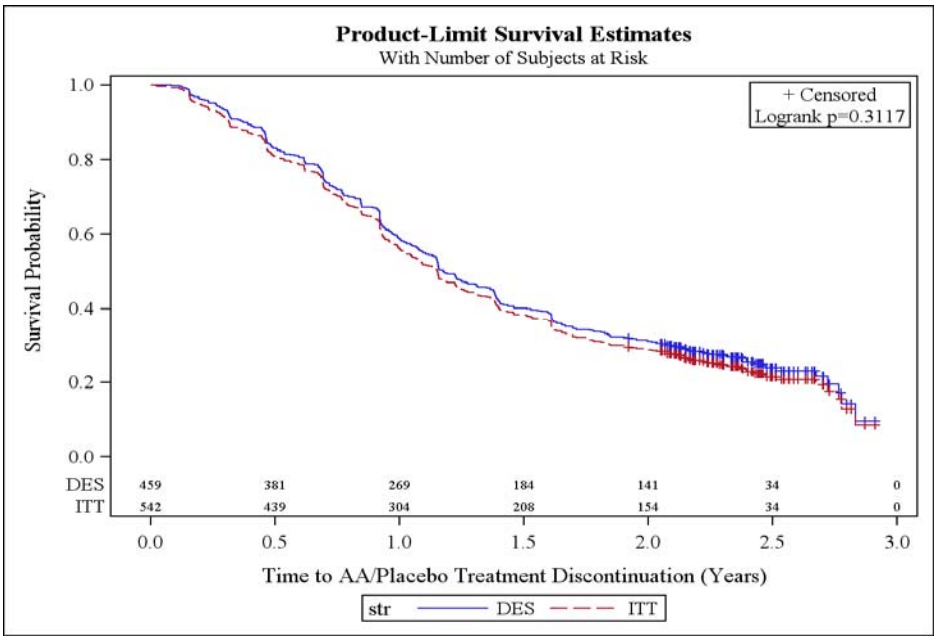


Figure 7: Comparison of Analysed Patients vs. ITT Population: OS, BSC (PP) Arm

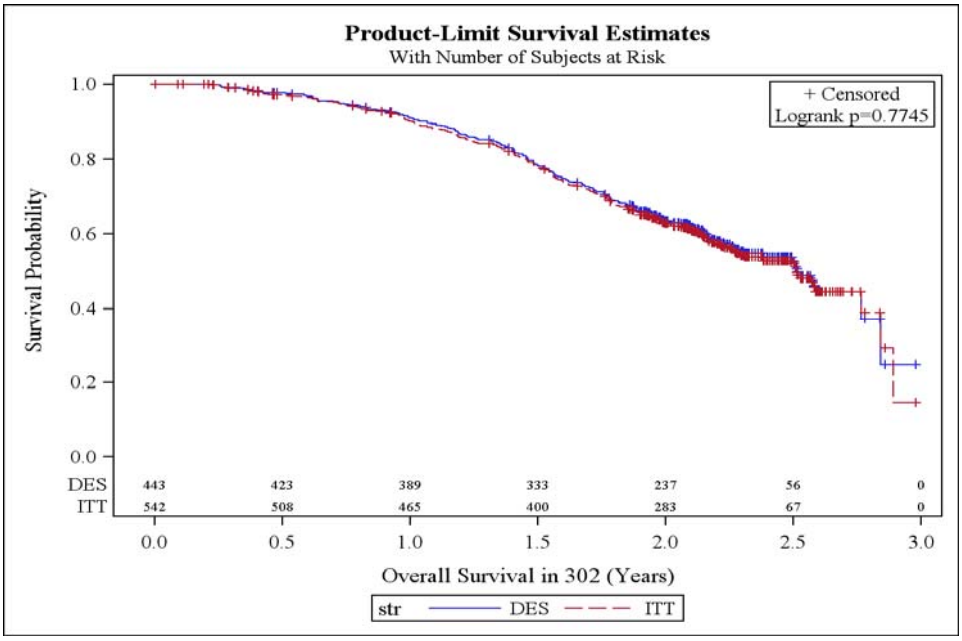
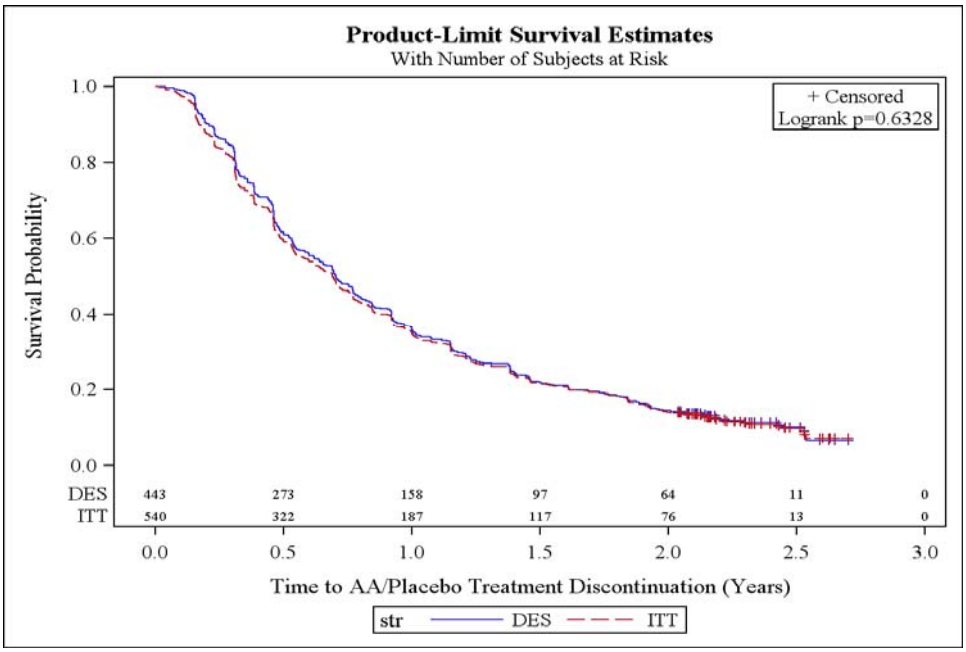


Figure 8: Comparison of Analysed Patients vs. ITT Population: TTD, BSC (PP) Arm



2.6 PAS administration costs

"The Committee noted that the administration costs of administering the PAS, although low, had not been included in the modelling and considered that these costs should have been included" [para 4.18]

Janssen acknowledges that the cost of administering the PAS should have been included in the modelled evaluation, and admits that this was simply an omission error. Consequently, we have

included this administration cost and its inclusion has a negligible impact on the ICER, see Table 4 below.

2.7 Price of docetaxel

"The Committee noted that generic versions of docetaxel have become available during the course of the appraisal…The Committee agreed that the cost of docetaxel may vary across the NHS, but it was likely to be closer to the eMIT cost than that modelled by the company" [para 4.18]

Janssen maintains that it is difficult to determine an accurate estimation of the national average price of docetaxel, and agrees with the Committee that the price is likely to vary across the UK. We also assert that it is most appropriate to use the British National Formulary (BNF) price in appraisals, and not tendered prices. Janssen believes the inclusion of tendered prices of genericised drugs, particularly when the prices change over the course of an appraisal, into NICE appraisals as a matter of course is not appropriate, as not only are these prices not agreed at a national level, but they also do not reflect the actual value that these drugs bring to the NHS. However, in response to the Committee's concerns, we have conducted a sensitivity analysis applying the significantly reduced, electronic market information tool (eMIT) price of docetaxel. The analysis shows that inclusion of the eMIT cost of docetaxel has a negligible impact on the ICER, see Table 4 below.

2.8 Compliance rate

"…in the COU-AA-302 trial, patients took 98% of the licensed dose on average and so the company's base-case model used 98% of the cost of the licensed dose of abiraterone. The Committee considered that the cost of unused tablets was unlikely to be recovered by the NHS, so the full cost of the licensed dose of abiraterone should be included in the model" [para 4.18]

Janssen appreciates that the cost of unused tablets is unlikely to be recovered by the NHS, however, we note that the treatment effect observed in the COU-AA-302 trial and consequently modelled in the economic evaluation represents the treatment effect associated with a compliance rate of 98%, not 100%. Adjustment of only the drug cost, without a corresponding adjustment assuming a treatment effect associated with 100% compliance will likely bias against abiraterone. However, in order to address the Committee's concern, we have included 100% of the cost of the licensed dose of abiraterone, which has a minimal impact on the ICER, see Table 4 below.

2.9 Adjustment for cabazitaxel

"The Committee noted that cabazitaxel is not recommended by NICE and is currently available on the Cancer Drugs Fund. The Committee accepted that it was appropriate to adjust for treatments that have a survival benefit and which are not available in the NHS…The Committee noted that adjusting for subsequent treatments had a modest impact on the ICER…the Committee concluded that adjustment for subsequent treatments in the abiraterone arm should be included in the analyses used for decision-making" [para 4.14]

Janssen notes that cabazitaxel is currently undergoing a NICE appraisal, and may receive a positive recommendation this year. If this is the case, then exclusion of cabazitaxel may not be appropriate. Consequently, we have conducted a sensitivity analysis which includes cabazitaxel as an acceptable post-docetaxel alternative. This results in a lower ICER, see Table 4 below.

2.10 Results using Committee's preferred assumptions

Table 4 below displays the cost-effectiveness results using each of the Committee's preferred assumptions, discussed under Sections 2.1-2.9 above. Importantly, the ICER is not very sensitive to these assumptions.

Table 4. Alternative ICERs based on Committee's preferred assumptions

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER, £/QALY
Original company base case							
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP				16,055	0.62	0.56	28,563
Base case + PAS administration costs							
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP				16,141	0.62	0.56	28,717
Base case + eMIT cost of docetaxel							
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP				16,648	0.62	0.56	29,618
Base case + 100% compliance rate for abiraterone							
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP				16,454	0.62	0.56	29,273
Base care + no adjustment to cabazitaxel							
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP				16,127	0.63	0.57	28,143
Base case + 1.2 weeks fixed duration between end of AAP or BSC treatment and start of docetaxel*							
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP				14,735	0.62	0.55	26,640
Base case + 2-segment curve (log-logistic+Weibull)**							
BSC (PP)	[redacted]	[redacted]	[redacted]				
AAP				15,855	0.54	0.48	32,849

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

** This scenario analysis has been presented to the Committee in November 2015 and was only added as it is also based upon one of the Committee's preferred assumptions.*

*** Refer to Section 2.4 for key assumptions on the 2-segment analyses*

3. Survival benefit associated with abiraterone

"Overall, the Committee concluded that abiraterone delayed disease progression and improved overall survival compared with placebo, but that there was uncertainty about the extent of the survival benefit" [para 4.7]

"For the abiraterone arm, for the time period (the trial period) for which data were available, the Committee agreed with the company that the log-logistic curve fitted the trial data better than the Weibull curve. However, it noted that the log-logistic curve predicted that some patients remained on abiraterone for a long time and about 4% took abiraterone for at least 8 years. The Committee heard from the company that there was anecdotal evidence that a few patients take abiraterone for several years. However, the Committee agreed that it had not seen data to support the extrapolation in the company's model because the maximum follow-up time in the trial was about 5 years" [para 4.12]

The COU-AA-302 trial is a well-designed, randomised controlled trial against the relevant comparator in the UK with over four years of follow-up. This trial has demonstrated a statistically significant survival benefit versus BSC and, therefore, Janssen strongly contends that there is little uncertainty surrounding the extent of the survival benefit associated with abiraterone.

We fully maintain that those patients who respond very well to treatment with abiraterone can remain on treatment for extended periods of time and can provide supporting evidence, firstly in the form of data from several centres across the UK that have treated patients with abiraterone and secondly, data from the US, where abiraterone has been available for longer than in the UK (Appendix 2).

Both sources of data demonstrate that there is in fact a proportion of patients that respond particularly well on abiraterone, and thus remain on the drug for several years in real life clinical practice. Janssen asserts that these data support our choice of extrapolation, and provide clinical plausibility to the modelled results.

4. End of life (EoL) criteria

Whilst we recognise that the Committee has determined that abiraterone in the pre-chemotherapy setting does not meet the life expectancy criterion of the EoL criteria, we wish to refer to the following quote taken from the current ACD: *"The Committee agreed that treatment switching and subsequent treatments that are not available in the NHS probably extended survival in both groups of COU-AA-302, but the effect was probably greater for the placebo group because more people took these treatments" [para 4.7].*

This lends credence to our contention that the control arm of the trial does not in fact reflect the true life expectancy of patients in UK clinical practice and has been associated with better results than patients would normally experience in normal clinical practice (conservative approach).

COU-AA-302 was an international study, and patients in the trial had significant exposure to other novel medications after the point of disease progression, which are not routinely available in the UK, and which would have the effect of extending survival over that which would be observed in usual practice (Table 5Table). Some of these medications, such as sipuleucel-T, cabazitaxel, ketoconazole and retreatment with abiraterone are not currently recommended by NICE and therefore do not align with current clinical practice in England and Wales. Of note, a higher proportion of patients received subsequent therapies in the control arm than in the abiraterone arm.

Table 5: Subsequent therapy for prostate cancer, COU-AA-302 study (3)

	Abiraterone plus prednisone (n=546), no. (%)	Prednisone alone (n=542), no. (%)
Patients with selected subsequent therapy for mCRPC	274 (50%)	348 (64%)
Docetaxel	239 (44%)	304 (56%)
Cabazitaxel	60 (11%)	70 (13%)
Ketoconazole	39 (7%)	63 (12%)
Abiraterone*	38 (7%)	78 (14%)
Sipuleucel-T	33 (6%)	28 (5%)

Note: Table reports cumulative incidence of subsequent therapy regardless of sequence after study drug discontinuation to the third interim analysis clinical cut-off date of 22 May 2012.
* Prior to unblinding and crossover from the prednisone arm to the abiraterone arm.

5. Conclusion

In this current appraisal in the pre-chemotherapy setting, the Committee made an initial decision to reject abiraterone, and Janssen has been responsive and offered a new PAS that increases the cost-effectiveness of the drug. Importantly, the new PAS is specifically designed to address the Committee's main identified area of uncertainty of long-term time on treatment and survival benefit. We strongly believe that the balance of evidence demonstrates that under the conditions of the PAS, abiraterone in the pre-chemotherapy setting is a cost-effective use of NHS resources. As demonstrated in Section 2.10, many of the Committee's key concerns and preferred assumptions have little impact the ICER. Moreover, the Committee's main concern regarding our choice of parametric extrapolation is significantly reduced by our supportive real-world data from the US and the UK, and hence Janssen believes that the Committee can be reassured that the ICER is below £30k.

If the Committee grants a positive recommendation to abiraterone in the current appraisal, the question regarding long term uncertainty in modelled treatment duration can in fact be answered. The Janssen portal associated with the complex PAS, which will become operational once positive NICE guidance is granted, will allow the NHS to track treatment duration, as it is based upon the Blueteq system already in place to monitor PbR excluded drugs. **Through this PAS portal, regular reports can be provided to NHS England and NICE to monitor the duration of treatment in real clinical practice, providing data for any future guidance review of abiraterone in this specific indication. This would allow the data to mature, and for the Committee to assess the accuracy of our modelled economic evaluation during the normal 3-year review associated with NICE guidance.**

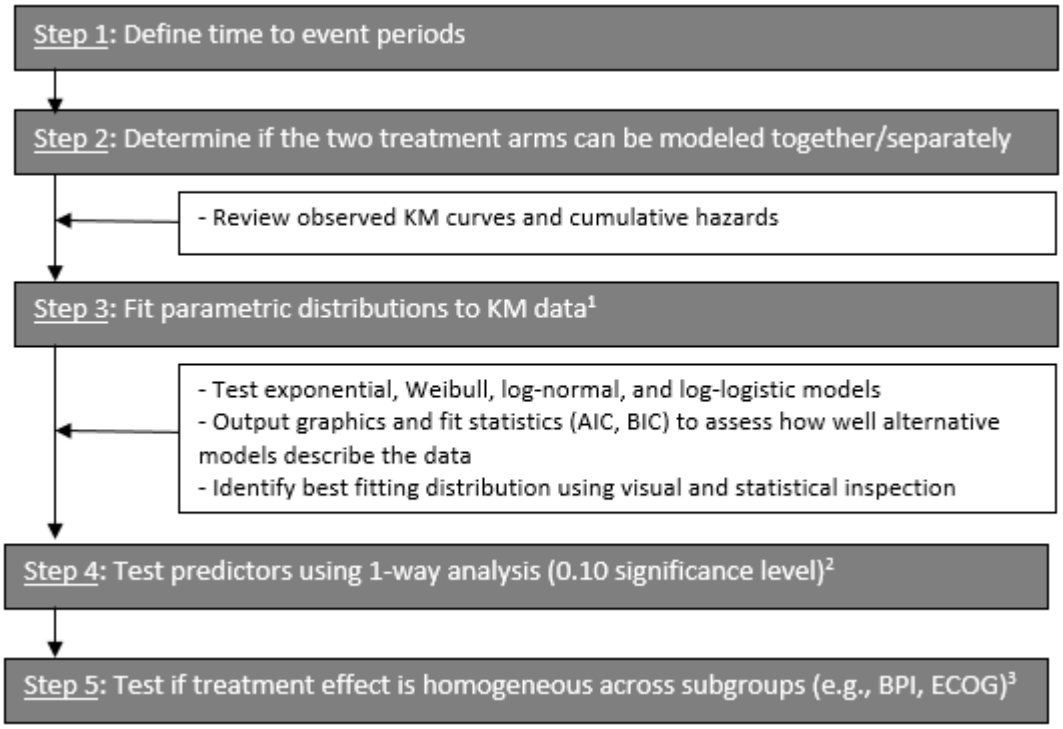
Janssen remain committed to finding a way forward that results in the routine commissioning of abiraterone in this earlier setting, as we have heard from the patient and clinical community that men with mCRPC would strongly benefit from delaying chemotherapy. This is particularly important given that enzalutamide has recently received a positive recommendation from NICE, and as sequential use of the two treatments is not permitted in the NHS, it is unlikely that patients will be offered abiraterone after chemotherapy if they have received enzalutamide in the pre-chemotherapy setting. From our extensive discussions with clinicians we note that they feel it is essential to have both treatments routinely available, as they recognise clear differences between the treatments due to their differing modes of action. Allowing both treatments to be available would permit clinicians to select the best option on an individual patient basis, depending upon individual patient characteristics. This need for choice can be observed by the continuing high numbers of requests for both agents through the CDF.

Appendix 1: Choice of covariates in the prediction equations

Steps for Determining Predictors and Parametric Distribution

A systematic approach specified a priori in a statistical analysis plan (SAP) was used to develop the prediction equations. The COU-AA-302 trial design and data collection provided the unique opportunity to follow patients over their treatment course and to subsequent treatments. The COU-AA-302 trial data were used to link individual patient characteristics (e.g., treatment, current ECOG, baseline BMI) to an event time (e.g., treatment start) using standard statistical procedures outlined in Figure A1.

Figure A.1. Statistical Procedure to Develop Time to Event Equations



AIC= Akaike Information Criterion; BIC= Bayesian Information Criterion; Brief Pain Inventory score; ECOG = Eastern Cooperative Oncology Group performance status

[1]The main goal of time to event equations was to predict the time to event outcomes for the overall population well.

[2]Note that adding predictors insures that variability in the outcomes between patients in the trial is captured correctly, which is important in individual simulation modeling. Also, if a specific distribution does not predict the outcome for the entire population well, adding predictors will not correct for that and therefore the current order of the steps to estimate and select predictors is the most logical.

[3]Only BPI is significant in the time to discontinuation AAP phase post-ADT.

The candidate variables for the prediction equations for the economic model were pre-specified in the SAP and consisted primarily of clinically relevant variables as indicated in pre-specified analysis for trial endpoints or from clinician feedback:

Trial-based variables	Clinician-recommended variables
Treatment group	BMI
Age	BSA
Baseline ECOG performance status grade	Days from diagnosis to randomization
Baseline BPI	Baseline haemoglobin
Baseline PSA	Analgesic use level in last 24 hours at baseline
Baseline bone metastasis	Worst Pain in Last 24 Hours Score at baseline
Baseline LDH value	
Baseline ALK	

For prediction equations beyond the first phase of time on treatment, additional time-dependent variables were added as specified in the SAP, such as ECOG at the start of each equation time, PSA progression, radiographic progression and opiate use at first line treatment discontinuation, and time spent in previous treatment to better capture and account for patient history and predictive power.

As indicated in step 4 of the process, to select predictors to be included in the predictive equation, we examined each potential predictor separately in univariate models. Significance was assessed based on a pre-specified p-value of <0.10. An initial multivariate model was then fitted by including all significant predictors identified in univariate models. This model was then trimmed down manually by removing predictors with the highest p-value one at a time, until the model included only significant variables.

For variables that were not independent from each other, but one portion met statistical significance, all components were included in the model following standard statistical practice.

For each equation, goodness of fit of the equation was assessed by comparing observed versus predicted outcomes using visual inspection as well (see Figures A4-A13 below). In this step, one deviation was made in the time from post-docetaxel treatment end to death, to (see section 1.3 below).

All of the equations fit the observed data well.

Additional Considerations in Model Selection Criteria and ICER Impacts on Different Assumptions

Deviations in Significant Predictors was Clinically and Statistically Appropriate

The predictors included in the company's model were based on statistical significance (p-value ≤10) with one exception described below in which statistical significance was likely compromised by small sample size and important prognostic factors showed a non-negligible effect size (one case):

- Time from post-docetaxel treatment end to death, in which the p-value = 0.1899. We keep treatment as a predictor in this equation because the Kaplan Meier graph shows clear survival difference between the two treatment groups (see Figure 3 and Figure 4). Only 125 patients are included in this analysis (other patients had not reached this point in 302 trial) experiencing 71 events. It is therefore likely that the treatment effect is not statistically significant due to the small sample size. Excluding AAP treatment as predictor in post-docetaxel treatment end to death, using strict significance criteria, leads to a prediction that

clearly does not match the observed data (see Figure A2). Including treatment as a predictor gives a more accurate estimate of time from post-docetaxel treatment end to death (see Figure A3).

Figure A2. Estimating Post-Docetaxel Treatment End to Death with Treatment Excluded as a Predictor

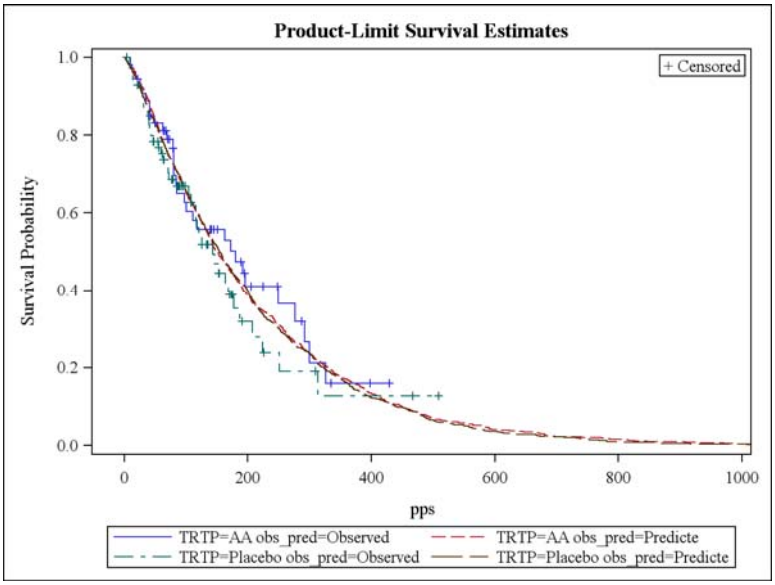
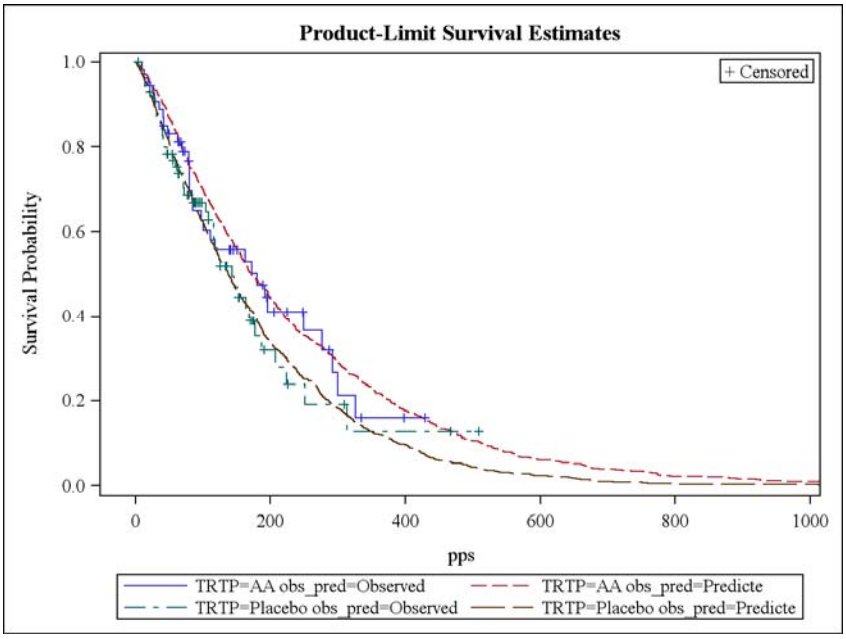


Figure A3. Estimating Post-Docetaxel Treatment End to Death with Treatment Included as a Predictor



In another case, a non-significant predictor was included as the predictor in question was not independent from other variables as is standard practice.

- In time to AAP/BSC (PP) end, BPI0-1 becomes non-significant only when the interaction term (BPI x treatment group) was added to the model, otherwise in both the univariate model and in the model with other significant predictors but without

interactions terms, BPI0-1 is statistically significant (p-value < 0.0001 in the univariate model and 0.004 in the model without interaction). In models including interaction terms (required for subgroup analysis), the standard approach and recommendation is to include main effects regardless of their significance after the interaction term is added. For this reason, the main effect (i.e., BPI0-1) was retained in the final equation. The interaction term was included to inform the pre-specified subgroup analysis. Both ECOG*AA and BPI*AA were tested but ECOG*AA was not statistically significant.

Finally, in other cases, some categories were not statistically significant but the overall effect of the categorical variables retained in the model was statistically significant at the 0.10 level. E.g., ECOG = 1 and ECOG = 1 were statistically significant, but not ECOG=2, however this is retained in the model following standard statistical practice.

As shown in Table A1, the impact of excluding non-significant predictors (based on p-value threshold of 0.10) had minimal impact on ICERs (£1,531).

Table A1. Impact of Excluding Non-Significant Predictors

Scenario	ICER (£/QALY)	Impact on ICER (absolute difference)
(a) No interaction term in time to AAP end	£29,312	£749
(b) No AAP Tx as predictor in post-docetaxel Tx end to death	£29,296	£733
(c) Both (a) and (b)	£30,094	£1,531

Base case ICER = £28,563/QALY

Goodness of Fit of Prediction Equations

Figure A4. Time to AAP/BSC (PP) End Estimates

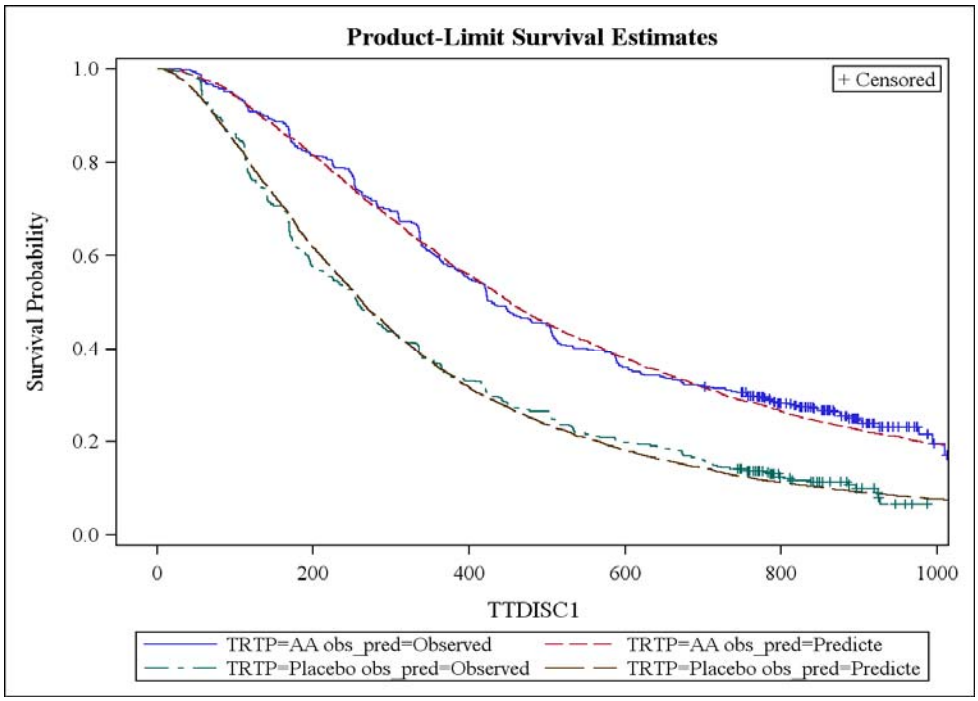


Figure A5. Time from AAP/BSC (PP) End to Docetaxel Start Estimates

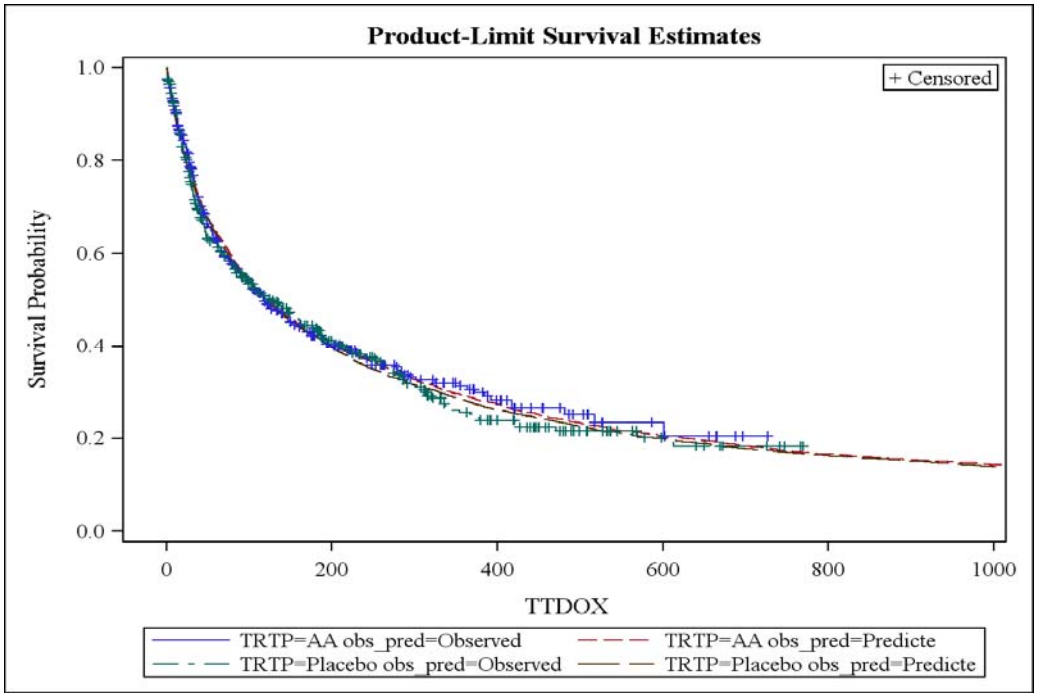


Figure A6. Time from Docetaxel Start to Docetaxel End Estimates

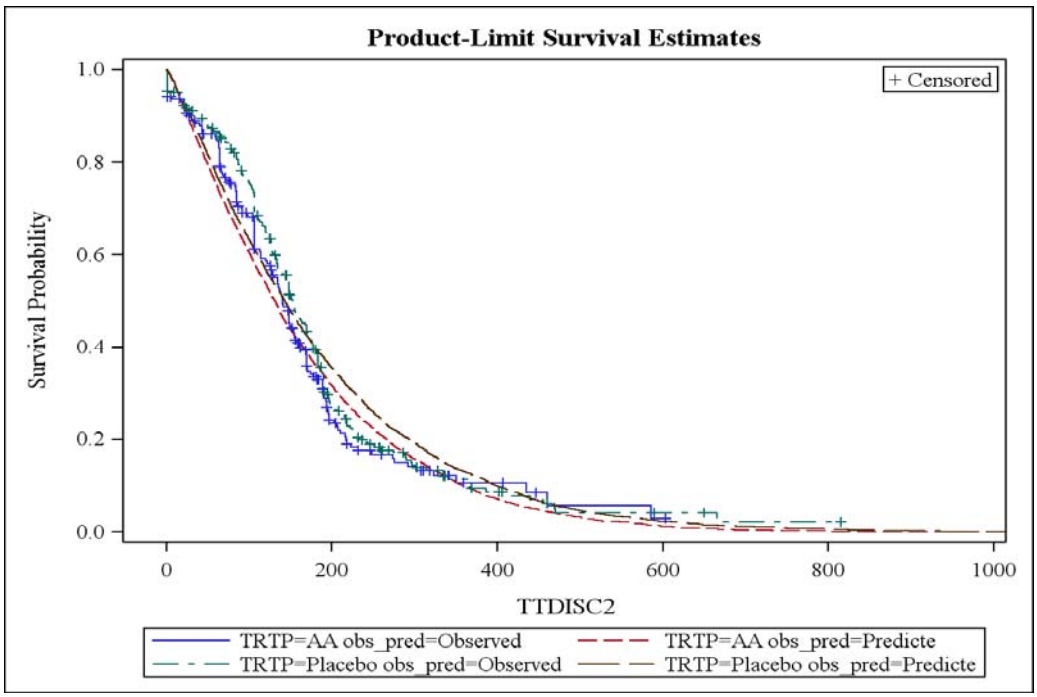


Figure A7. Time from Docetaxel End to Post-docetaxel Treatment Start Estimates

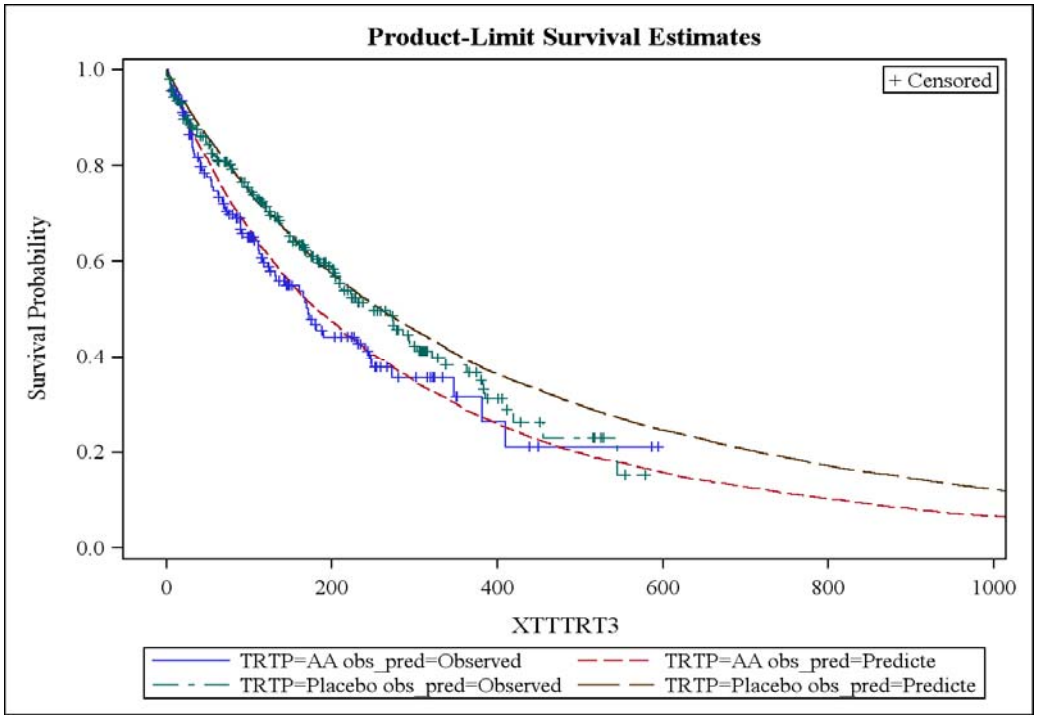


Figure A8. Time from Post-docetaxel Treatment Start to End Estimates

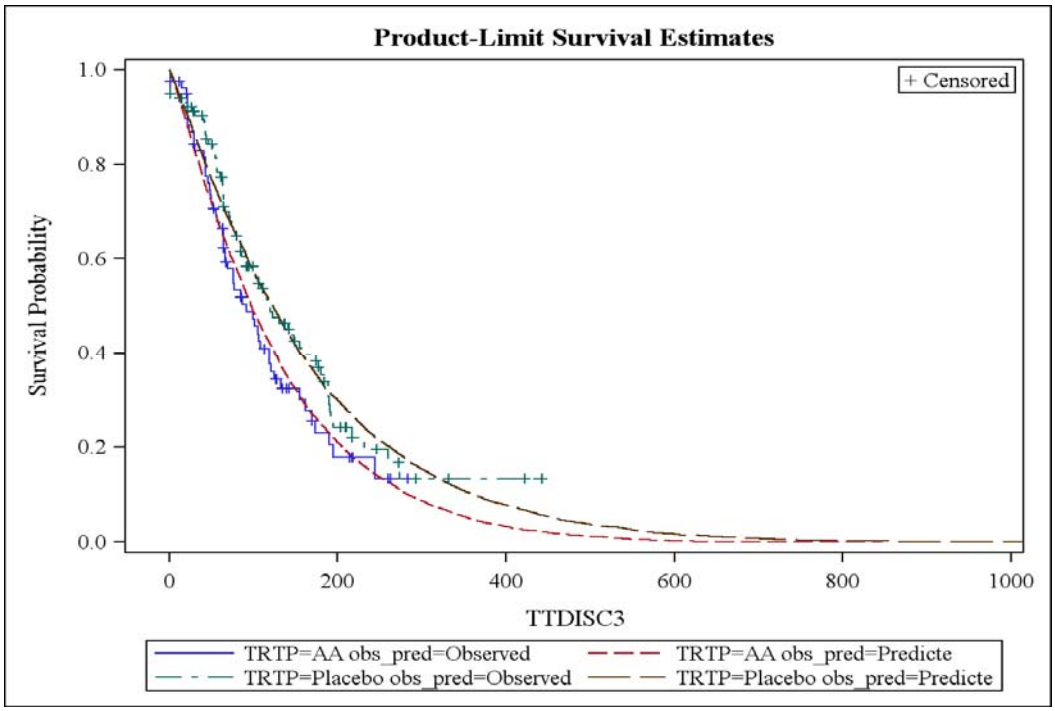


Figure A9. Time from AAP End to Death Estimates

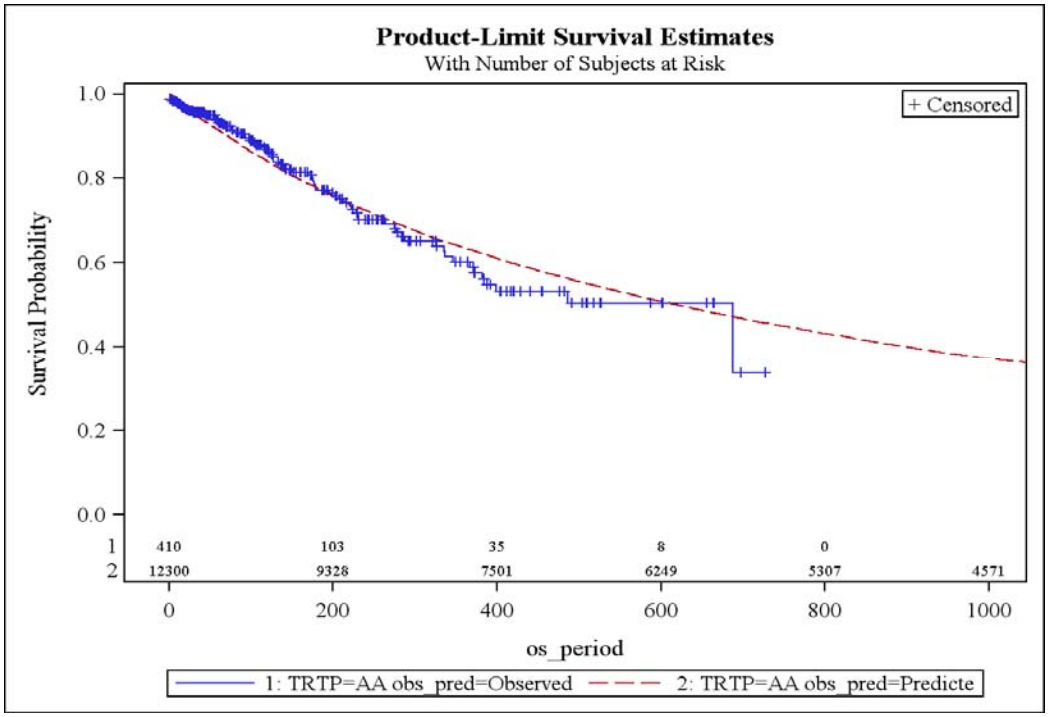


Figure A10. Time from BSC (PP) End to Death Estimates

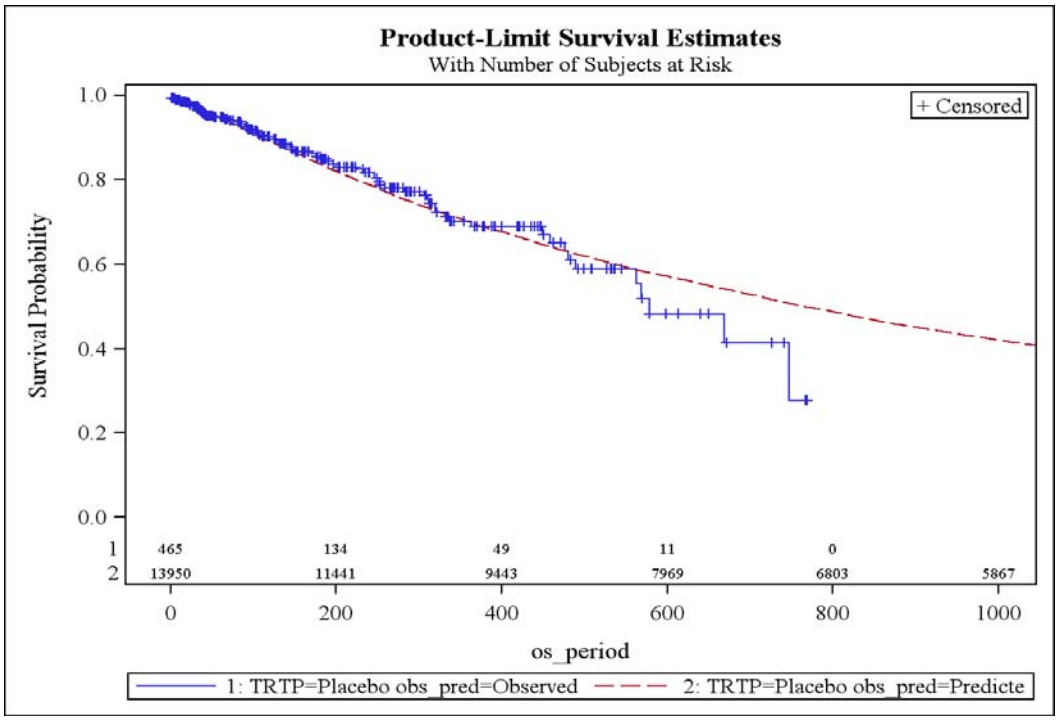


Figure A11. Time from Docetaxel Start to Death Estimates

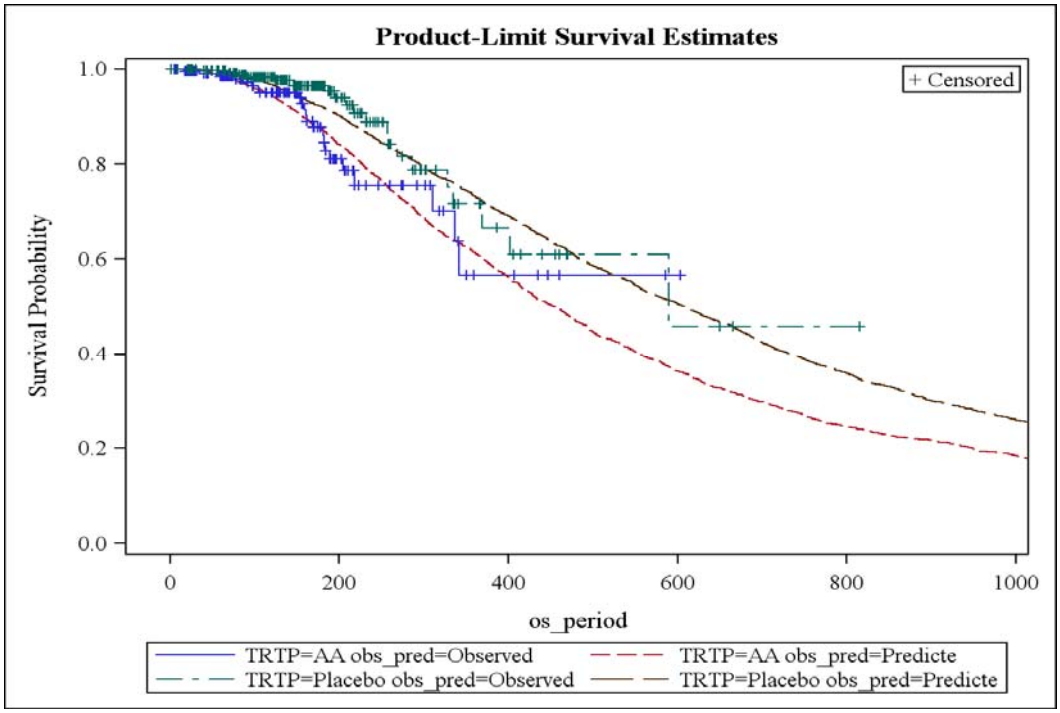


Figure A12. Time from Docetaxel End to Death Estimates

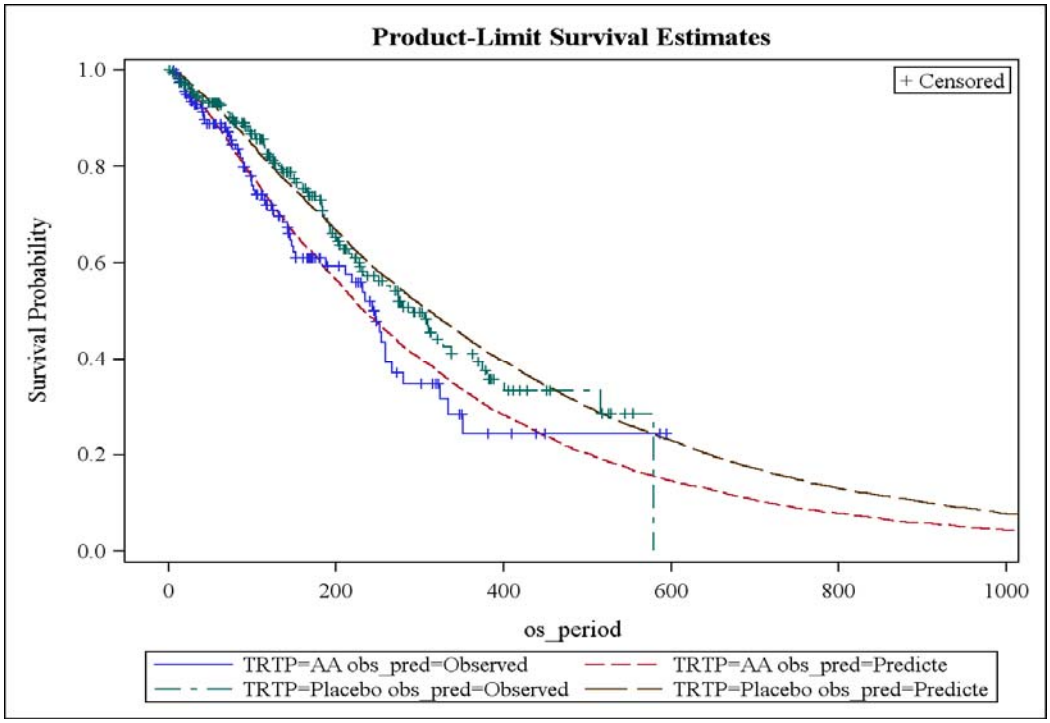
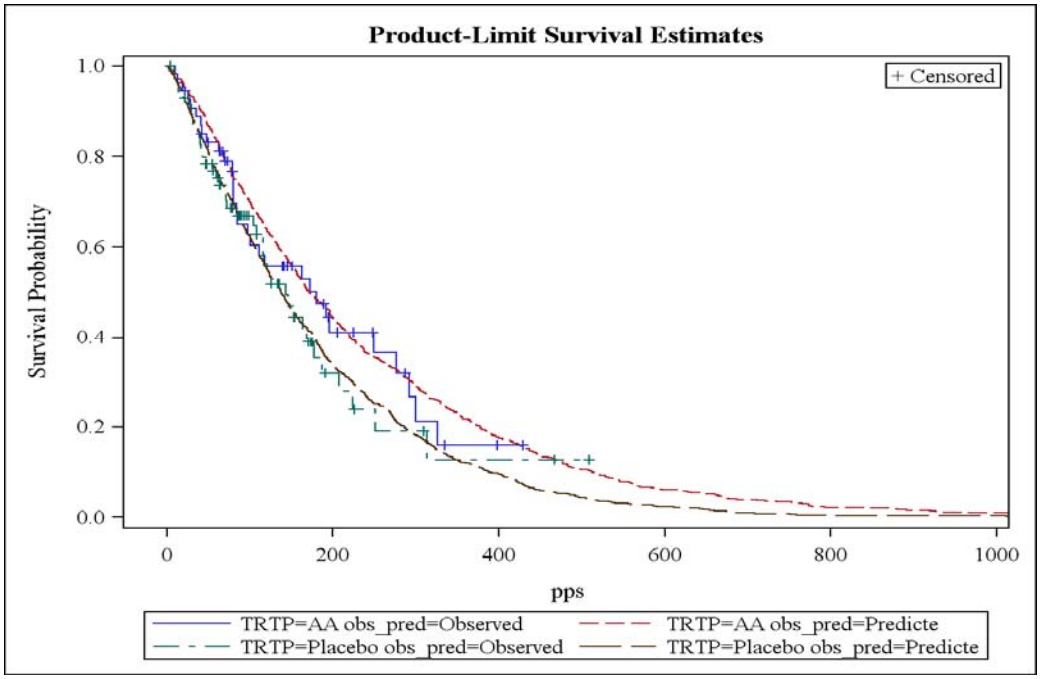


Figure A13. Time from Post-docetaxel Treatment End to Death Estimates



Appendix 2: Real world data to support the modelled duration of treatment extrapolations

According to the ACD (para. 4.12), the Committee agreed with Janssen that the log-logistic curve fitted the AAP trial data better than the Weibull curve. However, it noted that the log-logistic curve predicted that some patients remained on abiraterone for a long time, and approximately 4% took abiraterone for at least 8 years.

The economic model was developed to estimate the longer term benefit of abiraterone after the 4-year follow-up period of the clinical trial (COU-AA-302). The extrapolation method was selected to ensure the best fit to the trial data for the duration of the trial, and was used to determine the long term benefit that could be expected from abiraterone.

As the EU marketing authorization for abiraterone was obtained in 2012, it must be noted that the follow-up period for UK patients remains too short to allow a full view of the treatment duration that could be expected with AAP pre-chemotherapy. Moreover, English clinicians were only able to start routinely prescribing AAP in this setting since its listing on the National Cancer Drugs Fund in January 2013.

Janssen has approached 19 UK-based clinicians who have a wide experience of prescribing AAP. The clinicians report that many of their mCRPC patients treated pre-chemotherapy with AAP experience long treatment durations of over 1, 2 or 3 years. We have also contacted a number of oncology pharmacists from the cancer centres in the UK which prescribe the highest volumes of AAP (i.e. [redacted]). The rationale for choosing these centres is that their volume of patients on treatment with AAP represents more than 35% of the overall UK prescribing of AAP; in addition, as major centres, these hospitals have pharmacy and finance reporting systems in place to be able to more easily provide the information. Amongst these centres, 5 were able to provide information as to the proportion of mCRPC patients who had been treated with AAP either pre or post-chemotherapy for the following treatment durations (See Table A2). These results are very preliminary and are difficult to interpret as they include patients who had finished treatment as well as patients still on treatment.

Table A2. [redacted]

	%
≥ 12 months – 23 months	[redacted]
≥24 months – 35 months	
≥36 months – 47 months	

Note: [redacted].

Due to the limited data on treatment patterns with AAP in the UK, we have additionally sourced a US-based health claim database to provide more extensive treatment duration data.

[redacted]

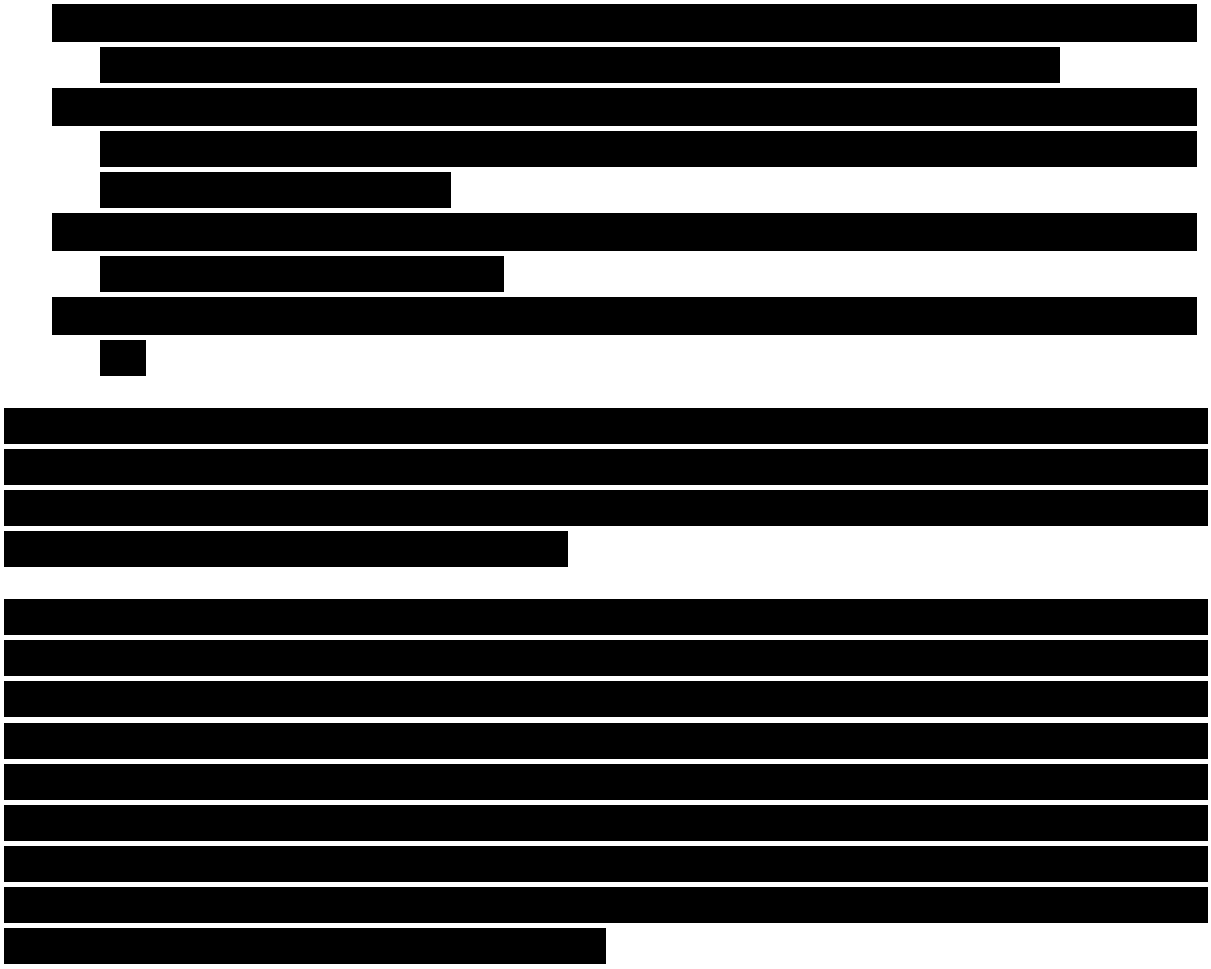


Figure A14. [redacted]

Tackle Prostate Cancer is dismayed and surprised that NICE has not recommended abiraterone for use in chemotherapy naive patients. This is despite the fact that the manufacturer has offered to pay for the treatment for anybody who is continuing to benefit from the medicine for longer than 10 months.

Abiraterone has already proved to be an excellent treatment for metastatic hormone relapsed prostate cancer in the post chemotherapy setting and trials show it is even more effective when given pre-chemotherapy. It is important that clinicians and patients are given a choice of treatments when there are so few options available. We urge the Panel to look at this recommendation again, taking into account all of the relevant facts.

15 January 2016

British Uro-oncology Group (BUG) Response to:

NICE Appraisal Consultation Document
Abiraterone for treating metastatic hormone-relapsed prostate cancer not previously treated with chemotherapy

Men with metastatic Castration Resistant Prostate Cancer (mCRPC), whose disease is asymptomatic or mildly symptomatic, and for whom chemotherapy may not be immediately appropriate or necessary, have limited treatment options. The British Uro-oncology Group (BUG) fails to understand NICE's preliminary recommendation that:

1.1 Abiraterone is not recommended for treating metastatic hormone relapsed prostate cancer in people who have no or mild symptoms after androgen deprivation therapy has failed and in whom chemotherapy is not yet clinically indicated.

BUG strongly urges NICE to re-consider its ACD recommendation on the basis that abiraterone in the pre-chemotherapy setting has the potential to prolong survival, palliate symptoms, and improve quality of life for men suffering from prostate cancer.

The importance of abiraterone in daily clinical practice has been demonstrated by the number of applications by oncologists to the Cancer Drugs Fund (CDF).

As experts in their field, oncologists recognise that there are patients who will respond very well to either abiraterone or enzalutamide so it is important to have both these treatment options available for men with asymptomatic or minimally symptomatic mCRPC who are chemotherapy naïve.

Some men with a history of seizures or neurological disorders would be unsuitable for treatment with enzalutamide and it would be vital for them to have the opportunity to benefit from abiraterone. Individual discussions with patients and their choices must be taken into account with regard to the different toxicities of therapy. These choices and discussions are apparent when prescribing from the CDF. Oncologists should be able to prescribe either enzalutamide or abiraterone having evaluated the individual's circumstances and co-morbidities.

Prostate cancer treatment should be individualised to the patient with the best choice of treatment based on evidence, patient characteristics and specific tumour and cancer response data; there can be no one size fits all approach without patient harm. The treatment decision for each individual man needs to be made on the basis of both potential side-effects and existing co-morbidities.

In summary, abiraterone demonstrates excellent efficacy and tolerability with meaningful endpoints and maintenance of QOL for men with mCRPC. The British Uro-oncology Group requests a positive NICE appraisal allowing the prescribing of abiraterone in chemotherapy naive patients. The addition of abiraterone as an option alongside enzaluatamide provides meaningful clinical benefit to men with metastatic castration resistant prostate cancer.

Yours faithfully

[redacted]

and on behalf of the BUG Executive Committee

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8 January 2016

Dear Mr Powell

Re: Abiraterone acetate for the treatment of metastatic hormone relapsed prostate cancer not previously treated with chemotherapy (ID889) – ACD 2

The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 31,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

The NCRI-RCP-ACP-RCR are grateful for the opportunity to respond jointly to the above ACD 2 consultation. We would like to make the following comments in response to the below:

The Appraisal Committee is interested in receiving comments on the following:

- **Has all of the relevant evidence been taken into account?**
- **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**
- **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**

Overall, we believe that all the relevant evidence has been taken into account, and the summaries seem reasonable interpretations of the evidence.

However, our experts believe that the decision will likely have a detrimental impact on patients, most particularly those who would not normally receive docetaxel. It is thought that up to half of Castration Resistant Prostate Cancer (CRPC) patients in the UK never get docetaxel. Until now they have been able to access abiraterone via the CDF. We believe that to deny these patients access to abiraterone, unless they have docetaxel first, is most regrettable.

Further to this, if a similar decision is made for enzalutamide it may have the unintended consequence of massively increasing the use of docetaxel (in order to get subsequent access to abiraterone or enzalutamide). This would place increased pressure on the capacity to deliver chemotherapy for all cancers.

Yours sincerely

Abiraterone for the treatment of metastatic hormone relapsed prostate cancer not previously treated with chemotherapy

Appraisal consultation document

Response from The Institute of Cancer Research, London
January 2016

The Institute of Cancer Research (ICR) welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) for abiraterone in the treatment of metastatic hormone-relapsed prostate cancer not previously treated with chemotherapy.

Abiraterone was discovered by the ICR, in what is now the Cancer Research UK Cancer Therapeutics Unit, and the ICR and The Royal Marsden carried out initial clinical development on the drug, as well as leading the UK arms of later-stage international clinical trials. ICR researchers have been treating patients with abiraterone for more than 10 years.

Abiraterone is now used as standard treatment after chemotherapy and has extended the lives of thousands of men in the UK with advanced prostate cancer. We are very disappointed that NICE did not recommend use of abiraterone for men with prostate cancer who are yet to receive chemotherapy in draft recommendations in this second ACD.

We understand that the manufacturer has discounted the costs of abiraterone, and we believe that it is crucial that the DH, NICE and the manufacturer continue to work together to ensure that this drug is made available and that more patients can benefit from it.

Cost-effectiveness

The Committee concluded that the incremental cost-effectiveness ratio (ICER) for use of abiraterone before chemotherapy was likely to be above the range normally considered a cost-effective use of NHS resources, calculated to lie between £35,500 and £59,600 per quality-adjusted life year (QALY) gained. The reason given for the large range in the potential cost-effectiveness was uncertainty in overall survival and how long people would receive abiraterone.

We believe the evidence is clear that abiraterone is effective when given before chemotherapy and can give men many extra months free of disease. We felt it was important to respond to questions raised by the committee about overall survival and the length of time that patients receive abiraterone.

The committee and the evidence review groups discussed the company's modelling, particularly the distributions used for extrapolating to long-term survival. The committee noted that the log-logistic curve used in the modelling predicted that some patients would remain on abiraterone for a long time, with some taking abiraterone for eight years. The committee felt that there wasn't data to support this extrapolation because the maximum follow-up time of the trial was about five years. It felt that the final data did not support use of this distribution for predicting time on treatment.

At the ICR, we would not claim to be experts in economic modelling and we cannot comment on the appropriateness of the extrapolation methods used by the company. However, ICR staff have great experience of treating patients with abiraterone and have treated a patient with abiraterone for more than eight years.

Innovation

The committee considered that abiraterone is innovative compared with best supportive care because it was the first active treatment available for this position in the treatment pathway. We think it is important to point out that abiraterone is also innovative in that it was a drug acting on a novel target with a completely new mechanism of action.

It is very important that NICE recognises the degree of innovation in the drugs it assesses, and takes this into account in making its judgements. It is much riskier and more expensive to produce drugs with novel mechanisms of action than to produce improved versions of what has come before. If NICE does not give innovation due recognition, there will be no incentive for companies or research institutes to create genuinely new and innovative treatments.

Benefit in delaying chemotherapy

We are very disappointed that abiraterone was not recommended in the ACD for men with prostate cancer who are yet to receive chemotherapy. This decision would deny many thousands of men the opportunity to access this drug earlier in their course of treatment, as well as some men who may never qualify for treatment with abiraterone as they are not in the position to receive chemotherapy as they might not be fit enough or might be too old. We understand – although are disappointed by – the decision taken by NICE to not apply end-of-life criteria in this case, even though they were applied in assessing abiraterone post chemotherapy. However, we would ask NICE to consider whether end-of-life criteria could be applied in the specific subset of men who are too frail to receive chemotherapy and for whom treatment options are therefore currently limited. These men would be expected to have significantly shorter survival than men with equivalent disease who are able to go on to receive further treatment.

Inequality across the UK

Since the last draft recommendation from NICE, abiraterone has been made available on the NHS in Scotland for men with advanced prostate cancer before treatment with chemotherapy, following a decision from the Scottish Medicines Consortium.

It is very disappointing that men in England and Wales will not be able to access the treatment – even though in Scotland it has been made available on the NHS. We want to see NICE follow the lead of Scotland so that this highly innovative drug can be made available for all men with prostate cancer in every part of the UK.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Location	England
Conflict	None declared
Notes	
Comments on the ACD	NICE is provisionally recommending that Abiraterone is not recommended for treating metastatic hormone relapsed prostate cancer in people who have no or mild symptoms after androgen deprivation therapy has failed and in whom chemotherapy is not yet clinically indicated. I would like to submit that NICE should change this recommendation, as many studies have shown that continued treatment with Abiraterone can have significant benefits for men with prostate cancer in this situation. This is born out by several studies and is supported by medical practitioners in my area (Morecambe Bay NHS Foundation Trust). The proposed cost saving measure will have a damaging impact on many men's quality of life.

Name	[redacted]
Role	Carer
Other role	
Location	England
Conflict	None declared
Notes	
Comments on the ACD	Please keep abiteraone pre-chemotherapy its a very important and necessary drug for treatment of prostate cancer (my father is a prostate cancer patient)

Name	[redacted]
Role	Patient
Other role	
Location	England
Conflict	None declared
Notes	
Comments on the ACD	As a Prostate cancer patient I feel the need to give any man with the disease all and any treatments that may help them with their plight, regardless of cost. I therefore strongly feel that the proposal to attempt the use of the treatment in the future to be wrong.

Name	[redacted]
Role	Patient
Other role	
Location	England

Conflict	None declared
Notes	
Comments on the ACD	There are a number of issues which occur to me, having read the report about the proposal to limit if not remove abiraterone from the approved list of treatments for metastatic prostate cancer. 1, The report seems to confine itself to the late stages of cancer development before the issue of abiraterone to the patient rather than when there are other early indications of the presence of metastatic cancer. The accepted wisdom is that treatment of cancer is most effective if the treatment starts early yet I can't seem to find any suggestions that abiraterone should be used in this way. The only reference to long term use is 4% who were on it for eight years (paragraph 4.12) which to me shows its effectiveness in extending life. 2. In proposing the withdrawal of abiraterone important matters are called into question. The human body as not a mechanical machine which responds in a predictable manner but can respond in unpredictable ways such as the patient suffering unacceptable side effects or not responding as anticipated. Allowing for that eventuality the clinicians must be allowed as many treatment options as possible which must include abiraterone The report acknowledges the effectiveness of abiraterone so why is there consideration to remove it from treatment options? As far as I can see, there is an unsubstantiated assumption that enzalutamide and abiraterone are equivalent. As noted above, the human body does not necessarily respond as hoped to a given treatment. I am sure that if medical records are examined there will be patients who are intolerant of one or the other making this assumption of equivalence a nonsense. As a person with metastatic prostate cancer I am aware from conversations with fellow sufferers that in some cases, this is true. At 546/542 patient numbers in some of the tables, I am curious as to the statistical significance of these numbers in terms of accuracy of interpretation of results. Considering the number of patients suffering from prostate cancer, I should have thought that there would be many more than this from which to obtain data to make the interpretation of that data more certain and believable(I am not saying that the report conclusions are inaccurate as such just that data from a larger population would give greater confidence). 3. Paragraphs 3.5 3.7 and other parts of the report indicate as far as I can see, the effectiveness of treatment with abiraterone which to me counters the decision in the introduction that

	abiraterone is not to be recommended for the treatment of metastatic hormone relapsed prostate cancer. 4. Section 4.3 'the Committee concluded that there is some uncertainty about the benefits or consequences of delaying chemotherapy but accepted the view of patients that delaying chemotherapy is of value to them' why was this not thoroughly investigated and assessed before reaching a decision? Section 4.7 last paragraph 'Overall the Committee concluded that abiraterone delayed disease progression and improved overall survival compared with placebo but there was uncertainty about the extent of the survival benefit' - Would it not be wise to clarify the extent of the survival benefit before denying patients the use of abiraterone? I find aspects of this report confusing if not conflicting. In Section 4.13 test results are mentioned which refer to treatment switching to drugs not available on the NHS. Why is this data included it simply confuses the decision making process and contributes nothing? That the company amend the data in 4.14 is not helpful and begs the question why did they include it in the first place? Why do the committee accept that it is appropriate to include drugs which have a survival benefit but are not available on the NHS? Does this mean they will consider making them available on the NHS?

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

ERG response to:
the Company's response to the 2nd ACD on 15 January 2016

Abiraterone acetate for the treatment of metastatic hormone relapsed prostate cancer not previously treated with chemotherapy

The ERG concludes that the Company's response to the 2nd ACD on 15 January 2016 does not affect any of the critiques raised, assumptions preferred (e.g. use of the intention to treat (ITT) population and treatment as only predictor) or any of the conclusions presented in the ERG report and previous addenda. See the ERG addendum submitted in April 2015 for an overview of our critiques. The ERG base case, as submitted to NICE on November 6th 2015, is presented in Table 1. Note that this analysis incorporated the new PAS for abiraterone and the old PAS for best supportive care (BSC). Additionally, an updated ERG base case is presented while incorporating the PAS administration fee for abiraterone acetate plus prednisolone (AAP).

Table 1: ERG base case submitted to NICE on November 6th 2015 and updated ERG base case

		Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
ERG base case	BSC	[redacted]	[redacted]			
	AAP			£16,098	0.425	£37,859
Updated ERG base case[a]	BSC	[redacted]	[redacted]			
	AAP			£16,184	0.425	£38,061

[a]This analyses incorporates the PAS administration fee (only applied to AAP).

Using the new PAS for AAP only seems justified given that the new PAS will only be implemented if AAP is recommended by NICE. Please note that in all analyses provided by the Company, the new PAS is used for both AAP and BSC (post-docetaxel abiraterone). Potentially resulting in an underestimation of the ICER.

Below the ERG will address the issues raised by the Company in its response to the 2nd ACD on 15 January 2016. Not all issues are considered in detail given the overlap with previous critiques and discussions.

In **section 2.1** the Company advocates not using the ITT population (as preferred by the ERG) for two reasons:

1. this does not reflect how clinical decisions are made and;
2. this would underestimate overall survival (OS) with AAP (based on Figures 1 and 2 in the Company's response).

The ERG is not convinced by these arguments. Firstly, the only clinical decision incorporated in the economic model is to decide which patients are suitable for docetaxel treatment (based on ECOG score). This is also incorporated in the ERG analyses based on the ITT population (as the baseline characteristics based on the "patient disease status" prediction equations are incorporated). Secondly, though the absolute AAP OS might be slightly underestimated compared with the Kaplan-Meier curves in the ERG base case after approximately 2.5 years (see Figure 1 in the Company's response), the most influential outcome for the cost-effectiveness is the incremental survival (i.e. relative treatment benefit) which seems overestimated when not using the ITT population. This is previously justified and discussed (see amongst others the ERG report section 5.2.6 and the addendum sent on April 2015). Moreover, Figures 1 and 2 in the Company's response indicate an overestimation of incremental survival during approximately the first 2 years, which seems larger when not using the ITT population. Therefore, the ERG has a preference for using the ITT population as it believes not using the ITT population might bias the results in favour of AAP.

The ERG would like to stress that it does not advocate against the inclusion of covariates, if done consistently. Rather the ERG advocates to use the ITT, for which it is not possible to include covariates without for instance using imputation methods. Hence, according to the ERG, the discussion should

primarily focus on the use of the ITT population or the "analysable" subset rather than whether to include covariates or not.

See section 5.2.6 of the ERG report and Table 3 (points 4-6) of the addendum sent in April 2015 for critiques regarding the selection of parametric distribution, inconsistent use of (candidate) covariates, interaction terms and stratified models.

Considering **sections 2.2 and 2.3** in the Company's response: we acknowledge that there is uncertainty regarding the impact of cross-over and subsequent treatments on overall survival and that post-docetaxel survival might be overestimated as a result. This is also apparent when comparing post-docetaxel survival between the COU-AA-301 and COU-AA-302 trials (see also Figure 7 in the Company's response to request for additional info; 301015). These sections do not provide any arguments to prefer the Company's base case above the ERG base case.

Considering **section 2.4** in the Company's response: the statement *"the final dataset from the COU-AA-302 trial provides longer follow up and captures more death events than the 55% data cut, there is less uncertainty around the long-term projection associated with the final data cut"* is confusing as it contradicts the Company's approach to use the *"55% data cut to check the best fit distribution for predicting time to AAP/BSC (PP) treatment discontinuation"*. No methods or data are provided considering the verification of the preferred parametric distribution with the final data cut data.

Moreover, it is unclear to the ERG why the publications printed under Figure 3 in the Company's response, focusing on hepatocellular carcinoma and metastatic colorectal cancer, advocate the use of log models for extrapolation in the specific case of AAP for metastatic hormone relapsed prostate cancer not previously treated with chemotherapy. Indeed, these publications state the importance of producing projections that are clinically plausible and external validation with a clinical expert or confirmation in similar populations; as done for AAP during previous appraisal committee meetings. One argument for selecting parametric distributions with long tails such as the log-logistic distribution is the ''survival of the fittest'' phenomenon, it is however unclear to the ERG whether this is applicable for this specific case.

Please note that the last paragraph on page 6 of the Company's response seems incorrect; the time to treatment discontinuation (TTD) in Figure 3 seems overestimated for both AAP and BSC (Company stated only for BSC) and hence it is questionable whether the approach is conservative as stated by the Company. Also, as stated above, the differences in modelled OS seems to be overestimated compared with the Kaplan-Meier curves from Figure 2 (for approximately the first 2 year), which is not considered conservative.

The ERG attempted to verify the first-line TTD two-part model scenario presented by the Company. This scenario initially uses the log-logistic distribution and after the point of extrapolations (approximately 2.5 years) outside of the COU-AA-302 trial, the Weibull distribution is used. The formulas in the Excel model seem correct and the ERG was able to reproduce the results presented by the Company in Table 1 of their response. However, the assumption of discontinuation for BSC after 1,000 days seems arbitrary and not conservative (also illustrated by the 'hitch' in the Model BSC line in Figure 4 of the Company's response).

As requested by NICE, Table 2 presents the ERG base case (including the PAS administration fee) while incorporating the two-part model for TTD with and without the 1,000 days limit for BSC.

Considering **section 2.5** in the Company's response: the results presented by the Company in Table 2, calculated using mean imputation, should be interpreted with caution. Mean imputation should be avoided in general; it underestimates variance/uncertainty, disturbs the relations between variables, biases almost

any estimate other than the mean and biases the estimate of the mean when data are not MCAR (Missing Completely at Random). See for instance the handbook by van Buuren S (2012) "Flexible Imputation of Missing Data".

Table 2: Additional analyses performed by ERG

		Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Updated ERG base case[a]	BSC	[redacted]	[redacted]			
	AAP			£16,184	0.425	£38,061
Updated ERG base case[a] + two-part model	BSC	[redacted]	[redacted]			
	AAP			£15,938	0.312	£51,026
Updated ERG base case[a] + two-part model[b]	BSC	[redacted]	[redacted]			
	AAP			£15,908	0.294	£54,091

[a]This analyses incorporates the PAS administration fee (only applied to AAP).
[b]In this analysis the BSC TTD is not limited to 1,000 days.

See above for arguments regarding the justification for the ERG's preference for using the ITT population. In addition, the comparison of the characteristics of the ITT population with the "analysable" population seems not informative to the ERG. The comparison of the "analysable" population and the patients excluded in this dataset might be more informative. However, independent of the comparison of patient characteristics, given that the incremental TTD is overestimated (see ERG report section 5.2.6 and Figure 5.3 and response to clarification question B4a wherein the Company mentioned that *"analysed patients who were treated with AAP had slightly longer TTD"*), the ITT population and the "analysable" population seem to be different either based on observed or unobserved patient characteristics. For convenience purposes, Figure 5.3 from the ERG report has been copied below (Figure 1). As previously reported in the ERG report: *"This is also illustrated by Table 5.4, comparing model and clinical trial results, indicating an increased median TTD and an increased median OS by 1.05 and 0.27 months respectively favouring AAP"*.

Figure 1: Time to AAP/BSC (PP) discontinuation for the ITT population versus the "analysable" dataset
[Figure is commercial-in-confidence.]

Source: Company submission Figure 37 (Appendix 16) and ERG report Figure 5.3
Abbreviations: AA, abiraterone acetate plus prednisolone; Placebo, placebo plus prednisolone; str, strata; TRTP, treatment arm.

The Company incorporated the PAS administration fee in the analysis described in **section 2.6**. These cost per patient per year were estimated to be £48. It is unclear to the ERG how these costs per patient per year were estimated. However, given that it is more conservative to incorporate these administration costs compared to not incorporating these costs, the ERG updated its base case to incorporate these costs (see Table 1 and Table 2). Moreover, the ERG was able to reproduce the results of this analysis as presented by the Company. Please note that the Company included the PAS administration costs for both AAP and BSC. Consistently with the usage of the old PAS for BSC, the ERG only applied the PAS administration costs to AAP in its updated base case.

The results presented by the Company in Table 4 and described in **sections 2.7-2.9** could not be reproduced by the ERG given the lack details and a copy of the model indicating how these scenarios are exactly implemented. However, the direction of the results (i.e. change in ICER compared with the base case ICER) presented in Table 4 do align with the ERG's expectations. For instance, incorporating a docetaxel price of £35.35 per 160 mg vial in the updated ERG base case would increase the ICER to £40,023.

Please note that the Company's argumentation in **section 2.8** seems flawed. Since unused tablets are unlikely to be recovered by the NHS, 100% of the drug costs are incurred to get a compliance of 98% (in this specific case). Hence no adjustment for treatment effect is necessary.

Regarding **section 3** – 'Survival benefit associated with abiraterone', as stated in the ERG report:

> *"Neither the second nor third interim analysis overall survival results met the pre-specified statistical significance levels (HR at third interim analysis: 0.79 (95% CI: 0.66, 0.96). Median overall survival was 35.3 months (95% CI: 31.2, 35.3) in the AAP group and 30.1 months (95% CI: 27.3, 34.1) in the PP group. The manufacturer did not provide mean survival for both groups or mean survival gain, despite explicit questions in the clarification letter."*

The pre-specified statistical significance level (0.0034) was used to correct for multiple endpoints (OS and rPFS) and multiple time points (after 15%, 40% and 55% of deaths). As can be seen from the trial results, the pre-specified statistical significance levels were not reached and because cross-over is now allowed, it is unlikely that the trial will ever show a significant survival benefit at this level of significance. Therefore, the ERG does not agree with the Company that there is little uncertainty surrounding the extent of the survival benefit associated with abiraterone.

The information in appendix 2 seems to suggest that [redacted], as suggested by the Company. Table 3 summarizes the data provided by the Company in Appendix 2 in comparison with the time to pre-docetaxel abiraterone treatment discontinuation in the model. Considering the differences between the UK and US (Optum health claims) data, it is questionable whether the US data are representative for the UK setting. However, given that the UK data also include post-docetaxel AAP treatment duration, which is expected to be shorter than pre-docetaxel AAP treatment duration (see Table 68 in the original Company submission), the UK data might be an underestimation for actual pre-docetaxel AAP treatment duration. Nevertheless, there is no evidence to suggest that the assumption that approximately 4% take abiraterone for at least 8 years, is valid.

Regarding **section 4** – End of life (EoL) criteria, the ERG still thinks that abiraterone for men with mCRPC in whom chemotherapy is not yet clinically indicated might not meet the end-of-life criteria because the life expectancy in this patient group is likely to be more than 24 months. The fact that some treatments used by control patients in the trial are not recommended by NICE does not change that conclusion.

Table 3: Time to pre-docetaxel abiraterone treatment discontinuation

	Log-logistic distribution (ERG)	Log-logistic distribution (Company)	Weibull distribution (ERG)	Weibull distribution (Company)	Two-part model (ERG)	Two-part model (Company)	[redacted] UK oncology centres[a]	Optum health claims data [redacted] [b]	Optum health claims data [c]
N	na	na	na	na	na	na	nr	[redacted]	[redacted]
>=12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>=24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>=27 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>=36 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>=48 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>=53 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>=60 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>=72 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>=84 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>=96 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: na, not applicable; nr, not reported

[a] It should be noted that these figures include [redacted]

[b] Selection criteria: [redacted]

[c] Selection criteria:

- [redacted]