Response to the Appraisal Consultation Document (ACD)

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

June 2014

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1. Overview

Janssen welcomes the opportunity to comment on the preliminary recommendation made by the Appraisal Committee detailed in the appraisal consultation document (ACD).

We are disappointed the Appraisal Committee's preliminary decision is that abiraterone is not recommended for patients with metastatic hormone-relapsed prostate cancer not previously treated with chemotherapy; however, we are committed to working with NICE in order to address all of the Committee's key concerns outlined in the ACD.

Our response addresses the following key issues:

- **End of life (EoL) criteria**: The ACD states that the Committee did not consider the EoL criterion for short life expectancy (< 24 months) was met. We believe this criterion is in fact met because the published literature on survival estimates for this patient group consistently show that the life expectancy of this population is less than 24 months.
- **Discrete event simulation (DES) model**: We are aware that the Committee has concerns over complexity and transparency of the DES model. We would like to clarify the steps taken when the model was constructed, and demonstrate that both the procedure followed and the outputs generated are robust.
- **Survival benefit of abiraterone**: The Committee has concluded that the survival benefit of abiraterone was overestimated in the COU-AA-302 study. However, we believe that the benefit was robustly demonstrated in the trial, which has high internal validity.
- **Early unblinding of the COU-AA-302 study**: The ACD notes that trial participants might regard early unblinding as unfair. Whilst ethical considerations surrounding randomised clinical trials are complex, we do not agree with this assertion as the unblinding decision was taken by theIndependent Data Monitoring Committee, in keeping with standard practice in oncology trials.
- **Benefits of delaying chemotherapy**: The ACD highlights that one of the benefits of abiraterone acetate is in delaying chemotherapy. Abiraterone offers significantly longer chemotherapy-free period for patients and their carers compared with current standard practice. It is important to recognise that such benefits cannot be readily captured in the standard cost per QALY framework.

Abiraterone, discovered at the Institute of Cancer Research in London, is an example of a UK discovered innovation, and has quickly established itself as the standard of care in the post-docetaxel setting. Moreover, it is the first novel therapy to be licensed in the post-ADT, pre-chemotherapy setting, offering a step-change to those patients who have not received chemotherapy. The clinical demand for abiraterone in this setting is high as evidenced by the fact that it is the second most requested medicine on the Cancer Drugs Fund (CDF).(1)

We believe this response document addresses the key concerns raised in the ACD, and provides the relevant information for the Appraisal Committee to take into account in the forthcoming Committee meeting.

2. End of life criteria

2.1 Short life expectancy, normally less than 24 months

According to the ACD (para. 4.18), the Committee considered that the end-of-life (EoL) criterion for short life expectancy (< 24 months) was not met for abiraterone in the post-ADT, pre-chemotherapy setting. It appears that the Committee's view was predominantly related to the fact that there was an average of 30.1 months survival observed in the control arm of the COU-AA-302 trial.

We believe it is important that the Committee recognises that the control arm of the clinical trial is not representative of average survival of metastatic prostate cancer patients in England and Wales and, as a result, should not be relied upon for determining whether EoL criteria are met. The COU-AA-302 study has high internal validity, which means that it is a robust source of evidence for estimating the effect size of benefit between the two treatment arms. However, Janssen believes that it is not appropriate to use the trial to estimate average absolute survival in UK patients in the absence of treatment is flawed for the following reasons:

- Firstly, this randomised controlled trial was carefully designed to assess the incremental clinical efficacy and safety of abiraterone compared to the control arm, but it is important to emphasise that this study was not designed to answer questions related to the average survival of patients at this stage of their disease in the absence of the new treatment. Therefore, the committee needs to be cognisant of the limitations of using the data in this way to answer a question the study was never designed to answer. Patients enrolled in clinical trials are generally a fitter selection of the target population than those in real life clinical practice due to specific inclusion criteria. Of critical importance to this fact is that, in the COU-AA-302 trial, a specific inclusion criteria was that patients could only participate in the study if they were expected to have a life expectancy of at least 6 months.(2) Patients who were at risk of dying within 6 months were therefore specifically excluded. This means that patients enrolled in the COU-AA-302 study would be, on average, expected to be fitter and thus have a longer survival compared with a general population of patients at this stage of the disease, as a specific subset of patients were pre-selected. Whilst randomisation enables the estimation of an effect size between treatments, this inclusion criteria has the impact of introducing an important element of bias, inflating the average survival estimate in the control arm upward.
- Secondly, this was an international study, and patients in the COU-AA-302 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 1). 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 1: 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.

We have extensively reviewed the published literature on survival estimates for this patient group and we believe our analysis consistently demonstrates that the balance of evidence consistently supports our conclusion that the life expectancy of this population is less than 24 months, as summarised below:

- The 2012-2014 European Association of Urology (EAU) guidelines state a mean survival of patients in this setting is between 9 and 27 months, depending upon the level of metastases.(4-6)
- The SWOG study shows that a PSA of ≤4 ng/mL after 7 months of ADT is a strong predictor of survival.(7) In the COU-AA-302 study, the median PSA at baseline was approximately 10-fold higher; 40ng/ml.(3) In the SWOG study, those patients with PSA >4ng/ml at the end of ADT demonstrated on average 13 months survival.(7)
- Lastly, a systematic literature review by Kirby et al. showed the median survival of patients with castrate-resistant prostate cancer (CRPC) to range between 9 to 30 months, with considerably shorter estimates for those with metastatic disease (9 to 13 months). A pooled sample-weighted survival estimate from populations included in the review was 14 months.(8)

In making a balanced judgement about whether this EoL criterion is met, we believe that the Committee should fully acknowledge the limitations of relying on the control arm of the COU-AA-302 study and take close account of the consistent evidence we have outlined above. This evidence, from different sources, all support the case for accepting the plausibility that survival in this group of patients would on average be less than 24 months.

Furthermore, this approach would be consistent with many other previous NICE TAs where the EoL criteria were considered. We reviewed both the NICE website and the HTAinSite database, searching all NICE TAs for which the EoL criteria were considered. This search, which was validated for accuracy by an independent consultancy (see Appendix 1), identified a total of 35 STAs and 4 MTAs. The source of evidence used to demonstrate a life expectancy of less than 24 months varied among TAs, with no single source of evidence being explicitly preferred by the Committee. In numerous cases, multiple sources were presented to support a life expectancy of less than 24 months. Whilst median OS from the control arm of the clinical trial(s) was a common source (n=27), published literature (including other published clinical trials in the disease area) (n=13) and expert clinical opinion were also used (n=6) (Table 2). This illustrates the importance of evaluating each appraisal on a case by case basis and recognising when the clinical trial may or may not be the best available evidence to assess suitability for EoL.

Table 2: EoL criterion of short life expectancy (<24 months) - Basis for decision making

Basis for decision making	No. of technologies
Control arm of clinical trial	27
Published literature	13
Clinical opinion	6
Model estimates	4

2.2 Extension to life, normally of at least an additional 3 months, compared to current NHS treatment

The COU-AA-302 trial demonstrated that, at the third interim analysis (IA3) with 55% of OS events (425 of 773), the median OS is 5.2 months longer in the abiraterone arm than in the control arm.(3) The *mean* OS from the IA3 would be misleading because 45% of OS events had not occurred and thus many patients were still alive, and thusthe median OS offers a better estimate of abiraterone's survival benefit.

Based on the economic model, the mean modelled OS benefit of abiraterone compared with the control arm is 9.3 months, which we believe demonstrates a significant survival advantage in favour of abiraterone.

Both the trial and model results indicate that abiraterone meets the EoL criterion of extension to life of at least 3 months.

This is consistent with previous TAs: Our analysis shows that in a significant proportion of TAs (n=21), the median OS reported from the relevant clinical trial(s) was the primary source of evidence and, in a minority of TAs (n=9), the modelled mean OS was also cited as an additional information source (Appendix 1).

2.3 The treatment is licensed or otherwise indicated for small patient populations

The ACD (para. 4.18) notes that we had presented an estimate of the population eligible for abiraterone in England and Wales, rather than that for England only. Table 3 displays the estimated split between England and Wales.

Table 3: Patients eligible for treatment with abiraterone in the pre- and post-docetaxel settings

	England and Wales	**England**	**Wales**
Population	56,784,200	53,698,373	3,085,827
Estimated number of mCRPC patients	11,085	10,483	602
Chemotherapy-naïve	60%	60%	60%
No. chemotherapy naïve	6,651	6,290	361
Asymptomatic or mildly symptomatic	70.5%	70.5%	70.5%
Eligible patient population (A)	**4,689**	**4,434**	**255**
Receive docetaxel	40%	40%	40%
No. receiving docetaxel	4,434	4,193	241
Assume 70% of these are eligible for AAP post-docetaxel	3,104	2,935	169
Eligible patients after the introduction of AAP in the post-ADT, pre-chemotherapy setting (B)	**2,483**	**2,348**	**135**
Total no. of patients eligible for AAP in both pre- and post-docetaxel settings (A+B)	**7,172**	**6,782**	**390**

AAP, abiraterone acetate plus prednisone/prednisolone; ADT, androgen deprivation therapy; mCRPC, metastatic castration resistant prostate cancer.

These estimates indicate that the eligible patient population is small, whether it is for England only, or for England and Wales combined.

Moreover, according to figures released by NHS England, 3,023 applications were received by the Cancer Drugs Fund regarding the use of abiraterone in the post-ADT, pre-chemotherapy setting between April 2013 and March 2014.(1) This confirms that abiraterone is indeed being used in a small patient population in UK clinical practice.

3. Discrete event simulation model

3.1 Model design

According to the ACD (para. 4.8), the "Committee agreed that using a discrete event simulation model was not unreasonable, but that the manufacturer's model was particularly complex". In its report, the ERG stated that a "less elaborate Markov model (using more health states than the regular three-state model) would have been as appropriate and would have allowed the ERG much more flexibility in performing additional analyses" (page 14).

We believe that, for this particular appraisal, a Markov approach would not necessarily be simpler than the discrete event simulation (DES) model for the following reasons:

- First, a patient's disease progression and treatment choice depends upon past experience and the specific time point at which they move to the next treatment phase. However, unlike the DES model, Markov models have no memory as noted in the technical support document (TSD) on patient-level simulation recently published by NICE DSU: "state-transition models often employ a Markovian assumption in which it is assumed that future events are independent of past events. This makes it difficult to model situations where the likelihood of future state transitions is dependent on the time since a previous transition (e.g. time on current treatment) or the history of previous events" (9)
- Second, for a Markov model to capture multiple lines of treatment and time dependent transition probabilities, it would have to be fairly complicated with a cohort in each cycle needing to be tracked separately, given the no memory limitation of the Markov approach.

In contrast, the DES is more efficient as indicated by the NICE DSU: "An individual patient-level methodology is likely to provide a more efficient and parsimonious solution than trying to implement a cohort model in situations where there is substantial non-Markovian behaviour due to its ability to track individual patients and record their event history and use this to update their risk of future events".(9)

3.2 Prediction equations

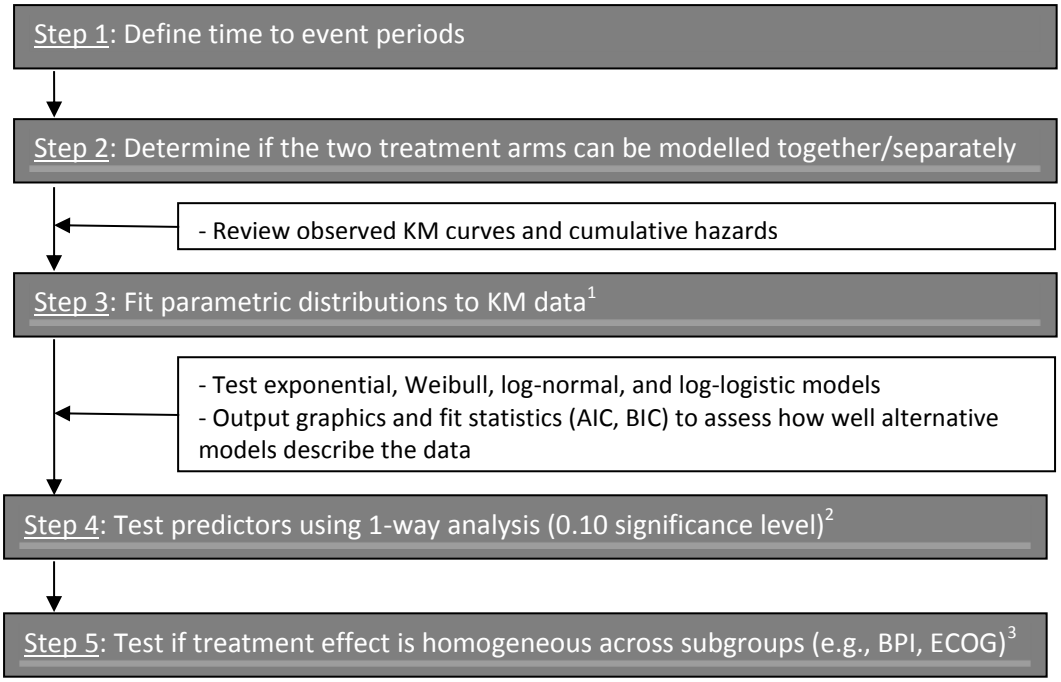
The ACD states: "for each of the model's 17 equations predicting time to events, the Committee noted that the manufacturer needed to make a large number of judgements when determining which variables to include in the prediction equations, which covariates to retain in the equations, and which parametric distribution to choose for extrapolation" (para. 4.8). The same paragraph also notes: "The manufacturer did not clearly pre-specify its approach to each of these judgements".

We would like to clarify the steps taken and the pre-specified statistical methodologies employed in order to derive the prediction equations.

Prediction equations are required for the DES model in order to predict when each patient transitions from one phase to another. Patient characteristics are included in the prediction equations because the model simulates one patient at a time, and using his characteristics can help us better replicate what actually happened in the trial.

The COU-AA-302 study data are 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 1.

Figure 1: Statistical procedure to develop time-to-event prediction equations



Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; BPI, Brief Pain Inventory score; ECOG, Eastern Cooperative Oncology Group performance status

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

[2]Note that adding predictors ensures that variability in the outcomes between patients in the trial is captured correctly, which is important in DES modelling. 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 procedure illustrated above generated a series of prediction equations as shown in Table 4 and Table 5.

Table 4: Time-to-event prediction equations

From →	To	Parametric distribution used
AAP / WW(PP) start	AAP / WW(PP) end	Log-logistic
AAP / WW(PP) end	Docetaxel start	Log-normal
Docetaxel start	Docetaxel end	Weibull
Docetaxel end	Post-docetaxel treatment start	Weibull
Post-docetaxel treatment start	Post-docetaxel treatment end	Weibull
AAP end	Death	Weibull
WW (PP) end	Death	Weibull
Docetaxel start	Death	Log-logistic
Docetaxel end	Death	Weibull
Post-docetaxel treatment end	Death	Weibull

Abbreviations: AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; PP, placebo plus prednisolone; WW, watchful waiting.

Table 5: Disease status prediction equations

ECOG status at AAP / WW(PP) end
ECOG status at docetaxel start
ECOG status at docetaxel end
ECOG status at post-docetaxel treatment start
PSA progression at AAP / WW (PP) end
Radiographic progression at AAP / WW (PP) end
Opiate use at AAP / WW (PP) end

Abbreviations: AAP, abiraterone acetate plus prednisolone; ECOG, Eastern Cooperative Oncology Group; PP, placebo plus prednisolone; PSA, prostate-specific antigen; WW, watchful waiting.

The ACD states: "the Committee appreciated that it is also important to take into account face validity and whether extrapolation predicts realistic outcomes, both for the event modelled by each equation, and for the model as a whole, but that this had not been done by the manufacturer" (para. 4.9). Janssen believes that this is not a fair conclusion because we followed a pre-defined protocol to assess the validity of the individual prediction equations (Figure 1). Also, comparisons between the fitted curves and the Kaplan-Meier curves from the trial have been previously provided to the ERG in our response to the clarification questions (see Figure 8 and Figures 10-28 in our response document).

In summary, in order to derive the prediction equations, we performed necessary statistical analyses by diligently following the pre-defined procedure and by checking face validity of the final equations.

3.3 Analysable population vs. ITT population

According to the ACD (para. 4.10), the "Committee was concerned that the selected group may not be representative of the ITT population, and of patients in England".

When developing the prediction equations, the number of patients contributing to each equation depended upon which characteristics or predictors were retained in the final prediction equation. A total of 902 patients from the COU-AA-302 study had full baseline data (459 for AA and 443 for placebo) to inform the statistical analysis and to derive the prediction equations.

The analysable dataset of 902 patients was also used to define the patient profiles in the model. We believe that missing of baseline information occurred completely at random and therefore does not bias the results. As Table 6 illustrates, baseline characteristics of the analysable population and the ITT population are very similar.

Table 6: Patient characteristics of analysable population vs. ITT population

	ITT population		**Analysable population**	
Characteristic	**AAP (N=546)**	**PP (N=542)**	**AAP (N=459)**	**PP (N=443)**
Age, years, median	71	70	70	70
<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
Black	2.8	2.4	2.6	2.5
Asian	0.7	1.7	0.9	1.6
Native Hawaiian / Other Pacific Islander	0	0.4	0.0	0.2
Other	1.1	1.1	1.1	1.1
Ethnicity, %				
Hispanic or Latino	4.6	4.5	3.7	4.8
Not Hispanic or Latino	95.4	95.5	96.3	95.2
Weight (kg), median	87.0	88.0	87.0	87.9
Height (cm), median	175.0	175.3	175.0	176.0
Mean time from diagnosis to first dose, years	6.7	6.5	6.79	6.5
Alkaline phosphatase, IU/L, median	93	90	93	90
Haemoglobin, g/dL, median)	13	13.1	13	13.1
Lactate dehydrogenase, IU/L, median	187	184	187	183
Baseline serum PSA, ng/mL				
Median	42	37.7	40.48	37.82
Range	0 – 3,927	1 – 6,606	0.04 – 3927.43	0.7 – 6606.44
BPI-SF #3 pain score, %				
0–1	68.6	64.8	74.07	69.75
2–3	23.9	27.5	25.93	30.25
≥4	7.4	7.7	0	0
Bone-only metastasis, %	50.4	49.3	51.85	50.11

As previously presented in our response to the ERG's clarification questions, Kaplan-Meier curves for both OS and time to treatment discontinuation (TTD) are very similar between the analysable and ITT populations (see Figure 2 to Figure 5).

Figure 2: Analysable vs. ITT populations – OS, abiraterone arm

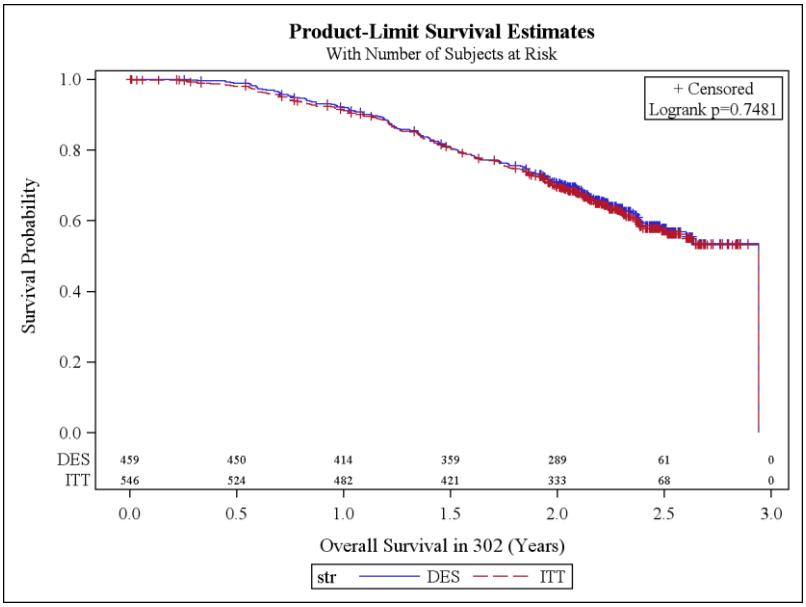


Figure 3: Analysable vs. ITT populations – time to treatment discontinuation (TTD), abiraterone arm

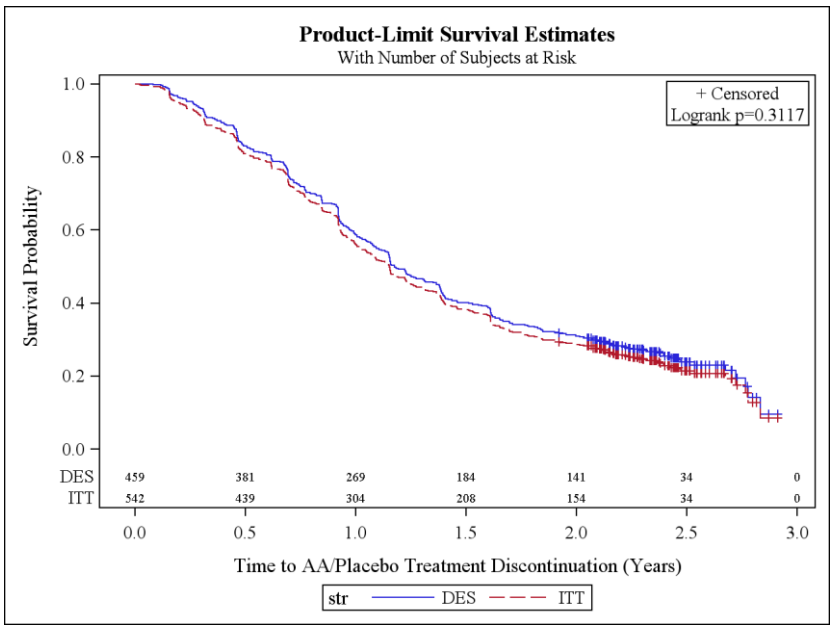


Figure 4: Analysable vs. ITT populations – OS, control arm

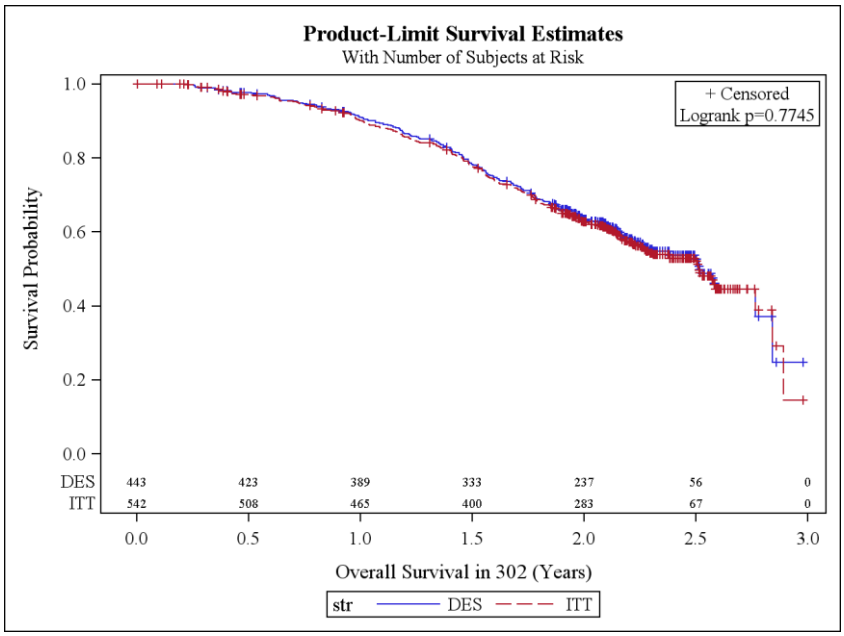
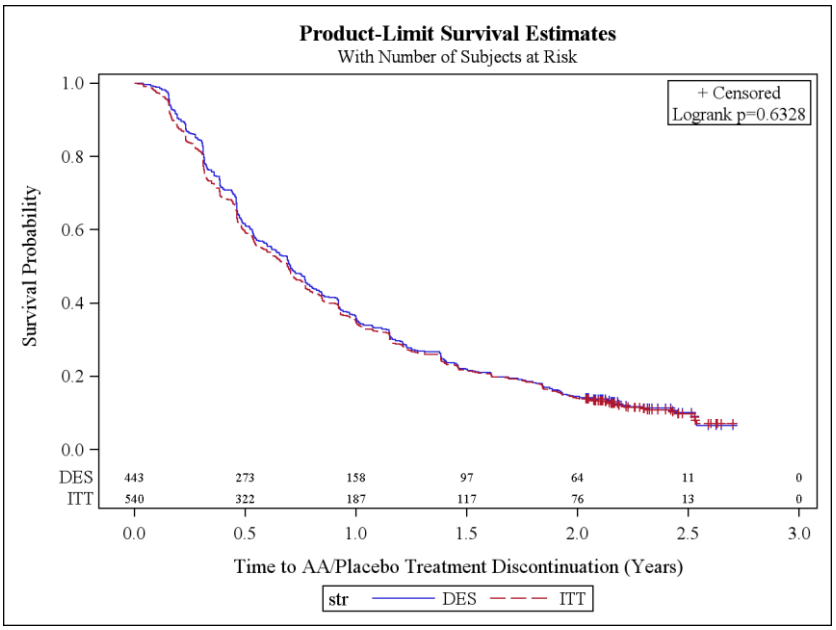


Figure 5: Analysable vs. ITT populations – time to treatment discontinuation (TTD), control arm



Comparisons between the analysable and ITT populations shown above illustrate that the two populations are indeed similar, and we believe that the ERG's concern ("the ITT population was not used (but a subset) and therefore the model results were probably not fully comparable with the ITT results of COU-AA-302" [para. 3.25]) are addressed by the results we present here.

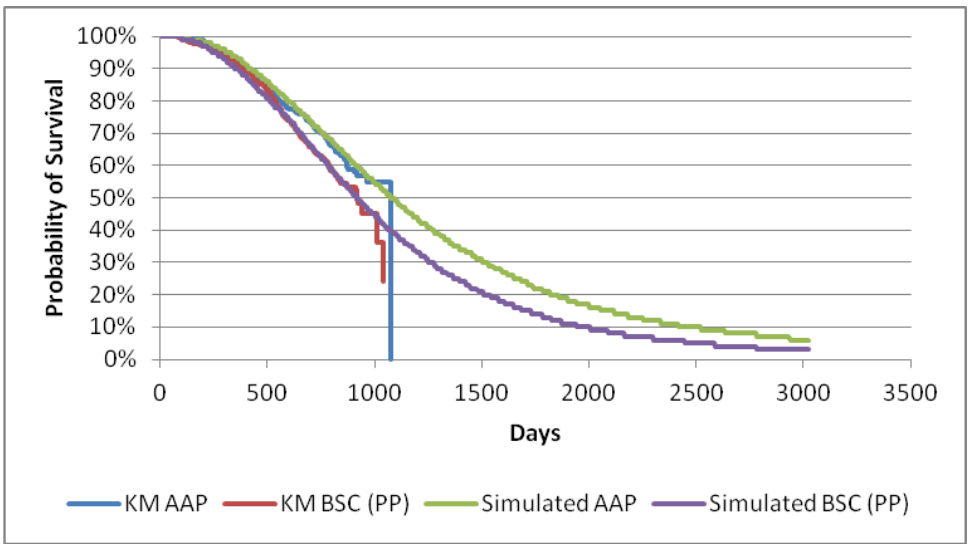
The ACD also states that the Committee "noted the ERG's comments that using the subgroup favoured abiraterone compared with best supportive care because people in the subgroup were treated with abiraterone for longer than people in the ITT population, and this would have the effect in the model that overall survival improved" (para. 4.10). Again, this is not a relevant issue that impacts the cost-effectiveness of abiraterone for the following reason:

- Contrary to the ERG's comment, the difference in TTD for abiraterone between two populations did not result in an overestimation of survival benefit of abiraterone over placebo. As Figure 6 illustrates, the model predicted the observed OS closely, particularly between year 1 and year 3 when most of treatment discontinuations occurred. This was also acknowledged in the ACD ("The Committee noted that the model results followed the trial results between day 540 and day 1080, at which point the trial data were unblinded." [para. 4.10])

Therefore, there is no evidence to suggest that the use of the analysable population, rather than the ITT population, favoured abiraterone compared against placebo. If anything, it may have resulted in a higher ICER than in a hypothetical situation where all relevant baseline characteristics were available for the overall ITT population.

It is also important to note that small variation between the ITT trial survival curves and the modelled curves is partially attributable to the way the model accounts for subsequent novel therapies. In the trial, patients went on to receive subsequent treatments with interventions not available to UK patients (which occurred more in the control arm [Table 1]), and therefore the modelled curves are more likely to reflect the survival benefit that can be expected in the NHS.

Figure 6: Overall survival - observations from COU-AA-302 trial vs. predictions from the economic model



4. Survival benefit of abiraterone

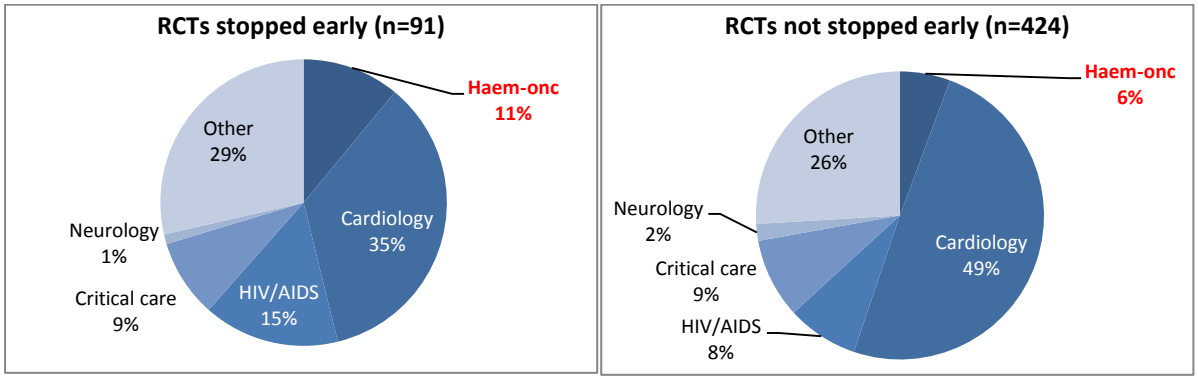
The ACD states that "the Committee concluded that it was likely that the treatment effect of abiraterone on survival was overestimated" (para. 4.5). It appears that this assertion was based on a verbal comment made by a committee member who was referring to a single systematic review conducted by Bassler et al.

We are surprised that this anecdotal comment, which if it were true would equally apply to many other appraisals, appears to have been used as a justification for questioning the robustness of the survival estimate. We have extensively reviewed this systematic review and are confident that it does not provide any robust justification for the Committee to conclude that the survival benefit of abiraterone is overestimated.

Firstly, in their publication, Bassler et al. did not state that "trials that stop early show a larger treatment effect than trials that run to completion, and that trials stopped early because of benefit are likely to overestimate benefit by approximately 40%" (ACD para. 4.5). In fact, their key finding was that the pooled ratio of relative risks in truncated RCTs (i.e. those stopped early) vs. matching non-truncated RCTs was 0.71.(10) This represents a 29% relative risk reduction, rather than 40%.

Secondly, and of most relevance, the majority of RCTs reviewed by Bassler et al. were in cardiology and HIV/AIDS, and only a small minority (11%) was from haematology-oncology (Figure 7).(10) Given that approximately 90% of the RCTs reviewed by Bassler et al. were from outside the haematology-oncology area, there is no clear relevance of these findings to this appraisal of patients with mCRPC.

Figure 7: Disease areas of RCTs reviewed by Bassler et al.(10)



Indeed, Bassler et al. quoted reviews of oncology studies conducted by others:

- "Korn and colleagues recently reviewed the results of cancer trials stopped early and that either continued with further follow-up or released results early. They found that substantial differences between results at the time of early stopping and subsequent follow-up seldom occurred."(10)
- "Freidlin and Korn published a related simulation study that supported these findings, suggesting that if the true effect is large, differences between stopped-early results and full follow-up results will differ little."(10)

These comments cast further doubts on whether the findings by Bassler et al. should be applied in the decision making process for this particular STA.

Therefore, the basis for the Committee's conclusion regarding the survival benefit of abiraterone, namely the review paper by Bassler et al., does not appear to have relevance for the current decision problem.

It is important to note that treatment with abiraterone resulted in a clinically meaningful improvement in OS. An estimated 21% decrease in the risk of death was observed (absolute risk reduction 6.6%), resulting in an additional 5.2 months of life.(3) Although the result did not cross the

boundary for statistical significance (p-value: observed 0.0151 vs. required 0.0034), this was due to the stringent pre-specified alpha-spending rules applied to the interim analyses.

We believe that the survival benefit of abiraterone was clearly demonstrated in the COU-AA-302 trial, and there is no reason to believe that abiraterone's benefit was either over- or under-estimated.

5. Early unblinding of the COU-AA-302 study

The ACD states that the Committee "noted that people consented to participate in the study based on the original protocol, and they were not given the opportunity to consider this deviation from the protocol. The Committee considered that trial participants might regard this as unfair, undermining the value of the results, and reducing the value of their having taken part in the trial."

We disagree with this assertion. Considered opinion on these matters is that it is unethical to knowingly harm patients by allowing those in the control arm to progress and die unnecessarily when sufficient evidence is available to determine whether or not there are substantial benefits of abiraterone compared with placebo.

There was some criticism of Janssen at the committee meeting, where some individuals appeared to have the incorrect understanding that it was the company that took the decision to stop the trial early. This is wholly inaccurate. We want to re-emphasise that the decision to unblind the study was taken entirely independently of the company. Janssen had no part in that decision. Regulatory trials of cancer medicines (and other trials) mandate the creation of an independent data monitoring committee (IDMC) to oversee trial results at pre-specified time points to ensure that participants are treated ethically during a trial. One of the core roles of an IDMC is to recommend stopping trials early for three key reasons. Firstly, if safety concerns arise, stopping a trial ensures that participants are not unnecessarily exposed to an unproven treatment. Alternatively if the data demonstrates an overwhelming benefit for participants at an interim analysis point, the IDMC will recommend that the trial should be stopped, as it would be unethical to withhold an efficacious treatment from patients in the control arm. Lastly, a trial may be stopped early if the results in the control arm are identical to those in the experimental arm. A monitoring role is essential in these decisions. However, the company sponsoring the trial is blinded, so they cannot perform this service in order to mitigate any conflict of interest. In the case of the COU-AA-302, the IDMC was tasked to review the results and provide one of the following three recommendations at each of the analysis time points:

- Recommend stopping study for safety reasons
- Recommend study continues to next interim analysis on OS
- Recommend stopping study for survival advantage and crossing over patients on the placebo arm

The IDMC made a unanimous decision to stop COU-AA-302 at IA2 as all committee members felt the ethical thing to do was to stop the study in view of the highly significant advantage seen for survival among patients on Arm X which turned out to be the abiraterone arm. This decision was further supported by the high significance observed in the secondary endpoints the IDMC evaluated. No other questions or concerns were raised by committee members. The committee's recommendation to the study sponsors (Janssen/Cougar Biotechnology) was to stop the study and permit crossover from placebo to abiraterone, and to inform the regulatory authorities of this decision.

Ethical considerations surrounding randomised clinical trials are indeed complex. However, the comment in the ACD (quoted above) is contrary to the generally accepted standard role of an IDMC, and also not plausible in the context of the COU-AA-302 study where it was clear that patients in the placebo arm would benefit from crossover to abiraterone.

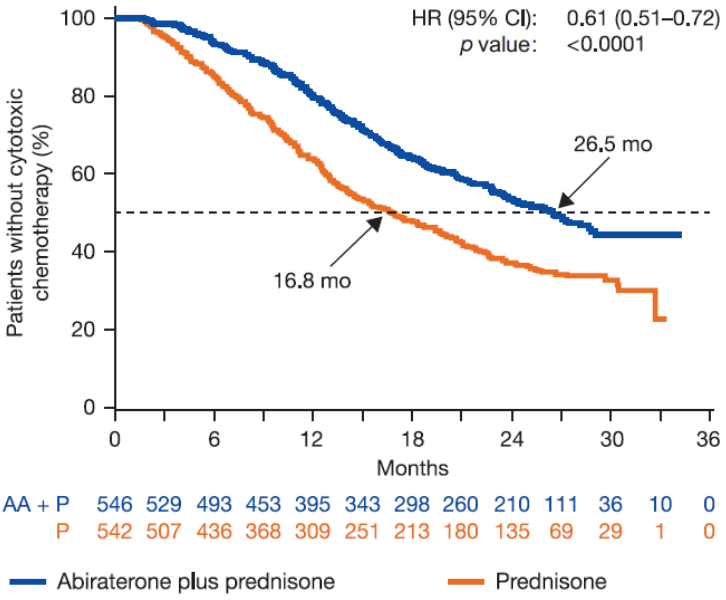
6. Benefits of delaying chemotherapy

An important benefit which was discussed by both the clinicians and patient groups during the Appraisal Committee meeting was the value of abiraterone in delaying or avoiding chemotherapy. This was mentioned numerous times in the ACD:

- "The Committee heard from the clinical specialists that older people and people with comorbidities are less likely to be fit enough to have docetaxel, and that some patients chose not to have docetaxel." (para. 4.1)
- "…clinicians would generally use [abiraterone], in addition to best supportive care, to treat people with few symptoms to delay chemotherapy, or to treat people who are unable or do not wish to have chemotherapy." (para. 4.1)
- "The Committee heard from the patient experts about how important it is for patients to have the option of delaying chemotherapy. The patient experts explained that the adverse effects of chemotherapy are severe and may be particularly poorly tolerated by people who are older or who lack support from a partner or carer. The patient experts further stated that some people choose not to have cytotoxic chemotherapy to avoid the debilitating adverse effects and to maximise the quality of what remains of their lives, even if it may mean dying sooner. The Committee concluded that chemotherapy can reduce a person's quality of life and that treatments that delay the need for chemotherapy are highly valued by patients." (para. 4.2)
- "The Committee noted the statements submitted by patient groups, which pointed out that patients usually can cope with the adverse effects of abiraterone that are usually mild and tolerable, particularly compared with those of docetaxel, and that one of the advantages of abiraterone is that it delays the debilitating effects of chemotherapy." (para. 4.6)

Time to initiation of cytotoxic chemotherapy, one of the secondary endpoints in the COU-AA-302 trial, was nearly 10 months longer in the abiraterone arm than in the control arm (26.5 months vs. 16.8 month [Figure 8]). Abiraterone reduced the risk of chemotherapy initiation by 39% and the hazard ratio (0.61) was statistically significantly below one (p<0.0001).(3)

Figure 8: Time to initiation of chemotherapy - COU-AA-302 [IA3] (3)



The trial results clearly demonstrate that, for those patients who eventually receive chemotherapy, abiraterone can allow them to stay chemotherapy-free significantly longer than under the current standard of care. Although docetaxel is recommended by NICE and widely used in today's UK clinical practice, it is associated with debilitating side effects and requires substantial emotional and physical support from nurses and carers.(11) The impacts of cytotoxic therapy on a patient's body may not be confined to time on treatment, but could also stretch into the longer term for those that experience serious side effects.(12)

There is also a group of patients who are unable to receive chemotherapy because they are not fit enough, or because they lack the social, family and emotional support that is necessary to cope with the rigors of chemotherapy with docetaxel. Indeed, as of IA3 of the COU-AA-302 study, a higher proportion of patients in the abiraterone arm still had not received docetaxel compared with the control arm (56% vs. 44%) (Table 1).(3) With current NICE guidance, this group of men cannot access novel agents such as enzalutamide or abiraterone in the post-chemotherapy setting, which means that they are left without access to NICE approved options other than best supportive care. This creates a natural inequity in access for both clinical and social reasons, which approval of abiraterone in the post-ADT, pre-chemotherapy setting could redress.

Furthermore, whilst this benefit of abiraterone is highly relevant to the patient and their carers in this setting, it is not adequately captured within the cost per QALY evaluation:

- The majority of patients who have metastatic prostate cancer are elderly, as the disease is most common in those over the age of 70.(13, 14) Many patients suffer co-morbidities, are likely to be reliant on family or carers and require emotional support to endure chemotherapy. Whilst abiraterone can delay or avoid the need for chemotherapy, such patient benefits cannot be adequately captured in the cost per QALY framework.
- Many men at this age live alone, for example having been widowed. Such social isolation can be a barrier to receiving chemotherapy.(11) Hence a patient's treatment pathway is determined not only by their health status, but is also highly dependent on social factors such as the support from nurses and carers, time spent with loved ones, practicalities of medical care and other day-to-day activities. Abiraterone's ability to alter the treatment pathway of this group of patients cannot be fully captured in the standard evaluation framework.
- Metastatic prostate cancer can also occur in younger men who may also lack a stable support network, or may otherwise be the financial provider for a household. As a result, these men would require the necessary social support to help minimise the impact of time off work and travel expenses on their family whilst they undergo treatment.(11) Again, the standard cost per QALY framework is not well suited to capture abiraterone's benefits for this group of patients.
- Detrimental impact of chemotherapy on carers is well documented. For example, Turkoglu and Kılıc concluded that QoL of carers of cancer patients undergoing chemotherapy decline as carer burden increases.(15). A recent UK study explored the needs of informal carers for patients having intravenous chemotherapy and illustrated different aspects of carer burdens.(16) By delaying or avoiding the need for chemotherapy, abiraterone can benefit QoL of carers as well as that of patients. However, the standard cost per QALY framework does not adequately capture this benefit.

Extending the stage of disease when mCRPC is still asymptomatic or mildly symptomatic means patients may enjoy prolonged quality of life and more time with loved ones whilst their disease is less severe. Since abiraterone can be taken at home, there is minimal interruption to daily life and less need for frequent visits to hospital. Elderly patients in particular can therefore avoid the social anxiety associated with outpatient clinics and the financial requirements of travel. In addition, the value of delaying chemotherapy is felt indirectly by the family and carers of the patient as there is less demand for continuous physical, emotional and financial support required throughout

chemotherapy. Indeed, such carer benefit appeals to a pivotal aspect of the NHS Outcomes Framework which recognises the vital role they play in supporting people who are ill and the importance of also maintaining their QoL (indicator 2.4 Health related quality of life for carers).(17)

As mentioned above, whilst many mCRPC patients are reliant on the care provided by others, some may not have a carer and hence would not cope with the arduous cycles of chemotherapy. These patients have no choice other than to receive best supportive care and would be excluded from receiving novel agents only available after chemotherapy. Elderly men are rarely naïve to their prognosis when diagnosed with metastatic prostate cancer, yet clinical opinion suggests that many would choose to avoid chemotherapy; Koedoot et al. found watchful waiting was preferred among cancer patients who expected severe toxicities from chemotherapy.(18)

7. Other issues

7.1 Sensitivity analysis around the treatment effects

The ACD states: "The Committee further recognised that the manufacturer had not performed a sensitivity analysis around the treatment effect of abiraterone" and "key areas of uncertainty had not been explored" (para. 4.14).

To address this concern, additional sensitivity analyses have been performed by varying coefficients for treatment effects by one standard error in each direction. Table 7 indicates that varying treatment effect-related coefficients results in the ICER range between £41k/QALY to £55k/QALY.

Table 7: Results of the sensitivity analyses – treatment effects

1) Treatment effect=mean – SE			
	AAP	**PP**	**Incremental**
LY	[redacted]	[redacted]	0.46
QALY	[redacted]	[redacted]	0.42
Cost	[redacted]	[redacted]	£23,136
Cost/QALY			£55,155
2) Treatment effect=mean + SE			
	AAP	**PP**	**Incremental**
LY	[redacted]	[redacted]	0.81
QALY	[redacted]	[redacted]	0.73
Cost	[redacted]	[redacted]	£29,996
Cost/QALY			£41,248

7.2 Docetaxel drug cost

Para. 4.13 of the ACD discusses the cost of docetaxel in the model, and notes that "the price used by the manufacturer in the model seemed high".

To test the sensitivity of the ICER estimate on docetaxel acquisition cost, an additional analysis was performed whereby docetaxel cost was reduced by 20%. As shown in Table 8, the ICER estimate in this sensitivity analysis (£46,998/QALY) is highly similar to the one from the base case (£46,722/QALY), suggesting the ICER is not particularly sensitive to the cost of docetaxel.

Table 8: Result of the sensitivity analysis – docetaxel cost

	AAP	**PP**	**Incremental**
QALY	[redacted]	[redacted]	0.57
Cost	[redacted]	[redacted]	£26,560
Cost/QALY			£46,998

8. Conclusion

Appraised in 2012 under end of life criteria, abiraterone in the post-chemotherapy setting was only recommended for use on the NHS following considerable efforts and a patient access scheme by Janssen to make the medicine available to NICE. [redacted]

In this current appraisal in the pre-chemotherapy setting, the Committee has made an initial decision to reject abiraterone as they believe it does not meet the EoL criteria in the same patient population earlier in the treatment pathway. We believe that the balance of evidence supports our arguments that abiraterone continues to meet these criteria at this stage in the patient pathway. Given that abiraterone has already been appraised under these criteria in an indication in which it is used in the same types of patients later on in the prostate cancer pathway, such a decision not to

apply the criteria on this occasion could illustrate the arbitrary nature of how these criteria are applied. It is important to note that the current indication under appraisal offers a range of clinically important benefits for men at an earlier stage of their disease, at a similar cost-effectiveness to the indication previously approved. It also provides an option for men who cannot go through chemotherapy for clinical or social reasons, and delays the time to chemotherapy for those who can. These are critically important benefits, but ones which are not easy to capture in a traditional cost per QALY framework. We therefore believe that there are a range of important benefits that are strongly under-represented in the economic analysis as it stands. If approved in the pre-chemotherapy setting, patients will receive abiraterone prior, as opposed to after, chemotherapy, providing more equitable access to this NICE approved medicine in the same group of patients, earlier in the course of their disease.

Appendix 1: Review of previous NICE HTAs in oncology

The search of previous NICE HTAs of oncology drugs were conducted using the NICE website and the HTAinSite database. All NICE TAs for which the EoL criteria were considered. This search has been validated for accuracy by Abacus International, an independent consultancy who administers the HTAinSite database.

Table 9: EoL criteria decisions by NICE Technology Appraisal Committees

EoL criteria fully met?	No. of technologies
Yes	19
No	25
TOTAL	44

Table 10: EoL criterion of short life expectancy (<24 months) - Basis for decision making

Basis for decision making	No. of technologies
Control arm of clinical trial	27
Published literature	13
Clinical opinion	6
Model estimates	4

Table 11: EoL criterion of survival gain (>3 months) - Basis for decision making

Basis for decision making	No. of technologies
Median OS from clinical trial	21
Median OS from clinical trial & modelled mean OS	9
Modelled mean OS	6
Mean OS from clinical trial	8

Table 12: List of NICE HTAs in oncology and EoL considerations

TA	Drug	Condition	Decision	EoL met	> 3 months survival gain based on.. (mean/median survival)	<24 months life expectancy based on.. (mean/median survival)
169	**Sunitinib (STA)**	Renal cell carcinoma	**Yes (restricted)**	**Yes**	- median OS (26.4 vs 21.8) - extrapolated mean OS given (46.6 vs 27.5)	- median OS estimates from CT control arms
171	**Lenalidomide**	Multiple myeloma	**Yes (restricted)**	**Yes**	- median OS from trial	- median OS from published lit - MRC data
172	**Cetuximab**	Recurrent and/or metastatic squamous cell cancer of the head and neck	**No**	**No**	- median OS gain from trial (2.7mo) - modelled OS gain (2.2mo) mean/median not specified	- life expectancy based on control arm - unlikely >24mo - potentially as low as 7mo
178	**Bevacizumab**	Renal cell carcinoma	**No**	**No**	- median OS from trial	- life expectancy based on median trial data
178	**Temsirolimus**	Renal cell carcinoma	**No**	**Yes**	- median OS gain from trial (10.9 vs. 7.3 months)	- life expectancy based on median trial data
179	**Sunitinib**	Metastatic GIST	**Yes**	**Yes**	- median OS gain from trial (73 vs 65 wks)	- published life expectancy lit - life expectancy from trial noted by committee - RPSFT adjusted BSC arm to 39 wks.
183	**Topotecan**	Recurrent cervical cancer	**Yes (restricted)**	**No**	- median OS gain from trial	- life expectancy proxy from clinical expert
184	**Topotecan**	Small-cell lung cancer	**Yes (restricted)**	**Yes**	- median OS from trial (25.9 vs. 13.9 wks) - extended survival from model	- published life expectancy lit - life expectancy from control arm
185	**Trabectedin**	Soft tissue sarcoma	**Yes (restricted)**	**Yes**	- median OS gain from trial	- median survival from published lit
189	**Sorafenib**	Advanced hepatocellular carcinoma	**No**	**Yes**	- modelled mean OS gain	- life expectancy based on median OS trial data - supported by other CT also median OS
190	**Pemetrexed**	Maintenance NSCLC	**Yes**	**Yes**	- median OS gain from trial (5.2 mo) - mean life extension exceeded 3months - modelled mean OS gain exceeded 3 months	- median OS from clinical trials
196	**Imatinib**	GIST	**No**	**No**	- No robust evidence in survival gain - median OS not reached	- mean life expectancy more than 24 months

202	**Ofatumumab**	Chronic lymphocytic leukaemia	**No**	**No**	- median OS gain from trial - modelled OS gain thought to be biased - non-comparative evidence not robust enough	- published life expectancy lit
208	**Trastuzumab**	HER2-positive metastatic gastric cancer	**Yes**	**Yes**	- median OS gain from trial (4.2mo & 5.6mo) - modelled mean OS exceeded 3 months (4.8mo & 7.4mo)	- median OS control arm of trial
209	**Imatinib**	Unresectable and/or metastatic gastrointestinal stromal tumours	**No**	**No**	- modelled mean OS exceeded 3 months (4.2 mo)	- published life expectancy lit
212	**Bevacizumab**	Metastatic colorectal cancer	**No**	**No**	- median OS gain <3 months	- median OS from CT
214	**Bevacizumab**	First-line treatment of metastatic breast cancer	**No**	**No**	- median OS gain <3mo (1.7mo)	median OS in BSC arm = 24.8mo
215	**Pazopanib**	Renal cell carcinoma	**Yes (restricted)**	**Yes**	- modelled median OS gain (27.8 vs 12.1 mo) - estimated using the RPSFT weighted method	- published life expectancy lit - sunitinib median survival from RCT - clinical specialist
218	**Azacitidine**	Myelodysplastic syndromes	**Yes (restricted)**	**Yes**	- median OS gain from trial	- life expectancy based on BSC arm in trial
219	**Everolimus**	Advanced renal cell carcinoma	**No**	**Yes**	- median OS gain from trial - mean OS calculated using IPCW - mean OS calculated using RPSFT - modelled mean OS gain	- median life expectancy thought <12 mo - median survival of 5.4 - 22 mo depending on severity - Clinical specialist: life expectancy for patients on BSC unlikely to be > 24 months and potentially as low as 5 months
222	**Trabectedin**	Relapsed ovarian cancer	**No**	**No**	- median OS from trial	- published life expectancy lit
227	**Erlotinib**	Lung cancer	**No**	**No**	- modelled (by ERG) mean OS gain (3.4mo)	- median survival 7-11mo - UK life expectancy - source not provided
239	**Fulvestrant**	Breast Cancer (metastatic)	**No**	**No**	- NMA submitted by manufacturer - no diff in OS gain	- mean survival estimated from trial & NMA - not met as mean OS with 2 of the drugs >24mo
241	**Dasatinib**	Imatinib-resistant chronic myeloid leukaemia	**No**	**No**	- median OS gain from trials	-Clinical specialists

241	**High-dose imatinib**	Imatinib-resistant chronic myeloid leukaemia	**No**	**No**	- median OS gain from trials	-Clinical specialists
242	**Bevacizumab**	Metastatic colorectal cancer after first-line chemotherapy	**No**	**No**	- median OS gain from trial (2.1mo) - OS gain considered irrelevant	- median OS estimates from BSC arm (10.8 mo)
242	**Cetuximab**	Metastatic colorectal cancer after first-line chemotherapy	**No**	**No**	- median OS gain from trial (4.7 mo) - modelled OS (mean/median not specified)	- median OS estimates from BSC arm (4.8 mo)
242	**Panitumumab**	Metastatic colorectal cancer after first-line chemotherapy	**No**	**No**	- mean OS gain from trial (after adj for crossover) - between 2.74 - 3.13 mo	- median OS estimate from BSC arm (7.6 mo)
250	**Eribulin**	Breast Cancer (locally advanced or metastatic)	**No**	**No**	- mean OS gain from ITT trial population (2.7 mo)	- committee stated short life expectancy - no source reported
255	**Cabazitaxel**	Prostate cancer (hormone-refractory metastatic)	**No**	**Yes**	- median OS gain from trial (2.4mo) - modelled mean OS gain >3mo	- survival estimated from BSC arms of trials (<15 months)
257	**Lapatinib**	Metastatic breast cancer	**No**	**No**	- median OS gain from trial (1mo) - no robust evidence for >3mo survival	- mean OS survival in comparator arm >24mo
257	**Trastuzumab**	Metastatic breast cancer	**No**	**No**	- median OS gain from trials (adj for crossover using RPSFT) - 4.6 mo, 5.5 mo, 6.6 mo	- Published life expectancy lit - median survival from trial > 24mo (23.9 - 31mo)
259	**Abiraterone**	mCRPC post-chemo	**Yes**	**Yes**	- median OS gain (4.6mo) - modelled mean OS gain	- Life expectancy from BSC arms < 15 months
263	**Bevacizumab**	First-line treatment of metastatic breast cancer	**No**	**No**	- median OS gain from trial (2.9 mo)	- Life expectancy from placebo arm (22.8mo)
268	**Ipilimumab**	Advanced melanoma	**Yes**	**Yes**	- median OS from trial data (3.5 mo, 3.7 mo) - modelled mean OS gain	- median OS data less than 24 months from trial data
269	**Vemurafenib**	BRAF V600 metastatic melanoma	**Yes**	**Yes**	- median OS gain from trial	- used life expectancy from trial data 3-9 months - verified with clinical specialists

272	**Vinflunine**	Urothelial tract carcinoma	**No**	**No**	- median OS gain from trial (2.3 - 2.6 months)	- committee stated life expectancy <6mo - source not reported in final guidance
285	**Bevacizumab**	Ovarian (inc. fallopian tube and primary peritoneal) cancer	**No**	**No**	- median OS gain from trial (not sig) - modelled survival	- assume median OS in control arm - not assessed as not small population
289	**Ruloxitinib**	Myelofibrosis	**No**	**No**	- no months gained reported - plausible survival gain but reason for gain unclear	- survival estimates range 1.3 to 2.3 yrs - not met due to uncertainty
295	**Everolimus**	Breast cancer	**No**	**No**	- modelled mean OS gain	- mean OS from model >24mo - 2 supporting trials with median OS were irrelevant
296	**Crizotinib**	Non-small-cell lung cancer	**No**	**Yes**	- mean OS gain 5.8 mo (adj for crossover using RPSFT) - other estimates also mean survivals	- current expected survival 6-8 months
299	**Bosutinib**	Chronic myeloid leukaemia	**No**	**Yes**	mean OS - uncertainty in estimates of survival extension	- survival estimate 6-16 months
307	**Aflibercept**	MCC	**No**	**No**	- modelled mean OS gain (4.7 mo) - mean estimates not robust (extrapolation methods)	- OS estimates from placebo arm median OS 12.1 mo & modelled mean 18.1 mo - preferred published lit estimates 10.5 mo
309	**Pemetrexed**	NSCLC (non squamous; maintenance)	**No**	**Yes**	- median OS from trial (2.85mo) - modelled mean OS gain (Manufacturer 4.22 mo & ERG estimate: 3.49 mo)	- life expectancy estimate from National Lung Cancer Audit (2013) - survival from placebo/BSC arm

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