NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Cabazitaxel for the second line treatment of hormone refractory, metastatic prostate cancer

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:
   - Sanofi
   - British Uro-Oncology Group
   - Royal College of Physicians, on behalf of the National Cancer Research Institute (NCRI) - Prostate Cancer Clinical Studies Group, the Royal College of Physicians (RCP), the Royal College of Radiologists (RCR), the Association of Cancer Physicians (ACP) and the Joint Collegiate Council for Oncology (JCCO)
   - The Prostate Cancer Charity
   - Prostate Cancer Support Federation
   - Department of Health
   - NHS Warwickshire
   - Commissioning Support Appraisals Service
   - MRC Clinical Trials Unit
   - School of Health and Related Research, University of Sheffield

3. **Comments on the Appraisal Consultation Document from experts:**
   - George Goldsmith, patient expert, nominated by the Prostate Cancer Support Federation

4. **Response to Sanofi comments on the ACD,** prepared by the School of Health and Related Research, University of Sheffield

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

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 CLINICAL EXCELLENCE

Health Technology Appraisal

Cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen

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

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

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 may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Sanofi	**End-of-life criteria** In the ACD, the Committee judges that "further exploration and validation of the modelled mean survival benefit using updated trial-based or observational data would be necessary before the mean extension to life of 4.2 months could be considered sufficiently robust for the end-of-life criteria to be met." (Section 4.21). • We consider that there is robust evidence that the estimated mean survival benefit of cabazitaxel is in excess of 3 months and that the conclusion of the Committee does not represent a balanced view of the available data. • It is usual in modelling the cost-effectiveness of oncology drugs to use extrapolation to calculate the mean overall survival benefit, as it is very rare to have complete follow-up data from a trial. NICE positive recommendations in oncology routinely rely on this type of information. • In addition to the views expressed by the ERG that a survival gain of approximately 4 months was robustly demonstrated, we would direct the Committee's attention to the fact that however the TROPIC overall survival data are extrapolated, the resulting mean survival improvement is always in excess of 3 months and very often longer. We show graphically below (Figure 1) and describe in the Appendix (section 4) a variety of alternative modelling approaches; all of these functions provide an estimate of mean OS in excess of 3 months. This is shown for our submitted base-case population; results for patients with ECOG performance status 0 – 1 and received ≥225 mg/m2 docetaxel based on the *entire* TROPIC population, not just the European cut, are provided in the Appendix. • Probabilistic sensitivity analysis using the ERG preferred population and all assumptions included in the ERG's preferred base-case, showed that the probability of the mean OS being >3 months was >93%. The ERG commented that probabilistic results were relatively robust in that cabazitaxel produced a survival advantage in each of the 2000 probabilistic analyses run by the ERG. • We note that other drugs have been judged as meeting end-of-life criteria based on similar evidence, for example sorafenib in hepatocellular carcinoma, where, similar to cabazitaxel, the median OS gain was <3	• The Committee considered the additional analyses which evaluated the robustness of modelled mean overall survival gain submitted following consultation on the Appraisal Consultation Document. The text of the FAD has been updated accordingly. See sections 3.32, 3.33, 3.34, 3.36 and 4.24 of the FAD. • Comment noted – see above • Comment noted – see above • Comment noted – see above • Comment noted – see above • Comment noted

Consultee	Comment	Response
	months, but the mean OS gain was >3 months. • We also believe that cabazitaxel is precisely the type of drug for which end-of-life criteria were introduced. Cabazitaxel is intended to be used in mHRPC patients who have progressed after docetaxel. This represents a population of fewer than 2000 patients in England and Wales. These patients have short survival times (mean OS of around 15 months) and extremely limited treatment options. The improvement in mean OS produced by cabazitaxel represents an increase of around 30% in life expectancy, which is clinically meaningful. The introduction of cabazitaxel therefore represents an important development in the treatment of patients at high clinical need.	• Comment noted
	Cardiac and renal safety profile "The Committee concluded that there remains substantial uncertainty about the effects of cabazitaxel on renal and cardiac adverse events." (Section 4.10). • We would like to take this opportunity to provide further clarification around the effects of cabazitaxel on renal and cardiac adverse events, noting that the assessment of safety of a medicinal product is properly the domain of the regulatory bodies, and that these data have already been explored in detail with these agencies. Indeed, the UK regulatory agency, the MHRA, was the co-rapporteur of the EMA review of cabazitaxel. Both the FDA and EMA concluded that there was a positive benefit-risk profile for cabazitaxel, with no need for a further risk-management plan beyond that proposed. After its consideration of the available safety data, the EMA stated: *"Due to the poor prognosis, high unmet clinical need and lack of alternative therapies, the observed benefits in terms of overall survival are considered clinically important. There are no major remaining uncertainties that have an impact on the benefit-risk balance".* • We also provide updates from post-marketing surveillance, which includes data from >5500 patients who have been treated worldwide. **Cardiac effects in TROPIC** • There were five cardiac-related deaths in TROPIC in the cabazitaxel arm, and none in the mitoxantrone arm (noted by the EMA and De Bono 2010; the FDA deemed four deaths to be cardiac-related). None of these were	Comments noted. • The Committee considered the additional information on cardiac and renal safety submitted following consultation on the Appraisal Consultation Document. The text of the FAD has been amended in section 3.11 and the Committee consideration of this is found in section 4.10 of the FAD • Comment noted – see above • Comment noted – see above

Consultee	Comment	Response
	considered by the investigators to be related to the study drug – this fact was highlighted by one of the clinical experts at the Appraisal Committee meeting, referring to the letter published by De Bono et al in the Lancet (De Bono 2011).	
	• In their analysis, the FDA commented that three patients also had confounding factors including diabetes, hypertension, atrial fibrillation, prior warfarin use, and history of pulmonary embolism, and stated that: "Hence, there is no clear relationship between cabazitaxel exposure and fatal cardiotoxicity".	• Comment noted – see above
	• In TROPIC, all Grade cardiac events were more common on cabazitaxel of which 6 patients (1.6%) had Grade ≥3 cardiac arrhythmias, compared with 1 patient (0.3%) on mitoxantrone. The incidence of tachycardia on cabazitaxel was 1.6%, none of which were Grade ≥3. The incidence of atrial fibrillation was 1.1% in the cabazitaxel group. Cardiac failure events were more common on cabazitaxel, the event term being reported for 2 patients (0.5%), versus none on mitoxantrone (EPAR 2011; TROPIC clinical study report). As expected, more events of LV dysfunction and EF decrease occurred on the mitoxantrone arm (all grades - 3 patients versus 1 patient) (TROPIC CSR). As stated in the EPAR, there is a lack of clear evidence to suggest that cabazitaxel contributed to these cardiac events. In light of the unknown aetiology of the increased incidence of cardiac deaths and arrhythmias, the potential risk for cardiac conduction disorders was included in the SmPC.	• Comment noted – see above
	• An evaluation of the effect of cabazitaxel on the QT/Qc interval in cancer patients has been undertaken in study TES10884. This study has been designed to meet the current ICH E14 guidance (standard FDA guidance applicable to all drugs). The results of this were reviewed and interpreted by an external cardiology expert who concluded that cabazitaxel does not affect the ventricular repolarisation in humans to an extent that would require substantial risk-benefit considerations. The overall conclusion was that cabazitaxel at a dose of 25 mg/m2 was well tolerated, with QTc changes from baseline below the level of regulatory concern and not clinically meaningful.	• Comment noted – see above
	Renal effects in TROPIC:	
	• The EMA and the De Bono study reported 3 renal deaths, although the FDA attributed 4 deaths to renal failure, on the cabazitaxel arm, versus none in	• Comment noted – see above

Consultee	Comment	Response
	the mitoxantrone arm. • After considering the available data, the CHMP commented: *"Renal failure was often multi-factorial in origin and a direct causal relationship with cabazitaxel cannot be determined. Haematuria is very common in patients with prostate cancer. Although more frequent in the cabazitaxel group, a possible explanation for the observed haematuria was found in most cases. Haematuria should be closely monitored".* • In response to the FDA review, an expert advisory board was convened to evaluate renal events occurring in the seven completed cabazitaxel studies (TROPIC, the Phase II breast cancer study, and the Phase I studies). This board concluded that, for the vast majority of the patients with an AE renal failure, at least one concomitant risk has been identified, such as an AE (e.g. diarrhoea, dehydration, severe infection plus or minus septic shock), local obstruction/progression, medications (e.g. NSAID, zoledronic acid, vancomycin, aminosides), contrast given for repeated CT scans, or co-morbidity (e.g. diabetes), and stated that: *"It is difficult to assess retrospectively the exact level of implication of each of these risk factors of renal failure in the completed studies."* • With regards to the pharmacokinetics of cabazitaxel, cabazitaxel is minimally excreted via the kidney (2.3% of the dose) (EPAR). No formal pharmacokinetic studies were conducted with cabazitaxel in patients with renal impairment. However, the population pharmacokinetic analysis carried out in 170 patients that included 14 patients with moderate renal impairment (creatinine clearance in the range of 30 to 50 ml/min) and 59 patients with mild renal impairment (creatinine clearance in the range of 50 to 80 ml/min) showed that mild to moderate renal impairment did not have meaningful effects on the pharmacokinetics of cabazitaxel. To further investigate the pharmacokinetics in patients with moderate and severe renal impairment, a study (POP12251) is underway as reflected in the Risk Management Plan. The safety of cabazitaxel has not been specifically evaluated in patients with renal disorders. The SmPC states that no dosage adjustment is necessary in patients with mild renal impairment, that patients with moderate and severe renal impairment should be treated with caution and monitored carefully during treatment and that dosage delay or reduction should be considered in the event of adverse drug reactions. **Post-marketing data:**	• Comment noted – see above • Comment noted – see above • Comment noted – see above

Consultee	Comment	Response
	• Two periodic safety update reports (PSUR) are now available, covering the period from 17 June 2010 to 16 June 2011. It is estimated that approximately [redacted] patients were exposed to cabazitaxel worldwide during this period (marketed drug). An additional [redacted] patients were enrolled in studies during this period. A review was conducted of cardiac safety issues, specifically cardiac arrhythmia, torsade de pointes or QT prolongation, cumulative analysis of cardiac arrhythmia terms (including bradyarrhythmia and tachyarrhythmias) and also peripheral neuropathies. No new safety signal was identified from these. From the data included in the PSURs and the cumulative analyses on specific reactions, no serious unlisted reactions, which would due to their frequency and/or the nature, severity, specificity, or outcome of the cases in which they occur, suggest a new risk not yet included in the current safety information for cabazitaxel.	• Comment noted – see above
Sanofi	**Utility data from the Early Access Programme** "The Committee concluded that because the utility data were based on such a small number of patients from a potentially select population, there is considerable uncertainty as to the validity of these data" – section 4.11. "The Committee concluded that there is uncertainty over the utility values used in the model, that it is likely that the manufacturer had overestimated the utility values and that the use of more realistic utility values would increase the ICER" – section 4.16. The Committee noted that "the manufacturer based the utility value for the stable disease state on a small selected sample of patients and that therefore the value had wide confidence intervals and may have been biased" – section 4.16. • The EQ-5D data were collected through a single-arm, UK-based, prospective trial of cabazitaxel which collected EQ-5D data (the Early Access Programme). As a formally conducted trial, this is a high quality source of information and the most appropriate data source for estimating the utility of patients treated with cabazitaxel. • We are unclear as to why the Committee would assume the utility data reported by the EAP would be "biased". The early access programme (EAP) was run as a clinical trial, with formal inclusion criteria (CABAZ_C_05331 protocol – see Appendix section 7 for details). Patients were selected by physicians purely on the basis of eligibility and suitability for this trial. The patients included in the EAP are entirely reflective of those who would be expected to receive cabazitaxel in UK practice – namely patients with good performance status and who have progressed after a sufficient trial of	The Committee considered the additional evidence submitted following consultation on the Appraisal Consultation Document and the updated utility values in the model. The text of the FAD has been amended to include the new utility values from the updated EAP. See sections 3.15, 3.16, 4.14 4.15, 4.16 and 4.17 of the FAD • The Committee welcomed the manufacturer's commitment and efforts to obtaining EQ–5D utility data in accordance with the reference case. The Committee concluded that there remains considerable uncertainty around the utility value for stable disease incorporated in the model, and that this value was likely to be overestimated.. See FAD section 4.15, 4.16 • Comment noted – see above

Consultee	Comment	Response
	previous docetaxel. • In relation to the comment on the overestimation of the utility values by the manufacturer, we remind the Committee that these utility data were taken directly from a prospective trial – the values have therefore been directly measured, and not estimated or in any way inflated by the manufacturer. The EQ-5D is a patient-reported outcome and hence does not carry assessor bias. • The Committee noted that the utility values for the stable disease state are close to those for the age- and gender-matched population, and consider this to be implausible. However, the Committee are perhaps not familiar with the prostate cancer patients who would meet the entry criteria for the trial and who would therefore be fit enough to receive cabazitaxel. The ECOG classification system describes ECOG Grade 0 as "Fully active, able to carry on all pre-disease performance without restriction". ECOG Grade 1 is described as "Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work". Considering these descriptions, we might expect a mixture of mainly level 1 and level 2 responses to the EQ-5D, which would be consistent with utility values in the range of 0.7 – 0.8. It should be noted that the general population of this age group would be expected to have a range of comorbidities that would reduce their utility somewhat from perfect health, thus it is not necessarily implausible that the EAP patients would show similar EQ-5D values to the age and gender-matched general population. • In addition, the EAP baseline value (representing progressing patients on 1st line treatment) of [redacted] is similar to what has been found elsewhere for estimates of progression after 1st line treatment; PORTREAT, a registry study collecting EQ-5D data in patients with mHRPC with progressive disease prior to initiation on second-line chemotherapy, reported a mean utility value for patients with ECOG 0 -1 status of 0.696 (based on 57 European patients, including 6 from UK). • A 2007 review found nine utility values in the literature for prostate cancer, of which only one value was less than 0.75 (Pickard 2007a). Although not confined to prostate cancer, a retrospective study of >500 patients with a variety of different types of advanced (Stage III/IV) cancer found a mean utility of 0.72 calculated by the UK tariff, with values of 0.85 for ECOG 0	• Comment noted – see above • Comment noted – see above • The Committee considered the references cited in support of modelled stable disease utility values. The text of the FAD has been updated to include this additional information (section 3.16 and 4.16 of the FAD). The Committee noted that the PROTREAT study indicated lower utility values than the baseline utility values from the second interim analysis of the early access programme. The Committee concluded that there remains considerable uncertainty as to the validity of the around the utility data value for stable disease incorporated in the model, and that thise

Consultee	Comment	Response
	patients, and 0.73 for ECOG 1 patients (Pickard 2007b). • There are no truly comparable values to the EAP utility data as this study is the first to report EQ-5D values from second-line mHRPC patients on treatment, but overall, the values we obtained are consistent with what is reported in literature, supporting the validity of the results. • The ERG and the Committee note the wide confidence intervals around the values, due to the small sample size available in the interim analysis. We are pleased to be able to provide updated data from a second interim analysis, based on a larger sample size. Although there are still limited data available for later timepoints due to the fact the EAP is an ongoing study, more data are now available for baseline, cycle 2, cycle 4 and cycle 6. These data are based on a larger sample size and thus have narrower confidence intervals. Similar values and trends are shown as those observed in the first interim analysis. These data have been submitted to ASCO GU in abstract form. • A comparison of the first and second interim utility analyses is presented in Table 1. Updated modeling results are presented based on the second interim analysis data, in section 3. To provide one value for the stable disease state in the model, we pooled the cycle 2 and cycle 4 values, on the basis that there are relatively large samples for both these timepoints. Pooling utility values from cycles 2, 4 and 6 produces a very similar estimate. • The percentage of patients at each level for each of the 5 domains of the EQ-5D is presented below (Figure 2). This shows that between baseline, cycle 2 and cycle 4, [redacted] Although this is interim data and requires further confirmation from the final dataset, this suggests that the small increase in mean utility score seen between baseline and on treatment (stable disease) is in fact due to a beneficial effect of the drug [redacted]. • As the sole source of EQ-5D data for patients with second-line mHRPC on active treatment (to our knowledge) we believe that the EAP is a valuable source of information to guide decision-making in this setting. • The Committee questioned whether the decrement applied upon the	utility value of the stable disease state in the model was likely to be overestimated • The Committee was of the view that since only small numbers of patients in some of the included studies could be assumed having hormone refractory metastatic prostate cancer these utilities values could not be assumed reflective of utility values in for population considered in this appraisal. • Comment noted. See above • Comment noted. See above • Comment noted. See above • Comment noted. See above • Comment noted. See above

Consultee	Comment	Response
	transition to the progressed health state was large enough, however, we consider the utility decrement of 0.07 (approximately 10% decline) whilst at the lower end of the spectrum, is nevertheless in line with that reported in literature and is therefore a clinically meaningful decrement. • A retrospective study of a variety of cancer types, which used both distribution-based and anchor-based approaches (based on performance status) to calculate the minimally important difference in EQ-5D score, found a range of 0.08 – 0.16 for UK scores by the distribution approach, and 0.09 – 0.16 by the anchor-based approach (Pickard 2007b). • As a further consideration, a decrement at the lower end of the range of values reported in other cancer areas could also be considered appropriate for this population on the basis of the definitions of progression used in the TROPIC trial. As noted by the ERG, the definition of progression in TROPIC is a conservative one. Included in this population are patients who progress based on PSA changes alone and are likely to have had asymptomatic progression; thus they would not have immediate decrease in utility. • At this time, there are too few data points from the EAP for patients in the progressed disease state; the second interim analysis of the EAP reports only 4 patients who have progressed. Therefore, an estimate of the utility decrement on moving from the stable to the progressed disease state can only be taken from the literature.	• The Committee concluded in light of this evidence on the minimally important difference in EQ-5D score (section 3.16) that the utility decrement associated with progressive disease in the economic model of 0.07 was likely to be too low. See FAD section 4.17 • Comment noted. See above • Comment noted. See above • Comment noted. See FAD section 3.15
Sanofi	**Choice of base-case population** "The Committee concluded that it is not appropriate to restrict the base-case population to patients recruited at European centres". This was also the judgement of the ERG. • The ERG judged that restricting the population to patients recruited at European centres was inappropriate because there was no a priori clinical reason for assuming a regional difference, and because there was no statistical heterogeneity in treatment effect across the three regions for the primary endpoint. The Committee appeared to adopt the same reasoning.	The Committee considered the information provided to support the rationale behind the manufacturer's base case population submitted following consultation on the appraisal consultation document. The Committee further considered information related to the regional differences for combing the North American and European population compared with patients from other regions. The Committee was aware that the manufacturer found no statistically significant differences in treatment by geographically defined

Consultee	Comment	Response
	• The lack of a statistically significant difference between subgroups is not unexpected because the trial was not powered to show such a difference. The absence of a statistically significant difference is not proof that there is no difference between subgroups. • Further exploration of the regional differences showed that although it is true that there is no statistically significant difference between Europe versus North America versus the other countries, a test for interaction for the European and North American regions combined compared to the "Other countries" region, had a p-value of [redacted] (in the whole population). [redacted] • The rationale for using the European subgroup for the base case can be clarified in three parts: i. While there was no a priori clinical rationale to expect a difference in treatment effect, there were clear and significant differences in adverse event rates (e.g. rate of clinical neutropaenia was 16.1%, 25.7%, and 35.1% in the EU, NA and Other countries regions respectively, p<0.1). This is thought to be the manifestation of differing care practices across the regions. This variation in management and in adverse event rates is particularly important because, with chemotherapy, management of adverse events has a bearing on efficacy because it is critical that patients can tolerate chemotherapy in order to derive the greatest benefits from it. ii. In light of these clinical practice and outcomes differences it was considered appropriate to restrict the base-case population to the pre-specified regional group which includes the UK, as this is most likely to be reflective of UK practice. The clinical experts informed the NICE Committee that the neutropaenia rates seen in this group could considered reflective of the UK	subgroup when it compared Europe, North America, and 'other countries'. The Committee further noted that the manufacturer did not present an ICER for this subgroup (European and North American patients). The Committee did not consider there to be a difference in the effectiveness of cabazitaxel treatment for European patients and therefore, concluded that it is not appropriate to restrict the base-case population to patients in TROPIC recruited at European centres. The text of the FAD has been updated (see sections 3.13 and 4.7). • Comment noted – see above • Comment noted – see above • Comment noted – see above

Consultee	Comment	Response
	experience. iii. To provide a relevant economic evaluation, consideration must be given to the circumstances under which the entirety of the clinical data – not just the primary endpoint – can be considered generalisable. The European subgroup is more generalisable to the UK than is the whole TROPIC dataset, due to regional variation in clinical management and the influence of such variation on adverse events and other clinical endpoints. • The third point above is arguably the same rationale applied by the ERG, and accepted by the Committee, in consideration of the analysis that removed the early deaths in TROPIC. The ERG and the Committee concluded that with better management of neutropaenia as expected in the UK, the early deaths observed in TROPIC could be avoided. • Neutropaenia was apparently managed more effectively in Europe (as shown in the rates of clinical neutropaenia observed) and consequently the European subgroup reported a lower rate of neutropaenic deaths than the whole TROPIC population. Arguably adoption of the European-subgroup for the base case achieves the same objective as the post-hoc analysis requested by the ERG, whilst having the advantage that the European subgroup approach employs all the 'relevant' data, not just an artificial adjustment to the primary endpoint. It is therefore contradictory for the Committee to accept an analysis which selectively removes one group of events (the early deaths) on the basis that these would not be expected to occur in the UK, while rejecting an analysis which more comprehensively accounts for regional differences in other outcomes.	• Comment noted – see above • The Committee noted that the incidence of neutropenia was lower among participants recruited at European centres than other centres which reflected clinical practice in the UK which follows best practice guidelines for managing neutropenia. The Committee further considered that it is appropriate to exclude the costs and effects of these deaths from the economic modelling either by excluding early deaths within 30 days of randomisation or by using the piecewise analysis. See FAD section 4.10, 4,13 and 4.22 • Comment noted – see above

Consultee	Comment	Response
Sanofi	**Curve-fitting** • In the base-case, Kaplan-Meier (KM) data from TROPIC were used directly, and mathematical extrapolation limited to the post-trial period only. The ERG judged that it would be more appropriate to use the parametric functions throughout; a sensitivity analysis presented in our original submission. • The rationale for using the Kaplan-Meier data for the initial time period was that these are the actual data from TROPIC. They therefore provide the most accurate reflection of what was observed in the TROPIC trial. We note that the use of Kaplan-Meier data, followed by extrapolation limited to the period beyond the trial follow-up has been adopted in previous technology appraisals (for example it was applied by the ERG in the recent eribulin appraisal). • The application of this methodology to the base case was criticised unfairly in the ACD. The 'choice' of time point at which the KM data was replaced by mathematical extrapolation was described as arbitrary. This was not the case; a decision rule was applied. The KM data were considered unreliable when four consecutive cycles reported zero events. Furthermore, the ACD also incorrectly asserts that the time point was 'chosen' to generate "the most favourable ICER". This is factually incorrect; the time point at which the switch occurs in the base case (cycle 37) does not generate the lowest ICER – the lowest ICER is seen when the switch is made at cycle 17. • While the choice of survival data modelling is clearly a matter for scientific debate – indeed our submission explored a variety of approaches, including the one favoured by the ERG – section 4.13 of the ACD states that "the parametric fitted curves more closely fit data from TROPIC…". We also reject this assertion as it cannot be the case that fitted curves could more closely fit data from TROPIC than the actual data from TROPIC itself. • At the Committee meeting, one member of the Committee suggested that, instead of either the parametric (Weibull) function or our base-case approach, it may be more appropriate to fit a piecewise survival analysis considering of a number of different curves fitted to the Kaplan-Meier data. While this approach is not explicitly mentioned in the ACD, we would have wished to respond to the Committee member's comments. We therefore requested clarification from NICE in relation to the point raised during the	The Committee considered the additional analysis on curve fitting submitted following consultation on the Appraisal Consultation Document. The text of the FAD has been updated (see sections 4.21-4.22. • The Committee concluded that the fitted parametric curves are more generalisable to the population outside the trial. • The text of the FAD has been changed to note that the ERG considered the time to replace Kaplan–Meier data on overall survival in the model with a fitted parametric curve to be based on an arbitrary decision rule and that the ICER was sensitive to the time point at which this change was made (section 3.25 of the FAD). • The ERG noted that 'Kaplan–Meier curves provide the most accurate reflection of the trial, but are less generalisable to other populations who are eligible for treatment' (section 3.25 of the FAD). • The Committee heard from the ERG that both the piecewise and the partitioned methods of curve fitting were more plausible than the method provided in the original model (which used the Kaplan–Meier data until they were considered unreliable and a single Weibull fit). The Committee concluded that of all the methods of curve fitting, it considered the

Consultee	Comment	Response
	meeting. In response to our request, we were provided with the ERG's understanding of this proposed approach, but no specific details which would enable us to investigate fully the suggestion made by the Committee member during the meeting. • In the absence of detailed guidance on this matter, we have nevertheless explored alternative approaches including a piecewise approach to find a better fit to the data. Full details of these methodologies are provided in the Appendix (section 5). The piecewise approach fitted different functions before and after 2.1 months. For our base-case population (European patients with ECOG status 0 -1 and who had received ≥225 mg/m2 docetaxel), this provided an estimate of the mean OS gain of [redacted] months. Incorporating this in the model provided an estimate of the ICER of £77,765. This is very similar to that obtained with our original methodology - £78,016 (both analyses run with updated utility data and the Committee's preference for post-second-line chemotherapy). Similarly, using the ERG/ Committee preferred population, the result obtained with this methodology was very similar to that obtained with our original methodology. Detailed modeling results are provided in the Appendix (section 5). • As an alternative curve-fitting approach, we also fitted partitioned survival functions to the Kaplan-Meier OS curves for cabazitaxel and for mitoxantrone. This was performed for our preferred base-case population (European patients with ECOG status 0 -1 and who had received ≥225 mg/m2 docetaxel). Details are provided in the Appendix (section 5). A partitioned approach incorporating 3 Weibull functions was indicated as the best fit for the data, for both cabazitaxel and for mitoxantrone. This approach provided an estimate of the mean OS gain of [redacted] months. Again, this is very close to what was obtained using the initial modelling approach we took (Kaplan-Meier followed by Weibull extrapolation – mean OS gain of [redacted] months). In conclusion, while the appropriate methodology for modeling the TROPIC survival data is clearly a matter for scientific debate, our original choice of base-case methodology was chosen in order to reflect the TROPIC data as closely as possible and minimise the level of data extrapolation.	piecewise analysis the most appropriate (section 4.22 of the FAD) • Comment noted – see above • Comment noted – see above • Comment noted – see above
Sanofi	Pg 3, 2.3 While this section is factually correct, we believe it is important to specify what	The definitions of 'very common' and common have been added to the FAD (sections 2.3).

Consultee	Comment	Response
	constitutes “very common” to aid in interpretation of this paragraph. In addition, peripheral neuropathy is not a very common adverse event, it is classed as common (≥1/100 – 1/10 instead of (≥1/10, as per the SmPC. The incidence of Grade ≥3 peripheral neuropathy was in fact notably low for a taxane chemotherapy, as remarked on in the De Bono 2010 Lancet publication.	
Sanofi	Pg 8, 3.11 The statement on febrile neutropaenia incidence is factually incorrect. The incidence in the cabazitaxel arm was 7.5% (28 patients) and in the mitoxantrone arm was 1.3% (5 patients).	The text of the FAD has been updated accordingly (FAD sections 3.11) Cabazitaxel was associated with higher rates of ≥ grade 3 neutropenia (82%) compared with mitoxantrone (58%), and infections and febrile neutropenia (7.5%) compared with mitoxantrone(1.3%)
	Pg 10, 3.14 This summary omits the per cycle costs of disease management included in the model. In the stable disease state, costs of hospitalisations, tests and imaging, and physician time (over and above that required for chemotherapy administration) are applied on a per cycle basis. Similarly, in the progressive disease state, a per cycle cost incorporating ongoing LHRH agonist medication, supportive care medications, hospitalisations, tests and imaging, and physician time was applied. This is important as the progressive disease costs are higher in the cabazitaxel arm due to the fact that cabazitaxel prolongs life, and thus these costs are accrued over a longer time period. The costs of best supportive care were not applied as a transition cost, but were applied on a per cycle basis throughout the progressive disease period.	The text of the FAD has been updated accordingly (FAD section 3.14).
Sanofi	Pg 10, 3.15 With regards to the statement “the manufacturer assumed that utility values within a health state were independent of time spent in the health state” – we would like to highlight that this is a widely accepted and commonly used assumption in oncology modelling. In addition, we would like to clarify that the early access programme was conducted in twelve, not nine centres.	The text of the FAD has been updated accordingly (section 3.15).
Sanofi	Pg 11, 3.16 It is factually inaccurate to state that we corrected the incidence of adverse events. These rates were correct in the submitted model. However, in response to a request from the ERG, we changed the calculation of QALY losses associated with adverse events to divide by 365.25 instead of 365.	The text of the FAD has been updated accordingly (FAD sections 3.16).
Sanofi	Pg 12, 3.21 The statement that TROPIC was not powered to detect differences in adverse	Text of FAD has been updated. See section 3.21No action required

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	events is true – to aid in interpretation, it should be added that this is the case with most registration trials designed for efficacy.	
Sanofi	Pg 12, 3.21 The statement that "The ERG noted that because of the stringent management of adverse events in the trial, the incidence of adverse events associated with cabazitaxel is likely to be higher in clinical practice in the UK" does not reflect input from the clinical experts at the Committee meeting, who expressed confidence in the ability and experience of UK physicians with managing the AEs commonly associated with taxane chemotherapies. It is also contradictory with statements elsewhere in the document – for example, the emphasis placed on a sensitivity analysis removing early neutropenic deaths, on the basis that it is believed these would NOT occur in UK practice, and the recognition that clinical neutropaenia rates were lower in Europe than in the rest of the trial population, which suggests that the good management practices prevalent in the UK and the rest of Europe would result in AE rates as low or lower than those observed in TROPIC.	The evidence section in the ACD summarises the evidence submitted by the manufacturer and ERG's critique. The Committee however noted that clinicians in the UK follow best practice guidelines for managing neutropenia and, as a result, few patients in the UK develop febrile neutropenia or neutropenic sepsis (FAD section 4.10).
Sanofi	Pg 12, 3.21 The statement that "The ERG stated that the trial provided insufficient information on the cardiac and renal complications associated with cabazitaxel" is disappointing. As discussed in detail above (section 1.2) these effects have been explored with the regulators, as part of their stringent assessment of drug safety. Additional information on the cardiac and renal complications in TROPIC beyond that presented in the submission, together with a summary of post-marketing data, is discussed in detail above.	The Committee considered the additional information on cardiac and renal safety submitted following consultation on the Appraisal Consultation Document. The text of the FAD has been amended (section 3.11) and the Committee consideration of this can be found in section 4.10 of the FAD
Sanofi	Pg 12,3.22 We comment on detail on the choice of base-case population in section 1.4.	See the comment above related to the base case population.
Sanofi	Pg 13, 3.23 See section 1.5 for further clarification on the curve-fitting methodology. Of note here, the choice of timepoint at which to switch from the Kaplan-Meier data to the parametric function was rule-based, not arbitrary.	See the comment above related to the curve fitting methodology.
Sanofi	Pg 13, 3.24 The request to remove the deaths which occurred within 30 days in TROPIC on the basis that these could have been prevented with more vigilant treatment of neutropaenia is contradictory with the statement in 3.21 that it is believed adverse event rates would be higher in UK practice than in TROPIC. It is also contradictory with the position that the European subgroup should be rejected. The European population has fewer deaths reflecting better management of neutropaenia, and it seems more reasonable to use the complete adverse event profile from the European subgroup rather than to selectively remove certain events from the trial	See the comment above related to the exclusion of early deaths (within 30 days of randomisation).

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	data. This is explored more fully in section 1.4.	
Sanofi	Pg 14, 3.25 We discuss extensively in section 1.3 the utility data. We profoundly disagree with the statement from the ERG that the utility value for stable disease was implausible because it was similar to the utility values observed in the general population. These data came from a prospective trial of UK patients receiving cabazitaxel and completing EQ-5D questionnaires and as such we judge to be the most reliable source available. We also highlight that the independent sampling of the stable and progressive disease utility values was an error in our model, but that this only affects the sensitivity analyses, and has no bearing on the deterministic ICER.	See the comment above related to the additional information related to the updated utility values.
Sanofi	Pg 14, 3.26 As in 3.25, we would highlight that the change to the sampling of the utility in stable and progressive disease only affects the sensitivity analyses and has no effect on the deterministic ICER of £89,476 quoted here.	Text of the FAD updated. See section 3.26
Sanofi	Pg 15, 3.27 This is correct, however we wish to clarify that the decrement of 0.085 was also applied in a sensitivity analysis included in our original submission.	Comment noted.
Sanofi	Pg 15, 4.2 The text notes that docetaxel re-treatment is not recommended by current NICE guidance. In addition we note that the benefits of docetaxel re-treatment have not been investigated in a RCT, and would not be expected to provide benefit patients who are resistant to docetaxel.	Comment noted.
Sanofi	Pg 16, 4.3 With regards to the comment on the lack of evidence that cabazitaxel improves health-related quality of life, we would like to draw attention to the updated analysis of EQ-5D from the cabazitaxel EAP.	See the comment above related to the updated utility values from the EAP
Sanofi	Pg 17, 4.4 The text comments that “The Committee noted that the manufacturer excluded from its submission the other comparators listed in the scope”. This is correct; indeed this is something we agreed with NICE at the decision problem meeting and the ERG report considered this to be appropriate.	Comment noted.
Sanofi	Pg 17, 4.4 The committee noted that TROPIC was susceptible to bias in the subjective outcomes included in progression-free survival. This is true, but we would point out that the results of these subjective outcomes were consistent with objective measures such as radiographic progression, and that progression-free survival results were consistent with purely objective outcomes such as overall survival.	Comment noted.

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	Also, it should be noted that the ERG considered the definition of progression in the TROPIC trial to be a conservative approach.	
Sanofi	Pg 17, 4.4 The text comments that the Committee heard from clinical specialists that participants in TROPIC were in many ways similar to those who would receive cabazitaxel in the UK, although on average younger (median age 68 years). We recollect that the clinical specialists at the meeting did not think TROPIC patients were younger than those who would receive cabazitaxel in the UK. Sixty-eight may be younger than the median age of the overall UK metastatic prostate cancer patient population, however it would be expected cabazitaxel would only be given to fitter patients with good performance status; these tend to be younger patients (although not exclusively). Data from our EAP shows that patients entered into this trial also had a median age of [redacted], suggesting that the TROPIC population may not be younger than the average UK patients receiving cabazitaxel	Text of the FAD has been updated. See FAD section 4.4
Sanofi	Pg 18, 4.5 We comment in section 1.1 on the survival benefit of cabazitaxel beyond the period of the trial.	Text has been amended. See FAD section 4.5
Sanofi	Pg 18 – 20, 4.6 – 4.10 The rationale for the European subgroup is discussed further in section 1.4. We note that in section 4.7, the statement "the clinical specialists commented that clinicians in other European centres manage adverse events similarly to clinicians in the UK" is supportive of the choice of the European subgroup.	See comment above related to the base case population
Sanofi	Pg 20, 4.10 As for section 3.21, we consider the point that the Committee noted that the incidence of neutropaenia was lower among participants recruited at European centres, is inconsistent with the rejection of the rationale for our European subgroup.	See comment above related to the base case population
Sanofi	Pg 20, 4.10 We discuss in detail in section 1.2 our response to the question of cardiac and renal adverse effects.	See comment above related to the base case population.
Sanofi	Pg 21, 4.11 We comment extensively on the utility data in section 1.3; we dispute the claim that there is uncertainty in the validity of these data.	See comment above related to the consideration of new utility data from the updated EAP data.
Sanofi	Pg 21, 4.13 The statement "the time point chosen by the manufacturer produced the most favourable ICER" is incorrect. There were several timepoints which in fact produced a lower ICER. The choice of this timepoint was based on a decision-rule. This issue is discussed further in section 1.5. With regards to the statement "The Committee concluded that the parametric fitted	See comment above related to the parameteric curve fitting.

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	curves more closely fit data from TROPIC" – this assertion is not reasonable; fitted curves not could more closely fit data from TROPIC than the actual data itself.	
Sanofi	Pg 22, 4.15 As discussed in section 1.4 and our response to 3.24, the conclusion that early deaths could have been avoided with the better management of neutropaenia clearly expected to occur in UK practice is inconsistent with the rejection of the European subgroup – we employ the European subgroup because we considered practice in Europe to be more reflective of what would occur in the UK and the results of the European subgroup provide a more comprehensive picture of the outcomes which would be expected in UK practice.	See comment above related to the base case population
Sanofi	Pg 22, 4.16 We discuss this issue fully in section 1.3. However, the suggestion that the data are biased and that the values obtained represent overestimates is unreasonable and appears to be based on the Committee's preconceived notion of this populations baseline utility. We also highlight that it is biased to report on page 23, only the impact of variability on the ICER using the lower limit of the 95% CI – which is the worst-case scenario – and not to report the equally probable scenario based on the upper 95%CI. We consider the utility values presented to be the most realistic utility values available, as they are sourced from a prospective UK-based trial collecting EQ-5D data.	See comments above related to the updated utility data from EAP.
Sanofi	Pg 24, 4.17 The text notes: "…the manufacturer had assumed that an improbably high proportion of patients received post second-line chemotherapy" and comments that the proportions from a UK audit would be more appropriate. This is misleading, since the base-case uses the proportion of patients receiving post second-line chemotherapy from the TROPIC database. Therefore we believe the description "improbably" is unjustified. A sensitivity analysis using the proportions from an audit of UK practice (more properly, a series of UK service evaluations) was also presented in the submission. As the ERG and the clinical experts considered the audit data acceptable we are happy to accept the Committee's choice that this would be a more appropriate input for the base-case. We note however that the impact on the ICER of using these alternative data is relatively small; the ICER increased by less than 2%. Therefore the statement "using the UK values for post second-line chemotherapy from the audit would increase the ICER" without qualification of by how much, alongside the emotive statement that the data used were "improbably high" is both misleading and unnecessarily critical of our submission.	Text of the FAD has been amended. See section 4.18

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Sanofi	Pg 24, 4.17 With regards to hospitalisations for febrile neutropaenia, the model did indeed include hospitalisations for febrile neutropaenia. In the base-case we took the hospitalisation rate for febrile neutropaenia recorded in the TROPIC database – this was 75%. If we assume that, in the UK, 100% of patients would be hospitalised for febrile neutropaenia, the ICER is increased by £254 in the base-case.	Text of the FAD has been amended. See FAD section 4.18
Sanofi	Pg 24, 4.19 We consider the statements on the robustness of the ICER to be inappropriate and incorrect. The utility data is discussed in section 1.3. The statement that "the costs of post second-line chemotherapy were not appropriately estimated" is incorrect because these costs were appropriately estimated based on the regimens received in TROPIC. Costs based on post-second-line chemotherapy regimens received in a UK audit were presented as a sensitivity analysis and the Committee judged that this would be a more appropriate set to use in the base-case; the impact on the ICER is small (<2%). The statement that "the costs associated with the management of adverse events were underestimated" is misleading, given that the only cost questioned was that of febrile neutropaenia, which was included in the model, and even if the hospitalisation rate is increased from the 75% rate observed in TROPIC to 100%, the impact on the ICER is only £254. The ERG report recognised that hospitalisations were appropriately included and that post second-line chemotherapy was appropriately costed.	Text of the FAD has been amended in the light of the comments and additional analyses presented. See FAD section 4.22
Sanofi	Pg 26, 4.21 We consider that the evidence for cabazitaxel providing a survival benefit in excess of 3 months is robust. This is discussed fully in section 1.1.	See comment above on mean extension in survival and FAD section 4.24
Sanofi	Pg 27, 4.23 The patient experts commented that the most important benefits were the extension to life, and **the hope that this affords**. We consider that the benefit of hope to patients and their families provided through offering an active treatment which can prolong survival, in a setting where no treatment has until now been available, is a considerable benefit which is not captured within the QALY calculation. In addition we note, that it is challenging to provide data to demonstrate innovation. Innovation by definition cannot always be demonstrated through hard outcomes. The innovativeness of cabazitaxel is that it was specifically designed to overcome a problem, namely taxane resistance, and has been demonstrated through RCT .	The Committee was not presented with a case, substantiated by data, showing that the treatment adds demonstrable and distinctive benefits of a substantial nature that have not already been adequately captured in the QALY measure. No action required
Sanofi	Pg 28, Key conclusions As stated in our response to 4.19, we consider that the statements that the "costs of post second-line chemotherapy were not appropriately estimated, and the costs associated with the management of adverse events were underestimated" are	Text has been amended. See FAD, Key conclusion

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	incorrect and misleading.	
Sanofi	Pg 28 – Innovation This is commented on in our response to section 4.23.	See comments on innovation above. No action required
Sanofi	Pg 29 – Position in pathway of care As stated above in our response to 4.2, we emphasise that in addition to the fact that docetaxel re-treatment is not recommended by NICE, there is no RCT evidence to support its use, and is unlikely to provide any benefit in the patient population cabazitaxel was designed to treat, namely patients whose tumours have developed resistance to docetaxel.	Comment noted.
Sanofi	Pg 29 – Adverse effects As noted above, we emphasise that the safety profile of cabazitaxel has been reviewed thoroughly by both European and North American regulatory bodies and the risk-benefit profile deemed adequate. We have provided further clarification on the cardiac and renal profile of the medicine.	Please see comment above related to the incidence or renal and cardiac events
Sanofi	Pg 29 – Availability, nature and quality of evidence With regards to the comment that TROPIC was susceptible to bias in the subjective outcomes included in progression-free survival, we note that it is true, but also point out that the results of these subjective outcomes were consistent with objective measures such as radiographic progression, and that progression-free survival results were consistent with purely objective outcomes such as overall survival.	Comment noted.
Sanofi	Pg 30 – Uncertainties generated by the evidence As in the comment above, we note that the outcomes subject to bias showed a similar trend to objective outcomes, all showing consistent evidence of benefit. With regards to the uncertainty in the long-term survival benefit, we note that it is usual for oncology trials to have incomplete follow-up data (i.e. for patients to remain alive beyond the trial cut-off point) and comment that we demonstrate that even the most conservative extrapolations show a survival benefit in excess of 3 months.	Comment noted.
Sanofi	Pg 30 – Estimate of the size of the clinical effectiveness including the strength of supporting evidence The same comment as above applies to the uncertainties around the long-term effects on overall survival. With regards to progression-free survival we note that there is no uncertainty in this outcome given that all patients had progressed by the trial cut-off point.	Comment noted.
Sanofi	Pg 31 – Uncertainties around and plausibility of assumptions and inputs in the economic model We consider these conclusions to be misleading and inappropriate – as commented on above in the response to section 4.19.	See comment above related to conclusion
Sanofi	Pg 31 – What are the key drivers of cost effectiveness?	Text has been amended. See FAD What are the

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	We do not accept that the ICER was sensitive to the cost of post second-line chemotherapies. The main sensitivity analysis on this (changing from post second-line chemotherapy used in TROPIC to the Committee's preferred approach, the chemotherapies recorded in a UK-based audit) changed the ICER by <2%.	key drivers of cost effectiveness?
Sanofi	Pg 32 – Most likely cost-effectiveness estimate (given as an ICER) As discussed in our main responses we believe that the updated data from the EAP provide greater confidence in the robustness of the ICER generated. We also believe that the subgroup of European patients with ECOG 0 -1 and who had received at least 225 mg/m2 of docetaxel is the most appropriate subgroup for evaluating the cost-effectiveness of cabazitaxel within the UK. The additional points referred to in this paragraph regarding costs of post second-line chemotherapy, and costs of adverse event management, have a minimal impact on the ICER. Therefore, we believe that the most plausible ICER is <£80,000 per QALY.	The Committee considered that the most plausible ICER would be above £87,500 per QALY gained. The Committee noted that there remains considerable uncertainty in the robustness of this ICER because the utility values that were used in the model were based on unpublished data from an interim analysis of a small number of patients, and the costs associated with managing febrile neutropenia were underestimated. See FAD Most likely cost-effectiveness estimate

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
National Cancer Research Institute (NCRI) - Prostate Cancer Clinical Studies Group, the Royal College of Physicians (RCP), the Royal College of Radiologists (RCR), the Association of Cancer Physicians (ACP) and the Joint Collegiate Council for Oncology (JCCO)	Point 3.21 - 'The ERG noted that because of the stringent management of adverse events in the trial, the incidence of adverse events associated with cabazitaxel is likely to be higher in clinical practice in the UK'. Our experts would respectfully disagree with this. There is little reason to believe that adverse events should be higher in routine UK practice compared to the TROPIC trial. As we understand the committee heard, the UK patient population that would be treated with this agent are likely to closely match the population in TROPIC. UK oncologists took part in TROPIC and its criteria for patient selection, drug dosage modification and management of complications are essentially the same as those that would be used off trial. Chemotherapy administration in this country is restricted to oncologists sub-specialised to particular tumour sites within specialist cancer centres and units. Consensus national guidelines exist for management of complications and acute oncology services exist in all NHS trusts. As such, the administration of chemotherapy is every bit as stringent outside of clinical trials as in TROPIC. Furthermore, the UK experience with cabazitaxel, initially in TROPIC and the cabazitaxel expanded access	Text has been amended .See FAD section 3.21

Nominating organisation	Comment	Response
	programme, and now in routine use in some parts of England through Cancer Drugs Fund access, has been found to be very similar to the use of other taxane based chemotherapy for solid tumours, not least docetaxel for prostate cancer. The community is highly experienced in the administration of this type of agent and increasingly with cabazitaxel itself. Discussions with colleagues from around the UK have indicated that we are not seeing an increase in adverse events when using cabazitaxel. Concerns from TROPIC relating to early deaths following trial entry in a small number of countries with less well established acute oncology practices have simply not materialised in the UK during off-trial use.	
NCRI/RCP/RCR/ACP/JCCO	Point 3.21 - 'The ERG stated that the trial provided insufficient information on the cardiac and renal complications associated with cabazitaxel'. The rates of these events were small in TROPIC in either arm of the study and it therefore remains unclear if an increased rate of either cardiac or renal toxicity occurs with the use of cabazitaxel. Further data are clearly required and of importance. We await data on renal toxicity from the ongoing phase I study specifically evaluating renal safety and from a current phase III trial (of differing cabazitaxel doses) in which a number of UK centres are participating which will address this question as a secondary endpoint. Some further data has been published by letter on the nature of cardiac toxicity seen in TROPIC by the trial authors (Lancet, 2011, volume 377, page 122) who also note that further data are due to emerge on QT interval effects of the drug. UK clinicians will of course engage fully with post-marketing surveillance for these and other potential emergent adverse events. In the mean time the view of UK oncologists is that the weight of evidence in TROPIC for a survival advantage over mitoxantrone clearly justifies its continued use albeit with appropriate care and surveillance of individual patients and pre-treatment counselling regarding the various potential risks.	Text of the FAD has been amended. See FAD section 3.22
NCRI/RCP/RCR/ACP/JCCO	Points 4.2 and 4.3 - It is noted that patients in some regions of England, but not in others or in Wales, are already able to access cabazitaxel through the Cancer Drugs Fund. UK oncologists therefore share strongly the concerns expressed by patient representatives to the committee that there is currently unequal access to this life prolonging treatment which a positive NICE	NICE recommendations are based on clinical and cost-effectiveness of new health technologies. NICE cannot comment on any issues related to the funding through the Cancer Drug Fund.

Nominating organisation	Comment	Response
	appraisal would remove. In the same section of the ACD it is noted that patients feel it important 'that clinicians should inform patients about the potential serious toxicity of cabazitaxel and the lack of evidence showing that cabazitaxel improves health-related quality of life before taking the decision to start cabazitaxel therapy'. It should be understood that detailed counselling of exactly these issues is provided to all patients and their families prior to commencing palliative chemotherapy of any sort. This would be viewed by oncologists as a routine prerequisite for the use of an agent such as cabazitaxel. Patients are always included in, and central to, the decision to treat and alternative options, including use of symptom control measures alone, are also presented.	This text has been deleted from the FAD.
NCRI/RCP/RCR/ACP/JCCO	Point 4.4 - the number of cycles of chemotherapy that would be administered is discussed. To clarify, mitoxantrone is limited to a maximum of 10 cycles because cardiac toxicity may occur with further administration. As a result, the clinical trials of both first line docetaxel and second line cabazitaxel were performed using the same maximum number of cycles to provide appropriate comparisons to be made in the relevant trials. It would not therefore be appropriate to consider treatment beyond 10 cycles for which we have no data outside of a clinical trial. As noted the median number of cycles of cabazitaxel administered in TROPIC was 6 (limited either by progression, excessive toxicity or death) and it is reasonable to assume a similar median would occur off trial in the UK.	Comment noted.
NCRI/RCP/RCR/ACP/JCCO	The NCRI/RCP/RCR/ACP/JCCO feel that there is overwhelming support among UK prostate cancer specialists for the use of cabazitaxel as a new life-prolonging treatment option for this disease. Our experience in counselling patients is in agreement with the views expressed to the committee by patient representative groups. Patients wish to have proven treatment options available to them following use of docetaxel and are deeply concerned by the possibility of restrictions in access. Members are clear that cabazitaxel can be administered safely and are impressed by the efficacy demonstrated in the TROPIC study. Many of those in TROPIC were	The Committee concluded that cabazitaxel was an effective, life-extending treatment but with an ICER of more than £87,500 per QALY gained, it was unlikely to represent a cost-effective use of NHS resource.

Nominating organisation	Comment	Response
	progressing while on docetaxel and were therefore in a particularly poor prognostic group. To achieve any sort of outcome in such a group is remarkable.	
British Uro oncology Group (BUG)	The overall response was of great disappointment at this decision. We recently conducted a survey of 80 expert urological oncologists in the UK (publication in press) to evaluate current management strategies for patients with advanced prostate cancer in order to identify key considerations in the decision making process and to gain insights into the possible role of emerging therapies in future UK practice. The respondents had an average of 189 new referrals for prostate cancer each year, with 24% reporting >200 new referrals annually. There was consensus that there is currently no 'Standard of Care' in the management of this group of patients. Forty-four percent of oncologists felt that they were very likely to be using cabazitaxel in their clinical practice within the next five years, with a further 35% stating that this was a possibility. Reasons for this included prior approval of cabazitaxel in the US, significant improvement in overall survival and progression free survival with cabazitaxel when compared to mitoxantrone in a randomised phase 3 study (Tropic), and the fact that the efficacy of cabazitaxel demonstrated in the second-line setting is superior to that seen for any of the currently available treatment options for patients at that time with advanced m castration resistant prostate cancer (CRPC). This enthusiasm for the use of cabazitaxel has increased with further availability following the clinical trial and many members have also submitted individual responses to NICE which reflects the strength of opinion that there is a great need for cabazitaxel as part of the management for men with metastatic CRPC and enthusiasm for UK oncologists to be able to offer their patients optimal care. We would be grateful if the committee would take the following points into consideration There was a consensus in replies to BUG that cabazitaxel should be made available to men with a performance status of 0-1, who have progressed on / during at least 3 cycles of docetaxel and who have been adequately counselled as to the potential toxicities and benefits	The Committee concluded that cabazitaxel was an effective, life-extending treatment but with an ICER of more than £87,500 per QALY gained, it was unlikely to represent a cost-effective use of NHS resource.

Nominating organisation	Comment	Response
British Uro oncology Group (BUG)	Until recently docetaxel has been the only systemic therapy to demonstrate a significant survival benefit in patients with stage IV castrate-refractory prostate cancer. Docetaxel was approved by NICE in July 2006. There is no standard NICE approved treatment for patients with progressive metastatic CRPC following docetaxel chemotherapy. The most efficacious alternative cytotoxic regimen to docetaxel is mitoxantrone plus prednisone. This combination significantly improves palliation of bone pain when compared to prednisone alone, but does not impact on survival. It has generally been used as a second line regimen following treatment with docetaxel chemotherapy and was the most robust comparison arm against which to assess cabazitaxel in this setting.	The Committee concluded that cabazitaxel was an effective, life-extending treatment but with an ICER of more than £87,500 per QALY gained, it was unlikely to represent a cost-effective use of NHS resource.
	NICE approved second-line palliative chemotherapy for other solid tumours generally only provides a small survival benefit. An example of this is seen in a study in lung cancer where docetaxel 75mg /m2 was compared with Best Supportive Care. The median survival improvement for docetaxel was 7.5 months compared with 4.6 months for Best Supportive Care. As a result of this study by Shepherd, docetaxel was approved in this setting by NICE in 2001. Other examples are seen in the management of breast cancer where docetaxel was approved by NICE in February 2009 for similar median survival benefits.	Comments noted.
	The TROPIC study upon which the cabazitaxel submission to NICE is based was conducted in patients who had already received docetaxel chemotherapy. In fact approximately 30% of patients in each arm had received 2 or more prior chemotherapy regimens and so were actually receiving at least 3rd line therapy. Therefore despite being administered to heavily pre-treated patients, and compared to a robust alternative cytotoxic agent, cabazitaxel still produced a significant increase in overall survival. It also matched mitoxantrone in its ability to palliate bone pain.	Comments noted
	The fact that other chemotherapy regimens with comparable advantages have been accepted by NICE whereas cabazitaxel has been rejected was viewed by many members as discriminatory and inconsistent. The major concerns regarding cabazitaxel were the haematological	Each Technology Appraisal considers the clinical and cost effectiveness of the technology on an individual basis in accordance with the scope of the appraisal, the methods guide and the evidence available for the appraisal. The Committee

Nominating organisation	Comment	Response
	toxicities, and cardiac/renal related mortality figures. The Tropic study included patients with an ECOG performance status of 0-2. However, in the UK it would be unusual to give chemotherapy to a patient with a performance status of 2 as they would not be considered fit enough to tolerate chemotherapy and gain the advantages of treatment. The inclusion of patients with a poor performance status in the Tropic study may have resulted in a higher toxicity profile in the study than would be expected in UK clinical practice. Reports to BUG from oncologists who have used cabazitaxel both in the Tropic study and the expanded access programme have been that this drug has an acceptable toxicity and provides very significant benefits to patients.	concluded that cabazitaxel was an effective, life-extending treatment but with an ICER of £87,500 per QALY gained, it was unlikely to represent a cost-effective use of NHS resource. The FAD notes that in clinical practice in the UK cabazitaxel would be used to treat people with a performance status of 0-1 because people with the performance status of 2 are considered by clinicians to be not fit enough to tolerate further chemotherapy (FAD section 4.9).
	Following the NCEPOD enquiry into UK deaths within 30 days of chemotherapy, and the subsequent NCAG recommendations for acute oncology services it would be expected that the UK has more stringent systems in place for managing the complications of chemotherapy than some of the centres in other countries who participated in the Tropic study. As pointed out in 3.2.4 the ERG state that the deaths in TROPIC within 30 days of randomisation could have been prevented with more vigilant treatment of neutropenia and so these were excluded from the analysis. This would seem entirely appropriate. However, the ERG also state that because of the stringent management of adverse events in the trial, the incidence of adverse events associated with cabazitaxel is likely to be higher in clinical practice in the UK. There was general disagreement with this statement form a number of BUG members who have commented that with more appropriate patient selection and the increased resources now available for acute oncology, any cabazitaxel-related toxicities are likely to be better managed now than in the study. It should therefore be accepted that the toxity of neutropenia with cabazitaxel is no more than would be anticipated for second line chemotherapy and that this as well as any symptoms of diarrhoea would be well managed in dedicated UK oncology centres	No change has been made to the ERG evidence. The FAD notes (section 4.10) that the management of neutropenia in the UK is in line with best practice guidance with the result that few patients in the UK develop febrile neutropenia or neutropenic sepsis.
	The five cardiac deaths in the cabazitaxel arm of the Tropic study were attributed to cardiac arrest (3), sudden death (1), and ventricular fibrillation (1). The individual investigators at the centres treating each of these	Please see comment above related to the consideration of cardiac and renal events.

Nominating organisation	Comment	Response
	patients did not think the deaths were directly related to the study drug, although that was a subjective opinion. The concerns regarding potential renal and cardiac toxicity have been reviewed and revaluated by the FDA and EMA and it has been concluded that there is no need for additional risk management to be put in place. Since these reviews a further 12 months of post marketing updates have become available for review and there have been no further concerns regarding cardiac or renal safety issues. There has been no recommendation for the need for additional cardiac or renal monitoring above good clinical practice associated with the administration of any other chemotherapy agents. Cardiac and renal complications have not been seen in the EAP	
British Uro oncology Group (BUG)	The UK Early access programme with cabazitaxel has shown that the data from the TROPIC study underestimated patient benefit from cabazitaxel in terms of quality of life. I understand that a letter has been forwarded to you from oncologists in this programme and many of these clinicians have also consulted BUG to state that the quality of life data from this trial was robust. Patients in the expanded access study were carefully selected and assessed with the usual inclusion and exclusion criteria in any other credible clinical trial. The second interim analysis of quality of life provides strong evidence in favour of cabazitaxel over mitoxantrone in this setting. The investigators are keen to point out that there was no bias in reporting and that this evidence should be regarded as that form any other clinical trial. The expanded access programme will continue to provide credible data with time as these patients continued to be monitored and carefully follow up. There is unequivocal evidence from UK clinicians who have used cabazitaxel, both through the Early Access Programme and through the Cancer Drug Fund, that health-related quality of life is significantly and dramatically improved, with improvements seen after one or two cycles. Patients feel better, their pain is better and their daily activities of life are achievable. The results of the Early Access programme validate this, with pain improvement seen in at least 50% of patients.	The Committee remained concerned that the utility values from the early access programme in a population with metastatic disease and limited life expectancy who had progressed after first-line therapy were similar to those of the age- and gender-matched general population. The Committee agreed this to be implausible because people with metastatic prostate cancer refractory to docetaxel treatment would be expected to have a poorer quality of life. Therefore, the Committee was concerned that the utility values as calculated from the early access programme overestimated the utility of the population with hormone-refractory metastatic prostate cancer refractory to docetaxel treatment. See FAD section 4.14, 4.15 and 4.16.
Prostate Cancer Charity	The Charity is disappointed to see that the preliminary recommendation is that cabazitaxel in combination with prednisone or prednisolone is not recommended for people with mCRPC which no longer responds to docetaxel treatment.	The Committee concluded that cabazitaxel was an effective, life-extending treatment but with an ICER of above £87,500 per QALY gained, it was unlikely to represent a cost-effective use of NHS resource.

Nominating organisation	Comment	Response
	There is currently only one other licensed second line treatment for people with mCRPC that has been shown to increase overall and progression-free survival once the cancer has progressed on or following docetaxel treatment. This treatment is abiraterone, which was only recently licensed and has not yet been appraised by NICE. It would be desirable to increase the range of clinically effective treatment options available for this patient population. A recommendation from NICE that cabazitaxel is effective for the above indication will help to provide standardised access and increased choice to a group of patients who currently have few other licensed treatments available to them and are facing a very limited lifespan. Should the Appraisal Committee's final recommendation match their preliminary recommendation, we are very concerned that this will lead to an inequality in access of eligible patients to cabazitaxel in England and Wales. Evidence given to the Committee by clinical specialists and the NHS commissioning expert highlighted that access to cabazitaxel varies by English region when it is made available through the local cancer drugs fund. It is also important to note that Wales does not have an equivalent cancer drugs fund. This is very likely to lead to eligible people being denied access to a drug that has could provide significant clinical benefit to them.	NICE recommendations are based on clinical and cost-effectiveness of new health technologies. NICE cannot comment on any issues related to the funding through the Cancer Drug Fund.
	However, the Charity does recognise that more data is required on the impact of cabazitaxel treatment on both renal function and health related quality of life to enable the Committee to more effectively appraise the drug's effectiveness. We would also want to see that the modelled mean survival benefit is further explored and validated to determine whether the mean extension to life of 4.2 months is sufficiently robust for NICE's end of life criteria to be met. We hope that the drug's manufacturer will be able to provide such information to the Committee at the earliest possible opportunity.	Following consultation on Appraisal Consultation Document, the manufacturer submitted further analyses on mean extension of life and additional data on cardiac and renal safety. The Committee concluded that an improvement of greater than 3 months mean overall survival had been robustly demonstrated and that therefore the end of life criteria were met. However with an ICER of above £87,500 per QALY gained, it was unlikely to represent a cost-effective use of NHS resource.
	We would also like to see patient-reported outcomes considered by the Committee as part of their appraisal. Consideration of patient-reported outcomes will ensure that the agent is not only clinically effective but also improves outcomes of great importance to this population, such as the extension of life. If cabazitaxel is not recommended by NICE, patients tells	The appraisal was done in accordance with NICE's published methods. This includes quantification of health benefits using QALYs as well as involvement of patient/carer groups in the appraisal process. However with an ICER of above

Nominating organisation	Comment	Response
	us that the main implication for them would be the loss of a chance to improve their survival and increased distress associated with not being able to access a clinically relevant drug, if it is not funded locally.	£87,500 per QALY gained, it was unlikely to represent a cost-effective use of NHS resource.
	The Charity was concerned that there was an excess number of deaths, mainly due to neutropenia, in the cabazitaxel arm of the TROPIC trial and that there was a higher probability of grade three adverse events in patients given the drug. However, it should be noted that in a recent survey of people affected by prostate cancer conducted by the Charity[1], only seven out of thirty respondents highlighted that the side effects of cabazitaxel were of serious concern to them. Of these, most commented that patients need balanced information to weigh up the pros and cons of cabazitaxel, if offered it, for themselves. Whether NICE ultimately recommends cabazitaxel or not, thought must be given to how clear and balanced information on both the benefits and the likelihood of serious adverse events can be best provided to patients so that they are able to make an informed choice if offered cabazitaxel by their clinician. If the drug will only be made available through the cancer drugs fund in England, or via an exceptional funding request in Wales, patients will also need clear information on how to apply for funding to cover the costs of this treatment.	Comment noted. NICE recommendations are based on clinical and cost-effectiveness of new health technologies. NICE cannot comment on any issues related to the funding through the Cancer Drug Fund.
Prostate Cancer Support Federation (PCSF) and Prostate Cancer Support Organisation (PCaSO)	1. Randomised trials include men who are passed the stage where the therapy has no impact and might even have a negative effect because of the side effects. This skews the results that otherwise would show a much longer extension of life and a lower cost QALY. We believe it is very relevant and economically sound to exclude these deaths from the results. Many things are left to the clinicians	1. Comment noted.

[1] Between 24th May and 3rd June 2011, The Prostate Cancer Charity surveyed people affected by prostate cancer living in England and Wales for their views on cabazitaxel. 30 people responded to an online and paper survey. 90% of respondents had been diagnosed with prostate cancer (the others were relatives or friends of someone diagnosed with the disease) and 33% of respondents had advanced prostate cancer. None had any experience of cabazitaxel.

Nominating organisation	Comment	Response
	judgement these days and matching suitable patients with this treatment is one. 2. There are side effects that require the clinicians to be vigilant about and treat them appropriately but they should not be life threatening. They do this all the time and it is wrong of NICE to make an issue of this for Cabazitaxel 3. The Prostate Cancer Support Federation (PCSF) has members whose Docetaxel regime has failed, been very successfully treated with Cabazitaxel and expect a significant life extension. I attach a document from one of the them. 4. The clinical specialists on the panel excluded vial sharing as a possibility but with careful management at centres of clinical excellence who have a higher throughput of patients, this could be possible thus lowering the cost of treatment. This is something that is currently undertaken with other chemo therapy treatments. With all the above said this is an of life treatment that gives men with CRPC and failed Docetaxel regime a further chance of extending their life with their family. No amount of science or economics can account for that. Men are important we are fathers and grandfathers whose families want us to have a long as possible on this planet and we want equality with women who need Herceptin as an end of life drug. To this present day we have not been treated with equality and now is the time for NICE to re-address this with Cabazitaxel.	2. Text has been amended. See FAD section 4.10 3. The Committee concluded that cabazitaxel was an effective, life-extending treatment but with an ICER of £87,500 per QALY gained, it was unlikely to represent a cost-effective use of NHS resource. 4. The Committee concluded that vial sharing could not be considered a feasible option in clinical settings. The Committee concluded that cabazitaxel was an effective, life-extending treatment but with an ICER of above £87,500 per QALY gained, it was unlikely to represent a cost-effective use of NHS resource.
Prostate Cancer Support Federation (patient representative)	Prostate Cancer is not self-inflicted. In my opinion, it is very much the 'poor relation' in the numerous cancer types and the sad thing is that accurate screening could prevent many men reaching the stage of treatment being considered here. In the days after the meeting in September I tried to understand further the various cases put forward. I, (mistakenly as it turned out), came to the conclusion that I expected the Committee to give approval for the treatment. I felt that there was confusion over the number vials required to be an adequate test period and there was quite a wide discrepancy over the 'proven' extended life expectancy. The question of the actual cost was, I thought, muddled. An important consideration is the quality of life resulting from the treatment. I may have missed something, but I felt that this was somewhat glossed over. There are numerous treatments available these days for the conditions	NICE's appraisals do not differentiate between treatments for diseases that may be 'self-inflicted' and others diseases. The average cost of one cycle of treatment with cabazitaxel is £3696 excluding VAT (FAD section 2.4). Vial sharing between patients was not considered to be routinely possible (FAD section 4.20). The methods used by technology appraisals do indeed rely on quality of life being described by

Nominating organisation	Comment	Response
	mentioned. The quality of life surely can only be appraised by the individual patient. I have since pointed out, that the 'numbers' being considered are actual people. I personally, found it difficult to connect with the tone of some of the presenters, in human terms. Any extension of life expectancy must be the hope of all patients. From investigating the treatments available for most illnesses, it is blatantly obvious that as time goes by, better drugs become available and adopted. Cabazitaxel is an 'end of life drug', so surely this must clearly be the case here. From the information available to me, and my comments above, I feel that Cabazitaxel must be given further consideration and extended trials.	patients themselves, and this was done in the Early Access Programme, which was the basis of the quality of life values used by the manufacturer. The Committee considered evidence from the patient representative on the value placed on cabazitaxel treatment, the extension to life and the hope it provides (FAD section 4.3). Following consultation and the additional evidence provided by the manufacturer, the Committee agreed that cabazitaxel fulfils the criteria for an end of life treatment (FAD section 4.24). However, the most plausible ICER was above £87,500 per QALY gained which does not represent a cost-effective use of NHS resource.

Comments received from commentators

Commentator	Comment	Response
ScHARR (ERG)	Page 9 section 3.2 … discounted at a rate of 3.5% Strictly speaking the model used a discount rate of 3.56% Page 9 section 3.2 Lifetime (15 years) Strictly speaking the model used a 14.4 year horizon Page 13 section 3.24 The ERG believed that these deaths in TROPIC could have been prevented…. Should be changed to The ERG believes that these deaths possibly could have been prevented. We do not know whether they definitely could have been prevented. Page 22 section 4.15 The committee considered hat Typo: 'hat' was intended to be 'that' Page 23 section 4.16 …resulted in ICERs of £65,000 to £89,000. This would be more informative if the reference ICER (£75,000 - taken from the manufacturer's base case) was provided	The Committee noted the ERGs comments related to the factual accuracy of the ACD. The text of the FAD has been amended accordingly.

Commentator	Comment	Response
	Page 31 First box …used data from Kaplan Meier curves to calculated transition probabilities Typo: 'calculated' should be 'calculate' Page 31 Last box …assigned to stable and progressive disease state Typo: 'state' should be 'states'	
Commissioning Support, Appraisals Service (CSAS)	We are in agreement with the recommendations in the ACD not to recommend cabazitaxel for this indication as on the basis of the evidence considered it is unlikely that this treatment can be considered clinically and cost effective. In particular we noted: • Cabazitaxel is not a cost effective use of NHS resources. The most plausible ICER for the committee's preferred patient population is in excess of £89,000 per QALY gained. • Cabazitaxel does not meet NICE criteria for consideration as a life extending end of life treatment. Based on evidence from the TRPOIC trial, median extension of life with cabazitaxel is 2.4 months. Modelling data from the manufacturer citing a mean extension of 4.2 months is not robust and should not be considered by the committee. • There is no reliable data on health-related QOL. The manufacturer submitted modelling estimates for QoL. The assumption made in the model that utility values within a health state are independent of time spent in that health state is clearly flawed. Additionally, inclusion of data from an early access programme in the modelling is not appropriate. • Haematological adverse events and diarrhoea in patients treated with cabazitaxel are of concern. There remains substantial uncertainty about the effects of cabazitaxel on renal and cardiac adverse events. The most common adverse events observed in the TROPIC trial were neutropenia, asthenic conditions and gastrointestinal toxicity. The fact that the TRPOIC trial was not powered to detect differences in specific adverse events between treatment groups is of real concern. • Potential cost savings from vial sharing is not considered feasible in the	Comments noted.

Commentator	Comment	Response
	clinical setting and indeed there are important licensing and clinical governance implications. This reduces the possibility that efficiencies or savings can be made in real life clinical practice. Additionally, clinical specialists report that cabazitaxel has a short shelf life and the number of patients treated at each centre would be small.	
MRC Clinical Trials Unit	I would note that the relative benefit in this very pre-treated population is rather encouraging. If this same benefit could be replicated much earlier in the disease, the absolute benefits could be quite large and one could imagine that a cost-effective benefit could be achieved at that point. Of course, the trial results are not in place and I am not sure whether the trials are even being undertaken. The STAMPEDE collaborations and the MRC Clinical Trials Unit have been in discussions with Sanofi-Aventis about potentially including a hormone therapy + cabazitaxel arm in the STAMPEDE trial (NCT00268476) in the future. STAMPEDE is a trial which recruits men starting first-line hormone therapy and is already assessing docetaxel in this setting. The trial will present results which are relevant to NICE in the future. If discussions to assess cabazitaxel in this adaptive trial are to proceed, accrual would not commence until after the recruitment has been completed to the docetaxel comparisons has been completed. In the meantime, perhaps NICE might conclude more strongly in encouraging the assessment of this (and other) agents earlier in the disease when they might have a greater impact.	The Committee concluded that cabazitaxel was an effective, life-extending treatment but with an ICER of above £87,500 per QALY gained, it was unlikely to represent a cost-effective use of NHS resource.

Comments received from members of the public

Role*	Section	Comment	Response
Investigators for the Cabazitaxel Early Access Programme (UK	4	We the undersigned investigators for the Cabazitaxel early Access Programme would like to express our concern regarding 4.11 'The Committee concluded that because the utility data were based on such a small number of patients from a potentially select population, there is	The Committee was concerned that the utility values as calculated from the early access programme overestimated the utility of the population with hormone-refractory metastatic

* 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	Response
		considerable uncertainty as to the validity of these data'. This particular study was conducted with the same rigours as a clinical trial with the protocol being followed to its entirety and therefore the statement regarding the selection bias and the uncertainity as to the validity of the data is unfounded. The patients were entered into this as per the inclusion criteria of the protocol (which was exactly the same as the TROPIC study inclusion criteria) and the data was collected according to the ICHGCP standards. This study recruited the total number of patients before the planned accrual date reflecting the confidence that both the clinicians and the patients had in the treatment being offered in this area of great unmet need. We have submitted the initial QOL data to ASCO GU and EAU2012 and if selected these data would be presented in these international meetings.	prostate cancer refractory to docetaxel treatment. See FAD section 4.15
Chief Investigator of the cabazitaxel Phase III TROPIC trial	1	In view of the critically important unmet need for treatment for this common disease, a cancer that causes so much suffering to our patients, as well as the impressive antitumour activity of this agent, I write to suggest that the NICE committee reconsider their preliminary recommendation to not support the use of this important anticancer drug	The Committee agreed that cabazitaxel was an effective, life-extending treatment but that the most plausible was higher than ICER £87,500 per QALY gained. Therefore, the Committee concluded that the additional weight that would need to be assigned to the QALY benefits would be too great to justify it as an appropriate use of limited NHS resources (FAD section 4.24).
Chief Investigator of the cabazitaxel Phase III TROPIC trial	2	We have shown that cabazitaxel has important antitumour activity against advanced prostate cancer with radiological tumour responses and PSA falls post-treatment. Critically we have also shown that this agent improves overall survival with one of the best hazard ratios ever described in a prostate cancer Phase III trial. At the cutoff for the final analysis, median overall survival was 15·1 months (95% CI 14·1—16·3) in the cabazitaxel group and 12·7 months (11·6—13·7) in the mitoxantrone group. The hazard ratio for death of men treated with cabazitaxel compared with those taking mitoxantrone was 0·70 (95% CI 0·59—0·83, p<0·0001). This impressive impact of this agent on this disease has led to its being	The Committee agreed that cabazitaxel was an effective, life-extending treatment but that the most plausible was higher than ICER £87,500 per QALY gained. Therefore, the Committee concluded that the additional weight that would need to be assigned to the QALY benefits would be too great to justify it as an appropriate use of limited NHS resources (FAD section 4.24).

Role*	Section	Comment	Response
		given regulatory approval in Europe and North America and it is being widely used by oncologists around the world.	
Chief Investigator of the cabazitaxel Phase III TROPIC trial	4	Cabazitaxel in my experience with it during Phase I, III and expanded access studies is well tolerated. Indeed, my experience indicates that it is better tolerated than docetaxel, which is used in the first line setting for the treatment of this disease. Critically, cabazitaxel rarely causes peripheral neuropathy which is arguably the most difficult toxicity induced by this class of agents – the tubulin binding drugs. The toxicity of cabazitaxel is otherwise very similar to that of other tubulin binding drugs in routine use. Finally, it is important to note with the TROPIC trial that the frequency of grade 5 toxicities was related to geographical region with the lowest risk in North America (being 0.8 and 0.9% in the mitoxantrone and cabazitaxel arms respectively) and a slightly higher risk in Europe including Eastern Europe (3.0% vs 4.9% in the mitoxantrone and cabazitaxel arms respectively). Finally, deaths from other causes on trial were 4.0% and 3.2% in the mitoxantrone and cabazitaxel arms respectively. Moreover, there was significantly more myelosuppression with mitoxantrone than seen with the same dose and schedule of mitoxantrone in the TAX327 trial because of the more advanced disease present in this subset of patients. Overall, these data indicate that a) administration of cabazitaxel earlier in the disease to fitter patients as practiced in North America decreases risk; and b) that better supportive care minimizes risk of grade 5 toxicities from myelosuppression.	The Committee agreed that cabazitaxel was an effective, life-extending treatment but that the most plausible was higher than ICER £87,500 per QALY gained. Therefore, the Committee concluded that the additional weight that would need to be assigned to the QALY benefits would be too great to justify it as an appropriate use of limited NHS resources (FAD section 4.24).
Not reported	1	We wish to express our concern at the refusal to supply the above drug to suffers of prostate cancer, under the N.H.S . We strongly feel these people have the right to this drug and therefore the hope of a longer life. This drug appears to have a lot of success, and we feel it should be available on prescription as life is so very precious and extra time to live should not be denied. We feel a decision should be made in favour of this drug being prescribed as soon as possible.	The Committee agreed that cabazitaxel was an effective, life-extending treatment but that the most plausible was higher than ICER £87,500 per QALY gained. Therefore, the Committee concluded that the additional weight that would need to be assigned to the QALY benefits would be too great to justify it as an appropriate use of limited NHS resources (FAD section 4.24).
Professor of Urological Oncology	4	I have reviewed the various documents and opinions on the NICE website. I think the comparator issue is clouded a little by US practices such as the use of estramustine and this concept of docetaxel challenge- both of these rarely if ever practiced in the UK (certainly docetaxel beyond 10 cycles). As a uro-oncologist who was not involved in TROPIC to me the TROPIC data was compelling if a little suprising in view of similar mechanism of action. Subsequently it has been clear the marked increase intubular	The Committee considered mitoxtrantrone to be the most appropriate comparator for cabazitaxel based on the evidence of clinical specialists (FAD section 4.4). The Committee agreed that cabazitaxel was an effective, life-extending treatment but that the most plausible was higher

Role*	Section	Comment	Response
		stabilisation conferred by carbazi may explain the clinical data. I think the OS data is difficult to argue and I would think that around 30% of docetaxel failures would be suitable for carbazi, and that is without abiraterone competing. We have large number of well informed patienst and our local prostate cancer charity is also intent on lobbying for access in light of the phase III evidence. We wont have much better opportunities to see the evidence in this way for carbazi as current studies are aimed at optimising dose. I think carbazitaxel does offer a rationale and quality of life improving option for our patients; I think clinicians are well aware of the high cost and would restrict use to optimal clinical scenarious and close monitoring by rodaiology and symptoms.	than ICER £87,500 per QALY gained. Therefore, the Committee concluded that the additional weight that would need to be assigned to the QALY benefits would be too great to justify it as an appropriate use of limited NHS resources (FAD section 4.24)..
Not reported	1	I am writing in support of the new trial drug Cabazitaxel for Prostrate Cancer. My uncle, Robert Harrison, has been trialling it and has responded really well to treatment and scans show that the tumours have shrunk.	The Committee agreed that cabazitaxel was an effective, life-extending treatment but that the most plausible was higher than ICER £87,500 per QALY gained. Therefore, the Committee concluded that the additional weight that would need to be assigned to the QALY benefits would be too great to justify it as an appropriate use of limited NHS resources (FAD section 4.24).
Patient	1	This response is made on behalf of the Bay Prostate Cancer Support group, a well-established, patient-led Group serving the Lancaster/Morecambe area of NW Lancashire. The Group is extremely disappointed and concerned by NICEs preliminary recommendation. Carbazitaxel offers significant life extension and improved quality of life to late-stage prostate Ca patients where first line chemotherapy has failed and prospects are otherwise bleak. Denying access to Carbazitaxel would be a cruel blow to these men, destroying all hope and putting them at an unfair disadvantage in comparison with patients with other tumour types, where successive lines of chemotherapy are already approved & in use. We urge NICE to take these factors into account, to reverse their initial decision and recommend the use of Carbazitaxel for advanced prostate cancer patients within the NHS.	The Committee heard and considered evidence from the patient representative on the value placed on cabazitaxel treatment. The Committee were mindful of the extension to life associated with cabazitaxel treatment and the hope that this brings. The Committee agreed that cabazitaxel was an effective, life-extending treatment but that the most plausible was higher than ICER £87,500 per QALY gained. Therefore, the Committee concluded that the additional weight that would need to be assigned to the QALY benefits would be too great to justify it as an appropriate use of limited NHS resources (FAD section 4.24).

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21st October 2011

Dear Professor Longson

Re: NICE Single Technology Appraisal of cabazitaxel for metastatic hormone-refractory prostate cancer previously treated with a docetaxel-containing regimen

Sanofi is disappointed by the Appraisal Committee's preliminary decision in this appraisal. Metastatic hormone-refractory prostate cancer that has progressed following treatment with docetaxel is an area of significant unmet need in which, until recently, no therapy had shown a survival benefit. Cabazitaxel is the only treatment to demonstrate an improvement in survival against mitoxantrone, the current standard chemotherapy in this setting, and is the first treatment to be licensed for this patient population.

We welcome the Committee's recognition that cabazitaxel is an effective second-line treatment for metastatic hormone-refractory prostate cancer. However, a 'not recommended' from NICE will deny many patients in England and Wales access to this effective second-line treatment, in a setting where there are currently no NICE-approved treatments.

The ACD describes several conclusions made by the Committee in reaching their decision, which we consider are unreasonable in light of the evidence presented, and which consequently lead to an unreasonable estimate of cabazitaxel's cost-effectiveness.

We present our detailed responses to the five main conclusions outlined in the ACD as detailed below:

- End-of- Life Criteria: the Committee judges that cabazitaxel does not meet the third End-of-Life criterion, despite the consistent evidence that cabazitaxel increases mean survival by at least 3 months.
- Safety profile: the Committee raises concerns over the cardiac and renal safety of cabazitaxel, in contrast to the conclusions from a more thorough review of the safety data undertaken by the EMA and FDA regulatory bodies.
- Utility data: the Committee disregards valid utility data from a trial of UK patients receiving cabazitaxel, and instead favours their own bleak assumptions about the quality of life of this patient population.
- Base-case population: the Committee judges the evidence of differences between the geographic subgroups were unimportant and thus disregards the base-case population which better reflects patient care in the UK.
- Survival extrapolation: the Committee believes that the mathematical extrapolation of the entire survival curve was more appropriate to use in the economic model than an approach which uses the real data from the trial with mathematical extrapolation limited only to the post-trial period.

In addition to our responses on the above topics, we have included a tabulated point-by-point response to the ACD (Table 2), in which we address other relevant comments and factual inaccuracies.

As agreed with the NICE secretariat, we present herein additional utility data from an updated interim analysis of the cabazitaxel Early Access Programme and additional modelling approaches to demonstrate the mean OS is in excess of 3 months.

We remain at the Committee's disposal and hope that our comments as outlined in this document will help the Committee to reconsider the evidence for cabazitaxel and recognise that the most likely ICER is somewhat lower than they have currently indicated.

Yours sincerely,

[redacted]

1. Responses to Key Criticisms

1.1 End-of-life criteria

In the ACD, the Committee judges that "further exploration and validation of the modelled mean survival benefit using updated trial-based or observational data would be necessary before the mean extension to life of 4.2 months could be considered sufficiently robust for the end-of-life criteria to be met." (Section 4.21).

- We consider that there is robust evidence that the estimated mean survival benefit of cabazitaxel is in excess of 3 months and that the conclusion of the Committee does not represent a balanced view of the available data.
- It is usual in modelling the cost-effectiveness of oncology drugs to use extrapolation to calculate the mean overall survival benefit, as it is very rare to have complete follow-up data from a trial. NICE positive recommendations in oncology routinely rely on this type of information.
- In addition to the views expressed by the ERG that a survival gain of approximately 4 months was robustly demonstrated, we would direct the Committee's attention to the fact that however the TROPIC overall survival data are extrapolated, the resulting mean survival improvement is always in excess of 3 months and very often longer. We show graphically below (Figure 1) and describe in the Appendix (section 4) a variety of alternative modelling approaches; all of these functions provide an estimate of mean OS in excess of 3 months. This is shown for our submitted base-case population; results for patients with ECOG performance status 0 – 1 and received ≥225 mg/m2 docetaxel based on the *entire* TROPIC population, not just the European cut, are provided in the Appendix.

Figure 1: Mean OS observed with alternative modelling approaches (Population: European patients with ECOG performance status 0 -1 and received ≥225mg/m2 docetaxel)

- Probabilistic sensitivity analysis using the ERG preferred population and all assumptions included in the ERG's preferred base-case, showed that the probability of the mean OS being >3 months was >93%. The ERG commented that probabilistic results were relatively robust in that cabazitaxel produced a survival advantage in each of the 2000 probabilistic analyses run by the ERG.

- We note that other drugs have been judged as meeting end-of-life criteria based on similar evidence, for example sorafenib in hepatocellular carcinoma, where, similar to cabazitaxel, the median OS gain was <3 months, but the mean OS gain was >3 months.

- We also believe that cabazitaxel is precisely the type of drug for which end-of-life criteria were introduced. Cabazitaxel is intended to be used in mHRPC patients who have progressed after docetaxel. This represents a population of fewer than 2000 patients in England and Wales. These patients have short survival times (mean OS of around 15 months) and extremely limited treatment options. The improvement in mean OS produced by cabazitaxel represents an increase of around 30% in life expectancy, which is clinically meaningful. The introduction of cabazitaxel therefore represents an important development in the treatment of patients at high clinical need.

1.2 Cardiac and renal safety profile

"The Committee concluded that there remains substantial uncertainty about the effects of cabazitaxel on renal and cardiac adverse events." (Section 4.10).

- We would like to take this opportunity to provide further clarification around the effects of cabazitaxel on renal and cardiac adverse events, noting that the assessment of safety of a medicinal product is properly the domain of the regulatory bodies, and that these data have already been explored in detail with these agencies. Indeed, the UK regulatory agency, the MHRA, was the co-rapporteur of the EMA review of cabazitaxel. Both the FDA and EMA concluded that there was a positive benefit-risk profile for cabazitaxel, with no need for a further risk-management plan beyond that proposed. After its consideration of the available safety data, the EMA stated:

  > *"Due to the poor prognosis, high unmet clinical need and lack of alternative therapies, the observed benefits in terms of overall survival are considered clinically important. There are no major remaining uncertainties that have an impact on the benefit-risk balance".*

- We also provide updates from post-marketing surveillance, which includes data from >5500 patients who have been treated worldwide.

- **Cardiac effects in TROPIC**

  - There were five cardiac-related deaths in TROPIC in the cabazitaxel arm, and none in the mitoxantrone arm (noted by the EMA and De Bono 2010; the FDA deemed four deaths to be cardiac-related). None of these were considered by the investigators to be related to the study drug – this fact was highlighted by one of the clinical experts at the Appraisal Committee meeting, referring to the letter published by De Bono *et al* in the Lancet (De Bono 2011).

  - In their analysis, the FDA commented that three patients also had confounding factors including diabetes, hypertension, atrial fibrillation, prior warfarin use, and history of pulmonary embolism, and stated that: *"Hence, there is no clear relationship between cabazitaxel exposure and fatal cardiotoxicity".*

  - In TROPIC, all Grade cardiac events were more common on cabazitaxel of which 6 patients (1.6%) had Grade ≥3 cardiac arrhythmias, compared with 1 patient (0.3%) on mitoxantrone. The incidence of tachycardia on cabazitaxel was 1.6%, none of which were Grade ≥3. The incidence of atrial fibrillation was 1.1% in the cabazitaxel group. Cardiac failure events were more common on cabazitaxel, the event term being reported for 2 patients (0.5%), versus none on mitoxantrone (EPAR 2011; TROPIC clinical study report). As expected, more events of LV dysfunction and EF decrease occurred on the mitoxantrone arm (all grades - 3 patients versus 1 patient) (TROPIC CSR). As stated in the EPAR, there is a lack of clear evidence to suggest that cabazitaxel contributed to these cardiac events. In light of the unknown aetiology of the increased incidence of cardiac deaths and arrhythmias, the potential risk for cardiac conduction disorders was included in the SmPC.

  - An evaluation of the effect of cabazitaxel on the QT/Qc interval in cancer patients has been undertaken in study TES10884. This study has been designed to meet the current ICH E14 guidance (standard FDA guidance applicable to all drugs). The results of this were reviewed and interpreted by an external cardiology expert who concluded that cabazitaxel does not affect the ventricular repolarisation in humans to an extent that would require substantial risk-benefit considerations. The overall conclusion was that cabazitaxel at a dose of 25 mg/m^2 was well tolerated, with QTc changes from baseline below the level of regulatory concern and not clinically meaningful.

- **Renal effects in TROPIC:**
    - The EMA and the De Bono study reported 3 renal deaths, although the FDA attributed 4 deaths to renal failure, on the cabazitaxel arm, versus none in the mitoxantrone arm.
    - After considering the available data, the CHMP commented: *"Renal failure was often multi-factorial in origin and a direct causal relationship with cabazitaxel cannot be determined. Haematuria is very common in patients with prostate cancer. Although more frequent in the cabazitaxel group, a possible explanation for the observed haematuria was found in most cases. Haematuria should be closely monitored".*
    - In response to the FDA review, an expert advisory board was convened to evaluate renal events occurring in the seven completed cabazitaxel studies (TROPIC, the Phase II breast cancer study, and the Phase I studies). This board concluded that, for the vast majority of the patients with an AE renal failure, at least one concomitant risk has been identified, such as an AE (e.g. diarrhoea, dehydration, severe infection plus or minus septic shock), local obstruction/progression, medications (eg, NSAID, zoledronic acid, vancomycin, aminosides), contrast given for repeated CT scans, or co-morbidity (e.g. diabetes) and stated: "It is difficult to assess retrospectively the exact level of implication of each of these risk factors of renal failure in the completed studies."
    - With regards to the pharmacokinetics of cabazitaxel, cabazitaxel is minimally excreted via the kidney (2.3% of the dose) (EPAR). No formal pharmacokinetic studies were conducted with cabazitaxel in patients with renal impairment. However, the population pharmacokinetic analysis carried out in 170 patients that included 14 patients with moderate renal impairment (creatinine clearance in the range of 30 to 50 ml/min) and 59 patients with mild renal impairment (creatinine clearance in the range of 50 to 80 ml/min) showed that mild to moderate renal impairment did not have meaningful effects on the pharmacokinetics of cabazitaxel. To further investigate the pharmacokinetics in patients with moderate and severe renal impairment, a study (POP12251) is underway as reflected in the Risk Management Plan.
    - The safety of cabazitaxel has not been specifically evaluated in patients with renal disorders. The SmPC states that no dosage adjustment is necessary in patients with mild renal impairment, that patients with moderate and severe renal impairment should be treated with caution and monitored carefully during treatment and that dosage delay or reduction should be considered in the event of adverse drug reactions.

- **Post-marketing data:**
    - Two periodic safety update reports (PSUR) are now available, covering the period from 17 June 2010 to 16 June 2011. It is estimated that approximately [redacted] patients were exposed to cabazitaxel worldwide during this period (marketed drug). An additional [redacted] patients were enrolled in studies during this period. A review was conducted of cardiac safety issues, specifically cardiac arrhythmia, torsade de pointes or QT prolongation, cumulative analysis of cardiac arrhythmia terms (including bradyarrhythmia and tachyarrhythmias) and also peripheral neuropathies. No new safety signal was identified from these. From the data included in the PSURs and the cumulative analyses on specific reactions, no serious unlisted reactions, which would due to their frequency and/or the nature, severity, specificity, or outcome of the cases in which they occur, suggest a new risk not yet included in the current safety information for cabazitaxel.

1.3 Utility data from the Early Access Programme

"The Committee concluded that because the utility data were based on such a small number of patients from a potentially select population, there is considerable uncertainty as to the validity of these data" – section 4.11. "The Committee concluded that there is uncertainty over the utility values used in the model, that it is likely that the manufacturer had overestimated the utility values and that the use of more realistic utility values would increase the ICER" – section 4.16. The Committee noted that "the manufacturer based the utility value for the stable disease state on a small selected sample of patients and that therefore the value had wide confidence intervals and may have been biased" – section 4.16.

- The EQ-5D data were collected through a single-arm, UK-based, prospective trial of cabazitaxel which collected EQ-5D data (the Early Access Programme). As a formally conducted trial, this is a high quality source of information and the most appropriate data source for estimating the utility of patients treated with cabazitaxel.

- We are unclear as to why the Committee would assume the utility data reported by the EAP would be "biased". The early access programme (EAP) was run as a clinical trial, with formal inclusion criteria (CABAZ_C_05331 protocol – see Appendix section 7 for details). Patients were selected by physicians purely on the basis of eligibility and suitability for this trial. The patients included in the EAP are entirely reflective of those who would be expected to receive cabazitaxel in UK practice – namely patients with good performance status and who have progressed after a sufficient trial of previous docetaxel.

- In relation to the comment on the overestimation of the utility values by the manufacturer, we remind the Committee that these utility data were taken directly from a prospective trial – the values have therefore been directly measured, and not estimated or in any way inflated by the manufacturer. The EQ-5D is a patient-reported outcome and hence does not carry assessor bias.

- The Committee noted that the utility values for the stable disease state are close to those for the age- and gender-matched population, and consider this to be implausible. However, the Committee are perhaps not familiar with the prostate cancer patients who would meet the entry criteria for the trial and who would therefore be fit enough to receive cabazitaxel. The ECOG classification system describes ECOG Grade 0 as "Fully active, able to carry on all pre-disease performance without restriction". ECOG Grade 1 is described as "Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work". Considering these descriptions, we might expect a mixture of mainly level 1 and level 2 responses to the EQ-5D, which would be consistent with utility values in the range of 0.7 – 0.8. It should be noted that the general population of this age group would be expected to have a range of comorbidities that would reduce their utility somewhat from perfect health, thus it is not necessarily implausible that the EAP patients would show similar EQ-5D values to the age and gender-matched general population.

- In addition, the EAP baseline value (representing progressing patients on 1st line treatment) of [redacted] is similar to what has been found elsewhere for estimates of progression after 1st line treatment; PORTREAT, a registry study collecting EQ-5D data in patients with mHRPC with progressive disease prior to initiation on second-line chemotherapy, reported a mean utility value for patients with ECOG 0 -1 status of [redacted]

- A 2007 review found nine utility values in the literature for prostate cancer, of which only one value was less than 0.75 (Pickard 2007a). Although not confined to prostate cancer, a retrospective study of >500 patients with a variety of different types of advanced (Stage III/IV) cancer found a mean utility of 0.72 calculated by the UK tariff, with values of 0.85 for ECOG 0 patients, and 0.73 for ECOG 1 patients (Pickard 2007b).

- There are no truly comparable values to the EAP utility data as this study is the first to report EQ-5D values from second-line mHRPC patients on treatment, but overall, the values we obtained are consistent with what is reported in literature, supporting the validity of the results.
- The ERG and the Committee note the wide confidence intervals around the values, due to the small sample size available in the interim analysis. We are pleased to be able to provide updated data from a second interim analysis, based on a larger sample size. Although there are still limited data available for later timepoints due to the fact the EAP is an ongoing study, more data are now available for baseline, cycle 2, cycle 4 and cycle 6. These data are based on a larger sample size and thus have narrower confidence intervals. Similar values and trends are shown as those observed in the first interim analysis. These data have been submitted to ASCO GU in abstract form.
- A comparison of the first and second interim utility analyses is presented in Table 1. Updated modeling results are presented based on the second interim analysis data, in section 3. To provide one value for the stable disease state in the model, we pooled the cycle 2 and cycle 4 values, on the basis that there are relatively large samples for both these timepoints. Pooling utility values from cycles 2, 4 and 6 produces a very similar estimate.

Table 1: Comparison of first and second interim utility analyses

Timepoint	First interim analysis (included in June submission)		Second interim analysis	
	N	Mean EQ-5D and 95% CI	N	Mean EQ-5D and 95% CI
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2	[redacted]		[redacted]	
Cycle 4	[redacted]		[redacted]	
Cycle 6	[redacted]		[redacted]	
Pooled cycle 2 and 4			[redacted]	

- The percentage of patients at each level for each of the 5 domains of the EQ-5D is presented below (**Error! Reference source not found.**). This shows that between baseline, cycle 2 and cycle 4, [redacted] Although this is interim data and requires further confirmation from the final dataset, this suggests that the small increase in mean utility score seen between baseline and on treatment (stable disease) is in fact due to a beneficial effect of the drug [redacted]
- As the sole source of EQ-5D data for patients with second-line mHRPC on active treatment (to our knowledge) we believe that the EAP is a valuable source of information to guide decision-making in this setting.

- The Committee questioned whether the decrement applied upon the transition to the progressed health state was large enough, however, we consider the utility decrement of 0.07 (approximately 10% decline) whilst at the lower end of the spectrum, is nevertheless in line with that reported in literature and is therefore a clinically meaningful decrement.
- A retrospective study of a variety of cancer types, which used both distribution-based and anchor-based approaches (based on performance status) to calculate the minimally important difference in EQ-5D score, found a range of 0.08 – 0.16 for UK scores by the distribution approach, and 0.09 – 0.16 by the anchor-based approach (Pickard 2007b).
- As a further consideration, a decrement at the lower end of the range of values reported in other cancer areas could also be considered appropriate for this population on the basis of the definitions of progression used in the TROPIC trial. As noted by the ERG, the definition of progression in TROPIC is a conservative one. Included in this population are patients who progress based on PSA changes alone and are likely to have had asymptomatic progression; thus they would not have immediate decrease in utility.
- At this time, there are too few data points from the EAP for patients in the progressed disease state; the second interim analysis of the EAP reports only 4 patients who have progressed. Therefore, an estimate of the utility decrement on moving from the stable to the progressed disease state can only be taken from the literature.

1.4 Choice of base-case population

- "The Committee concluded that it is not appropriate to restrict the base-case population to patients recruited at European centres". This was also the judgement of the ERG.

- The ERG judged that restricting the population to patients recruited at European centres was inappropriate because there was no *a priori* clinical reason for assuming a regional difference, and because there was no statistical heterogeneity in treatment effect across the three regions for the primary endpoint. The Committee appeared to adopt the same reasoning.

- The lack of a statistically significant difference between subgroups is not unexpected because the trial was not powered to show such a difference. The absence of a statistically significant difference is not proof that there is no difference between subgroups.

- Further exploration of the regional differences showed that although it is true that there is no statistically significant difference between Europe versus North America versus the other countries, a test for interaction for the European and North American regions combined compared to the "Other countries" region, had a p-value of [redacted] (in the whole population). [redacted]

- The rationale for using the European subgroup for the base case can be clarified in three parts:

    i. While there was no *a priori* clinical rationale to expect a difference in treatment effect, there were clear and significant differences in adverse event rates (e.g. rate of clinical neutropaenia was 16.1%, 25.7%, and 35.1% in the EU, NA and Other countries regions respectively, $p<0.1$). This is thought to be the manifestation of differing care practices across the regions. This variation in management and in adverse event rates is particularly important because, with chemotherapy, management of adverse events has a bearing on efficacy because it is critical that patients can tolerate chemotherapy in order to derive the greatest benefits from it.

    ii. In light of these clinical practice and outcomes differences it was considered appropriate to restrict the base-case population to the pre-specified regional group which includes the UK, as this is most likely to be reflective of UK practice. The clinical experts informed the NICE Committee that the neutropaenia rates seen in this group could considered reflective of the UK experience.

    iii. To provide a relevant economic evaluation, consideration must be given to the circumstances under which the entirety of the clinical data – not just the primary endpoint – can be considered generalisable. The European subgroup is more generalisable to the UK than is the whole TROPIC dataset, due to regional variation in clinical management and the influence of such variation on adverse events and other clinical endpoints.

- The third point above is arguably the same rationale applied by the ERG, and accepted by the Committee, in consideration of the analysis that removed the early deaths in TROPIC. The ERG and the Committee concluded that with better management of neutropaenia as expected in the UK, the early deaths observed in TROPIC could be avoided.

- Neutropaenia was apparently managed more effectively in Europe (as shown in the rates of clinical neutropaenia observed) and consequently the European subgroup reported a lower rate of neutropaenic deaths than the whole TROPIC population. Arguably adoption of the European-subgroup for the base case achieves the same objective as the *post-hoc* analysis requested by the ERG, whilst having the advantage that the European subgroup approach employs all the 'relevant' data, not just an artificial adjustment to the primary endpoint. It is

therefore contradictory for the Committee to accept an analysis which selectively removes one group of events (the early deaths) on the basis that these would not be expected to occur in the UK, while rejecting an analysis which more comprehensively accounts for regional differences in other outcomes.

1.5 Curve-fitting

- In the base-case, Kaplan-Meier (KM) data from TROPIC were used directly, and mathematical extrapolation limited to the post-trial period only. The ERG judged that it would be more appropriate to use the parametric functions throughout; a sensitivity analysis presented in our original submission.

- The rationale for using the Kaplan-Meier data for the initial time period was that these are the actual data from TROPIC. They therefore provide the most accurate reflection of what was observed in the TROPIC trial. We note that the use of Kaplan-Meier data, followed by extrapolation limited to the period beyond the trial follow-up has been adopted in previous technology appraisals (for example it was applied by the ERG in the recent eribulin appraisal).

- The application of this methodology to the base case was criticised unfairly in the ACD. The 'choice' of time point at which the KM data was replaced by mathematical extrapolation was described as arbitrary. This was not the case; a decision-rule was applied. The KM data were considered unreliable when four consecutive cycles reported zero events. Furthermore, the ACD also incorrectly asserts that the time point was 'chosen' to generate "the most favourable ICER". This is factually incorrect; the time point at which the switch occurs in the base case (cycle 37) does not generate the lowest ICER – the lowest ICER is seen when the switch is made at cycle 17.

- While the choice of survival data modelling is clearly a matter for scientific debate – indeed our submission explored a variety of approaches, including the one favoured by the ERG – section 4.13 of the ACD states that "the parametric fitted curves more closely fit data from TROPIC…". We also reject this assertion as it cannot be the case that fitted curves could more closely fit data from TROPIC than the actual data from TROPIC itself.

- At the Committee meeting, one member of the Committee suggested that, instead of either the parametric (Weibull) function or our base-case approach, it may be more appropriate to fit a piecewise survival analysis considering of a number of different curves fitted to the Kaplan-Meier data. While this approach is not explicitly mentioned in the ACD, we would have wished to respond to the Committee member's comments. We therefore requested clarification from NICE in relation to the point raised during the meeting. In response to our request, we were provided with the ERG's understanding of this proposed approach, but no specific details which would enable us to investigate or consider the suggestion made by the Committee member during the meeting.

- In the absence of detailed guidance on this matter, we have nevertheless explored alternative approaches including a piecewise approach to find a better fit to the data. Full details of these methodologies are provided in the Appendix (section 5). The piecewise approach fitted different functions before and after 2.1 months. For our base-case population (European patients with ECOG status 0 -1 and who had received ≥225 mg/m2 docetaxel), this provided an estimate of the mean OS gain of [redacted] months. Incorporating this in the model provided an estimate of the ICER of £77,765. This is very similar to that obtained with our original methodology - £78,016 (both analyses run with updated utility data and the Committee's preference for post-second-line chemotherapy). Similarly, using the ERG/ Committee preferred population, the result obtained with this methodology was very similar to that obtained with our original methodology. Detailed modeling results are provided in the Appendix (section 5).

- As an alternative curve-fitting approach, we also fitted partitioned survival functions to the Kaplan-Meier OS curves for cabazitaxel and for mitoxantrone. This was performed for our preferred base-case population (European patients with ECOG status 0 -1 and who had received ≥225 mg/m2 docetaxel). Details are provided in the Appendix (section 5). A

partitioned approach incorporating 3 Weibull functions was indicated as the best fit for the data, for both cabazitaxel and for mitoxantrone. This approach provided an estimate of the mean OS gain of [redacted] months. Again, this is very close to what was obtained using the initial modelling approach we took (Kaplan-Meier followed by Weibull extrapolation – mean OS gain of [redacted] months).

- In conclusion, while the appropriate methodology for modeling the TROPIC survival data is clearly a matter for scientific debate, our original choice of base-case methodology was chosen in order to reflect the TROPIC data as closely as possible and minimise the level of data extrapolation.

2. Point-by-point response

Table 2: Detailed point-by-point response

Comment within ACD	Comment
Pg 3, section 1	No comment
Pg 3, 2.1/2.2	No comment
Pg 3, 2.3	While this section is factually correct, we believe it is important to specify what constitutes “very common” to aid in interpretation of this paragraph. In addition, peripheral neuropathy is not a very common adverse event, it is classed as common (≥1/100– 1/10 instead of (≥1/10, as per the SmPC. The incidence of Grade ≥3 peripheral neuropathy was in fact notably low for a taxane chemotherapy, as remarked on in the De Bono 2010 Lancet publication.
Pg 4, 2.4	No comment
Pg 4, 3.1	No comment
Pg 5, 3.2	No comment
Pg 5, 3.3	No
Pg 6, 3.4	No comment
Pg 6, 3.5	No comment
Pg 6, 3.6	No comment
Pg 7, 3.7	No comment
Pg 7, 3.8	No comment
Pg 8, 3.9	No comment
Pg 8, 3.10	No comment
Pg 8, 3.11	The statement on febrile neutropaenia incidence is factually incorrect. The incidence in the cabazitaxel arm was 7.5% (28 patients) and in the mitoxantrone arm was 1.3% (5 patients).
Pg 9, 3.12	To clarify, the model compares cabazitaxel and mitoxantrone in combination with prednisolone. Prednisone is not available in the UK.
Pg 9, 3.13	No comment
Pg 10, 3.14	This summary omits the per cycle costs of disease management included in the model. In the stable disease state, costs of hospitalisations, tests and imaging, and physician time (over and above that required for chemotherapy administration) are applied on a per cycle basis. Similarly, in the progressive disease state, a per cycle cost incorporating ongoing LHRH agonist medication, supportive care medications, hospitalisations, tests and imaging, and physician time was applied. This is important as the progressive disease costs are higher in the cabazitaxel arm due to the fact that cabazitaxel prolongs life, and thus these costs are accrued over a longer time period. The costs of best supportive care were not applied as a transition cost, but were applied on a per cycle basis throughout the progressive disease period.

Pg 10, 3.15	With regards to the statement "the manufacturer assumed that utility values within a health state were independent of time spent in the health state" – we would like to highlight that this is a widely accepted and commonly used assumption in oncology modelling. In addition, we would like to clarify that the early access programme was conducted in twelve, not nine centres.
Pg 11, 3.16	It is factually inaccurate to state that we corrected the incidence of adverse events. These rates were correct in the submitted model. However, in response to a request from the ERG, we changed the calculation of QALY losses associated with adverse events to divide by 365.25 instead of 365.
Pg 11, 3.17	No comment
Pg 11, 3.18	No comment
Pg 12, 3.19	No comment
Pg 12, 3.20	No comment
Pg 12, 3.21	The statement that TROPIC was not powered to detect differences in adverse events is true – to aid in interpretation, it should be added that this is the case with most registration trials designed for efficacy.
Pg 12, 3.21	The statement that "The ERG noted that because of the stringent management of adverse events in the trial, the incidence of adverse events associated with cabazitaxel is likely to be higher in clinical practice in the UK" does not reflect input from the clinical experts at the Committee meeting, who expressed confidence in the ability and experience of UK physicians with managing the AEs commonly associated with taxane chemotherapies. It is also contradictory with statements elsewhere in the document – for example, the emphasis placed on a sensitivity analysis removing early neutropenic deaths, on the basis that it is believed these would NOT occur in UK practice, and the recognition that clinical neutropaenia rates were lower in Europe than in the rest of the trial population, which suggests that the good management practices prevalent in the UK and the rest of Europe would result in AE rates as low or lower than those observed in TROPIC.
Pg 12, 3.21	The statement that "The ERG stated that the trial provided insufficient information on the cardiac and renal complications associated with cabazitaxel" is disappointing. As discussed in detail above (section 1.2) these effects have been explored with the regulators, as part of their stringent assessment of drug safety. Additional information on the cardiac and renal complications in TROPIC beyond that presented in the submission, together with a summary of post-marketing data, is discussed in detail above.
Pg 12,3.22	We comment on detail on the choice of base-case population in section 1.4.
Pg 13, 3.23	See section 1.5 for further clarification on the curve-fitting methodology. Of note here, the choice of timepoint at which to switch from the Kaplan-Meier data to the parametric function was rule-based, not arbitrary.
Pg 13, 3.24	The request to remove the deaths which occurred within 30 days in TROPIC on the basis that these could have been prevented with more vigilant treatment of neutropaenia is contradictory with the statement in 3.21 that it is believed adverse event rates would be higher in UK practice than in TROPIC. It is also contradictory with the position that the European subgroup should be rejected. The European population has fewer deaths reflecting better management of neutropaenia, and it seems more reasonable to use the complete adverse event profile from the European subgroup rather than to selectively remove certain events from the trial data. This is explored more fully in section 1.4.
Pg 14, 3.25	We discuss extensively in section 1.3 the utility data. We profoundly disagree with the statement from the ERG that the utility value for stable disease was implausible because it was similar to the utility values observed in the general population. These data came from a

	prospective trial of UK patients receiving cabazitaxel and completing EQ-5D questionnaires and as such we judge to be the most reliable source available. We also highlight that the independent sampling of the stable and progressive disease utility values was an error in our model, but that this only affects the sensitivity analyses, and has no bearing on the deterministic ICER.
Pg 14, 3.26	As in 3.25, we would highlight that the change to the sampling of the utility in stable and progressive disease only affects the sensitivity analyses and has no effect on the deterministic ICER of £89,476 quoted here.
Pg 15, 3.27	This is correct, however we wish to clarify that the decrement of 0.085 was also applied in a sensitivity analysis included in our original submission.
Pg 15, 4.1	No comment.
Pg 15, 4.2	The text notes that docetaxel re-treatment is not recommended by current NICE guidance. In addition we note that the benefits of docetaxel re-treatment have not been investigated in a RCT, and would not be expected to provide benefit patients who are resistant to docetaxel.
Pg 16, 4.3	With regards to the comment on the lack of evidence that cabazitaxel improves health-related quality of life, we would like to draw attention to the updated analysis of EQ-5D from the cabazitaxel EAP.
Pg 17, 4.4	The text comments that “The Committee noted that the manufacturer excluded from its submission the other comparators listed in the scope”. This is correct; indeed this is something we agreed with NICE at the decision problem meeting and the ERG report considered this to be appropriate.
Pg 17, 4.4	The committee noted that TROPIC was susceptible to bias in the subjective outcomes included in progression-free survival. This is true, but we would point out that the results of these subjective outcomes were consistent with objective measures such as radiographic progression, and that progression-free survival results were consistent with purely objective outcomes such as overall survival. Also, it should be noted that the ERG considered the definition of progression in the TROPIC trial to be a conservative approach.
Pg 17, 4.4	The text comments that the Committee heard from clinical specialists that participants in TROPIC were in many ways similar to those who would receive cabazitaxel in the UK, although on average younger (median age 68 years). We recollect that the clinical specialists at the meeting did not think TROPIC patients were younger than those who would receive cabazitaxel in the UK. Sixty-eight may be younger than the median age of the overall UK metastatic prostate cancer patient population, however it would be expected cabazitaxel would only be given to fitter patients with good performance status; these tend to be younger patients (although not exclusively). Data from our EAP shows that patients entered into this trial also had a median age of [redacted], suggesting that the TROPIC population may not be younger than the average UK patients receiving cabazitaxel
Pg 18, 4.5	We comment in section 1.1 on the survival benefit of cabazitaxel beyond the period of the trial.
Pg 18 – 20, 4.6 – 4.10	The rationale for the European subgroup is discussed further in section 1.4. We note that in section 4.7, the statement “the clinical specialists commented that clinicians in other European centres manage adverse events similarly to clinicians in the UK” is supportive of the choice of the European subgroup.
Pg 20, 4.10	As for section 3.21, we consider the point that the Committee noted that the incidence of neutropaenia was lower among participants recruited at European centres, is inconsistent with the rejection of the rationale for our European subgroup.
Pg 20, 4.10	We discuss in detail in section 1.2 our response to the question of cardiac and renal adverse effects.

Pg 21, 4.11	We comment extensively on the utility data in section 1.3; we dispute the claim that there is uncertainty in the validity of these data.
Pg 21, 4.12	No comment.
Pg 21, 4.13	The statement "the time point chosen by the manufacturer produced the most favourable ICER" is incorrect. There were several timepoints which in fact produced a lower ICER. The choice of this timepoint was based on a decision-rule. This issue is discussed further in section 1.5. With regards to the statement "The Committee concluded that the parametric fitted curves more closely fit data from TROPIC" – this assertion is not reasonable; fitted curves could not more closely fit data from TROPIC than the actual data itself.
Pg 22, 4.14	No comment
Pg 22, 4.15	As discussed in section 1.4 and our response to 3.24, the conclusion that early deaths could have been avoided with the better management of neutropaenia clearly expected to occur in UK practice is inconsistent with the rejection of the European subgroup – we employ the European subgroup because we considered practice in Europe to be more reflective of what would occur in the UK and the results of the European subgroup provide a more comprehensive picture of the outcomes which would be expected in UK practice.
Pg 22, 4.16	We discuss this issue fully in section 1.3. However, the suggestion that the data are biased and that the values obtained represent overestimates is unreasonable and appears to be based on the Committee's preconceived notion of this populations baseline utility. We also highlight that it is biased to report on page 23, only the impact of variability on the ICER using the lower limit of the 95% CI – which is the worst-case scenario – and not to report the equally probable scenario based on the upper 95%CI. We consider the utility values presented to be the most realistic utility values available, as they are sourced from a prospective UK-based trial collecting EQ-5D data.
Pg 24, 4.17	The text notes: "…the manufacturer had assumed that an improbably high proportion of patients received post second-line chemotherapy" and comments that the proportions from a UK audit would be more appropriate. This is misleading, since the base-case uses the proportion of patients receiving post second-line chemotherapy from the TROPIC database. Therefore we believe the description "improbably" is unjustified. A sensitivity analysis using the proportions from an audit of UK practice (more properly, a series of UK service evaluations) was also presented in the submission. As the ERG and the clinical experts considered the audit data acceptable we are happy to accept the Committee's choice that this would be a more appropriate input for the base-case. We note however that the impact on the ICER of using these alternative data is relatively small; the ICER increased by less than 2%. Therefore the statement "using the UK values for post second-line chemotherapy from the audit would increase the ICER" without qualification of by how much, alongside the emotive statement that the data used were "improbably high" is both misleading and unnecessarily critical of our submission.
Pg 24, 4.17	With regards to hospitalisations for febrile neutropaenia, the model did indeed include hospitalisations for febrile neutropaenia. In the base-case we took the hospitalisation rate for febrile neutropaenia recorded in the TROPIC database – this was 75%. If we assume that, in the UK, 100% of patients would be hospitalised for febrile neutropaenia, the ICER is increased by £254 in the base-case.
Pg 24, 4.18	No comment
Pg 24, 4.19	We consider the statements on the robustness of the ICER to be inappropriate and incorrect. The utility data is discussed in section 1.3. The statement that "the costs of post second-line chemotherapy were not appropriately estimated" is incorrect because these costs were appropriately estimated based on the regimens received in TROPIC. Costs based on post-second-line chemotherapy regimens received

	in a UK audit were presented as a sensitivity analysis and the Committee judged that this would be a more appropriate set to use in the base-case; the impact on the ICER is small (<2%). The statement that "the costs associated with the management of adverse events were underestimated" is misleading, given that the only cost questioned was that of febrile neutropaenia, which was included in the model, and even if the hospitalisation rate is increased from the 75% rate observed in TROPIC to 100%, the impact on the ICER is only £254. The ERG report recognised that hospitalisations were appropriately included and that post second-line chemotherapy was appropriately costed.
Pg 25, 4.20	No comment.
Pg 26, 4.21	We consider that the evidence for cabazitaxel providing a survival benefit in excess of 3 months is robust. This is discussed fully in section 1.1.
Pg 26, 4.22	No comment
Pg 27, 4.23	The patient experts commented that the most important benefits were the extension to life, and **the hope that this affords**. We consider that the benefit of hope to patients and their families provided through offering an active treatment which can prolong survival, in a setting where no treatment has until now been available, is a considerable benefit which is not captured within the QALY calculation. In addition we note, that it is challenging to provide data to demonstrate innovation. Innovation by definition cannot always be demonstrated through hard outcomes. The innovativeness of cabazitaxel is that it was specifically designed to overcome a problem, namely taxane resistance, and has been demonstrated through RCT evidence.
Pg 28, Key conclusions	As stated in our response to 4.19, we consider that the statements that the "costs of post second-line chemotherapy were not appropriately estimated, and the costs associated with the management of adverse events were underestimated" are incorrect and misleading.
Pg 28 – Innovation	This is commented on in our response to section 4.23.
Pg 29 – Position in pathway of care	As stated above in our response to 4.2, we emphasise that in addition to the fact that docetaxel re-treatment is not recommended by NICE, there is no RCT evidence to support its use, and is unlikely to provide any benefit in the patient population cabazitaxel was designed to treat, namely patients whose tumours have developed resistance to docetaxel.
Pg 29 – Adverse effects	As noted above, we emphasise that the safety profile of cabazitaxel has been reviewed thoroughly by both European and North American regulatory bodies and the risk-benefit profile deemed adequate. We have provided further clarification on the cardiac and renal profile of the medicine.
Pg 29 – Availability, nature and quality of evidence	With regards to the comment that TROPIC was susceptible to bias in the subjective outcomes included in progression-free survival, we note that it is true, but also point out that the results of these subjective outcomes were consistent with objective measures such as radiographic progression, and that progression-free survival results were consistent with purely objective outcomes such as overall survival.
Pg 30 – Uncertainties	As in the comment above, we note that the outcomes subject to bias showed a similar trend to objective outcomes, all showing consistent evidence of benefit. With regards to the uncertainty in the long-term survival benefit, we note that it is usual for oncology trials to have

generated by the evidence	incomplete follow-up data (i.e. for patients to remain alive beyond the trial cut-off point) and comment that we demonstrate that even the most conservative extrapolations show a survival benefit in excess of 3 months.
Pg 30 – Estimate of the size of the clinical effectiveness including the strength of supporting evidence	The same comment as above applies to the uncertainties around the long-term effects on overall survival. With regards to progression-free survival we note that there is no uncertainty in this outcome given that all patients had progressed by the trial cut-off point.
Pg 31 – Uncertainties around and plausibility of assumptions and inputs in the economic model	We consider these conclusions to be misleading and inappropriate – as commented on above in the response to section 4.19.
Pg 31 – What are the key drivers of cost effectiveness?	We do not accept that the ICER was sensitive to the cost of post second-line chemotherapies. The main sensitivity analysis on this (changing from post second-line chemotherapy used in TROPIC to the Committee's preferred approach, the chemotherapies recorded in a UK-based audit) changed the ICER by <2%.
Pg 32 – Most likely cost-effectiveness estimate (given as an ICER)	As discussed in our main responses we believe that the updated data from the EAP provide greater confidence in the robustness of the ICER generated. We also believe that the subgroup of European patients with ECOG 0 -1 and who had received at least 225 mg/m2 of docetaxel is the most appropriate subgroup for evaluating the cost-effectiveness of cabazitaxel within the UK. The additional points referred to in this paragraph regarding costs of post second-line chemotherapy, and costs of adverse event management, have a minimal impact on the ICER. Therefore, we believe that the most plausible ICER is <£80,000 per QALY.

3. Additional modelling results

We present below revised modelling results. The main change here is that we use updated utilities for the stable disease state from the second interim analysis of our early access programme (EAP).

In addition, we have corrected the minor error in the discount rate identified by the ERG. Following feedback at the Committee meeting, we use the rates of post-second-line chemotherapy usage identified in the UK audit as the base-case, rather than the rates from TROPIC. Updated results are shown in Table 3.

We also present revised sensitivity analyses and scenario analyses in Table 4. These are based on the revised deterministic base-case. We have revised the way the SD and PD utilities are varied, in line with the ERG comments, to remove the possibility that the PD utility value can be higher than the SD utility value. Additional sensitivity analyses are included varying the SD utility estimate according to the lower and upper 95% confidence intervals. The updated EAP analysis based on greater patient numbers reduces the variation in the ICER with this parameter. These results are for our submitted base-case population, namely European patients with ECOG 0 -1 and received ≥225 mg/m2 docetaxel. For brevity we have excluded scenario analyses deemed irrelevant in the ERG report or already discussed elsewhere.

Table 3: Updated cost-effectiveness results

Population	European patients with ECOG 0 -1 and received ≥225 mg/m2 docetaxel		Patients with ECOG 0 -1 and received ≥225 mg/m2 docetaxel		European patients		Whole TROPIC population	
	Cabazitaxel	Mitoxantrone	Cabazitaxel	Mitoxantrone	Cabazitaxel	Mitoxantrone	Cabazitaxel	Mitoxantrone
Technology acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	£35,493	£11,845	£33,474	£11,736	£33,729	£11,615	£33,102	£11,460
Difference in total costs	N/A	£22,649	N/A	£21,739	N/A	£22,115	N/A	£21,643
LYG	1.585	1.172	1.528	1.168	1.508	1.146	1.472	1.134
LYG difference	N/A	0.414	N/A	0.360	N/A	0.362	N/A	0.338
QALYs	1.117	0.827	1.076	0.823	1.063	0.810	1.037	0.800
QALY difference	N/A	0.290	N/A	0.253	N/A	0.253	N/A	0.237
ICER	N/A	£78,016	N/A	86,008	N/A	87,348	N/A	91,134

Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALY = quality-adjusted life-year
*Includes administration, premedication and concomitant medication.

Table 4: Revised modelling estimates - univariate sensitivity analyses (European patients with ECOG 0 -1 and received ≥225 mg/m2 docetaxel)

Scenario	Incremental cost	Incremental QALYs	ICER per QALY
Base case	**£22,649**	**0.29**	**£78,016**
Utilities			
AE disutilities excluded	£22,649	0.29	£77,586
SD utility and PD utility +20%	£22,649	0.35	£64,104
SD utility and PD utility -20%	£22,649	0.23	£99,640
PD utility decrement +20%	£22,649	0.29	£79,277
PD utility decrement -20%	£22,649	0.29	£76,794
SD utility – lower 95% CI	£22,649	0.27	£83,438
SD utility – upper 96% CI	£22,649	0.31	£73,255
Utility decrement from Sandblom (0.085 versus 0.07)	£22,649	0.29	£79,369
Model structure			
Parametric curves used throughout	£23,417	0.271	£86,373
Weibull distribution used for mitoxantrone PFS	£23,273	0.271	£85,935
Time horizon			
1 year	£20,023	0.05	£443,942
2 years	£20,739	0.12	£176,209
3 years	£21,842	0.22	£97,847
5 years	£22,602	0.29	£78,839
10 years	£22,649	0.29	£78,016
Discount rates			
Costs: 0%, Effects: 0%	£23,015	0.31	£73,703
Costs: 3.5%, Effects: 0%	£22,663	0.31	£72,577
Costs: 0%, Effects: 3.5%	£22,994	0.29	£79,305
Costs: 6%, Effects: 6%	£22,391	0.28	£81,363

Appendix

4. Further detail on mean OS obtained with alternative survival analysis assumptions

- **Submitted base-case population (ECOG 0 -1 status and who had received at least 225 mg/m2 docetaxel based on European data):**
    - As shown in the graph in the main body of the text (Figure 1), the mean OS calculated in the model, using the Kaplan-Meier data followed by Weibull extrapolation, as submitted in our base-case, is [redacted] months. Using the fitted Weibull function, the mean OS gain is estimated as [redacted] months. As presented in the submission, we originally fit a range of alternative standard parametric functions to the Kaplan-Meier data to identify the function with the best fit. Notably, all of these gave an estimate of mean OS in excess of that used in the base-case (Table 5).
    - Even without extrapolation, and restricting survival in both arms to the timepoint at which the last death occurred in the mitoxantrone arm (26.9 months), the mean OS estimated from under the Kaplan-Meier curve is 3.0 months. In this population, at this timepoint, 28% patients were still alive in the cabazitaxel arm compared to 8% in the mitoxantrone arm. If, over the long-term, we assume all patients are dead in both arms at 33 months (6 months after the last death observed in the mitoxantrone arm) the incremental mean OS is 3.7 months (Table 6). This is still a very conservative assumption for cabazitaxel given that 28% of patients were still alive at 26.9 months – this is best illustrated on the graph in Figure 2).
    - Following comments at the Committee meeting, we also explored fitting piecewise functions the data. Details are provided above in section 1.5 and more extensively below in section 5). This provided an estimate of [redacted] months for the mean OS gain for our base-case population. In addition, we explored fitting a partitioned survival function (section 6) which provided an estimate of the mean OS gain of [redacted] months.
    - In conclusion, all of these provided estimates of the mean OS gain of 3 months or greater.

Table 5: European patients with ECOG PS 0 -1 and who received≥225 mg/m2 docetaxel – alternative parametric functions

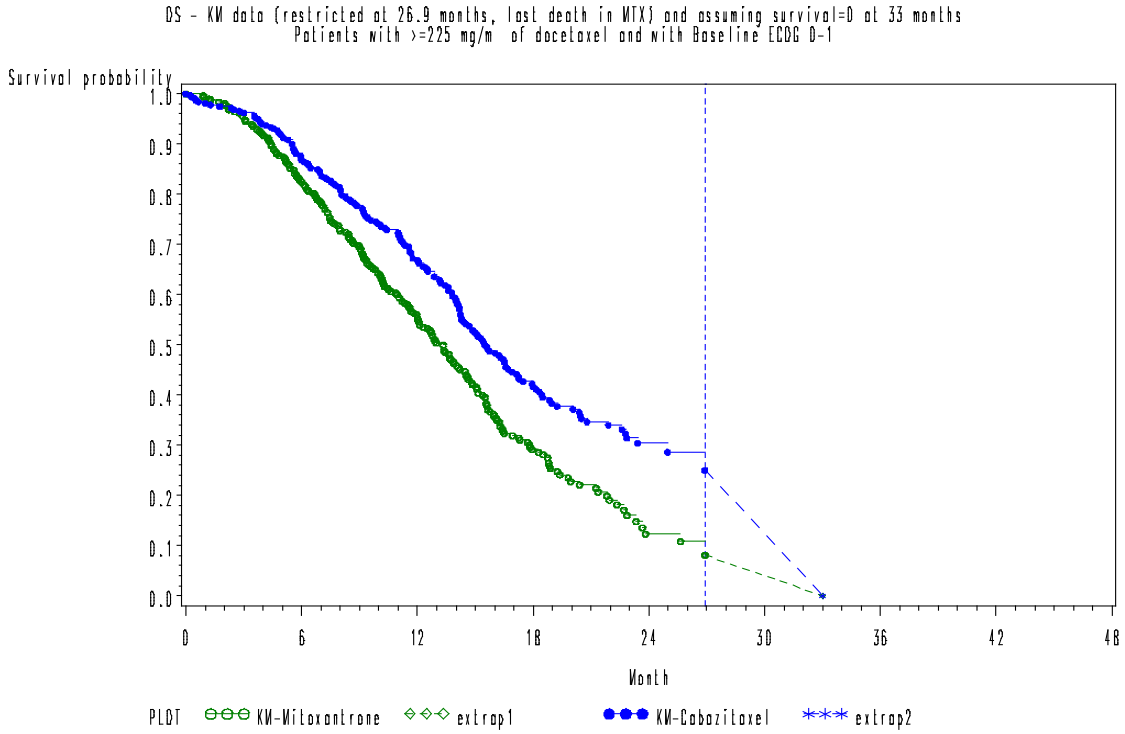
	Mitoxantrone arm			Cabazitaxel arm			Difference
Distribution	AIC	BIC	Mean OS (months)	AIC	BIC	Mean OS (months)	Incremental mean OS (months)
Exponential (λ)	379.2	382.2	16.78	421.5	424.7	[redacted]	[redacted]
Weibull (λ. σ) *	343.8	349.9	14.48 [13.1 ; 15.8]	397.6	404.0	[redacted]	[redacted]
Lognormal (λ. σ)	356.0	362.1	17.07	406.4	412.8	[redacted]	[redacted]
Loglogistic (λ. σ) *	350.5	356.6	18.16	397.0	403.4	[redacted]	[redacted]

AIC: Akaike's Information criteria, BIC: Bayesian Information Criteria (BIC)

Table 6: European patients with ECOG PS 0 -1 and who received≥225 mg/m2 docetaxel – Kaplan-Meier curve followed by linear extrapolation

	Mitoxantrone arm Mean OS (months)	Cabazitaxel arm Mean OS (months)	Difference Incremental mean OS (months)
Within trial (under-estimated): AUC under KM data restricted in both arm to the last death observed in MTX arm (at 26.9 months)	13.9 (restricted mean)	16.9 (restricted mean)	3.0 (restricted mean)
If all patients are dead at 33 months in both arms	14.1	17.8	3.7
If all patients are dead at 40 months in both arms	14.4	18.7	4.3
If all patients are dead at 50 months in both arms	14.8	20.1	5.3

Figure 2: Illustration of Kaplan-Meier followed by linear extrapolation to 33 months



- **ERG / Committee base-case population: (ECOG 0 -1 status and who had received at least 225 mg/m2 docetaxel):**
    - We ran similar analyses for the population preferred by the ERG and Committee.The mean OS benefit for the population with an ECOG 0 -1 and who had received at least 225 mg/m2 docetaxel is estimated as [redacted] months using the Weibull distribution, which provides the best fit to the data (by AIC, BIC criteria and graphical comparison) and is the function we used. Using alternative standard parametric functions all provided estimates in excess of this (Table 7).
    - Even without extrapolation, and restricting survival in both arms to the timepoint at which the last death occurred in the mitoxantrone arm (26.9 months), the mean OS estimated from under the Kaplan-Meier curve is 2.7 months. It should be noted that this scenario, in which nobody survives in either arm beyond the trial cut-off, is very unlikely and is biased against cabazitaxel given that 25% of patients in the cabazitaxel arm were still alive at this point, in comparison with 8% in the mitoxantrone arm. If, over the long-term, we assume all patients are dead in both arms at 33 months (6 months after the last death observed in the mitoxantrone arm), which is still a very conservative assumption, the incremental mean OS is 3.3 months (Table 8).
    - Following comments at the Committee meeting, we also explored fitting piecewise functions to the data. Details are provided above in section 1.5 and more extensively below in section 5). This provided an estimate of [redacted] months for the mean OS gain.
    - In conclusion, all of these provided estimates of the mean OS gain of 3 months or greater, with the sole exception of the analysis where it is assumed nobody survives beyond the trial cut-off, which is an analysis which is somewhat biased against cabazitaxel.

Table 7: Patients with ECOG PS 0 -1 and who received≥225 mg/m2 docetaxel – alternative parametric functions

	Mitoxantrone arm			Cabazitaxel arm			Difference
Distribution	**AIC**	**BIC**	**Mean OS (months)**	**AIC**	**BIC**	**Mean OS (months)**	**Incremental mean OS (months)**
Exponential (λ)	741.9	745.6	16.97	741.5	745.3	[redacted]	[redacted]
			14.40			[redacted]	[redacted]
Weibull (λ. σ) *	665.4	672.9		701.1	708.7		
			[13.5 ; 15.3]				
Lognormal (λ. σ)	678.0	685.5	16.70	730.4	737.9	[redacted]	[redacted]
Loglogistic (λ. σ)	671.0	678.5	17.68	703.6	711.1	[redacted]	[redacted]

AIC: Akaike's Information criteria, BIC: Bayesian Information Criteria (BIC)

Table 8: Patients with ECOG PS 0 -1 and who received≥225 mg/m2 docetaxel – Kaplan-Meier curve followed by linear extrapolation

	Mitoxantrone arm Mean OS (months)	**Cabazitaxel arm Mean OS (months)**	**Difference Incremental mean OS (months)**
Within trial (under-estimated): AUC under KM data restricted in both arm to the last death observed in MTX arm (at 26.9 months)	13.9 (restricted mean)	16.6 (restricted mean)	2.7 (restricted mean)
If all patients are dead at 33 months in both arms	14.1	17.4	3.3
If all patients are dead at 40 months in both arms	14.4	18.2	3.8
If all patients are dead at 50 months in both arms	14.8	19.5	4.7

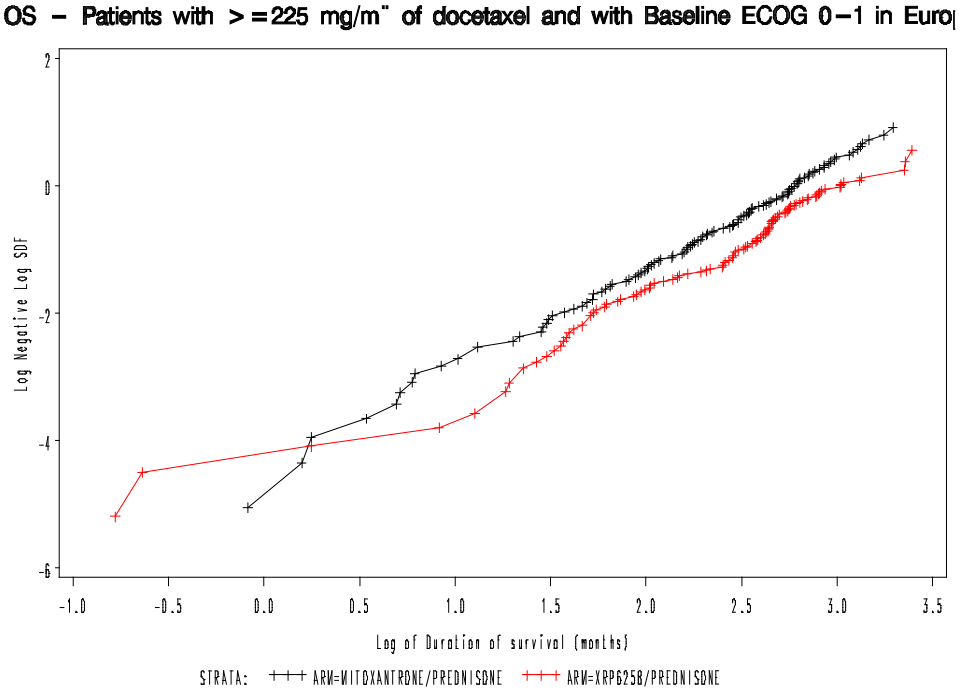
5. Piecewise OS analysis

To follow up on the discussion at the Committee meeting, we explored the possibility of fitting different curves over different time periods in the Kaplan-Meier data. These results are provided below for two populations: our base-case population, and the base-case population preferred by the ERG and Committee.

1: European patients with ECOG PS 0 -1 and who received ≥225 mg/m2 docetaxel

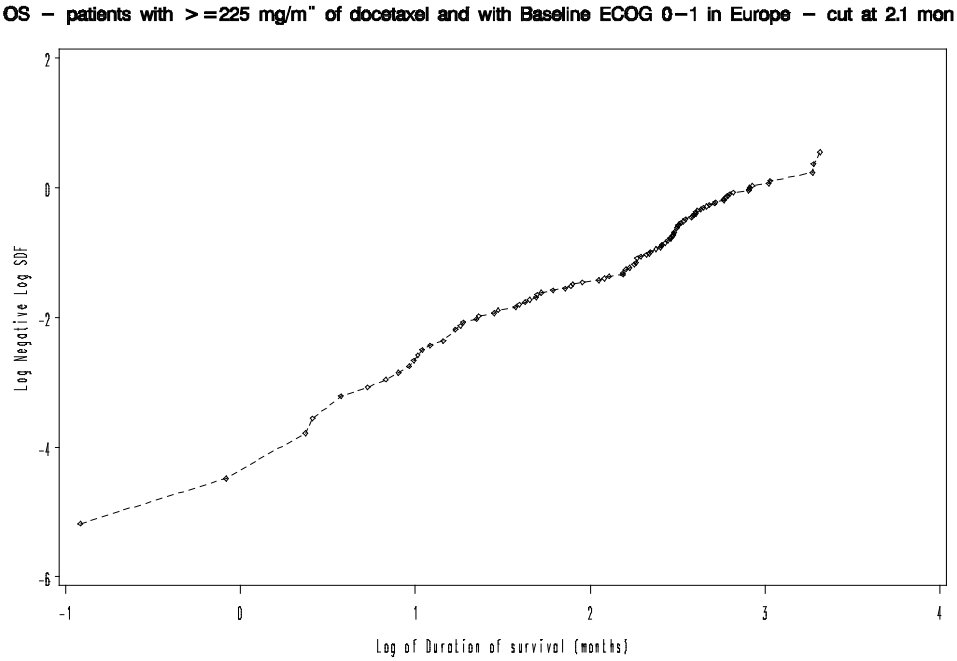
To do this, we performed a diagnostic graph, of log(-log(S(t))) versus log(t). If such a graph is relatively linear, this indicates that the underlying distribution is likely to be a Weibull distribution. This plot is shown in Figure 3. The diagnostic graph indicates that a Weibull distribution seems appropriate all over the curve in the mitoxantrone arm. In the cabazitaxel arm a different shape may be seen before and after ln(t)= 0.8, i.e. t=2.2 months (close to 3 cycles), suggesting it may be appropriate to fit a different curve over this initial time period.

Figure 3: Diagnostic plot - European patients with ECOG PS 0 -1 and who received ≥225 mg/m2 docetaxel



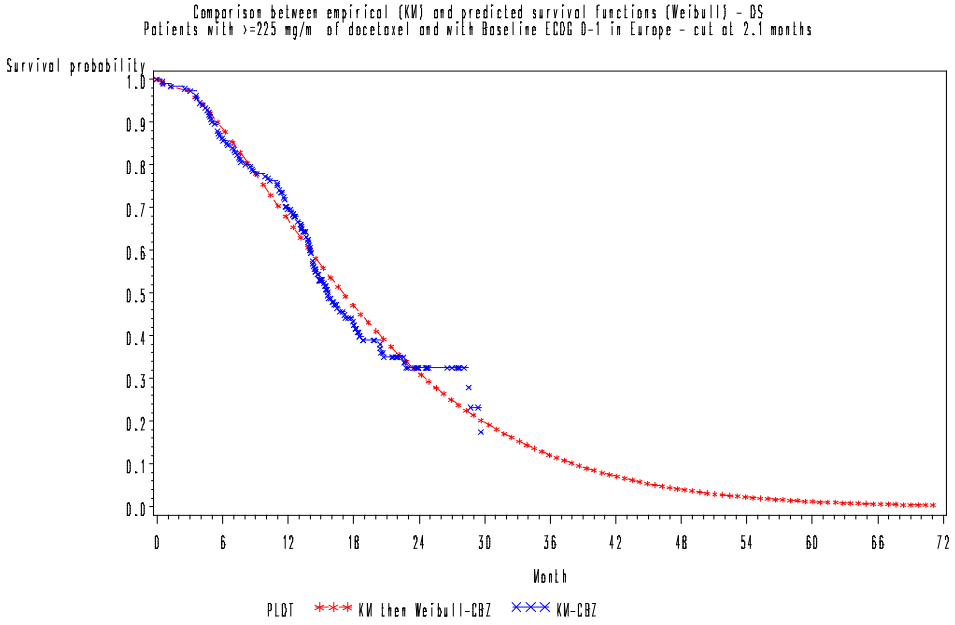
Therefore, the cabazitaxel data was cut at 2.1 months (i.e. 3 cycles). For information, no event occurred between 2.1 and 2.2 months. At 2.1 months, 8/319 (2.5%) patients died or were censored (S(t)=0.9749)). A diagnostic graph of log(-log(S(t))) vs log(t) for patients alive after 2.1 months (i.e. excluding patients who died or were censored before 2.1 months) is shown in Figure 4.

Figure 4: Diagnostic plot for patients alive after 2.1 months - European patients with ECOG PS 0 -1 and who received ≥225 mg/m2 docetaxel



The diagnostic graph indicates that a Weibull distribution seems appropriate all over the curve for this period. The Weibull parameters identified for this period were: lambda = 0.0162; sigma = 1.3808.
As this initial period is quite short, we used the Kaplan-Meier data for this portion of the curve, then after 2.1 months the Weibull fitted on patients alive after 2.1 months was applied via conditional probability of survival. It should be highlighted this is a different approach to our original methodology – in this new approach, the Weibull function was fitted specifically to the population surviving after 2.1 months.
Using this fit, we obtained an estimate of [redacted] months for mean OS in the cabazitaxel arm. This provides an estimate of mean OS gain of [redacted] months.
The graph below (Figure 5) displays the KM curve and the fitted curve (KM curve for the 3 cycles followed by the Weibull distribution).

Figure 5: KM data followed by Weibull - cut at 2.1 months - patients with ECOG PS 0 -1 and who received ≥225 mg/m2 docetaxel



Using this methodology in the model provides an estimate of the ICER of £77,765. This is similar to the ICER obtained using our original methodology (£78,016) and all the same assumptions. Results are calculated using the updated utility data, the post-second-line chemotherapy use from the UK audit, and the additional modelling changes described above. Comparisons are provided in Table 9.

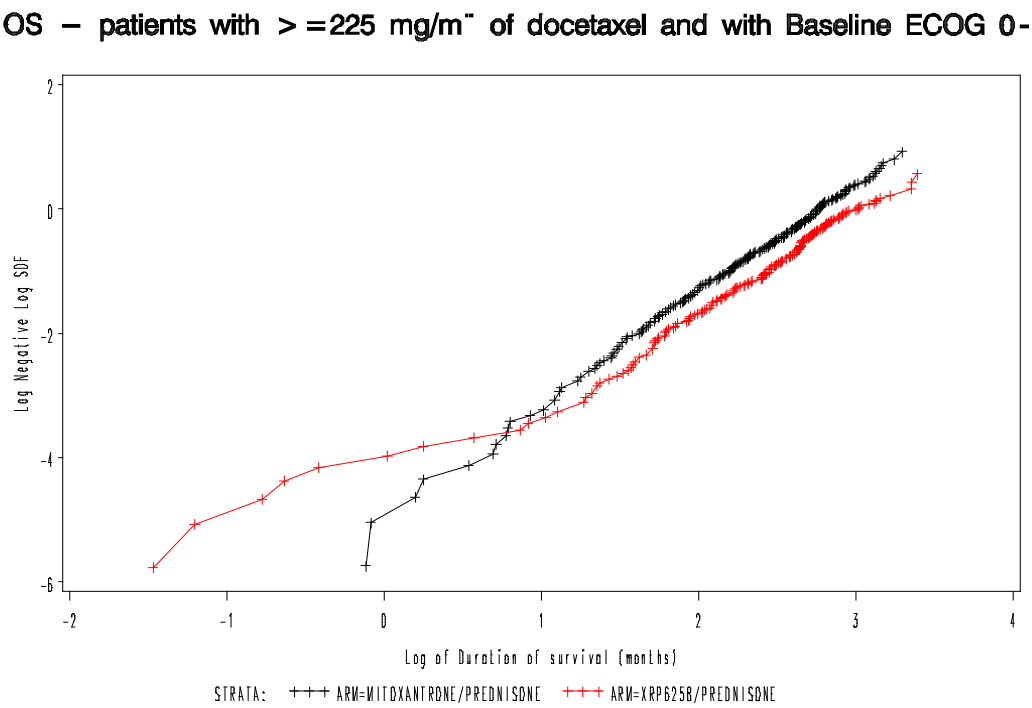
Table 9: Comparison of model results using piecewise curve-fitting versus original curve-fit - European patients with ECOG performance status 0 – 1 and who had received at least 225 mg/m2 docetaxel

	Mean OS gain (months)	ICER
Original curve-fitting methodology	[redacted]	£78,017
Piecewise curve-fitting methodology	[redacted]	£77,765
Single Weibull fit	[redacted]	£86,373

2: Patients with ECOG PS 0 -1 and who received ≥225 mg/m2 docetaxel

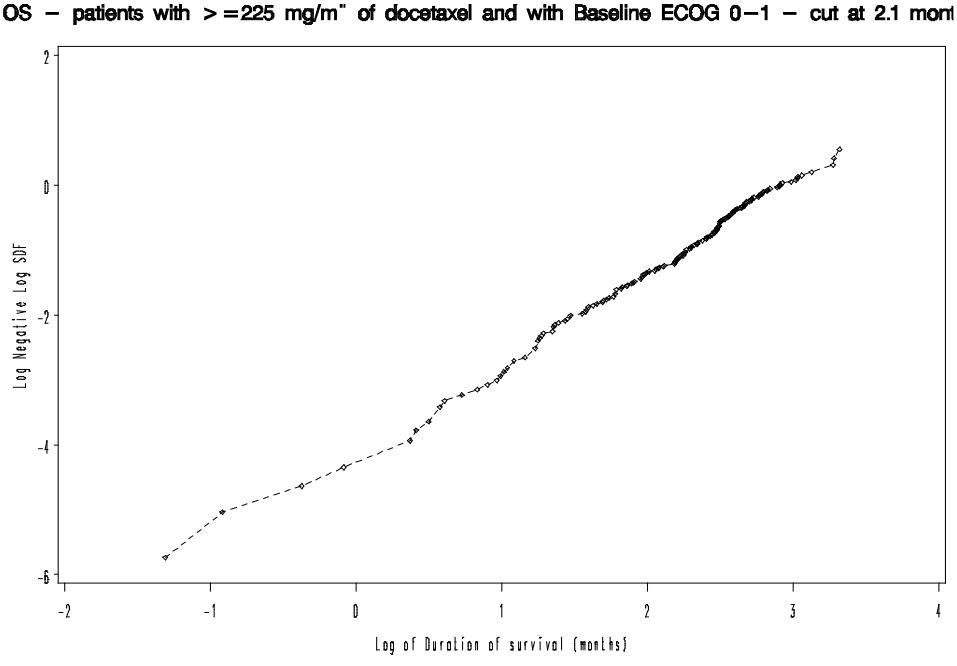
We performed a diagnostic graph, of log(-log(S(t))) versus log(t). If such a graph is relatively linear, this indicates that the underlying distribution is likely to be a Weibull distribution. This plot is shown in Figure 6. The diagnostic graph indicates that a Weibull distribution seems appropriate all over the curve in the mitoxantrone arm. In the cabazitaxel arm a different shape may be seen before and after ln(t)= 0.8, i.e. t=2.2 months (close to 3 cycles), suggesting it may be appropriate to fit a different curve over this initial time period.

Figure 6: Diagnostic plot - patients with ECOG PS 0 -1 and who received ≥225 mg/m2 docetaxel



Therefore, the cabazitaxel data was cut at 2.1 months (i.e. 3 cycles). For information, no event occurred between 2.1 and 2.2 months. At 2.1 months, 8/319 (2.5%) patients died or were censored (S(t)=0.9749)). A diagnostic graph of log(-log(S(t))) vs log(t) for patients alive after 2.1 months (i.e. excluding patients who died or were censored before 2.1 months) is shown in Figure 7.

Figure 7: Diagnostic plot for patients alive after 2.1 months - patients with ECOG PS 0 -1 and who received ≥225 mg/m2 docetaxel

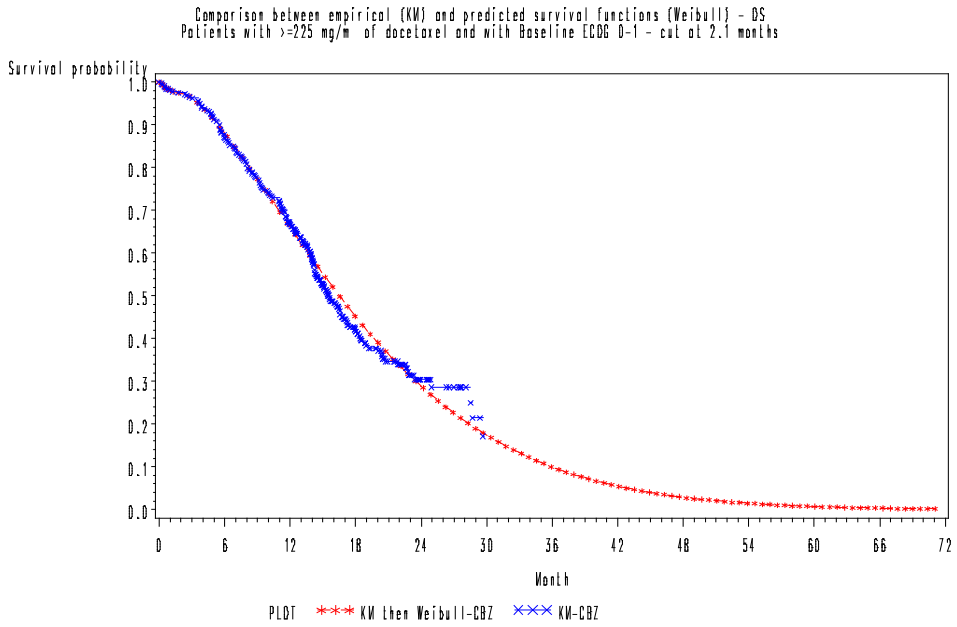


The diagnostic graph indicates that a Weibull distribution seems appropriate all over the curve for this period. The Weibull parameters identified for this period were: lambda = 0.0145; sigma = 1.438. Taking this function, we used the KM data for the first 2.1 months (3 cycles), then after 2.1 months the Weibull fitted on patients alive after 2.1 months was applied via conditional probability of survival.

Using this fit, we obtained an estimate of [redacted] months for mean OS in the cabazitaxel arm. This provides an estimate of mean OS gain of [redacted] months.

The graph below (Figure 8) displays the KM curve and the fitted curve (KM curve for the 3 cycles followed by the Weibull distribution).

Figure 8: KM data followed by Weibull - cut at 2.1 months - patients with ECOG PS 0 -1 and who received ≥225 mg/m2 docetaxel



Using this methodology in the model provides an estimate of the ICER of £87,518. This is similar to the ICER obtained using our original methodology (£86,088) and all the same assumptions. A comparison is provided in Table 10.

Table 10: Comparison of model results using piecewise curve-fitting versus original curve-fit - patients with ECOG performance status 0 – 1 and who had received at least 225 mg/m2 docetaxel

	Mean OS gain	ICER
Original curve-fitting methodology	[redacted]	£86,008
Piecewise curve-fitting methodology	[redacted]	£87,518
Single Weibull fit	[redacted]	£93,299

6. Partitioned OS analysis

A partitioned survival analysis was performed, as was done for a previous NICE submission, for docetaxel in early breast cancer (TA109). Partitioned survival functions were fitted to the Kaplan-Meier OS curves for cabazitaxel and mitoxantrone using the solver function in Excel. Three alternative functions were fitted: Weibull + loglogistic; 2 Weibull functions, and 3 Weibull functions. 100 solutions were run for each partitioned function using different starting values. The best fit was selected based on the minimum value for the residual sum of squares (weighted for the number at risk). Results are summarised in Table 11. Similar degrees of fit, mean OS estimates and mean OS benefits were estimated using the 3 approaches. The 3 Weibull function achieved a slightly superior fit in terms of wRSS, and gave the most conservative mean OS benefit estimate, [redacted] months. The fitted partitioned functions are plotted alongside the K-M curves for each partitioned function below (Figure 9 - Figure 11).

Table 11: Results from partitioned survival analysis

Function	wRSS_C	wRSS_M	Mean OS_C	Mean OS_M	Mean OS benefit
Weibull + loglogistic	1.4974	0.4716	[redacted]	[redacted]	[redacted]
2 Weibulls	1.5541	0.4710			
3 Weibulls	0.4949	0.4155			

C = CABAZITAXEL/PREDNISONE; M = MITOXANTRONE/PREDNISONE; OS = overall survival in months; wRSS = residual sum of squares weighted for the number at risk

Figure 9: 3 Weibull functions fitted

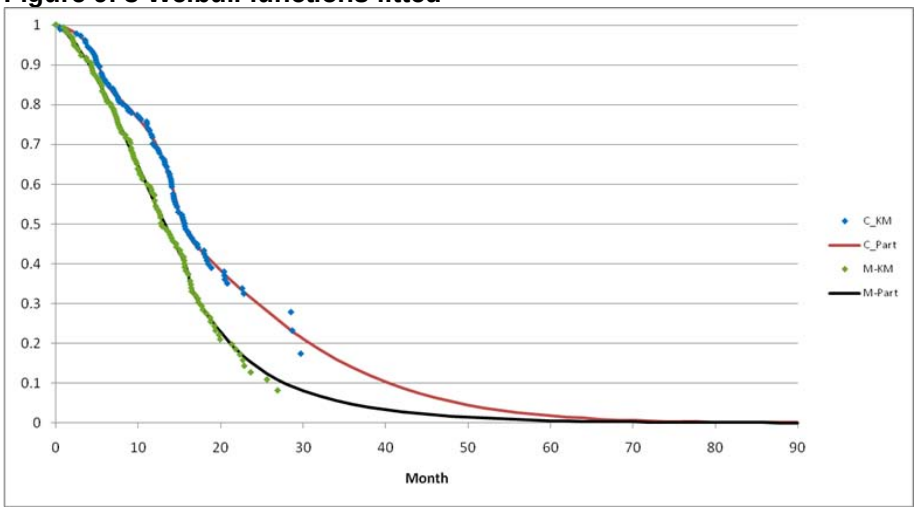


Figure 10: Weibull + log-logistic fit

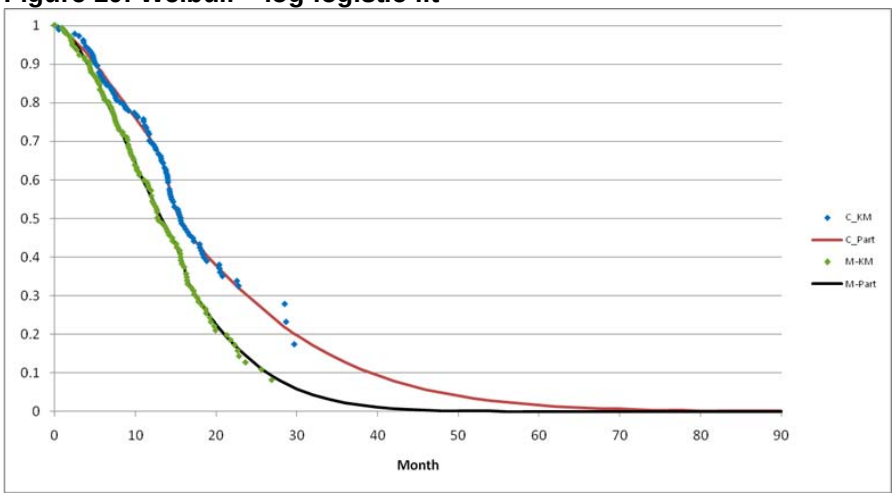
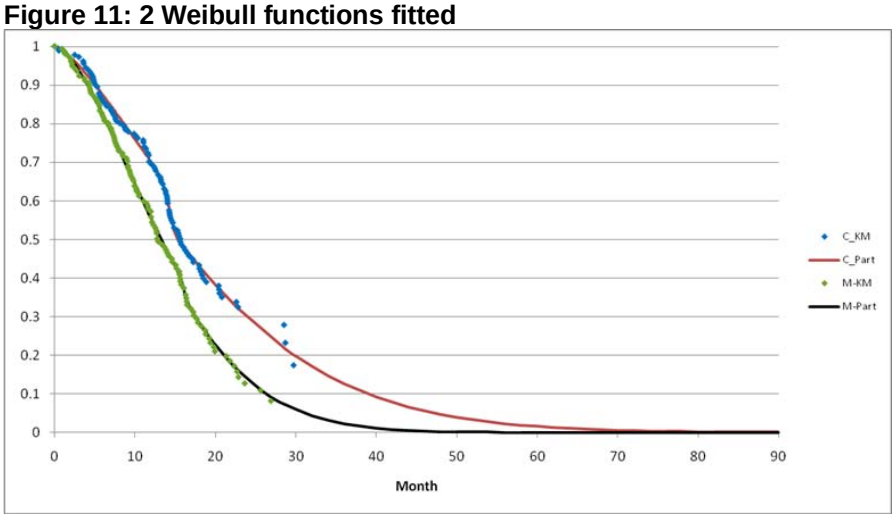


Figure 11: 2 Weibull functions fitted



7. Inclusion criteria and patient demographics for cabazitaxel EAP

Inclusion/ exclusion criteria for the Cabaz_C_05331 trial were as follows:

[redacted]

[redacted]

Patient demographics

A summary of patient demographics of the patients who have been included in the EAP and who provided EQ-5D questionnaires was included in the abstract submitted to ASCO GU. The median age was [redacted] years and [redacted] had experienced disease progression during or within 3 months of docetaxel and the remaining [redacted] within 3-6months after completing docetaxel.

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Response from the British Uro oncology Group (BUG) to the NICE Appraisal Committee's preliminary recommendations on the use of cabazitaxel in combination with prednisone or prednisolone for the treatment of hormone refractory prostate cancer previously treated with a docetaxel-containing regimen.

This reply is written on behalf of the British Uro oncology Group (BUG) and reflects the responses to the NICE Appraisal recommendations on the use of cabazitaxel in combination with prednisolone for the treatment of hormone refractory prostate cancer in men previously treated with a docetaxel-containing regime. The reply summarises the responses of members from the British Uro oncology Group who are all oncologists with a specialist interest in the management of urological malignancies.

The overall response was of great disappointment at this decision.

We recently conducted a survey of 80 expert urological oncologists in the UK (publication in press) to evaluate current management strategies for patients with advanced prostate cancer in order to identify key considerations in the decision making process and to gain insights into the possible role of emerging therapies in future UK practice. The respondents had an average of 189 new referrals for prostate cancer each year, with 24% reporting >200 new referrals annually. There was consensus that there is currently no 'Standard of Care' in the management of this group of patients. Forty-four percent of oncologists felt that they were very likely to be using cabazitaxel in their clinical practice within the next five years, with a further 35% stating that this was a possibility. Reasons for this included prior approval of cabazitaxel in the US, significant improvement in overall survival and progression free survival with cabazitaxel when compared to mitoxantrone in a randomised phase 3 study (Tropic), and the fact that the efficacy of cabazitaxel demonstrated in the second-line setting is superior to that seen for any of the currently available treatment options for patients at that time with advanced m castration resistant prostate cancer (CRPC). This enthusiasm for the use of cabazitaxel has increased with further availability following the clinical trial and many members have also submitted individual responses to NICE which reflects the strength of opinion that there is a great need for cabazitaxel as part of the management for men with metastatic CRPC and enthusiasm for UK oncologists to be able to offer their patients optimal care.

We would be grateful if the committee would take the following points into consideration

There was a consensus in replies to BUG that cabazitaxel should be made available to men with a performance status of 0-1, who have progressed on / during at least 3 cycles of docetaxel and who have been adequately counselled as to the potential toxicities and benefits

Until recently docetaxel has been the only systemic therapy to demonstrate a significant survival benefit in patients with stage IV castrate-refractory prostate cancer. Docetaxel was approved by NICE in July 2006**.** There is no standard NICE approved treatment for patients with progressive metastatic CRPC following docetaxel chemotherapy. The most efficacious alternative cytotoxic regimen to docetaxel is mitoxantrone plus prednisone. This combination significantly improves palliation of bone pain when compared to prednisone alone, but does not impact on survival. It has generally been used as a second line regimen following

treatment with docetaxel chemotherapy and was the most robust comparison arm against which to assess cabazitaxel in this setting.

NICE approved second-line palliative chemotherapy for other solid tumours generally only provides a small survival benefit. An example of this is seen in a study in lung cancer where docetaxel 75mg /m^2 was compared with Best Supportive Care. The median survival improvement for docetaxel was 7.5 months compared with 4.6 months for Best Supportive Care. As a result of this study by Shepherd, docetaxel was approved in this setting by NICE in 2001. Other examples are seen in the management of breast cancer where docetaxel was approved by NICE in February 2009 for similar median survival benefits.

The TROPIC study upon which the cabazitaxel submission to NICE is based was conducted in patients who had already received docetaxel chemotherapy. In fact approximately 30% of patients in each arm had received 2 or more prior chemotherapy regimens and so were actually receiving at least 3rd line therapy. Therefore despite being administered to heavily pre-treated patients, and compared to a robust alternative cytotoxic agent, cabazitaxel still produced a significant increase in overall survival. It also matched mitoxantrone in its ability to palliate bone pain.

The fact that other chemotherapy regimens with comparable advantages have been accepted by NICE whereas cabazitaxel has been rejected was viewed by many members as discriminatory and inconsistent.

The major concerns regarding cabazitaxel were the haematological toxicities, and cardiac/renal related mortality figures.

The Tropic study included patients with an ECOG performance status of 0-2. However, in the UK it would be unusual to give chemotherapy to a patient with a performance status of 2 as they would not be considered fit enough to tolerate chemotherapy and gain the advantages of treatment. The inclusion of patients with a poor performance status in the Tropic study may have resulted in a higher toxicity profile in the study than would be expected in UK clinical practice. Reports to BUG from oncologists who have used cabazitaxel both in the Tropic study and the expanded access programme have been that this drug has an acceptable toxicity and provides very significant benefits to patients.

Following the NCEPOD enquiry into UK deaths within 30 days of chemotherapy, and the subsequent NCAG recommendations for acute oncology services it would be expected that the UK has more stringent systems in place for managing the complications of chemotherapy than some of the centres in other countries who participated in the Tropic study. As pointed out in 3.2.4 the ERG state that the deaths in TROPIC within 30 days of randomisation could have been prevented with more vigilant treatment of neutropenia and so these were excluded from the analysis. This would seem entirely appropriate. However, the ERG also state that because of the stringent management of adverse events in the trial, the incidence of adverse events associated with cabazitaxel is likely to be higher in clinical practice in the UK. There was general disagreement with this statement form a number of BUG members who have commented that with more appropriate patient selection and the increased resources now available for acute oncology, any cabazitaxel-related toxicities are likely to be better managed now than in the study. It should therefore be accepted that the toxity of neutropenia with cabazitaxel is no more than would be anticipated for second line chemotherapy and that

this as well as any symptoms of diarrhoea would be well managed in dedicated UK oncology centres

The five cardiac deaths in the cabazitaxel arm of the Tropic study were attributed to cardiac arrest (3), sudden death (1), and ventricular fibrillation (1). The individual investigators at the centres treating each of these patients did not think the deaths were directly related to the study drug, although that was a subjective opinion. The concerns regarding potential renal and cardiac toxicity have been reviewed and revaluated by the FDA and EMA and it has been concluded that there is no need for additional risk management to be put in place. Since these reviews a further 12 months of post marketing updates have become available for review and there have been no further concerns regarding cardiac or renal safety issues. There has been no recommendation for the need for additional cardiac or renal monitoring above good clinical practice associated with the administration of any other chemotherapy agents. Cardiac and renal complications have not been seen in the EAP

The UK Early access programme with carbazitaxel has shown that the data from the TROPIC study underestimated patient benefit from cabazitaxel in terms of quality of life. I understand that a letter has been forwarded to you from oncologists in this programme and many of these clinicians have also consulted BUG to state that the quality of life data from this trial was robust. Patients in the expanded access study were carefully selected and assessed with the usual inclusion and exclusion criteria in any other credible clinical trial. The second interim analysis of quality of life provides strong evidence in favour of cabazitaxel over mitoxantrone in this setting. The investigators are keen to point out that there was no bias in reporting and that this evidence should be regarded as that form any other clinical trial. The expanded access programme will continue to provide credible data with time as these patients continued to be monitored and carefully follow up. There is unequivocal evidence from UK clinicians who have used cabazitaxel, both through the Early Access Programme and through the Cancer Drug Fund, that health-related quality of life is significantly and dramatically improved, with improvements seen after one or two cycles. Patients feel better, their pain is better and their daily activities of life are achievable. The results of the Early Access programme validate this, with pain improvement seen in at least 50% of patients.

There has also been considerable strength of opinion for UK oncologists that cabazitaxel is without doubt an end of life drug and should be considered by NICE to fulfil the criteria to be considered in this category.

Members of BUG have expressed disappointment and concerns that men with metastatic CRPC may be denied an effective 2nd line chemotherapy agent that not only significantly improves life expectancy but also quality of life if the NICE committee do not reconsider their ruling for cabazitaxel.

We thank you for considering this submission and await your final decision

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Professor Carole Longson
Director, Centre for Health Technology Evaluation
By e-mail

[redacted]

21 October 2011

Dear Professor Longson

Re: Cabazitaxel for the second line treatment of hormone refractory, metastatic prostate cancer – Appraisal Consultation Document (ACD)

I write on behalf of the National Cancer Research Institute (NCRI) - Prostate Cancer Clinical Studies Group, the Royal College of Physicians (RCP), the Royal College of Radiologists (RCR), the Association of Cancer Physicians (ACP) and the Joint Collegiate Council for Oncology (JCCO) with regard to the above ACD consultation. We are grateful for the opportunity to respond and also grateful to Dr Simon Crabb (NCRI/RCP/RCR/ACP/JCCO nominated clinical expert for this appraisal) who has coordinated this response across our experts. We would like to make the following points.

Point 3.21 - 'The ERG noted that because of the stringent management of adverse events in the trial, the incidence of adverse events associated with cabazitaxel is likely to be higher in clinical practice in the UK'.

Our experts would respectfully disagree with this. There is little reason to believe that adverse events should be higher in routine UK practice compared to the TROPIC trial. As we understand the committee heard, the UK patient population that would be treated with this agent are likely to closely match the population in TROPIC. UK oncologists took part in TROPIC and its criteria for patient selection, drug dosage modification and management of complications are essentially the same as those that would be used off trial. Chemotherapy administration in this country is restricted to oncologists sub-specialised to particular tumour sites within specialist cancer centres and units. Consensus national guidelines exist for management of complications and acute oncology services exist in all NHS trusts. As such, the administration of chemotherapy is every bit as stringent outside of clinical trials as in TROPIC. Furthermore, the UK experience with cabazitaxel, initially in TROPIC and the cabazitaxel expanded access programme, and now in routine use in some parts of England through Cancer Drugs Fund access, has been found to be very similar to the use of other taxane based chemotherapy for solid tumours, not least docetaxel for prostate cancer. The community is highly experienced in the administration of this type of agent and increasingly with cabazitaxel itself. Discussions with colleagues from around the UK have indicated that we are not seeing an increase in adverse events when using cabazitaxel. Concerns from TROPIC relating to early deaths following trial entry in a small number of countries with less well established acute oncology practices have simply not materialised in the UK during off-trial use.

Point 3.21 - 'The ERG stated that the trial provided insufficient information on the cardiac and renal complications associated with cabazitaxel'.

The rates of these events were small in TROPIC in either arm of the study and it therefore remains unclear if an increased rate of either cardiac or renal toxicity occurs with the use of cabazitaxel. Further data are clearly required and of importance. We await data on renal toxicity from the ongoing phase I study specifically evaluating renal safety and from a current phase III trial (of differing cabazitaxel doses) in which a number of UK centres are participating which will address this question as a secondary endpoint. Some further data has been published by letter on the nature of cardiac toxicity seen in TROPIC by the trial authors (Lancet, 2011, volume 377, page 122) who also note that further data are due to emerge on QT interval effects of the drug. UK clinicians will of course engage fully with post-marketing surveillance for these and other potential emergent adverse events. In the mean time the view of UK oncologists is that the weight of evidence in TROPIC for a survival advantage over mitoxantrone clearly justifies its continued use albeit with appropriate care and surveillance of individual patients and pre-treatment counselling regarding the various potential risks.

Points 4.2 and 4.3 - It is noted that patients in some regions of England, but not in others or in Wales, are already able to access cabazitaxel through the Cancer Drugs Fund. UK oncologists therefore share strongly the concerns expressed by patient representatives to the committee that there is currently unequal access to this life prolonging treatment which a positive NICE appraisal would remove.

In the same section of the ACD it is noted that patients feel it important 'that clinicians should inform patients about the potential serious toxicity of cabazitaxel and the lack of evidence showing that cabazitaxel improves health-related quality of life before taking the decision to start cabazitaxel therapy'. It should be understood that detailed counselling of exactly these issues is provided to all patients and their families prior to commencing palliative chemotherapy of any sort. This would be viewed by oncologists as a routine prerequisite for the use of an agent such as cabazitaxel. Patients are always included in, and central to, the decision to treat and alternative options, including use of symptom control measures alone, are also presented.

Point 4.4 - the number of cycles of chemotherapy that would be administered is discussed. To clarify, mitoxantrone is limited to a maximum of 10 cycles because cardiac toxicity may occur with further administration. As a result, the clinical trials of both first line docetaxel and second line cabazitaxel were performed using the same maximum number of cycles to provide appropriate comparisons to be made in the relevant trials. It would not therefore be appropriate to consider treatment beyond 10 cycles for which we have no data outside of a clinical trial. As noted the median number of cycles of cabazitaxel administered in TROPIC was 6 (limited either by progression, excessive toxicity or death) and it is reasonable to assume a similar median would occur off trial in the UK.

The NCRI/RCP/RCR/ACP/JCCO feel that there is overwhelming support among UK prostate cancer specialists for the use of cabazitaxel as a new life-prolonging treatment option for this disease. Our experience in counselling patients is in agreement with the views expressed to the committee by patient representative groups. Patients wish to have proven treatment options available to them following use of docetaxel and are deeply concerned by the possibility of restrictions in access. Members are clear that cabazitaxel can be administered safely and are impressed by the efficacy demonstrated in the TROPIC study. Many of those in TROPIC were progressing while on docetaxel and were therefore in a particularly poor prognostic group. To achieve any sort of outcome in such a group is remarkable.

Yours sincerely

[redacted]

Jeremy Powell
Technology Appraisal Project Manager
National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
London
WC1V 6NA

21 October 2011

Dear Jeremy

Please find below The Prostate Cancer Charity's response to the Appraisal Consultation Document (ACD) on "Cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen".

About us
The Prostate Cancer Charity is the UK's leading charity working with people affected by prostate cancer. We fund research, provide support and information, and campaign to improve the lives of people affected by prostate cancer. The Charity is committed to ensuring that the voice of people affected by prostate cancer is at the heart of all we do.

Response to the ACD on cabazitaxel
The Prostate Cancer Charity welcomes the National Institute for Health and Clinical Excellence (NICE) single technology appraisal (STA) on cabazitaxel for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) that has been previously treated with a docetaxel-containing regimen. We believe that cabazitaxel would make a difference to these patients by providing an additional treatment option that may significantly extend their lives, as well as offer hope of extra time with family and friends. Data from the TROPIC trial indicates that treatment with cabazitaxel is likely to increase both progression-free and overall survival within the eligible patient population[1].

The Charity is therefore disappointed to see that the preliminary recommendation is that cabazitaxel in combination with prednisone or prednisolone is not recommended for people with mCRPC which no longer responds to docetaxel treatment.

There is currently only one other licensed second line treatment for people with mCRPC that has been shown to increase overall and progression-free survival once the cancer has progressed on or following docetaxel treatment. This treatment is

[1] De Bono, JS et al (2010) *Lancet* **376**(9747):1147-54

THE PROSTATE CANCER CHARITY

abiraterone, which was only recently licensed and has not yet been appraised by NICE. It would be desirable to increase the range of clinically effective treatment options available for this patient population. A recommendation from NICE that cabazitaxel is effective for the above indication will help to provide standardised access and increased choice to a group of patients who currently have few other licensed treatments available to them and are facing a very limited lifespan.

Should the Appraisal Committee's final recommendation match their preliminary recommendation, we are very concerned that this will lead to an inequality in access of eligible patients to cabazitaxel in England and Wales. Evidence given to the Committee by clinical specialists and the NHS commissioning expert highlighted that access to cabazitaxel varies by English region when it is made available through the local cancer drugs fund. It is also important to note that Wales does not have an equivalent cancer drugs fund. This is very likely to lead to eligible people being denied access to a drug that has could provide significant clinical benefit to them.

However, the Charity does recognise that more data is required on the impact of cabazitaxel treatment on both renal function and health related quality of life to enable the Committee to more effectively appraise the drug's effectiveness. We would also want to see that the modelled mean survival benefit is further explored and validated to determine whether the mean extension to life of 4.2 months is sufficiently robust for NICE's end of life criteria to be met. We hope that the drug's manufacturer will be able to provide such information to the Committee at the earliest possible opportunity.

We would also like to see patient-reported outcomes considered by the Committee as part of their appraisal. Consideration of patient-reported outcomes will ensure that the agent is not only clinically effective but also improves outcomes of great importance to this population, such as the extension of life. If cabazitaxel is not recommended by NICE, patients tells us that the main implication for them would be the loss of a chance to improve their survival and increased distress associated with not being able to access a clinically relevant drug, if it is not funded locally.

The Charity was concerned that there was an excess number of deaths, mainly due to neutropenia, in the cabazitaxel arm of the TROPIC trial and that there was a higher probability of grade three adverse events in patients given the drug. However, it should be noted that in a recent survey of people affected by prostate cancer conducted by the Charity[2], only seven out of thirty respondents highlighted that the side effects of cabazitaxel were of serious concern to them. Of these, most commented that patients need balanced information to weigh up the pros and cons of cabazitaxel, if offered it, for themselves.

Whether NICE ultimately recommends cabazitaxel or not, thought must be given to how clear and balanced information on both the benefits and the likelihood of serious

[2] Between 24th May and 3rd June 2011, The Prostate Cancer Charity surveyed people affected by prostate cancer living in England and Wales for their views on cabazitaxel. 30 people responded to an online and paper survey. 90% of respondents had been diagnosed with prostate cancer (the others were relatives or friends of someone diagnosed with the disease) and 33% of respondents had advanced prostate cancer. None had any experience of cabazitaxel.

adverse events can be best provided to patients so that they are able to make an informed choice if offered cabazitaxel by their clinician. If the drug will only be made available through the cancer drugs fund in England, or via an exceptional funding request in Wales, patients will also need clear information on how to apply for funding to cover the costs of this treatment.

Conclusion

The Prostate Cancer Charity believes that NICE's preliminary recommendation on cabazitaxel is disappointing, but recognises that the lack of evidence related to quality of life, renal toxicity and mean extension to life is an important factor in this decision. We urge the drug manufacturer to provide the necessary evidence to NICE at the earliest possible opportunity. If this data is not available before this single technology appraisal process is completed, we also strongly suggest that NICE reviews the guidance on this technology as soon as new evidence is presented, rather than in 2015 (as currently proposed). It will also be important to ensure that clear information is provided to patients in England and Wales on the benefits and risks of the drug, as well as how to access it.

Yours sincerely

[redacted]

From: [redacted]
Sent: 10 October 2011 11:06
Subject: Cabazitaxel Consultation

Dear Jeremy

As the original respondent for the Prostate Cancer Support Federation (PCSF) and Prostate Cancer
Support Organisation (PCaSO) to this consultation I am disappointed that during the first round this application was refused. I have read the summary appraisal report and have the following comments
to make:

1. Randomised trials include men who are passed the stage where the therapy has no impact and might even have a negative effect because of the side effects. This skews the results that otherwise would show a much longer extension of life and a lower cost QALY. We believe it is very relevant and economically sound to exclude these deaths from the results. Many things are left to the clinicians judgement these days and matching suitable patients with this treatment is one.
2. There are side effects that require the clinicians to be vigilant about and treat them appropriately but they should not be life threatening. They do this all the time and it is wrong of NICE to make an issue of this for Cabazitaxel
3. The Prostate Cancer Support Federation (PCSF) has members whose Docetaxel regime has
failed, been very successfully treated with Cabazitaxel and expect a significant life extension. I attach a document from one of the them.
4. The clinical specialists on he panel excluded vial sharing as a possibility but with careful management at centres of clinical excellence who have a higher throughput of patients, this could be possible thus lowering the cost of treatment. This is something that is currently undertaken with other chemo therapy treatments.

With all the above said this is an of life treatment that gives men with CRPC and failed Docetaxel regime a further chance of extending their life with their family. No amount of science or economics can account for that. Men are important we are fathers and grandfathers whose families want us to have a long as possible on this planet and we want equality with women who need Herceptin as an end of life drug. To this present day we have not been treated with equality and now is the time for NICE to re-address this with Cabazitaxel.

Kind regards
[redacted]

[redacted]

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http://www.nice.org.uk/nicemedia/live/13237/56544/56544.pdf

is one of the most recent documents produced by NICE, page 96 shows the conclusions and infers more research and information is required to determine the risk of Neutropenia. It does discuss the costs at £89,000 per patient but this is work in progress . Frequently guidance by NICE is altered once all of the evidence has been collected and therefore its not unusual for this type of newspaper article to be published earlier than perhaps it should be. It does seem that journalists are keen to make others aware of these reports but this one only tells of a narrow angle rather than a balanced view. Extracting and reporting on a single issue from a 130 page report shows a level of unnecessary alarm when considering very important drugs, particularly as Cabazitaxel could become a standard treatment post Docetaxel (Taxotere). Have a read of the summary starting at page 9.

so, the reason for posting,
I am a patient (aged 50 but 49 at the time Cabazitaxel was prescribed) that has failed Docetaxel with no standard treatment offered to me, very difficult for someone like me as a family man with progressive disease to read I am not worth the investment. To publish half truth before any final decision is made, it feels like they have put a value on my life as a human interest story with only a small part of the picture considered.

Advancements in treatment at present are incredible, I am lucky enough to have been offered Cabazitaxel on compassionate grounds and have been told its working. The plan is for ten treatments but due to reported success and reducing risk of Neutropenia I have reconsented to allow me as many treatments that would be considered beneficial. This means I can go way past ten if I still gain benefit. I am uncertain if NICE has this information as yet, it is an influencing factor. Once the treatment is fully completed other drugs will be made available to me, revisiting Abiraterone has already been mentioned along with any current open trials at the time, this makes a mockery of any prognosis the current data offers. The reporting of mortality from Cabazitaxel needs much more detailed explanation, similar to Abiraterone giving you 4 extra months of life, this needs reporting and explaining accurately.

As the Cabazitaxel is working, this means my prognosis is now uncertain again, to put a date on my demise is now thankfully irrelevant and I personally think the newspaper report is missing this type of real life issue and doesn't consider those who are doing well on the drug. Furthermore, there is another live trial to establish the most appropriate dose for Cabazitaxel, either 250 or 200ml, surely no final conclusions will be made by NICE without this information.

The staff at the RMH promised me they would always do their very best for me as a 'young man' with mCRPC , they have constantly reassured me that there are no real budgetary constraints for my treatment, my age and family circumstances and willingness to assist with their pioneering trials again infer that they will always make their best effort for me.

To summarise my reply, the information regarding Cabazitaxel is only half there, once the appeals process and all relevant information has been supplied to NICE its just as possible and even likely they will approve the only post Docetaxel treatment available.

Advancements in available treatments means that all they need to do for me is keep me well enough to get the the next drug, I could and fully plan to live way past the 12 months they would have you believe if you read about those of us that fail Docetaxel.

So, when reading the information out there, take it with a pinch of salt and always consider that some of us think about their mortality far too early in life

My personal opinion would support a journalist who reported the information accurately with no bias leading us to believe good treatments will not be used as the current climate has picked up on the cost of treating cancer patients.

Development, research and trialling new drugs means they are expensive when first used, I understand Abiraterone is around £3,000 per month at the moment, I did try and find out how much Paracetamol was when first discoverred but I was unable to, the point being once development costs and expected profits are regained, costs inevitably reduce.

From: [redacted] on behalf of
[redacted]
Sent: 21 October 2011 08:30
To: TA Comm B
Subject: NICE STA - Prostate cancer - cabazitaxel - ACD:

Dear NICE

Thank you for the opportunity to comment on the appraisal consultation document and evaluation
report for the above single technology appraisal.

I wish to confirm that the Department of Health has no substantive comments to make regarding
this consultation.

Many thanks and best wishes

[redacted]
NICE Sponsor Team
Department of Health

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Warwickshire

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17th October 2011

National Institute for Health and Clinical Excellence

Dear Mr Powell,

ACD: Cabazitaxel for hormone-refractory, metastatic prostate cancer previously treated with a docetaxel-containing regimen

On behalf of NHS Warwickshire, I would like to submit our comments on the appraisal consultation document for cabazitaxel for hormone-refractory, metastatic prostate cancer previously treated with a docetaxel-containing regimen.

We are in agreement with the recommendations in the ACD not to recommend cabazitaxel for this indication as on the basis of the evidence considered it is unlikely that this treatment can be considered clinically and cost effective.

In particular we noted:

- **Cabazitaxel is not a cost effective use of NHS resources.** The most plausible ICER for the committee's preferred patient population is in excess of £89,000 per QALY gained.

- **Cabazitaxel does not meet NICE criteria for consideration as a life extending end of life treatment.** Based on evidence from the TROPIC trial, median extension of life with cabazitaxel is 2.4 months. Modelling data from the manufacturer citing a mean extension of 4.2 months is not robust and should not be considered by the committee.

- **There is no reliable data on health-related QOL.** The manufacturer submitted modelling estimates for QoL. The assumption made in the model that utility values within a health state are independent of time spent in that health state is clearly flawed. Additionally, inclusion of data from an early access programme in the modelling is not appropriate.

- **Haematological adverse events and diarrhoea in patients treated with cabazitaxel are of concern.** There remains substantial uncertainty about the effects of cabazitaxel on renal and cardiac adverse events. The most common adverse events observed in the TROPIC trial were neutropenia, asthenic conditions and gastrointestinal toxicity. The fact that the TROPIC trial was not powered to detect differences in specific adverse events between treatment groups is of real concern.

- **Potential cost savings from vial sharing are not considered feasible in the clinical setting and indeed there are important licensing and clinical governance implications**. This reduces the

possibility that efficiencies or savings can be made in real life clinical practice. Additionally, clinical specialists report that cabazitaxel has a short shelf life and the number of patients treated at each centre would be small.

- **Based on estimates that 3 patients per 100,000 population would meet the appraised indication there would be 15 patients eligible for treatment with cabazitaxel in NHS Warwickshire.** This would equate to a cost of £330,000 per annum for cabazitaxel. We would not consider that this expenditure would be justified for the small benefit in the small number of patients. There would be a significant opportunity cost, e.g. reduction in patient/ family support services, disinvestment in non-essential clinical services (e.g. fertility services) or major transformation such as closing community hospitals. The local QIPP target for high cost drugs in 2011/12 is £1.6m and a new cost pressure of circa £300, 000 would have significant impact on this, leading to disinvestment in other non-NICE approved technologies.

Please do not hesitate to contact me if you require further information.

Yours sincerely,

[redacted]
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COMMISSIONING SUPPORT

Appraisals

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14th October 2011

National Institute for Health and Clinical Excellence

Dear Mr Powell

ACD: Cabazitaxel for hormone-refractory, metastatic prostate cancer previously treated with a docetaxel-containing regimen

On behalf of Commissioning Support, Appraisals Service (CSAS), I would like to submit our comments on the appraisal consultation document for cabazitaxel for hormone-refractory, metastatic prostate cancer previously treated with a docetaxel-containing regimen.

We are in agreement with the recommendations in the ACD not to recommend cabazitaxel for this indication as on the basis of the evidence considered it is unlikely that this treatment can be considered clinically and cost effective.

In particular we noted:

- **Cabazitaxel is not a cost effective use of NHS resources.** The most plausible ICER for the committee's preferred patient population is in excess of £89,000 per QALY gained.

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- **Haematological adverse events and diarrhoea in patients treated with cabazitaxel are of concern.** There remains substantial uncertainty about the effects of cabazitaxel on renal and cardiac adverse events. The most common adverse events observed in the TROPIC trial were neutropenia, asthenic conditions and gastrointestinal toxicity. The fact that the TRPOIC trial was not powered to detect differences in specific adverse events between treatment groups is of real concern.

- **Potential cost savings from vial sharing is not considered feasible in the clinical setting and indeed there are important licensing and clinical governance implications**. This reduces the

possibility that efficiencies or savings can be made in real life clinical practice. Additionally, clinical specialists report that cabazitaxel has a short shelf life and the number of patients treated at each centre would be small.

If you require any further information please [redacted] directly.

Yours sincerely

[redacted],
Email: [redacted]

[redacted]
Email: [redacted]

Dear Professor Longson,

Thank you for sending me these documents for comment. I have no substantive comments on the quality of the report nor on the recommendations.

I would note that the relative benefit in this very pre-treated population is rather encouraging. If this same benefit could be replicated much earlier in the disease, the absolute benefits could be quite large and one could imagine that a cost-effective benefit could be achieved at that point. Of course, the trial results are not in place and I am not sure whether the trials are even being undertaken.

The STAMPEDE collaborations and the MRC Clinical Trials Unit have been in discussions with Sanofi-Aventis about potentially including a hormone therapy + cabazitaxel arm in the STAMPEDE trial (NCT00268476) in the future. STAMPEDE is a trial which recruits men starting first-line hormone therapy and is already assessing docetaxel in this setting. The trial will present results which are relevant to NICE in the future. If discussions to assess cabazitaxel in this adaptive trial are to proceed, accrual would not commence until after the recruitment has been completed to the docetaxel comparisons has been completed.

In the meantime, perhaps NICE might conclude more strongly in encouraging the assessment of this (and other) agents earlier in the disease when they might have a greater impact.

Kind regards,

MRC Clinical Trials Unit
Aviation House
125 Kingsway
London WC2B 6NH

Response from ScHARR regarding the ACD for Cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen.

All comments can be considered minor.

page	section	Current Text	Comment
9	3.2	… discounted at a rate of 3.5%	Strictly speaking the model used a discount rate of 3.56%
9	3.2	Lifetime (15 years)	Strictly speaking the model used a 14.4 year horizon
13	3.24	The ERG believed that these deaths in TROPIC could have been prevented….	The ERG believes that these deaths *possibly* could have been prevented. We do not know whether they definitely could have been prevented.
22	4.15	The committee considered hat	Typo: 'hat' was intended to be 'that'
23	4.16	…resulted in ICERs of £65,000 to £89,000.	This would be more informative if the reference ICER (£75,000 - taken from the manufacturer's base case) was provided
31	First box	…used data from Kaplan Meier curves to calculated transition probabilities	Typo: 'calculated' should be 'calculate'
31	Last box	…assigned to stable and progressive disease state	Typo: 'state' should be 'states'

[redacted]

[redacted]

[redacted]

19th October 2011

Jeremy.powell@nice.org.uk

Cabazitaxel

I was the Patient Representative for The Prostate Cancer Support Federation at the NICE Single Technology Appraisal Meeting on 6th September 2011.

My personal experience of the treatments available to patients is limited to my Radical Prostatectomy carried out at The Churchill Hospital in Oxford in 2009. I had studied the various technical presentations and submissions prior to the meeting, and did point out my limited knowledge at the start.

Since the meeting, I have spoken to Specialists and patients directly involved with 'late stage' Prostate Cancer. It is, not surprisingly, very clear to me that patients cling to the hope that they will be given every opportunity available to extend their life expectancy. Life is a very precious thing.

Prostate Cancer is not self-inflicted. In my opinion, it is very much the 'poor relation' in the numerous cancer types and the sad thing is that accurate screening could prevent many men reaching the stage of treatment being considered here.

In the days after the meeting in September I tried to understand further the various cases put forward. I, (mistakenly as it turned out), came to the conclusion that I expected the Committee to give approval for the treatment. I felt that there was confusion over the number vials required to be an adequate test period and there was quite a wide discrepancy over the 'proven' extended life expectancy. The question of the actual cost was, I thought, muddled.

An important consideration is the quality of life resulting from the treatment. I may have missed something, but I felt that this was somewhat glossed over. There are numerous treatments available these days for the conditions mentioned. The quality of life surely can only be appraised by the individual patient. I have since pointed out, that the 'numbers' being considered are actual people. I personally, found it difficult to connect with the tone of some of the presenters, in human terms. Any extension of life expectancy must be the hope of all patients.

From investigating the treatments available for most illnesses, it is blatantly obvious that as time goes by, better drugs become available and adopted. Cabazitaxel is an 'end of life drug', so surely this must clearly be the case here.

From the information available to me, and my comments above, I feel that Cabazitaxel must be given further consideration and extended trials.

Yours sincerely

W.G. Goldsmith

Response to Sanofi comments on the ACD

General Comment

It is noted that the new analysis provided by the manufacturer have not incorporated the most recent data on deaths. In response to the clarification process of the STA, the manufacturer discusses data presented at ASCO in 2010, after 585 deaths had occurred. This analysis found that, while the median survival values were unchanged, the hazard ratio increased slightly to 0.72. The analyses presented appears to be based on 513 deaths. Thus it is likely that the results are favourable to cabazitaxel. The effect of this on the ICER was explored when a single Weibull curve was used which indicated no material change, but this may not be generalisable to scenarios where piecewise curves are used.

1.1 End of life.

The manufacturer has presented a variety of different analyses, all of which demonstrate an improvement in mean survival of at least 3 months. The ERG believes that an improvement of more than 3 months in mean survival is robust given the current data.

1.2 Cardiac and renal safety profile.

These have been responded to in the detailed responses below.

1.3 Utility data from the EAP.

The ERG notes the updated data from the EAP. The manufacturer has provided additional references to support its use of utility values. However, the relevance of these to their patient population is, as they admit, limited. The ERG notes that these references were not used in the original manufacturer's submission. The main thrust of the section is to contest the judgement made by the appraisal committee which will not be responded to by the ERG.

1.4 Choice of base-case population.

The ERG would like to reinforce the importance of having *a priori* clinical reasons for assuming that there would be regional differences in the relative survival advantage conveyed by cabazitaxel when compared to patients who do not receive cabazitaxel.

The manufacturer indicates that the test of 'Europe & North America' vs 'Others' is proof of a statistically significant difference by regions. However, there are no prior justifications for this test, and it is noted that the AE results for North America are (marginally) closer to those for 'Others' than for Europe. Neutropenia by region was shown to be significantly different, although a multivariate analysis was not presented and it is unclear whether this would still be significant if age was also included. It is commented that there are 6 different combinations of regions that can be compared (e.g. 'Europe vs Other', 'Europe & Other vs North America), which would increase the probability of a significant finding if the specific test had not been defined *a priori*.

The manufacturer claims that the ERG's suggestion of removing deaths within the first 30 days is a justification for their restriction to a European population. It is noted that the occurrence of deaths within the first 30 days led to trial protocols on dose delay and modification, and treatment of neutropenia to be followed more strictly, as described on page 64 of the manufacturer's submission. It is for this reason that the ERG recommended modelling this aspect of the trial separately (or excluding it). Similarly, removing deaths within the initial 30 days for the entire TROPIC population may be justified if such deaths will be prevented by more vigilant treatment of neutropenia.

1.5 Curve fitting.

The ERG does not dispute the manufacturer's claim that the Kaplan-Meier data "provide the most accurate reflection of what was observed in the TROPIC trial". However, they note that the target population for the Committee's decision is not the patients enrolled in the TROPIC trial (nor is it the European subset). When generalising from one population to another, mathematical models are widely used as they model (assumed) underlying phenomena, and minimise the impact of 'chance' results that may not occur again.

It was seen that the ICER in the manufacturer's base-case was sensitive of to the chosen point of swap-over, as shown in Figure 10 of the ERG report. The manufacturer contests that the point of switching to the parametric distribution was arbitrary but was determined from a decision rule. The ERG would respond that the decision rule was arbitrary. A more natural cross-over point could be determined as the point at which the Kaplan Meier curve and the parametric distribution cross.

The manufacturer has provided two additional analyses of the overall survival data; 'piecewise' and 'partitioned'. The ERG do not have enough information to provide a detailed critique of the partitioned analysis, but note the following:

- A penalty term should be incorporated for the additional (mixtures of) distributions, and potentially also for the additional time-points at which the distributions switch rather than relying on a value such as residual sum of squares

- The three results presented all fall between those presented for the manufacturer's base-case and the ERG's base-case. The three results are all greater than three months, although the uncertainty about these estimates is not quantified.
- An ICER was not presented based on the partitioned analyses.

The ERG has more information available to critique the piecewise analysis, and note the following:

- The justification for partitioning the data (and the choice of where to do so) is based on a graphical test that is often used for model validation.
- The fitting of a Weibull distribution to patients surviving 2.1 months, and its application in the economic model, appear to have been applied correctly.
- The manufacturer justifies using Kaplan-Meier curves prior to 2.1 months (3 cycles) due to the shortness of the time period. The ERG acknowledges that this is a valid argument, but note that this has the drawback of not allowing the generation of information criteria, to facilitate comparisons with other methods.
- The analysis appears plausible; the reduction in ICER (compared to using the Weibull throughout) arises because the new Weibull estimates a slightly lower probability of death in the tail of its distribution.
- Only deterministic results are presented. The probabilistic ICER is not provided.
- The ERG had previously pointed out the high number of early deaths in the Cabazitaxel arm, and suggested that these be modelled separately (Clarification question A11). In their reply the manufacturer pointed out that this was mainly due to neutropenic events, and that as a result investigators were advised to be stricter in following trial protocols. It is likely that the piecewise approach reflects this reaction to early neutropenic events. If so, advice was given to both arms of the trial and so it may be better to conduct the same piecewise analysis for both drugs. Doing this [redacted] the ICER for the manufacturer's base-case from [redacted] to [redacted].The ERG do not have the data to replicate this analysis for the ERG base-case, but it may also result in a change in the ICER.
- If it is believed that strict adherence to trial protocols would eliminate the risk of early deaths then the full data set, which includes such deaths may not be appropriate. The removal of such deaths and the fitting of survival curves (either singly or in a piecewise manner) may provide a more appropriate ICER than the current method of including all data. Ideally the results from such analyses would be present so that the appraisal committee had greater information within their deliberations.

Point-by-point response to Sanofi

2.3	We agree that adverse events described as "very common" are those which occur ≥1/10 cases, and that therefore peripheral neuropathy should indeed be classified as "common" rather than "very common"
3.11	We agree with Sanofi that the incidence of Grade ≥3 febrile neutropaenia should be 7.5% with cabazitaxel and 1.3% with mitoxantrone (as indeed it was in the ERG report)
3.12	We accept that the model compares cabazitaxel and mitoxantrone in combination with prednisone, since prednisolone is not available in the UK. However, the model is based on the results of the TROPIC trial in which cabazitaxel and mitoxantrone were given in combination with either prednisolone or prednisone, depending on availability; consequently, the majority of participants are likely to have received prednisone.
3.14	We agree that additional information relating to per-cycle costs have been omitted, and that costs of best supportive care were applied on a per cycle basis in addition to the one-off costs (which did consider the duration of treatment within the one off coss). These costs were , however, relatively low at £87.63 per cycle, independent of prior treatment.
3.15	The comment re utility being independent of time spent in state was factually correct. The text from the original submission states that "As of 20 May 2011, nine UK sites were active, with a further three initiated." The initial data thus appeared to come from nine rather than twelve centres.
3.16	Sanofi's comment is factually correct.
3.21	The ACD statement is factually correct.
3.21	There appears to be conflation over the stringent criteria and the choice of population, which should be viewed as separate issues. The ERG believes that the definition of (non-fatal) AEs were stringent, and that these are likely to be greater in real life prescribing than seen in the RCT, for a chosen population, for example, Europe. The analyses re deaths associated with neutropenia is again not area specific, but good practice specific, as noted with the instruction to follow the trial protocols more strictly. Without further evidence the ERG would be unable to support a claim that deaths due to neutropenia could be avoided in one area, but not another.
3.21	The ERG report stated that "Cardiac and renal complications other than deaths appear to be poorly reported". The data now provided by Sanofi from the TROPIC trial on all grade cardiac events, cardiac arrhythmias, tachycardia, atrial fibrillation, and cardiac failure were not published in the Lancet article; the data for atrial fibrillation and tachycardia (but not cardiac failure) associated with cabazitaxel were published by EMEA but could not be interpreted in the absence of data from the mitoxantrone arm (which Sanofi still fail to present for tachycardia and atrial fibrillation). Furthermore, during the fact check process, Sanofi indicated that they had information from a trial evaluating the effect of cabazitaxel on the QTc interval (presumably study TES10884). They stated that these data could be could be provided, but did not offer them within the timescale of the ERG report.

	In addition, during the fact check process Sanofi indicated that they had information from the report of the expert review of renal toxicity which was recommended by the FDA, and which included data from all currently available cabazitaxel trials. They stated that these data could be could be provided, but did not offer them within the timescale of the ERG report. Sanofi now report that the expert advisory panel convened by the FDA concluded that, for the vast majority of the patients with "an AE renal failure" (sic), at least one concomitant risk has been identified, and that the panel stated that: *"It is difficult to assess retrospectively the exact level of implication of each of these risk factors of renal failure in the completed studies."* The post-marketing reports now referred to by Sanofi have not been made available to the ERG. However, we are prepared to accept that they indicate no new risk not included in the current safety information for cabazitaxel.
3.22	See separate response to 1.4
3.23	See separate response to 1.5
3.24	See response to 2.1 and detailed response to 1.4
3.25	There appears to be misrepresentation of the actual ERG comment [redacted] and the statement in the ACD, "The ERG also noted that the utility values for stable disease and progressive disease were sampled independently, which led to the utility value for progressive disease being higher than the utility for stable disease in some instances. The ERG considered this implausible." Our statement is factually correct, and allowed the appraisal committee to deliberate whether on the value from the EAP was plausible. The comment on the independent sampling was factually correct (as acknowledged). We agree that the independent sampling of utility values had no bearing on the deterministic ICER, but would comment that an ICER calculated probabilistically would be preferred.
3.26	Sanofi's comment is factually correct.
3.27	Sanofi's comment is factually correct.
4.2	We agree that the benefits of docetaxel re-treatment have not been investigated in an RCT, and that it seems unlikely that such re-treatment would provide benefit to patients who are resistant to docetaxel.
4.3	From the data provided by Sanofi it is not currently possible to categorically claim that cabazitaxel is proven to improve health-related quality of life. Corresponding data from patients not receiving cabazataxel would be needed to provide suitable evidence. Additionally it is noted that the confidence intervals for the values at all time points are relatively wide.
4.4	Sanofi's comment is factually correct in relation to the comments from the ERG. We did not attend the NICE decision problem meeting and offer no comment.
4.4	Sanofi are correct in stating that the ERG considered the definition of progression in the TROPIC trial to be a conservative approach because it included biochemical (PSA) progression, which frequently precedes symptomatic or radiological progression. Consequently, it was likely to underestimate the clinical PFS experienced by patients with mHRPC who receive cabazitaxel therapy in clinical practice.

	We agree that the TROPIC study's definition of PFS included subjective pain outcomes which were susceptible to bias because the study was unblinded. Sanofi state that these results were consistent with objective measures; we suggest that, as the pain outcomes are not statistically significant, it might be more accurate to say that they do not contradict them.
4.4	The ERG recalls remarks made by the clinical expects that support Sanofi's comment
4.5	See response to 1.1
4.6-4.10	The ERG recalls remarks made by the clinical experts that support Sanofi's comment. However we note that this is not the only factor to consider in the choice of patient population. This is dealt with in more depth in the response to 1.4.
4.10	It is true that, in the TROPIC trial, more patients died of cardiac or renal AEs in the cabazitaxel arm than in the mitoxantrone arm, and that cardiac and renal complications other than deaths appear to be poorly reported (see comments on 3.21 above)
4.11	We have provided a separate response to section 1.3..
4.13	We agree that Sanofi did not choose the most favourable time-point, but would highlight that the time point chosen produced a favourable ICER. We also agree that the sentence "…parametric fitted curves more closely fit data from TROPIC" is misleading. We would like to draw attention to our separate response to 1.5.
4.15	See comment on 4.6-4.10 and the separate response to 1.4.
4.16	Sanofi's comment is factually correct. See also the response to 1.3
4.17	Sanofi's comment is factually correct.
4.17	Sanofi's comment is factually correct.
4.19	This is comment on a judgement made by the committee and will not be responded to by the ERG.
4.21	This is comment on a judgement made by the committee and will not be responded to by the ERG.
4.23	This is comment on a judgement made by the committee and will not be responded to by the ERG.
Key conclusions	The response to 3.14 indicates that additional per cycle costs for post second-line treatment were included. As detailed in 3.21 the stringent criteria for (non-fatal) AEs is expected to underestimate the costs associated with AEs in real-life prescribing.
Innovation	See response to 4.23
Position in pathway	See 4.2
AEs	See response to 3.21
Availability, nature, and quality of evidence	As noted above, the subjective pain outcomes included in progression-free survival yielded results which were not statistically significant, and it might therefore be more accurate to say that they do not contradict objective measures such as radiographic progression rather than that they were consistent with them. However, we agree that the progression-free results were consistent with the results relating to overall survival.
Uncertainties generated by the evidence	The analysis presented by Sanofi indicate a mean survival of greater than 3 months.
Estimate of effect	We accept that the length of follow-up in the TROPIC trial was such that

size	overall survival data were incomplete, in that some patients remained alive after the end of follow-up, but that all patients had progressed by that date.
Uncertainty around model inputs	This is comment on a judgement made by the committee and will not be responded to by the ERG.
Key drivers	We would support thr statement that the costs of post-second-line treatment was not a key driver of the ICER.
Cost-effectiveness estimate	Further discussion on the most appropriate patient population is provided in the response to 1.4

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

Role	Investigators for the Cabazitaxel Early Access Programme (UK)
Other role	
Location	
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	We the undersigned investigators for the Cabazitaxel early Acc Programme would like to express our concern regarding 4.11 'T Committee concluded that because the utility data were based such a small number of patients from a potentially select populati there is considerable uncertainty as to the validity of these data'. This particular study was conducted with the same rigours a clinical trial with the protocol being followed to its entirety a therefore the statement regarding the selection bias and uncertainity as to the validity of the data is unfounded. The patie were entered into this as per the inclusion criteria of the proto (which was exactly the same as the TROPIC study inclusion crite and the data was collected according to the ICHGCP standards. This study recruited the total number of patients before the plan accrual date reflecting the confidence that both the clinicians a the patients had in the treatment being offered in this area of gr unmet need. We have submitted the initial QOL data to ASCO GU and EAU2(and if selected these data would be presented in these internatio meetings.
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	Chief Investigator of the cabazitaxel Phase III TROPIC trial
Other role	Professor in Experimental Cancer Medicine and Honorary Consultant in Medical Oncology
Location	England
Conflict	
Notes	Prostate cancer is the commonest cancer in men and the second commonest cause from cancer mortality in men in the

	United Kingdom. Despite this urgent unmet medical need, until recently only two treatments had any impact on overall survival for this disease: androgen deprivation by the blockade of testicular hormone synthesis and docetaxel. There therefore remains a desperate need to develop drugs that can positively impact outcome from this disease with one man dying every hour from this disease in the United Kingdom
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	In view of the critically important unmet need for treatment for this common disease, a cancer that causes so much suffering to our patients, as well as the impressive antitumour activity of this agent, I write to suggest that the NICE committee reconsider their preliminary recommendation to not support the use of this important anticancer drug
Section 2 (The technology)	We have shown that cabazitaxel has important antitumour activity against advanced prostate cancer with radiological tumour responses and PSA falls post-treatment. Critically we have also shown that this agent improves overall survival with one of the best hazard ratios ever described in a prostate cancer Phase III trial. At the cutoff for the final analysis, median overall survival was 15·1 months (95% CI 14·1—16·3) in the cabazitaxel group and 12·7 months (11·6—13·7) in the mitoxantrone group. The hazard ratio for death of men treated with cabazitaxel compared with those taking mitoxantrone was 0·70 (95% CI 0·59—0·83, p<0·0001). This impressive impact of this agent on this disease has led to its being given regulatory approval in Europe and North America and it is being widely used by oncologists around the world.
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	Cabazitaxel in my experience with it during Phase I, III and expanded access studies is well tolerated. Indeed, my experience indicates that it is better tolerated than docetaxel, which is used in the first line setting for the treatment of this disease. Critically, cabazitaxel rarely causes peripheral neuropathy which is arguably the most difficult toxicity induced by this class of agents – the tubulin binding drugs. The toxicity of cabazitaxel is otherwise very similar to that of other tubulin binding drugs in routine use. Finally, it is important to note with the TROPIC trial that the frequency of grade 5 toxicities was related to geographical region with the lowest risk in North America (being 0.8 and 0.9% in the mitoxantrone and cabazitaxel arms respectively) and a slightly higher risk in Europe including Eastern Europe (3.0% vs 4.9% in the mitoxantrone and cabazitaxel arms respectively). Finally, deaths from other causes on trial were 4.0% and 3.2% in the mitoxantrone and cabazitaxel arms respectively. Moreover, there was significantly more myelosuppression with mitoxantrone than seen with the same dose and schedule of mitoxantrone in the TAX327 trial because of the more advanced disease present in this subset of patients. Overall, these data indicate that a) administration of cabazitaxel earlier in the disease to fitter patients as practiced in North America

	decreases risk; and b) that better supportive care minimizes risk of grade 5 toxicities from myelosuppression.
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	
Other role	
Location	
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	We wish to express our concern at the refusal to supply the above drug to suffers of prostate cancer, under the N.H.S . We strongly feel these people have the right to this drug and therefore the hope of a longer life. This drug appears to have a lot of success, and we feel it should be available on prescription as life is so very precious and extra time to live should not be denied. We feel a decision should be made in favour of this drug being prescribed as soon as possible.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	Professor of Urological Oncology
Other role	
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	I have reviewed the various documents and opinions on the NICE website.I think the comparator issue is clouded a little by US practices such as the use of estramustine and this concept of docetaxel challenge- both of these rarely if ever practiced in

	the UK (certainly docetaxel beyond 10 cycles). As a uro-oncologist who was not involved in TROPIC to me the TROPIC data was compelling if a little suprising in view of similar mechanism of action. Subsequently it has been clear the marked increase intubular stabilisation conferred by carbazi may explain the clinical data. I think the OS data is difficult to argue and I would think that around 30% of docetaxel failures would be suitable for carbazi, and that is without abiraterone competing. We have large number of well informed patienst and our local prostate cancer charity is also intent on lobbying for access in light of the phase III evidence. We wont have much better opportunities to see the evidence in this way for carbazi as current studies are aimed at optimising dose. I think carbazitaxel does offer a rationale and quality of life improving option for our patients; I think clinicians are well aware of the high cost and would restrict use to optimal clinical scenarious and close monitoring by rodaiology and symptoms.
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	
Other role	
Location	
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I am writing in support of the new trial drug Cabazitaxel for Prostrate Cancer. My uncle, [redacted] has been trialling it and has responded really well to treatment and scans show that the tumours have shrunk.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	Patient
Other role	[redacted]
Location	England
Conflict	no
Notes	

Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	This response is made on behalf of the Bay Prostate Cancer Support group, a well-established, patient-led Group serving the Lancaster/Morecambe area of NW Lancashire. The Group is extremely disappointed and concerned by NICEs preliminary recommendation. Carbazitaxel offers significant life extension and improved quality of life to late-stage prostate Ca patients where first line chemotherapy has failed and prospects are otherwise bleak. Denying access to Carbazitaxel would be a cruel blow to these men, destroying all hope and putting them at an unfair disadvantage in comparison with patients with other tumour types, where successive lines of chemotherapy are already approved & in use. We urge NICE to take these factors into account, to reverse their initial decision and recommend the use of Carbazitaxel for advanced prostate cancer patients within the NHS. [redacted] Bay Prostate Cancer Support Group
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	NHS Professional
Other role	
Location	England
Conflict	yes
Notes	For clarity, to expand on my conflict of interest, I am a Consultant in Clinical Oncology with a particular interest in Urological cancers, and am one of a few centres where we are recruiting patients to a study funded by industry randomising pts to this drug at 2 different dose levels.
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Without stressing the incidence / mortality rates etc of prostate cancer , there is clearly considerable disease burden which makes this of major importance. The concern is that by not recommending this treatment option, it severely limits treatment choices in this setting, n whilst a no of pts may not be candidates for 2nd line therapy, there are some pts of good performance status for whom this is an important clinical option, n NONE of whom will be allowed access without NICE approval.
Section 2 (The technology)	In my clinical practice, pts are increasingly well informed about

	their disease, n available treatments, n even before chemotherapy agents are licensed, there is considerable interest. Undoubtedly pts suitable for this treatment are a relative minority of all those with HRPC, but with appropriate selection Cabazitaxel is a significant step forward in prostate cancer management. A no of my pts are interested in finding out about this, but without NICE approval the avenue will be closed off completely for all. In my practice, therei s judicious use even of Taxotere 1st line, supported by NICE, despite concerns about s/es etc, n it would be similar in the use of Cabazitaxel.
Section 3 (The manufacturer's submission)	In my clinical experience of 4 pts on this drug, the early fall in PSA is encouraging n appears to be profound, however, all these pts had a marked n durable response to 1st line Taxotere, completed at least 6 months before starting 2nd line therapy, which overall is a much better prognostic group than in the Tropic study extrapolating from tha study from pts off Taxotere for 3mths, the likely OVERALL benefit for my highlyselected pts would be considerably more than 2.4 mths. To have NO access to such an active agent in 2nd line setting would be extremely disappointing for pts n their families.
Section 4 (Consideration of the evidence)	Finally, there needs to be clarity about management of side effects in a proactive way, n from my personal clinical experience, the toxicity profile is not as much as a concern as expected - close monitoring esp initially, early intervention eg gi toxicity, makes this no more dificult to manage than many other agents, again case selection being paramount n good pt information. The blunt instrument of cost per QALY remains as flawed as ever, n health economic analysis, used by NICE have varied with different appraisals. The figures quoted are undermined by extrapolating to too broad a group of pts.
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	The remarkable success n promise of drug development for this long neglected group of pts means that a further review should be done considerably sooner than in over 3 yrs time!

Role	other
Other role	wife of a man with advanced prostate cancer
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	my husband is having cabazitaxel on a clinical trial.it was with quite a shock when we heard that NICE at their preliminary hearing had decided not to recommend the use of this drug for men who are hormone refractory metastatic prostate cancer patients previously treated with a docetaxel containing regimen.WHY! Cabazitaxel has changed my husbands life so much.he was pre cabazitaxel a very poorly man after all other treatments had failed he is 59years old and was diagnosed

	18months ago. pre cabazitaxel his PSA was 3024 it has come down to 440. he was on liquid morphine and morphine tablets to control his pain whilst in between treatments,he now may take 4 co codamel per day as his pain has almost gone. we could not have afforded cabazitaxel and feel very lucky to have been able to take part in a trial for it.this chemo should be made available on the NHS for men requiring 2nd line chemo why should this group of men be at a disadvantage compared to other cancer sufferers e.g breast cancer patients who indeed can have on the NHS 2nd and 3rd and even 4th line chemo.please dont deny these men a longer and better quality of life.
Section 2 (The technology)	my husband has not suffered from side effects apart from being tired but he is less tired now than pre cabazitaxel,he has no nausea or sickness no back pain and he did pre cabazitaxel he was in a lot of pain and some days he didnt want to be here.he now plans ahead which is amazing. as for the cost well how do we put a price on a life? many men as my husband has will have worked all their lives and paid their taxes and nat.ins.many of them will not get their pension.parliment members used our taxes to buy houses the goverment is owed millions from helping people on the NHS from other countries.dont deny these men a drug that does work.obviously not for all men but it does work very well for a lot of men,my husband is proof and he strongly believes he would not be here now if he had not got cabazitaxel.
Section 3 (The manufacturer's submission)	i have read all of the above and realise you are in a difficult situation in having to determine what the best treatment is for these men that could and are being helped by cabazitaxel,the goverment is always wanting to save money but i live with a man whos life has changed since having cabazitaxel.there is good evidence that cabazitaxel works i know it works.i realise there is insufficent info [or was] on the cardiac and renal complications that some men suffered but like any other drug people react differently.please do not refuse men the chance to have cabazitaxel on the NHS.you know it can work on a lot of men please give them the chance to stay with their loved ones for that extra time cabazitaxel can give them.
Section 4 (Consideration of the evidence)	cabazitaxel does work and surely even if it only gives a man an extra 4months of life that is very significant to that person and their family.cabazitaxel one of the only other treatments that can be used for these men is paramount for them needing it.
Section 5 (Implementation)	people know that the goverment doesnt agree in main with the NHS and money is a big factor but these men deserve too be offered cabazitaxel on the NHS.why shouldnt they have 2nd line chemo.they have paid their taxes and nat.ins.breast cancer patients get 2nd 3rd and 4th line chemo and quite rightly to.let them that could benefit from cabazitaxel have it.
Section 6 (Related NICE guidance)	i understand NICE clinical guidelines but as a wife of a man being treated with cabazitaxel and seeing how well he is doing after 6cycles i feel strongly that NICE reconsider their preliminary decision not to allow men to have cabazitaxel on the NHS.
Section 7 (Proposed date of review	february 2015 is too far away please reconsider this date.

of guidance)	

Role	other
Other role	Relative of a patient on the Cabazitaxel trial.
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Having seen the dramatic improvement of my Uncles standard of living, since being submitted to this trial, I am hoping that, like myself, other family/friends/carers of improved trialists will take the time to comment and submit enough first hand evidence that will, hopefully, at least give enough voice to make the committee reconsider their preliminary recommendation.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	It would seem that Cabazitaxel has been the most successful of the drugs trialled for this area. It also seems that there are no other treatments, at the moment at least, for these patients to be offered. Unfortunately I do not have access to my Uncles actual stats over the period of the trial which, I fear, may make my submission seem worthless. What I can say is that last Christmas he was actively seeking addresses and numbers of overseas Euthanasia Clinics, and exploring the legal consequences that this would have on his wife. This was because the pain and discomfort, brought on by both the progression of his disease and his treatment, was becoming too much to bare. 10 months later(after being placed upon this trial in January) he has recently celebrated his 59th birthday and is currently making plans for the New Year. He claims he actually felt the difference within days of the first treatment of Cabazitaxel. Everyone is well aware that this is not a cure, but the quality of life it has provided has been absolutely remarkable and desperately appreciated.
Section 5 (Implementation)	I would like to ask all of the NICE committee members - if they themselves, or one of their loved ones, were to be in the position of these patients, would they wish for Cabazitaxel to be available as a treatment? The childlike optimist in me would like to think that the possible answer to this question could have an influence on the outcome of the second appraisal. I guess the truth is though, there is no room for emotional context in these decisions. I find this so disheartening as the fact is, emotional ramifications - on both the patient and surrounding loved ones - are a massive factor in the whole concept of producing End of Life Treatments, such as Cabazitaxel.

Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	NHS Professional
Other role	
Location	England
Conflict	yes
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Treatment of patients with metastatic prostate cancer is an area of great unmet need and this drug offers them improvement in survival and early data suggests improvement in Quality of life as well.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	Point 4.11 is concerning as it questions the selection of patients and the validity of the data. This study was conducted as per strict trial criteria and the data was collected in accordance with the protocol and maintaining ICH GCP standards. This data is extremely relevant for the UK population of metastatic prostate cancer patients post-docetaxel treatment who receive Cabazitaxel. This data is robust and should be considered seriously.
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	These developments are eagerly awaited to optimise the management pathway for this group of patients who prior to drugs like Cabazitaxel and Abiraterone had precious little on offer for their disease management.
Section 7 (Proposed date of review of guidance)	

Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	There is clear level one evidence in the TROPIC Trial re: Survival benefit. More young and fit patients are diagnosed now a days with Castration Resistant Carcinoma of Prostate.Carbazitaxel in post Docetaxel chemotherapy setting is an essential treatment option. The decision of not recommending Carbazitaxel could potentially reduce life expectancy of this group of patients significantly.
Section 2 (The technology)	Although Carbazitaxel could cause Neutropaenia effective precausion ie GCSF inj could reduce this. Patients known to me who had treatment with Carbazitaxel found the drug well tolerated and better tolerated than Docetaxel. My fellow

	colleagues in other hospitals who had experience with Carbazitaxel shared the same view.
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	In Tropic Trial Carbazitaxel was compared with Mitoxantrone than best supportive care. Even though there is statistically significant survival and progression free survival and response rate, which has not been shown in any other trials so far. One could speculate that if Carbazitaxel was compared with best supportive care it would have had even better clinical outcome.
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	As the need for Carbazetaxel is growing it would be helpful to have the review date much earlier than Feb 2015, perhaps early next year.

Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Apart from the discussions around QUALY there is a distinct group of patients for whom a clinical decision would be made to start Carbazitaxel. Within our network there was support for the use of Carbazitaxel in this select group of patients.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	Support an earlier review taking into account our experience of using this drug through the Cancer Drugs Fund. This might change the cost effectiveness calculations

Role	Patient
Other role	n/a
Location	England
Conflict	no
Notes	Dear Sirs I wish to add my support to the retention of cabazitaxel in the treatment of prostate cancer. Being a patient of this disease I feel if the drug is proven to help patients and gives them hope to prolong their lives the cost should not be a deciding factor in this matter, or any other life thretening disease. The cost could be raised by a 50por£1 parking fee at all UK superstores with

	the proceeds being chanelled to all life thretening illnesses. Regards [redacted]
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	no/comment
Section 2 (The technology)	no/comment
Section 3 (The manufacturer's submission)	no/comment
Section 4 (Consideration of the evidence)	no comment
Section 5 (Implementation)	no comment
Section 6 (Related NICE guidance)	no/ comment
Section 7 (Proposed date of review of guidance)	no/comment

Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	A very disappointing decision. Treatment options are limited in patients post docetaxel and in patients who are of good performance status, it is unfair to deny them a treatment which has a survival advatage.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Given the paucity of evidence (single RCT) support the appraisal, even the most optimistic sensitivity analyses would not suggest that Cabazitaxel is cost effective for the treatment

	of this group of patients with prostate cancer. levels of side effects also high, suggesting that the value of any extension of life might well be offset by reductions in quality of life. Unless significant new evidence becomes available, we agree with these preliminary recommendations.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	We support the Appraisal Commitees recommendation that Cabazitaxel should not be recommended for the treatment of hormone-refractory prostate cancer. Cabazitaxel is not a cost effective use of NHS resources and does not meet NICE criteria for consideration as a life extending end of life treatment.Health-related QOL is an important measure and there is no reliable data on this. There are concerns about the side effect profile, particularly in respect of haematological adverse events and diarrhoea.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	Cabazitaxel does not meet NICE criteria for consideration as a life extending end of life treatment. Based on evidence from the TRPOIC trial, median extension of life with cabazitaxel is 2.4 months. Modelling data from the manufacturer citing a mean extension of 4.2 months is not robust and should not be considered by the committee. We consider health-related QOL an important consideration. The manufacturers submitted modelling estimates for QoL are flawed as they did not properly consider the time spent in health state. Inclusion of data from an early access programme in the modelling is not appropriate. There are concerns about the side effect profile of cabazitaxel in particular haematological adverse events and diarrhoea. The TROPIC trial was not powered to detect differences in specific adverse events between treatment groups and this is a real concern. There remains substantial uncertainty about the effects of cabazitaxel on renal and cardiac adverse events. The most common adverse events observed in the TROPIC trial were neutropenia, asthenic conditions and gastrointestinal toxicity.

Section 4 (Consideration of the evidence)	Cabazitaxel is not a cost effective use of NHS resources. The most plausible ICER for the committee?s preferred patient population is in excess of £89,000 per QALY gained. It seems that the potential cost savings from vial sharing would be very difficult to realise in practice. Clinical specialists said that cabazitaxel has a short shelf life and the number of patients treated at each centre would be small. This means that unused drug would be wasted reducing cost effectiveness.
Section 5 (Implementation)	From the information available we estimate that the cost of implementing treatment with Cabazitaxel for the PCT are in the region of £230,000 - £345,000 pa. The opportunity costs are significant. Funding would very likely have to be released from other services - for example this equates to 1,770 -2,653 radiotherapy fractions.
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	Public
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	Dear Sirs I am writing in support of the Cabazitaxel drug, which my father in law is currently trialling to treat his prostate cancer. He has had several sessions of this chemotherapy drug and it has so far proved very effective for him both in the extension and quality of his life. The outwards signs of usual chemotherapy are much reduced, as are other side effects, and this in turn contributes to his sense of well being. In my opinion it should be used by the NHS as a second line drug for the treatment of this type of cancer as I have seen first-hand the many benefits of it for my father in law and we are very grateful that he has been given the opportunity to have it. Everyone at the same stage of this cancer should have that opportunity. Manufacturers should also be encouraged to develop more similar drugs to treat prostate cancer, as it seems that there are very few out there to treat this type of cancer which is becoming

	much more common in men in their sixties and seventies.
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	other
Other role	Wife of patient receiving cabazitaxel
Location	England
Conflict	no
Notes	no
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	My husband has received six treatments of Cabazitaxel in combination with prednisolone. I cannot recommend this drug to you more highly. It has given him back his purpose in life. He has suffered minimum side effects and only on days three to seven. From day seven he looks and feels well and is able to resume his normal activities. There has been a dramatic improvement across all blood tests. It has greatly improved his quality of life! Second-line chemotherapy is routinely used in every other tumour type, other than in prostate cancer and when an active second-line chemotherapy drug is available, denying access disadvantages men with prostate cancer when compared to other tumour types, such as breast cancer where third or fourth line chemotherapy is the norm.
Section 2 (The technology)	My husband has suffered minimum side effects from the Cabazitaxel and those only on days three to seven. From day seven he is able to resume normal activities. His concentration is good, he is able to go walking (up to two miles a day), he looks and feels well. He has not needed to take any anti-sickness or anti-diahorroea drugs. He has no pain. There are no noticeable signs of chemotherapy, ie:alopecia, weight gain, nail deformity,confusion, loss of self-confidence. His quality of life is good.
Section 3 (The manufacturer's submission)	I do not feel qualified to comment on this.
Section 4 (Consideration of the evidence)	My husband has shown significant and dramatic improvement in quality of life from his first treatment of Cabazitaxel. His daily activities are achievable.He looks and feels well. His blood test results show a dramatic improvement which indicates prolonged survival. The side effects are insignificant by comparison to those of the Docetaxel.
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	I consider that Cabazitaxel has greatly benefited my husband in terms of quality of life and life expectancy. The side effects are minimal by comparison to those on the Docetaxel which left him with very poor life quality. I urge you to encourage manufacturers to research and develop new drugs to treat patients with castrate resistant metastatic prostate cancers as

	there are so few second-line treatments available and yet the condition is so prevalent! Second-line chemotherapy is routinely used in every other tumour type other than in prostate cancer and when an active second-line chemotherapy drug is available, denying access disadvantages men with prostate cancer when compared to other tumour types such as breast cancer where third or fourth line chemotherapy is routinely available.
Section 7 (Proposed date of review of guidance)	Could this date be brought forward as it could benefit many patients suffering from prostate cancer.

Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Although I have not yet had personal cabazitaxel experience, my cancer centre has had significant clinical experience of management of patients within the extended access programme. The clinicians involved in treating patients are convinced that cabazitaxel significantly improves quality of life in patients with metastatic prostate cancer, with significant advantages over mitoxantrone as the previous choice of active second line drug. Toxicity and safety concerns have not been substantiated with careful patient selection and education. The opportunity to offer cabazitaxel to patients with metastatic prostate cancer who are fit enough for further chemotherapy is a significant advance for their symptomatic managment and allows the possibility of more normal life and activity for this group of patients with advanced disease.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	In the Early Access Programme, pain responses of 50% are seen. These data are from a standard UK population of men with metastatic CRPC and is therefore a reflection of the efficacy of the drug. Patients also have significant improvement in all domains of daily activities as evidenced by the EQ5D data collected as part of the EAP. This reflects real life practice and whilst the numbers may be smaller than in TROPIC (100 patients) are directly relevant to UK practice and should not be dismissed. UK cancer networks are required to have guidelines for management of neutropenic sepsis and toxcity of chemotherapy. Within the Early Access Programme the centre I work in has experienced minimal toxicity with this drug, because patients are counselled to commence anti diarrhoeal agents promptly if needed and have nadir full blood counts performed. The use of prophylactic GCSF is 15%, only in patients with previous documented neutropenic sepsis, patients with extensive previous pelvic or spinal radiotherapy or patients aged over 75.
Section 4 (Consideration of the	

evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	other
Other role	Related to a patient
Location	England
Conflict	no
Notes	My name is [redacted], my Uncle is receiving Cabazitaxel treatment. Ten months ago he was in a great deal of pain, so much so that he was on the brink of giving up completely. Then luckily his nurse chose him to receive this treatment. His life has completely changed because of this. He actually sleeps now, he doesnt have agonising pain every day and he is enjoying each day. He renewed his wedding vows, celebrated his Sisters 60th birthday and he himself had a great birthday. These may sound trivial to you, but for us its a great thing, considering what he couldnt do before. I appreciate that you are in a tough situation, not only are you having to determine the treatment best for patients, but you also have the Government pushing you to save money. My argument for the Cabazitaxel is, it works, it really does. I know that its mainly over 65 year olds that have the side effects and that it costs a lot more money than Mitoxantrone. So could you not treat under 65 year olds with Cabazitaxel and over 65 year olds with Mitoxantrone? Or at least give the patients the choice of treatment? Only treating patients who go private is unfair to those that cant afford that way of treatment. People pay their National Insurance and Taxes and have done for years. Some have also donated money to cancer research to find a better way of treating it. So do you not think it unfair to ask them again to pay for treatment that will help them while they are already suffering? When reading the information about both treatments, the main issue that stood out to me was the money side. Its quite obvious that the Government doesnt like the way the NHS is run, but the fact is, people have the right to be treated, they pay National Insurance and taxes for this. I think NICE is a great organisation, but I think it unfair the responsibility you have right now. You will receive many emails of discontent if you decide that Cabazitaxel will not be given to patients through the NHS as we know it works

	The NHS has over £50 million in unpaid bills from treating Foreigners because they dont pay British taxes. So couldnt something be done there to save money instead of making this decision that will effect people who have paid their taxes? Please take into consideration that not all people are wealthy and that we are all human regardless of our financial situation. Thank you for your time Sincerely [redacted]
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	My Uncle has prostate cancer and ten months ago he was in a great deal of pain, so much so that he was on the brink of giving up completely. Then luckily his nurse chose him to receive the Cabazitaxel treatment. His life has completely changed because of this. He actually sleeps now, he doesnt have agonising pain every day and he is enjoying each day. He renewed his wedding vows, celebrated his Sisters 60th birthday and he himself had a great birthday this year. These may sound trivial to you, but for us its a great thing, considering what he couldnt do before.
Section 2 (The technology)	To my understanding, isnt it mainly over 65 year olds that have the side effects? So could you not treat under 65 year olds with Cabazitaxel and over 65 year olds with Mitoxantrone? Or at least give the patients the choice of treatment?
Section 3 (The manufacturer's submission)	When reading the information about both treatments, the main issue that stood out to me was the money side. Both treatments obviously work. Knowing that you have a disease that is killing you and that you cant do anything to change that is hard to deal with. Having family and friends is great, but you know that one day you wont be around to be with your loved ones any more and they will feel the loss. Cabazitaxel gives patients more chance of life. To spend quality time with people they care for and enjoy each day they have without the excruciating pain.
Section 4 (Consideration of the evidence)	I appreciate that you are in a tough situation, not only are you having to determine the treatment best for patients, but you also have the Government pushing you to save money. Obviously you can see that Cabazitaxel works well. My Uncle is looking great since being on it, he is enjoying himself more and he is happy. Only treating patients who go private is unfair to those that cant afford that way of treatment. People pay their National Insurance and Taxes and have done for years. Some have also donated money to cancer research to find a better way of treating it. So do you not think it unfair to ask them again to pay for

	treatment that will help them while they are already suffering?
Section 5 (Implementation)	Its quite obvious that the Government doesnt like the way the NHS is run, but the fact is, people have the right to be treated, they pay National Insurance and taxes for this. I think NICE is a great organisation, but I think it unfair the responsibility you have right now. You will receive many emails of discontent if you decide that Cabazitaxel will not be given to patients through the NHS as we know it works The NHS has over £50 million in unpaid bills from treating Foreigners because they dont pay British taxes. So couldnt something be done there to save money instead of making this decision that will effect people who have paid their taxes?
Section 6 (Related NICE guidance)	Obviously treatments for various diseases change over time when something new is found to work better. Cabazitaxel works for prostate cancer patients. Abiratone to my understanding is still a relatively new drug. So while this drug is still in the testing stage, could Cabazitaxel be offered to patients now?
Section 7 (Proposed date of review of guidance)	If this means that whatever treatment is decided to be offered via the NHS can not be changed until that time, then I feel that maybe 2015 is a date too far into the future. I believe that if the wrong decision is made or if another treatment that is better comes along, NICE will want to make the change. I feel NICE is an organisation that will make a difference to the NHS for the benefit of the patients.

Role	Patient
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	Regardlessv of cost the hope that the extention of life and the resulting benifits that the patient and their family gain is immeasurable. No economic model can take this into account and the drug should be available for those that the clinician sees a benefit.
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	Patient

Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	Regardlessv of cost the hope that the extention of life and the resulting benifits that the patient and their family gain is immeasurable. No economic model can take this into account and the drug should be available for those that the clinician sees a benefit.
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	Public
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	There are very few medication alternatives for castration resistant prostate cancer so I believe that every possibility should be utilised to the full. Cabazitaxel is proven to work where Docotaxel doesnt and if the 10,000 + per year death toll is to be reduced,Cabazitaxel should be available for prescription by doctors.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	NHS Professional
Other role	consultant medical oncologist, [redacted]

	[redacted]
Location	England
Conflict	no
Notes	I attended a foreign meeting funded by Sanofi-Aventis four years ago.
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Disease progression in prostate cancer patients who have received docetaxel is a common problem. The efficacy of cabazitaxel in this situation seems real and an improvement on current treatments. The drug appears to be a better one than docetaxel as neurotoxicity in particular is much less prominent. Retreatment with docetaxel is often effective but not possible in some because of neuropathy. Cabazitaxel makes a valuable alternative. Myelosuppression is seen with the majority of cytotoxic drugs and I have no doubt that British oncologists awill learn to use this one safely. The ICER number calculations seem reasonable and the figure is high. If this means the agent will be unavailable to those treating metastatic prostate cancer in the UK, there will be much disappointment.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	Patient
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Please reconsider the the advantage of a second-line chemotherapy which works with some of the twenty-four varieties of prostate cancer.
Section 2 (The technology)	As a patient I am aware that side effects will occur with chemotherapy. With use, many of these effects can be reduced with experience from patients. This already happens with Docetaxel with discussions amongst patients.
Section 3 (The manufacturer's submission)	Patients are aware such trials are carried out on patients with poor prognosis & weakened health. Earlier use of chemotherapy may well provide advantages.
Section 4	Mitoxantrone we know only helps with some pain relief at best.

(Consideration of the evidence)	We need chemotherapies that, in combinations, can provide tumour reduction. These are the first steps in proste cancer chemotherapy. "Are there specific groups of people for whom the technology is particularly cost effective?" Not applicable ? What about the younger men in their forties & fifties ? What about the revitalisation of hormone treatments which occur after chemotherapy ?
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	Public
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	As a friend of a patient who is suffering from prostate cancer, I would like to express my deep concern over NICEs decision not to license CARBAZITAXEL for the second-line treatment of this disease. It is my understanding that trial results provide firm evidence of its efficacy not only in enhancing quality of life for patients but also in prolonging their survival. I further understand that CARBAZITAXEL is licensed for use in many other tumour types. Not to extend this treatment to men with prostate cancer would seem to be extremely disadvantageous to this group of our population and unfairly discriminatory. I strongly urge you to review current policy and to consider the needs of the increasing number of men who fall victim to this nasty disease. Prostate cancer is by now a widespread condition amongst the population and for this reason alone, every opportunity must be taken to address this situation.
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	Patient
Other role	Retired
Location	England
Conflict	no
Notes	DoB 2/6/49
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	The report indicates that insufficient evidence has been submitted. It would seem sensible to identify and request the further evidence required before a decision is made. The decision is made on grounds of cost effectiveness per QALY, what would be an acceptable cost is not identified. Approaching this from both ends - it is clear further evidence on effectiveness is required. In addition the poor quality of NHS procurement effectiveness is well know. If both of these aspects were tackled it may be possible to meet the QALY cost effectiveness requirements. As one of the patients under the death sentence it would be reassuring to know that all possible and reasonable steps had been taken before the decision to not extend my life has been taken AND that the decision is the correct one when taken in conjunction with all NHS spending. I am aware the amount we give to the NHS is not limitless, but I am not comfortable that the available resources are well prioritised/spent. When I die I would like to be able to reassure my wife, family and friends that everything that reasonably could be done had been done.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	Patient
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	This is a necessary therapy for those whose Docetaxel regimes have failed. This will give those men extra time with their families which, something a price cannot be put on.
Section 2 (The technology)	If the manufacturer wants agreement from NICE then it must reduce its unit price significantly. Once in use the manufacturer will then be better able to recover its R&D costs.
Section 3 (The manufacturer's	If the manufacturer wants agreement from NICE then it must reduce its unit price significantly. Once in use the manufacturer

submission)	will then be better able to recover its R&D costs.
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	submission on behalf of the uro-oncologists at the Sussex Cancer Centre, Brighton UK: [redacted]
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	As Consultant Clinical Oncologists treating urological cancers within the Sussex Cancer Network, we feel that Cabazitaxel offers a unique and beneficial therapeutic option in a subset of those patients with castration refractory metastatic prostate cancer that progress following first line Docetaxel chemotherapy. Only the fittest patients would be considered eligible for second line chemotherapy, and within this patient group Cabazitaxel is of proven benefit, is likely to be well tolerated and in our opinion unlikely to result in costly inpatient treatment. We would encourage NICE to consider approving Cabazitaxel for use in mCRPC.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	Patient
Other role	
Location	England
Conflict	no
Notes	The reason for my message is regarding the recent news that

	Cabazitaxel is unlikely to be fully funded and licensed as a standard treatment post Docetaxel due to the initial seemingl high cost. I wish to share my experience of this drug which is priceless to my wife, children and granchildren in the hope that my experience may influence the final decisions regarding funding for Cabazitaxel. I am a 50 year old man that has had 3 cycles of Cabazitaxel at the Royal Marsden Hospital. This was only available to me on compassionate grounds when it was prescribed earlier this year. I previously had four doses of Docetaxel chemotherapy that failed meaning my disease progressed with no standard treatment available. I was informed I would be unlikely to survive longer than a year or so. For me, Cabazitaxel is working, it has halved my PSA, significantly reduced my Oedema and the tumours in my spine must be decreasing in size because the pain is reducing week by week. My pain medication particularly the morphine has almost halved. If my short message is able to influence any final decision I would be very happy, as a prostate cancer patient with limited options, I am very grateful to the developers and supportes of Cabazitaxel and hope the final decision is favourable
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	The reason for my message is regarding the recent news that Cabazitaxel is unlikely to be fully funded and licensed as a standard treatment post Docetaxel due to the initial seemingl high cost. I wish to share my experience of this drug which is priceless to my wife, children and granchildren in the hope that my experience may influence the final decisions regarding funding for Cabazitaxel. I am a 50 year old man that has had 3 cycles of Cabazitaxel at the Royal Marsden Hospital. This was only available to me on compassionate grounds when it was prescribed earlier this year. I previously had four doses of Docetaxel chemotherapy that failed meaning my disease progressed with no standard treatment available. I was informed I would be unlikely to survive longer than a year or so. For me, Cabazitaxel is working, it has halved my PSA, significantly reduced my Oedema and the tumours in my spine must be decreasing in size because the pain is reducing week by week. My pain medication particularly the morphine has almost halved. If my short message is able to influence any final decision I would be very happy, as a prostate cancer patient with limited options, I am very grateful to the developers and supportes of

	Cabazitaxel and hope the final decision is favourable
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	Patient
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	As someone who is on hormone therapy but thankfully not yet with hormone refractory disease can I please ask for this preliminary decision to be reconsidered. It needs to be remembered that the hope given by this drug is immeasurable in monetary terms for men who have reached the hormone refractory position. The effect of not having this drug and not having this extra tool in the armoury against prostate cancer is equally immeasurably harmful on mens state of mind and psychological well being. Looking at how Herceptin gained approval (for equally limited benefit) are we again being faced with the a reality of men being treated as second class citizens
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	Patient
Other role	
Location	England
Conflict	no
Notes	I am at present a patient receiving Cabazitaxel as part of its trial. I have just received my sixth treatment.

	The Cabazitaxel has shown an improvement in all blood counts and leaves me feeling I have a future! Four or five days after the treatment I feel able to go out walking, use the computer and generally feel useful. I am free of pain.I look and feel well! The side effects have been minimal. I havent needed to take either the anti-sickness or anti-diahorroea drugs. I have regained my self confidence and self purpose. Previously I was treated with Docetaxel. I became more tired and confused with each treatment and struggled to get upstairs. I lost my hair and gained weight.I was unable to derive much pleasure from life, after six treatments I was exhausted and depressed. The resulting blood tests showed nowhere near the improvement in comparison to those on the Cabazitaxel. Please support Cabazitaxel as prostate cancer sufferers have very few second line treatments available and yet the condition is so prevalent. I was diagnosed in my fifties and was told then that my life expectancy was three years at the most. With Cabazitaxel I feel I have prolonged life expectancy and very importantly, quality of life!
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I can only comment as a patient oncabazitaxel, and feel in my case it is far superior to docetaxel.
Section 2 (The technology)	I have suffered very few side effects and far fewer than when on docetaxel. I have had the pre meds
Section 3 (The manufacturer's submission)	I do not feel qualified to comment on this section.
Section 4 (Consideration of the evidence)	I feel cabazitaxel to be an excellent drug ,and has on the face of it so far,been very beneficial. I am not so breathless , improve from day five after treatment,have suffered no hair loss ,in fact my hair has grown back quite vigorously and dark.I am able to go for short walks , two miles or so. I have arthritis in my hips and have virtually no pain at present,when not on chemo I was taking pain killers nearly daily .
Section 5 (Implementation)	Not qualified to answer.
Section 6 (Related NICE guidance)	Speed in my case is imperative as there seems to be so few treatments available to prostate cancer sufferers.
Section 7 (Proposed date of review of guidance)	This seems a long way off to someone with a finite life of months rather than years.

Role	Public
Other role	
Location	England
Conflict	no
Notes	Dear Appraisal Committee, As a friend of a patient who is suffering from prostate cancer, I would like to express my deep concern over NICE?s decision

	not to license CARBAZITAXEL for the second-line treatment of this disease. It is my understanding that trial results provide firm evidence of its efficacy not only in enhancing quality of life for patients but also in prolonging their survival. I further understand that CARBAZITAXEL is licensed for use in many other tumour types. Not to extend this treatment to men with prostate cancer would seem to be extremely disadvantageous to this group of our population and unfairly discriminatory. I strongly urge you to review current policy and to consider the needs of the increasing number of men who fall victim to this nasty disease. Prostate cancer is by now a widespread condition amongst the population and for this reason alone, every opportunity must be taken to address this situation. Yours sincerely, [redacted]
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Dear Appraisal Committee, As a friend of a patient who is suffering from prostate cancer, I would like to express my deep concern over NICE?s decision not to license CARBAZITAXEL for the second-line treatment of this disease. It is my understanding that trial results provide firm evidence of its efficacy not only in enhancing quality of life for patients but also in prolonging their survival. I further understand that CARBAZITAXEL is licensed for use in many other tumour types. Not to extend this treatment to men with prostate cancer would seem to be extremely disadvantageous to this group of our population and unfairly discriminatory. I strongly urge you to review current policy and to consider the needs of the increasing number of men who fall victim to this nasty disease. Prostate cancer is by now a widespread condition amongst the population and for this reason alone, every opportunity must be taken to address this situation. Yours sincerely, [redacted]
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	NHS Professional
Other role	Health professional within private sector
Location	England
Conflict	no
Notes	I am a consultant clinical oncologist treating prostate cancer
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	As a consultant oncologist I have frequently found myself in the situation where I am faced with a prostate cancer patient who has been through all conventional treatment options but is still fit for further treatment if it were available, in contrast with my colleagues treating breast or colorectal cancer where there are many treatment options that can be used sequentially. It is an exciting time to be treating prostate cancer, therefore, with the recent licensing of cabazitaxel and abiraterone, and the new data on Alpharadin, as the survival gains from each seem likely to be cumulative. My experience of prescribing cabazitaxel is in the private sector, and I have found it to be better tolerated than other cytotoxic agents, and to give very good symptomatic responses even in heavily pre-treated individuals. My NHS patients certainly deserve to have access to the same benefits.
Section 2 (The technology)	In my experience the toxicity seems to be equivalent to docetaxel at 60mg/m2, the standard prostate cancer dose being 75 mg/m2, so it is less toxic than the drugs the patients have already received and therefore better tolerated. Regarding cost: a typical dose would be 40 - 50mg (assuming surface area is capped at 2 square metres) so possibly two vials could be used to make up three doses, bringing down the cost. At a cancer centre serving a population of 2,000,000 or so it should certainly be possible to arrange for several patients to receive their treatment on the same day. Also no oncologist would give six cycles (outside a clinical trial) without clear evidence of both tolerance and a good response, possibly reducing the median number of cycles given.
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	Regarding insufficient evidence of cardiac and renal safety, there is still a clear survival benefit even so, and any such toxicity has to be balanced against the risks of the cancer itself. In any case the difference in cardiac and renal deaths may have been a statistical fluke. I have all but stopped using mitoxantrone as its toxicity and the poor response in advanced prostate cancer limits its usefulness. Conversely, my patients starting cabazitaxel have by-and-large reported feeling better almost immediately, which is not something that I see very often even with docetaxel.
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	Patient
Other role	
Location	England
Conflict	no
Notes	I am terminally ill with prostrate cancer, some months ago I was given the opportunity to take part in a trial using Cabazitaxel, I am now in the 9th month of treatment and the improvement in my health since having Cabazitaxel has been remarkable and has significantly improved my quality of life, this has also been the case for others involved with the trial. I am absolutely outraged at the NICE preliminary decision, not to recommend the use of Cabazitaxel for the treatment of prostate cancer patients on the NHS. Without this drug being available many patients will suffer and indeed die prematurely which is an unacceptable situation, when there is a proven drug that could help extend their life. I appeal to NICE to overturn their decision and allow this amazing drug to be made available to all NHS affected patients. Yours Sincerely, [redacted]
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I am terminally ill with prostrate cancer, some months ago I was given the opportunity to take part in a trial using Cabazitaxel, I am now in the 9th month of treatment and the improvement in my health since having Cabazitaxel has been remarkable and has significantly improved my quality of life, this has also been the case for others involved with the trial. I am absolutely outraged at the NICE preliminary decision, not to recommend the use of Cabazitaxel for the treatment of prostate cancer patients on the NHS. Without this drug being available many patients will suffer and indeed die prematurely which is an unacceptable situation, when there is a proven drug that could help extend their life. I appeal to NICE to overturn their decision and allow this amazing drug to be made available to all NHS affected patients. Yours Sincerely,

	[redacted]
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	I have arranged and attended educational meetings sponsored by the manufacturers. I have also received honorariums in the past for speaking at such educational meetings (but on radiotherapy - unrelated to products produced by the manufacturer)
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I am a consultant Clinical Oncologist at Guy?s & St. Thomas? NHS Trust with a specialist interest in Uro&#8208oncology. I am writing to express my disappointment at the initial recommendations from NICE regarding the use of cabazitaxel in stage IV castrate refractory prostate cancer after disease progression post docetaxel chemotherapy. I believe it should be made available to men with a performance status of 0&#82081, who have progressed on / during at least 3 cycles of docetaxel and who have been adequately counselled as to the potential toxicities and benefits ? which is the cornerstone of the consent process. Until recently docetaxel was the only systemic therapy to demonstrate a significant survival benefit in patients with stage IV castrate&#8208refractory prostate cancer (Tannock 2004: 18.9months v 16.5months HR 0.76 NICE approved 2006). There is no NICE approved treatment for patients with progressive disease post docetaxel. The most efficacious alternative cytotoxic to docetaxel is mitoxantrone plus prednisone. This combination significantly improves palliation of bone pain (compared to prednisone alone), but does not impact significantly on survival
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	a. Second-line palliative chemotherapy for solid tumours generally provides a small survival benefit if any eg Lung Cancer: Shepherd 2000: 2.9 months (sig): NICE approved 2006 Breast Cancer: Nabholtz 1999: 2.7 months (sig): NICE approved 2009

	b. The TROPIC study was conducted in patients who had already received docetaxel chemotherapy, and ~30% of patients in each arm had received at least 2 previous cytotoxic regimens. TROPIC: de Bono 2010: 2.4 months (sig) HR 0.7 Therefore in a heavily pre-treated population, when compared to a robust alternative cytotoxic agent, cabazitaxel still produced a significant increase in overall survival, and matched mitoxantrone in its ability to palliate bone pain.
Section 4 (Consideration of the evidence)	a. The Tropic study included patients with an ECOG performance status (PS) 2082. In the UK it would be unusual to treat a PS 2 patient with chemotherapy, as the accosiated toxicity is too great. b. 2nd line palliative chemotherapy for solid tumours is associated with greater toxicity than 1st line eg: Lung Cancer: Shepherd 2000: G3/4 neutropenia 67.3% febrile neutropenia 1.8% treatment related death 1.8%: NICE approved 2006 Breast Cancer: Nabholtz 1999: G3/4 neutropenia 93.1% febrile neutropenia 9% treatment related death 2%: NICE approved 2009 c. NCEPOD and NCAG recommendations for UK acute oncology services should result in better management of chemotherapy related complications than were in place at the time of the study (NICE did comment in 3.2.4 that deaths could have been prevented by better management of neutropenia). d. Data from patients on the expanded access programme and QT interval studies should be analysed to investigate the renal and cardiac toxicity. e. Mitoxantrone patients had more stringent cardiac monitoring in TROPIC so the study is biased towards minimising cardiac toxicity in this arm
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	As a specialist in the treatment of prostate cancer , I am extremely familiar with the evidence from the TROPIC study and have also used Cabazitaxel extensively since January 2011 in men with castrate resistant metastatic prostate cancer refractory to docetaxel chemotherapy. Despite some initial reservations, I am convinced that this drug dramatically improves the quality of life in men with this disease as well as prolonging survival. Second-line chemotherapy is routinely used in every other tumour type other than in prostate cancer and

	when an active second line chemotherapy drug is available, denying access disadvantages men with prostate cancer when compared to other tumour types such as breast cancer where third or fourth line chemotherapy is the norm. Cabazitaxel is not a difficult drug to administer, what is paramount is patient selection. The UK Early access programme with cabazitaxel has shown that the data from the TROPIC study underestimated patient benefit from carbaxitaxel in terms of quality of life, and in terms of potential side-effects such as diarrhoea or febrile neutropenic which are easily and proactively managed.
Section 2 (The technology)	Nausea, vomiting, constipation, back pain, peripheral neuropathy, dysponea cough and arthlagia are not common side effects. When consenting for chemotherapy, commons side effects are those that are deemed to occur 30% of the time. The TROPIC trial showed diarrhoea not constipation and the rate of diarrhoea is low in real life practice and easily managed
Section 3 (The manufacturer's submission)	6 Survival 25% of patients in TROPIC had liver metastases, which would usually carry a prognosis in this setting of weeks. Despite this, 1 in 5 patients in the study were alive at 24 months.mitoxantrone is an active drug in prostate cancer, licensed in the USA for its pain benefit. In the TROPIC study, time to pain progression for patients on carbaxitaxel was 11.1 months. In the early Access programme, pain responses of 50% are seen (data available and submitted to GU ASCO meeting). These data are from a standard UK population of men with metastatic CRPC and is therefore a reflection of the efficacy of the drug. Patients also have significant improvement in all domains of daily activities as evidenced by the EQ5D data collected as part of the EAP. This reflects real life practice and whilst the numbers may be smaller than in TROPIC (100 patients) are directly relevant to UK practice and should not be dismissed. Patients are cable to carry on with their normal life and use words such as ?transformed?, ? fantastic?.In the UK we are used to delivering chemotherapy safely and have robust mechanisms for management of chemotherapy related toxicity and neutropenic sepsis.
Section 4 (Consideration of the evidence)	There is unequivocal evidence from UK clinicians who have used carbaxitaxel, both through the Early Access Programme and through the Cancer Drug Fund, that health-related quality of life is significantly and dramatically improved, with improvements seen after one or two cycles. Patients feel better, their pain is better and their daily activities of life are achievable. The resuts of the Early Access programme validate this, with pain improvement seen in at least 50% of patients.patients were not receiving placebo as the comparator. They were receiving mitoxantrone, an active agent in prostate cancer, licensed for its improvements in quality of life. Clinicians are trained in assessment of symptoms, patients are aware they are having active treatment and therefore bias is likely to be low.The survival benefit for cabazitaxel in the second line setting is very similar to that seen in the pivotal TAX327 study of docetaxel versus mitoxantrone in first line chemotherapy. in

	TROPIC, patients who had a rise in PSA but who were clinically benefiting from cabazitaxel had treatment stopped in real life practice, clinical benefit dictates treatment.
Section 5 (Implementation)	In my professional experience, cabazitaxel clearly benefits patients in contemporary UK practice in terms of quality of life, and the survival benefit is likely to be greater than that seen in the TROPIC study. This appraisal preliminary result disadvatges an entire patient group: the population disadvantaged are all men in the UK with metastatic CRPC resistant to first line chemotherapy who remain fit for further chemotherapy yet have impaired quality of life from their illness affecting their daily activities.
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	NHS Professional
Other role	
Location	England
Conflict	yes
Notes	I hold a research grant from Sanofi-Aventis for a Clinical Study.
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I was disappointed to hear of NICE?s decision not to recommend the use of cabazitaxel for the treatment of hormone refractory prostate cancer. As a clinician who manages advanced prostate cancer, I recognise the huge unmet need that currently exists in hormone refractory disease. Whilst chemotherapy with docetaxel has become a standard of care, subsequent therapeutic options have been very limited until recently. The TROPIC trial demonstrated a significant benefit in patient outcome with cabazitaxel/ prednisone over the previous standard of mitoxantrone/ prednisone. Whilst there was extra toxicity with the cabazitaxel group, my feeling is that this was generally predictable and manageable. The indications are that optimal management of neutropenic sepsis episodes would probably have largely prevented the excess in deaths within 30 days of last drug observed in the cabazitaxel arm of the study. Moreover, there is considerable uncertainty that the cardiac and renal toxicities observed in the cabazitaxel group were treatment-related. More recent Quality of Life data also seems to favour the use of cabazitaxel in this advanced disease setting. The TROPIC trial was a significant step forward in the management of the disease. Clearly, the clinician would be expected to play an important role in assessing the suitability of patients for this treatment. For appropriate patients though, I strongly believe cabazitaxel should be a therapeutic option, and I am disappointed that my patients are being denied this potentially valuable treatment.
Section 2	

(The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	Public
Other role	
Location	England
Conflict	no
Notes	1 We have knowledge of someone who has been treated with Cabazitaxel and have seen for ourselves the effectiveness of this drug. Quality of life is much improved, he is free from pain and has regained his previous sense of purpose and outward appearance. There have been no noticeable signs of chemotherapy:ie weight gain, hair loss, lack of colour, confusion and lack of self confidence. He looks and feels well . 2 This drug dramatically improves the quality of life in men with prostate cancer as well as prolonging survival. 3 We know of so many men in their sixties and early seventies suffering from this disease. Their prospects of good life quality are being denied if Cabazitaxel and other second-line drugs are not going to be made available. 4 Second-line chemotherapy is routinely used in every other tumour type, other than prostate cancer and when an active second-line chemotherapy drug is available, denying access disadvantages men with prostate cancer when compared to other tumour types, such as breast cancer, where third or fourth-line chemotherapy is the norm. 5 In conclusion, I would urge you to encourage manufacturers to research and develop more drugs to treat prostate cancer as there are so few available at present and yet the condition is so prevalent!
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	1 We have knowledge of someone who has been treated with Cabazitaxel and have seen for ourselves the effectiveness of this drug. Quality of life is much improved, he is free from pain and has regained his previous sense of purpose and outward

	appearance. There have been no noticeable signs of chemotherapy:ie weight gain, hair loss, lack of colour, confusion and lack of self confidence. He looks and feels well . 2 This drug dramatically improves the quality of life in men with prostate cancer as well as prolonging survival. 3 We know of so many men in their sixties and early seventies suffering from this disease. Their prospects of good life quality are being denied if Cabazitaxel and other second-line drugs are not going to be made available. 4 Second-line chemotherapy is routinely used in every other tumour type, other than prostate cancer and when an active second-line chemotherapy drug is available, denying access disadvantages men with prostate cancer when compared to other tumour types, such as breast cancer, where third or fourth-line chemotherapy is the norm. 5 In conclusion, I urge you to encourage manufacturers to research and develop drugs to treat prostate cancer
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	Currently, for this group of patients, there are no treatment options which improve survival. Re-challenge with docetaxel can be useful but only if there has been a reasonable length of time between its initial use and the time of disease progression. The mean time to progressive disease post-docetaxel is only 3 months and hence re-challenge is unlikely to be effective re-challenge is also not NICE approved and hence not funded in many areas. My clinical experience of cabazitaxel is that it is generally well tolerated, and I have sen meaningful clinical responses with

	clear quality of life benefits.
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	The drug has an overall survival advantage in pts who have progressed post docetaxel. This is a growing group in whom until recently we have had no treatments that offs an os advantage.
Section 2 (The technology)	the drug costs are high, but in my experience if it is poorly tolerated you stop soon, and if it works the improvement in quality of life exceeds what has been published.
Section 3 (The manufacturer's submission)	in reality many pts will stop after less than 6 cycles, and those who do well the the results and potential economic gains are real.
Section 4 (Consideration of the evidence)	oOS survival advantages for second line treatments are rarely demonstrated in any tumour type. It seems wrong to deny pts access to this drug which provides real options for this group of pts
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	await this review
Section 7 (Proposed date of review of guidance)	

Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I have been asked by a Sanofi representative to comment on whether I think there is a clinical need to use cabazitaxel, and to provide support for NICE to enter into discussion with Sanofi regarding a patient access scheme. I think a small proportion of patients would be fit enough to have further chemotherapy following docetaxel, and it is disappointing the cost per QALY of cabazitaxel is so high. I believe some patients will be very keen to have cabazitaxel simply for potential improvement in survival, even in the absence of data on quality of life. I would support negotiation on pricing which might allow widespread use of cabazitaxel, rather than variation through regional cancer drug funds.

Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	Attended Advisory board for Sanofi Aventis
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I participated in the TROPIC study and the subsequent EAP.We were the largest recruiters in the UK to both of these research programmes.In my experience cabazitaxel is a highly effective agent that is well tolerated in appropiately selected patients.I have noticed an early and sustained improvement in symptomotology with resultant improvements in patients quality of life as well as well as survival benefit. In view of the above I would request the commitee to reconsider their preliminary recommendation. I feel that this drug fulfils an unmet need with trial evidence from patients who have advanced disease resistant to docetaxel or progressing within 3 months in 70% of the cases, showing survival benefits.It is ironic that we have so many drugs available in metastatic breast cancer post 1st line yet only eribulin has demonstrated a survival benefit.Currently there is no NICE endorsed option post 1st line and I would urge the commitee to review this and help in addressing some of the inequalities faced by prostate cancer patients. Definitely,my patients have tolerated this treatment well with obvious clinical benefit as well as improvements in QoL enabling them to live their life.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	It is disappointing that the committee have come to this decision. There is a clear clinical need to improve treatments for men with castrate resisitant prostate cancer . The drug improves survival compared to the only realistic comparator in this situation and would provide patients with a clear alternative. The survival advantage is greater than many other targetted agents that have been approved. I note concern over toxicity but this was much greater in countries with less good infrastructure than UK oncology being much lower in US and Europe. Some of the patients who died of cardiac and renal problems may have been less fit than ideal and recommending a higher PS as recommended in the guidance might avoid these problems. From discussions with those who have experience with the drug the toxicity is not felt to be significant. I also believe that in the real world patients failing to respond/having toxicity are likely to receive less treatment than in the trial where there would be protocol driven need to complete certain amount of treatments. This would reduce potential costs in non responders. I would question whether 10 cycles of therapy is desirable for this gr
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	I agree that the use of this technology meets NICEs end of life technology I suspect most patients will require less than 10 cycles of treatment and costs are likely to be less than suggested in trial data End of life care without palliation are likely to be considerable
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	NHS Professional
Other role	Professor of Clinical Oncology
Location	England
Conflict	yes
Notes	Advisory Boards for Sanofi-Aventis
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary	

recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	3.21 One feature of the trial was that SAE?s, particularly fatal ones, were more likely outside the EU/North America. It is likely that methods for dealing with sick patients on chemotherapy are less well organized outside of these areas.
Section 4 (Consideration of the evidence)	4.2 On the basis of experience with the agent in pts with PS2, I would not offer treatment to PS 2 patients. 4.4 I generally agree, however, I review chemotherapy in this setting at every cycle, not after 6. Patients not benefiting will stop much earlier than 6 cycles. 4.5 Given the survival benefit observed and the population treated, it seems unlikely that the survival gap will close at a later date. In the TAX327 study comparing docetaxel with mitozantrone in the first line setting, a similar hazard ratio was observed at both initial and long term analysis. 4.11. The study referred to is ongoing. We entered patients in the study and in essence these are the patients we would envisage treating if the agent were made available. 4.21. On the basis of audit of our own practice, these numbers are too high. At most 60% of HRPC pts are able to receive chemotherapy. Of these, no more than 20% would be fit for further chemotherapy giving around 1000 pts per annum.
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Having seen the data presented, I do feel that this drug would benefit my patients in the post-docetaxel setting. Quite frankly, I find it difficult to believe that the committee would reject a drug that increases overall survival in this population.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6	

(Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	none
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I am a specialist in the treatment of prostate cancer and am extremely familiar with the evidence from the TROPIC study. I have some experience with Cabazitaxel in men with castrate resistant metastatic prostate cancer refractory to docetaxel chemotherapy. I am convinced that this drug improves the quality of life in men with this disease as well as prolonging survival. Second-line chemotherapy is routinely used in every other tumour type other than in prostate cancer and when an active second line chemotherapy drug is available, denying access disadvantages men with prostate cancer when compared to other tumour types such as breast cancer where third or fourth line chemotherapy is the norm
Section 2 (The technology)	Nausea, vomiting, constipation, back pain, peripheral neuropathy, dysponea cough and arthlagia are not common side effects. When consenting for chemotherapy, commons side effects are those that are deemed to occur 30% of the time.
Section 3 (The manufacturer's submission)	3.6 Survival 25% of patients in TROPIC had liver metastases, which would usually carry a prognosis in this setting of weeks. Despite this, 1 in 5 patients in the study were alive at 24 months, 3.9 Mitoxantrone is an active drug in prostate cancer, licensed in the USA for its pain benefit. In the TROPIC study, time to pain progression for patients on carbaxitaxel was 11.1 months. In the early Access programme, pain responses of 50% are seen (data available and submitted to GU ASCO meeting). These data are from a standard UK population of men with metastatic CRPC and is therefore a reflection of the efficacy of the drug. Patients also have significant improvement in all domains of daily activities as evidenced by the EQ5D data collected as part of the EAP. This reflects real life practice and whilst the numbers may be smaller than in TROPIC (100 patients) are directly relevant to UK practice and should not be dismissed. Patients are cable to carry on with their normal life and use words such as ?transformed?, ? fantastic?. These patients are receiving second line chemotherapy. Therefore the expected rates of neutropenia are higher than in the first line setting.
Section 4 (Consideration of the evidence)	Subjective outcome bias: patients received mitoxantrone, an active agent in prostate cancer, licensed for its improvements in quality of life. Clinicians are trained in assessment of symptoms, patients are aware they are having active treatment and therefore bias is likely to be low.

	4.5. 25% of patients in TROPIC had liver metastases with PSA levels of 100. These patients would usually have a survival measured in terms of weeks yet in TROPIC one in five of such patients were alive at 24 months. 4.10. Cardiac and renal complications have not been seen in the EAP. In the TROPIC study, patients with these complications were relatively few. 4.15 The survival advantage with cabazitaxel and therefore the ICER would be significantly higher if deaths due to poorly managed neutropenic sepsis in non-northern European countries was taken out of consideration.
Section 5 (Implementation)	acceptable
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	acceptable

Role	Public
Other role	
Location	England
Conflict	no
Notes	Cabazitaxel could make a massive difference to prostate cancer sufferers,not only in prolonging their lives but also to their quality of life and to that of their families. I believe that similar drugs are prescribed for other forms of cancer and do not understand why prostate cancer patients seem to be the "poor relations".
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	No comment.
Section 2 (The technology)	No comment.
Section 3 (The manufacturer's submission)	No comment.
Section 4 (Consideration of the evidence)	Having read the above, I realize that Cabazitaxel is very expensive, however, if treatment is targeted only to the most "suitable" prostate cancer sufferers, costs could be minimized. Cabazitaxel could make a massive difference, not only in prolonging their lives but also to their quality of life and to that of their families.
Section 5 (Implementation)	No comment.
Section 6 (Related NICE guidance)	No comment.
Section 7 (Proposed date of review of guidance)	No comment.

Role	NHS Professional
Other role	

Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	It is not fair as there is a sub group of relatively young and fit for 2nd line chemotherapy who will be suitable for cabazitaxel and being denied the chance of a drug clearly showing survival benefit in a situation with limited treatment options otherwise. In my opinion, this drug should be allowed for 2nd line usage in HRPC cancer patients who in clinicians view are suitable for it.
Section 2 (The technology)	I am afraid It is costly drug like any other new technology . Its cost could be adjusted by negotioation with the manufacturer as NICE have done with many other drugs companies through reimbursement program. Side effects are mangaeable in experienced hands like other taxanes. I do not think it will be a major issue in terms of controlling toxicity if clinicians choose / select patients carefully for this treatment
Section 3 (The manufacturer's submission)	Manufacturer has obviously done the calculations wrong in terms of QUALY gained and may have used a different model than NICE. The economiacl element based on the tropic trial may not make sense but from patients perspective it is important that these drugs should be made available with a certain pre defined criteria
Section 4 (Consideration of the evidence)	Fair consideration by NICE
Section 5 (Implementation)	Fair
Section 6 (Related NICE guidance)	awaited
Section 7 (Proposed date of review of guidance)	I think it will be too late. Some where 2012 will be more appropriate with more local evidence through local UK based audits via expanded access program or CDF provision

Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	nothing to disclose
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	As an oncologist treating prostate cancer I feel very disappointed about this decision. Not all patients would be offered this option of treatment however many with good Performance status can benefit a lot and this drugs has an impact on overall survival. I feel very strongly this option should be available for patients with prostate cancer
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	

Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	Recruited patients to the TROPIC trial Recruited patients to QOL study Received consultancy and Lecture fees, and Conference sponsorship from Sanofi Aventis
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Since the NICE approval of Docetaxel, there are many very fit mCRPC patients who have progressed after Docetaxel chemotherapy and did not have any proven second line chemotherapy option until the licensing of Carbazitaxel. Unlike the other major hormonally driven cancer ie breast cancer, prostate cancer patients have limited access to proven second line chemotherapy options. Carbazitaxel would satify this unmet need. Many fit patients would be deprived of a proven therapy if NICE does not approve Cabazitaxel. In out network, Carbazitaxel is not available via CDF unlike other networks.
Section 2 (The technology)	Cabazitaxel, although a taxane, shows considerable clinically meaningful activity in Docetaxel refractory prostate cancer patients.
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	Carer
Other role	wife of patient
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	

Section 4 (Consideration of the evidence)	I get incresingly annoyed at the attitude of NICE to patients who have life limiting illnesses. If there is a drug that can extend their lives for even a short time it should be used. NICE is not God and should not refuse a patient life extending drugs. Even a short extension is worth having for the family friends and patient to enjoy time together. I am aware that new drugs are costly BUT so much money is wasted in the NHS that NICE should either be looking at that scenario or get another quango to do so. The UK is treating too many people who have not contrbuted to the NHS at the expense of those, who like my husband and I,have paid our way all our lives. This drug should be made available to all those who need it.
Section 5 (Implementation)	It seems that those who shout loudest get the drugs they need: hercepti being a case in point. I admired the women who fought so hard for it. As a breast cancer patient many years ago when treatments wre very few I was lucky to need only radiotherapy. Today the Drs have many more options. NOW WE MUST GIVE THE MEN THE OPTIONS TOO.
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I would like to comment that there is a defined group of patients who will benefit greatly from cabazitaxel as second line chemotherapy for prostate cancer and NICE should recommend the drug for the specific group. the group includes patients who are still in a good performance status, who never responded well to any hormone manipulation.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	Patient
Other role	
Location	England
Conflict	no

Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I believe women with breast cancer do have the option of a second treatment if the first treatment fails. It would be wrong to discriminate against men with prostate cancer if they dod not have the same second opportunity
Section 2 (The technology)	If the choice is between earlier death or longer life with risk of some adverse reactions most men would choose the latter. At least they should have the option.
Section 3 (The manufacturer's submission)	No comment
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	No comment
Section 6 (Related NICE guidance)	No comment
Section 7 (Proposed date of review of guidance)	

Role	Patient
Other role	[redacted]
Location	England
Conflict	no
Notes	Yet another attempt to put finance before patients life The trial shows that it does give a valuable extension of life to men whose Docetaxel regime has failed and no amount of econometric modelling can put a price on that.
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Role	NHS Professional
Other role	
Location	Wales
Conflict	no
Notes	Attended ASCO urogenital cancer congress March 2010 as a guest of Sanofi-Aventis

Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	cabazitaxel showed an impressive PSA response rate and significant improval in median survival even in patients who had not responded/ were no longer responding to docetaxel, and would be the 2nd line treatment of choice for patients who had never had a good or sustained response to previous hormone therapy
Section 2 (The technology)	acceptible toxicity in patients of good performance score
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	I agree that the cost appears prohibitive and would ask whether any arrangement could be made with the Manufacturer to reduce this cost, eg free first cycle, or some refund if no response?
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	Abiraterone will be in direct competion as therapy for patients no longer responding to docetaxel, and will be the treatment of choice for many patients (of good performance score), but cabazitaxel may be preferable for patients who had a poor resonse to androgen deprivation previously
Section 7 (Proposed date of review of guidance)	