Cabazitaxel for hormone-relapsed metastatic prostate cancer previously treated with a docetaxel-containing regimen (review of TA255)

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The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Ben Kearns and Matt Stevenson critiqued the health economic analysis submitted by the company. Abdullah Pandor and Duncan Chambers summarised and critiqued the clinical effectiveness data reported within the company's submission. Jean Sanderson critiqued the statistical analyses undertaken by the company. Mark Clowes critiqued the company's search strategy. John Graham and Satish Kumar provided clinical advice to the Evidence Review Group throughout the project. Ben Kearns, Matt Stevenson, Abdullah Pandor, Duncan Chambers, Jean Sanderson and Mark Clowes were involved in drafting the final report. All authors were involved in commenting on the final report.

CONTENTS

LIST OF TABLES

LIST OF FIGURES

Abbreviations

AEs	Adverse events
AIC	Akaike's Information Criterion
BIC	Bayesian Information Criterion
BSA	Body Surface Area
BSC	Best Supportive Care
CDF	Cancer Drugs Fund
CS	Company Submission
CI	Confidence Interval
CrI	Credible Interval
CUP	Compassionate Use Programme
EAP	Early Access Programme
ECOG	Eastern Cooperative Oncology Group
eMIT	Electronic market information tool
EQ-5D	EuroQol 5 Dimensions
ERG	Evidence Review Group
FDA	Food and Drug Administration
G-CSF	Granulocyte-Colony Stimulating Factors
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
ICER	Incremental Cost Effectiveness Ratio
ITC	Indirect Treatment Comparison
ITT	Intention To Treat
LHRH	Luteinising Hormone-Releasing Hormone
mCRPC	Metastatic Castrate Resistant Prostate Cancer
mHRPC	Metastatic Hormone Refractory Prostate Cancer
NHS	National Health Service
NMA	Network Meta-Analysis
OS	Overall Survival
PAS	Patient Access Scheme
PBRE	Periodic Benefit Risk Evaluation
PFS	Progression Free Survival
PS	Performance Status
PSA	Prostate Specific Antigen
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
RECIST	Response Evaluation Criteria in Solid Tumors

rPFS	Radiographic Progression Free Survival
SD	Standard Deviation
SIGN	Scottish Intercollegiate Guidelines Network
SPC	Summary of Product Characteristics
STA	Single Technology Appraisal

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company's submission (CS) to the National Institute for Health and Care Excellence (NICE) aimed to provide evidence relating to the clinical and cost effectiveness of cabazitaxel used within its licensed indication in combination with prednisolone or prednisone for the treatment of metastatic hormone-refractory prostate cancer (mHRPC) previously treated with a docetaxel-containing regimen. The CS represents an update to a previous submission (TA255), for which the final appraisal determination was issued in January 2012. This determination did not recommend cabazitaxel (in combination with prednisone or prednisolone) for the treatment of hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen. The Appraisal Committee agreed that cabazitaxel was an effective, life-extending treatment but that the most plausible incremental cost effectiveness ratio (ICER) was likely to be above £87,500 per quality-adjusted life years (QALYs) gained. Nevertheless, cabazitaxel was made available via the Cancer Drugs Fund (CDF) until its removal in January 2015. After an agreement had been reached with NHS England, it was later re-instated on the CDF in May 2015 as an interim measure pending NICE re-review. Following TA255, the terminology for the population for which cabazitaxel is suitable has evolved. A distinction has been made between people with mHRPC and metastatic castrate resistant prostate cancer (mCRPC), with the latter more likely to respond to subsequent hormonal therapy than the former. The main focus of the CS was mCRPC, and the ERG shall refer to the population of interest as people with mCRPC.

The NICE final scope identified five relevant comparators: abiraterone in combination with prednisone or prednisolone; enzalutamide; mitoxantrone in combination with prednisolone; best supportive care (BSC); and radium-223 dichloride for the subgroup of people with bone metastasis only (no visceral metastasis). However, the CS only formally considered three comparators omitting BSC and radium-223 dichloride. It was assumed by the company that mitoxantrone could be considered to be at least equivalent to BSC as there was no demonstrable survival advantage associated with using mitoxantrone instead of BSC. The clinical advisors to the Evidence Review Group (ERG) concurred with this view. The company did not include radium-223 dichloride as a comparator for two main reasons. Firstly, evidence on the clinical effectiveness of cabazitaxel and radium-223 dichloride came from different patient populations as radium-223 dichloride is only licensed for use in a sub-population of adults who have mCRPC with symptomatic bone metastases and no known visceral metastases, and radium-223 dichloride is contra-indicated in people with liver metastases. Secondly, it was not possible to compare radium-223 dichloride with either abiraterone or enzalutamide due to differences in the definitions of progression-free survival (PFS) used. However, the ERG notes that whilst the reasons provided make comparisons of clinical and cost effectiveness difficult, they are not a sufficient rationale for excluding radium-223 dichloride as a comparator. The

potential cost-effectiveness of cabazitaxel when compared with radium-223 dichloride is discussed in Section 1.7.

The CS addressed the outcomes specified within the NICE final scope. However, one of the outcomes was PFS. Whilst the comparison between cabazitaxel and mitoxantrone used the same definition of PFS, an alternative definition was required for comparisons with abiraterone and enzalutamide. The company noted that analyses using this alternative definition, (radiographic PFS (rPFS)) should be interpreted with caution. The ERG agreed with this view.

1.2 Summary of clinical effectiveness evidence submitted by the company

The CS included a systematic review of the clinical effectiveness literature. The TROPIC trial, which forms the main supporting evidence for the intervention, was a phase III, manufacturer-sponsored, multi-centre (146 centres in 26 countries including the UK), randomised, open-label, active-controlled trial. TROPIC was designed to evaluate the efficacy and safety of cabazitaxel (25mg/m^2 intravenously over 1 hour, n=378) with mitoxantrone (12mg/m^2 intravenously over 15 to 30 minutes, n=377) in 755 men aged over 18 years with mHRPC, with an Eastern Cooperative Oncology Group (ECOG) performance score of 0–2, and with evidence of disease progression during or after treatment with a docetaxel-containing regimen. All patients received oral prednisone 10mg daily (or prednisolone where prednisone was unavailable). Exposure to the study treatment varied between the groups. In the cabazitaxel group, patients received a median of six cycles of treatment, of which 10% of cycles required a dose reduction, with a median relative dose intensity of 96.1%. In contrast, patients in the mitoxantrone group completed a median of four cycles of treatment, of which 5% of cycles required a dose reduction, with a median relative dose intensity of 97.3%.

The CS provided updated results from the TROPIC study. The results for the whole trial population were originally published after a median follow-up of 12.8 months, at which point 513 deaths had occurred (final analyses had been planned after 511 deaths). An updated analysis, with extended follow-up, was carried out when 585 deaths had occurred. In this analysis, after a median follow-up of 20.5 months, 277 (73.3%) deaths had occurred in the cabazitaxel group compared with 308 (81.7%) in the mitoxantrone group. Median overall survival (OS) (a primary efficacy endpoint) was 15.1 months in the cabazitaxel group and 12.8 months in the mitoxantrone group, thus, cabazitaxel plus prednisone or prednisolone was associated with an estimated median OS gain of 2.3 months relative to mitoxantrone plus prednisone or prednisolone. The hazard ratio (HR) was 0.72 (95% confidence interval [CI] 0.61 to 0.84, $p<0.0001$). Median PFS (a composite endpoint defined as time to progression as measured by a rise in prostate-specific antigen (PSA) level, tumour progression, pain progression or death) was significantly greater statistically in the cabazitaxel group (2.8 months) than in the mitoxantrone group (1.4 months) with an estimated 25% reduction in the risk of

progression (HR 0.75, 95% CI: 0.65 to 0.87, p=0.0002). The CS did not report any results for the following secondary outcomes and no explanations were provided for these omissions: tumour response; time to tumour progression; PSA response; PSA progression; pain response; and pain progression. Data on health related quality-of-life were not collected in the TROPIC study.

In NICE TA255, the Appraisal Committee considered a subgroup of patients with an ECOG performance score of 0 or 1 and who had received at least 225 mg/m^2 of prior docetaxel to be the most appropriate population to receive cabazitaxel in UK clinical practice. Patients with an ECOG performance score of 2 would not be deemed not fit enough to tolerate further chemotherapy and patients would need to receive at least 225 mg/m^2 of docetaxel to gain the full benefit of first-line treatment before going on to receive cabazitaxel. In this post-hoc subgroup analysis (representing 83.7% [632/755] of the total TROPIC trial population), the median OS was 15.6 months in the cabazitaxel group and 13.4 months in the mitoxantrone group with a HR of 0.69 (95% CI 0.57 to 0.82, p<0.001) corresponding to a 31% reduction in the risk of death. Thus, cabazitaxel plus prednisone or prednisolone was associated with an estimated median OS gain of 2.2 months relative to mitoxantrone plus prednisone or prednisolone. A statistically significant improvement in median PFS was also observed. PFS was 2.8 months in the cabazitaxel group and 1.4 months in the mitoxantrone group (HR 0.76, 95% CI: 0.65 to 0.89, p=0.001) corresponding to a 24% reduction in the risk of progression.

In the TROPIC study, treatment emergent adverse events (AEs) of grade ≥3 occurred in 213/371 (57.4%) patients in the cabazitaxel group and 146/371 (39.4%) patients in the mitoxantrone group. The proportion of patients withdrawing from study treatment permanently due to any treatment emergent AE was higher in the cabazitaxel group (18.3%) compared with the mitoxantrone group (8.4%). The most common AEs associated with cabazitaxel of grade ≥3 requiring medical intervention (i.e. dose reduction, dose modifications, use of supportive treatment or treatment discontinuation) compared with mitoxantrone were: neutropenia and its complications (neutropenia: 21% versus 7.3%; febrile neutropenia, 7.3% versus 1.6%); asthenic conditions (asthenia: 4.6% versus 2.4%; fatigue: 4.9% versus 3.0%); and gastrointestinal toxicity (diarrhoea: 6.2% versus 0.3%; nausea: 1.9% versus 0.3%), respectively. A similar frequency of AEs were also observed in the subgroup of patients with an ECOG performance score of 0 or 1 and who had received at least 225 mg/m^2 of prior docetaxel.

Deaths within 30 days of the last dose of study drug in the TROPIC study were more common with cabazitaxel (5%) than mitoxantrone (2%). The most common causes of such deaths were neutropenia and its complication in patients receiving cabazitaxel (accounting for seven deaths in the cabazitaxel group compared with one death in the mitoxantrone group), and disease progression in patients

receiving mitoxantrone (accounting for six deaths in the mitoxantrone group compared with zero deaths in the cabazitaxel group). Additional safety data, in the post-docetaxel setting, from 112 patients with mCRPC treated with cabazitaxel in the UK Early Access Programme (EAP) (which is part of an international phase IIIB/IV study with participants from 12 UK cancer centres) indicate lower rates of grade 3 or 4 treatment-emergent AEs: neutropenia, 9.8%; diarrhoea, 4.5%; and cardiac toxicity (0%), and that cabazitaxel is generally well tolerated with manageable toxicity. Seven patients (6.3%) experienced neutropenic sepsis during treatment in the UK EAP; however, none of these patients had received prophylactic granulocyte-colony stimulating factor.

In the absence of any direct head-to-head randomised controlled trials (RCTs) comparing cabazitaxel and other second-line agents for the treatment of mCRPC, a network meta-analysis (NMA) was conducted (termed as an indirect treatment comparison by the company). The NMA conducted by the company compared cabazitaxel, abiraterone, enzalutamide, mitoxantrone and BSC for the following outcomes: OS; rPFS; and selected AEs. The company only considered three studies relevant to the decision problem and these were included in the NMA. The TROPIC study compared cabazitaxel plus prednisone or prednisolone with mitoxantrone plus prednisone or prednisolone; the AFFIRM study compared enzalutamide plus placebo with placebo with or without prednisone; and the COU-AA-301 study compared abiraterone plus prednisone with prednisone plus placebo. For the purpose of this analysis, the CS noted that the three control arms from these trials were considered equivalent for the OS endpoint in the previous NICE Single Technology Appraisals (STAs) for cabazitaxel (TA255), abiraterone (TA259) and enzalutamide (TA316). The CS provided evidence to suggest that mitoxantrone does not improve survival and therefore a regimen comprising mitoxantrone plus prednisone together with BSC can be considered equivalent to BSC alone. The ERG's clinical advisors concurred with this view. As no consistent definition of PFS was employed across the pivotal trials for cabazitaxel, abiraterone and enzalutamide, the rPFS endpoint (defined as the time from randomisation to the first occurrence of: tumour progression [based on RECIST criteria] or death due to any cause) was analysed to facilitate a more coherent comparison across the three studies. Based on results from the fixed effects NMA, the CS showed that the treatment effects for cabazitaxel, abiraterone and enzalutamide are broadly similar for OS. With regards to rPFS the results of the fixed effects NMA indicate that the disease appears to progress more slowly when patients are treated with enzalutamide rather than when patients are treated with cabazitaxel or abiraterone. For AE outcomes, the fixed effect NMA indicates a significant increase in occurrences of anaemia and nausea for cabazitaxel compared with BSC, abiraterone and enzalutamide. For diarrhoea there is a statistically significantly increase in AEs for cabazitaxel compared with BSC and abiraterone.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The systematic review process followed by the company was reasonably comprehensive. Despite minor limitations in the company's search strategy, the ERG is confident that all relevant studies of cabazitaxel in combination with prednisone or prednisolone were included in the CS, including data from ongoing or planned studies. The specified inclusion and exclusion criteria were (mostly) appropriate and generally reflect the decision problem. However, studies that included radium-223 dichloride were excluded in the CS for the reasons described in Section 1.1. Nevertheless, the ERG's clinical advisors and the expert submissions indicate that radium-223 dichloride is a valid treatment option for people with symptomatic bone metastases and no known visceral metastases. Moreover, preliminary NICE guidance recommends radium-223 dichloride as an option for treating adults with hormone-relapsed prostate cancer, symptomatic bone metastases and no known visceral metastases, only if: they have had treatment with docetaxel, and the company provides radium-223 dichloride with the discount agreed in the confidential patient access scheme. The validity assessment tool used to appraise the included studies was considered appropriate by the ERG.

The CS includes the only RCT of cabazitaxel plus prednisone or prednisolone which is known to have been undertaken in the relevant population. This study, the TROPIC study, is an open-label study and is therefore susceptible to bias. In the guidance issued by NICE for cabazitaxel in 2011 (TA255) the Appraisal Committee accepted that, 'as an open-label study, TROPIC was susceptible to bias in the subjective outcomes included in progression-free survival, such as pain and deterioration in symptoms'. In addition, the assessment of clinical AEs is susceptible to bias because of lack of blinding, although the assessment of laboratory AEs is unlikely to have been affected. In the TROPIC trial, cabazitaxel was associated with higher rates of neutropenic complications (febrile neutropenia and infection), renal failure, and cardiac toxicity compared with mitoxantrone, however, after consideration of additional evidence (provided by the company during the consultation process) for TA255, the Appraisal Committee concluded that '…there is no evidence of additional risk other than that included in the SPC [Summary of Product Characteristics]'. Moreover, as noted earlier, additional safety data from post-docetaxel patients with mCRPC treated with cabazitaxel in the UK EAP suggest that cabazitaxel is generally well tolerated with manageable toxicity.

In the company's NMA, the ERG considered that the results presented may have underestimated the uncertainty in treatment effects since fixed effects models were used, despite clear evidence of heterogeneity amongst the trials included in the network. Results from an amended random effects model, conducted by the ERG, confirm the finding of broadly similar treatment effects for OS but also indicate that no active treatments are significantly more effective than other active treatments for rPFS. Furthermore, given the use of HRs, the relative treatment effects are assumed to be constant over time, with no justification for this assumption. The ERG consider that the NMA results presented

by the company should be interpreted with caution since they were based on an assumption of no between-study variance (using a fixed effects model) and because of concerns related to differences in patient populations between the trials and in the assumption that control treatments are exchangeable.

1.4 Summary of cost effectiveness submitted evidence by the company

The manufacturer supplied a *de novo* cohort Markov model constructed in Microsoft Excel©. Three states are modelled: stable disease; progressive disease; and death. All patients begin in the stable disease state, from which transitions to progressive disease or death are possible. Following progression the only transition possible is to death, which is an absorbing state.

The main comparison considered by the company was between cabazitaxel and mitoxantrone. Effectiveness data for the main comparison came from the subgroup of the TROPIC trial, as described in Section 1.2. In scenario analyses the manufacturer compared cabazitaxel with abiraterone and separately with enzalutamide. As there were no trials comparing cabazitaxel with abiraterone or enzalutamide, effectiveness data for the two scenario analyses was taken from an NMA performed by the company, which used the entire trial populations. Health-related quality of life was incorporated by attaching utility values to each of the health states; evidence from these was taken from the company's UK EAP. Evidence on resource use came from the TROPIC trial, supplemented by both expert clinical opinion and a UK clinical audit. Unit costs came from standard national sources. List prices were used for mitoxantrone, abiraterone and enzalutamide as directed by NICE, although commercial in confidence PASs are in place for abiraterone and enzalutamide.

In their base-case analysis the company estimated a probabilistic cost per QALY gained of £50,682 when comparing cabazitaxel with mitoxantrone. Based on scenario analyses, use of cabazitaxel was estimated to be both cheaper and more effective than use of abiraterone. Compared with enzalutamide, cabazitaxel was estimated to be cheaper but less effective, resulting in an ICER of £212,038 for enzalutamide compared with cabazitaxel.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG notes that the company did not consider radium-223 dichloride as a comparator despite its inclusion in the NICE final scope. However, for people with mCRPC, symptomatic bone metastases and no known visceral metastases, radium-223 dichloride is a valid treatment option. Hence excluding it leads to uncertainty regarding the cost-effectiveness of cabazitaxel. The comparison between cabazitaxel and mitoxantrone is relevant when either abiraterone or enzalutamide are used in the pre-chemotherapy setting (as neither would then be a comparator for cabazitaxel). The ERG notes that for the alternative setting of using either abiraterone or enzalutamide post-chemotherapy the company did not perform a fully incremental analysis: such an analysis should also include BSC. Radium-223

dichloride is a valid comparator (for the indicated sub-group) in both settings. The ERG notes that due to these omissions there is uncertainty in the cost effectiveness of cabazitaxel in both settings, and that it is unclear which setting represents standard National Health Service practice.

The ERG agrees with the company that the results of the NMA (and hence the cost-effectiveness results when cabazitaxel is compared with enzalutamide or abiraterone) should be viewed with caution.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The company undertook a reasonably comprehensive systematic review (no major limitations were noted) of cabazitaxel (in combination with prednisone or prednisolone) in patients with mCRPC previously treated with a docetaxel-containing regimen. The TROPIC study was a large, multicentre RCT of reasonable methodological quality (with some limitations, as noted in Section 1.3) that measured a range of clinically relevant outcomes.

The conceptual model used appears robust and transparent and contained the functionality to assess the impact of changing parameters and structural uncertainties on the ICER. A number of built-in alternative scenarios were included.

1.6.2 Weaknesses and areas of uncertainty

The key area of uncertainty in the clinical evidence concerned the absence of any head-to-head RCTs comparing cabazitaxel with other second-line agents such as abiraterone or enzalutamide for the treatment of mCRPC post docetaxel. In addition, there is no high quality evidence from prospective controlled trials to guide optimum sequencing of these agents after docetaxel treatment in patients with mCRPC and there is uncertainty over the optimal dose and frequency of cabazitaxel administration in men with mCRPC. Results from the PROSELICA trial (a study examining the dosage of cabazitaxel [either 25 or 20 mg/m^2] to optimise treatment benefits in relation to potential toxicity) are expected to be reported within the next 12 months.

Indirect comparisons between the treatments are subject to increased uncertainty due to concerns over differences between patient populations and exchangeability of control treatments. Results of the fixed effects NMA conducted by the company are likely to underestimate the uncertainty in treatment effects. Furthermore, the relative treatment effects are assumed to be constant over time, with no justification for this assumption.

Within the CS the clinical effectiveness of radium-223 dichloride and its cost effectiveness when compared with cabazitaxel were not formally considered. As radium-223 dichloride is a comparator for the subgroup of people with bone metastasis and no known visceral metastases, this exclusion leads to uncertainty regarding the cost-effectiveness of cabazitaxel.

Cost-effectiveness results were sensitive to the utility values that should be assigned to progressive disease, and to the choice of parametric model used for extrapolating the clinical effectiveness data. It is unclear how resolving these uncertainties would impact on the cost-effectiveness of cabazitaxel.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The probabilistic base-case ICER presented in the CS comparing cabazitaxel with mitoxantrone was £50,682. The ERG made six changes to the company's base case. These were: the use of Electronic market information tool prices in preference to British National Formulary prices for generic drug costs (including mitoxantrone); modelling vial wastage; not modelling discontinuation for reasons other than disease progression; not modelling a reduced disutility in the last three months of progressive disease; basing post-second line treatment resource use from a UK audit for all treatments; and using results from the NMA adjusted by the ERG. When taken in isolation each of these changes led to an increase in the ICER, with the largest increase attributable to the modelling of vial wastage. The combined effect of these changes was to increase the probabilistic ICER from £50,682 to [redacted]. If vial wastage is not modelled then the probabilistic ICER is £54,126.

The ERG also performed exploratory analyses regarding the long-term modelling of effectiveness data and using different utility values for progressive disease. It was noted that these uncertainties led to both increases and decreases in the base-case ICER depending on the assumptions made.

The ERG used the results from the NMA adjusted by the ERG to assess the cost-effectiveness of cabazitaxel when compared to BSC, abiraterone and enzalutamide. The ICER comparing enzalutamide with cabazitaxel was £141,363 when vial wastage was modelled and £155,014 when it was not modelled. Clinical advice given to the ERG suggests that vial wastage would be likely. Abiraterone was extendedly dominated by enzalutamide irrespective of how vial wastage was modelled. The ICER comparing cabazitaxel with BSC was £109,325 when vial wastage was modelled and £88,766 when it was not modelled: this was greater than estimated from the direct comparison with mitoxantrone and may indicate the inappropriateness of assuming proportional hazards. Analyses using the PAS-adjusted prices of abiraterone and enzalutamide, along with sensitivity analyses, are provided in a confidential appendix prepared for the Appraisal Committee only.

The ERG noted that, whilst it was not possible to include radium-223 dichloride in the cost-effectiveness analyses within the timelines of an STA, this comparator appeared to have similar clinical efficacy to cabazitaxel. [redacted]. A comparison with the PAS price of radium-223 dichloride is provided in a confidential appendix.

2 BACKGROUND

This report provides a review of the evidence submitted by the company for cabazitaxel for hormone-relapsed metastatic prostate cancer previously treated with a docetaxel-containing regimen. Cabazitaxel is licensed within the EU for use in combination with prednisone or prednisolone for the treatment of patients with metastatic hormone-refractory prostate cancer (mHRPC) previously treated with a docetaxel-containing regimen.[1]

Cabazitaxel was previously appraised as part of the NICE Single Technology Appraisal (STA) process (TA255), with the final appraisal determination issued in January 2012.[2] The Committee considered that the most plausible ICER was likely to be above £87,500 per quality-adjusted life years (QALYs) gained, and so did not recommend treatment with cabazitaxel. The Committee noted that key uncertainties related to the company's modelling of clinical effectiveness data and the utility values used. Cabazitaxel was available via the National Cancer Drugs Fund (CDF) until its removal in January 2015. It was later re-instated on the CDF in May 2015.

2.1 Critique of the company's description of underlying health problem

The company's submission (CS[3]) provides an appropriate overview of prostate cancer noting that prostate cancer can be heterogeneous with regards to both treatment response and the types of disease progression observed. Prostate cancer is the most common form of cancer in men in the UK, and the second most common cause of cancer death. There were 41,736 incident cases, and 10,837 deaths from prostate cancer in the UK in 2012, the most recent year for which data are available.[4]

For metastatic prostate cancer (cancer that has spread to other parts of the body), there is a distinction between mHRPC and metastatic castrate resistant prostate cancer (mCRPC).[5] Tumours that progress with castrate levels of testosterone (typically taken to be lower than 50 ng per deciliter[6]) are classified as mCRPC; tumours that progress after conventional luteinising hormone-releasing hormone (LHRH) and newer hormone therapies such as abiraterone and enzalutamide are classified as mHRPC. First line therapy is typically androgen deprivation therapy or LHRH with patients with mCRPC more likely to respond to further hormonal therapies than people with mHRPC.[5] As the advanced hormonal therapies abiraterone and enzalutamide were not available at the time of the company's original submission, the terminology used for TA255 was people with mHRPC. As terminology has subsequently evolved, for the purposes of this report, the ERG shall refer to the population of interest as people with mCRPC.

There are no published data for the incidence of mCRPC. However, a report from the National Cancer Intelligence Network[7] reveals that of the 36,287 diagnoses in England in 2013, 5836 (16%) were classified as Stage 4 (or metastatic) cancers, with a further 6661 diagnoses (18%) having an unknown

stage. As mCRPC represents a sub-group of stage 4 cancers, the incidence of mCRPC will be less than 12,497 (if all of the unknown stages were stage 4). Both clinical advisors to the ERG and the company noted that a large proportion of prostate cancer deaths will be amongst people with mCRPC – in England there were 9133 deaths attributable to prostate cancer in 2012.[4]

The company estimates that there are 6,147 people with mCRPC, a value that appears plausible given the calculations previously detailed. The company further estimate that, of people with mCRPC, 50% would receive first-line treatment with docetaxel, and of this group, and further 55% (therefore 27.5% of the mCRPC group) would be eligible to receive second-line chemotherapy. These two proportions are based on market research performed by the company, and result in an estimated 3073 people receiving docetaxel of whom 1690 people who would be eligible for cabazitaxel. In comparison, data from the CDF reveal that there were 805 notifications for cabazitaxel in 2014/15[8], whilst data from the Systemic Anti-Cancer Therapy Dataset for the calendar year 2014 record that (excluding clinical trials) 1,920 people received docetaxel and 551 people received cabazitaxel.[9]

The company considered life expectancy for people with mCRPC for both people receiving first line docetaxel and for people receiving post-docetaxel treatment. In the former case, the company cite a systematic review which calculated a median overall survival (OS) of 19 months (inter-quartile range: 17 to 20 months) based on 11 trials.[10] In the post-docetaxel setting, control-arm data from the pivotal trials for cabazitaxel, abiraterone, enzalutamide and radium-223 dichloride showed that median OS ranged from 11.2 months to 13.6 months.[11, 12,13, 14]

2.2 Critique of the company's overview of current service provision

A description of the company's overview of current service provision is provided below, followed by the ERG's critique of this overview.

For people with mCRPC, the company detailed two possible clinical care pathways under which patients may be eligible for cabazitaxel in England. These two pathways are re-produced from the CS in

Figure 1. The key difference between the two pathways is where abiraterone or enzalutamide is used: either in the pre- chemotherapy setting (left-hand side of

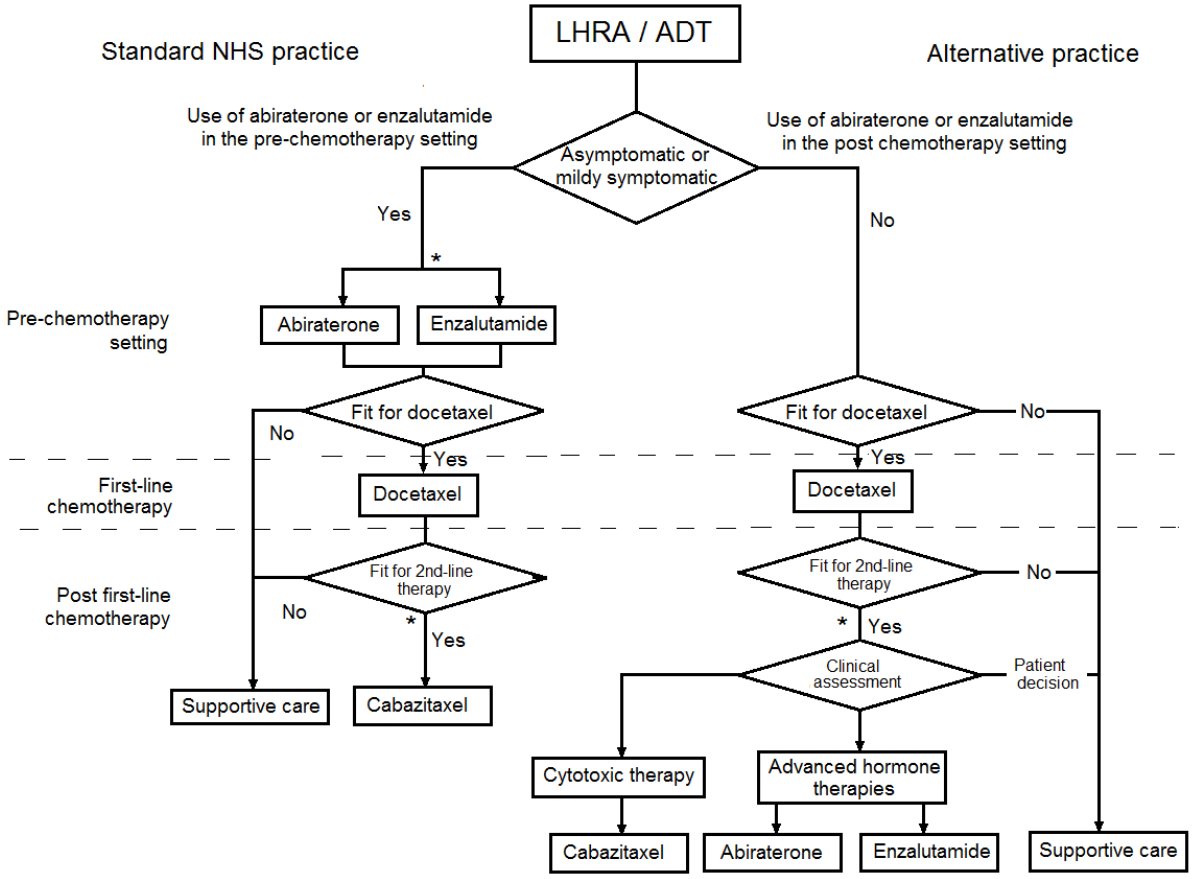
Figure 1) or post- chemotherapy (right-hand side). In both instances the chemotherapy was assumed to be docetaxel. At the time of the CS, use of either abiraterone or enzalutamide in the pre-chemotherapy setting was not approved by the National Institute for Health and Care Excellence (NICE), and was instead funded by the CDF. The two advanced hormonal therapies both had however, NICE approval in the post-chemotherapy setting. The company noted that sequential use of abiraterone and enzalutamide is not allowed in the CDF, and that due to concerns about cross-resistance only one of the two therapies is likely to be used in clinical practice.

Cabazitaxel is licensed only following the use of a docetaxel containing regimen. In the pathway where abiraterone and enzalutamide are used in the pre-chemotherapy setting this would mean that only best supportive care (BSC) is an alternative treatment option to cabazitaxel. Where abiraterone and enzalutamide are used in the post-chemotherapy setting these interventions are also comparators in addition to BSC.

The company denote the use of abiraterone or enzalutamide in the pre-chemotherapy as standard (established) National Health Service (NHS) practice. In response to clarification question A2, the company justified this definition of standard NHS practice based on market research undertaken on behalf of Sanofi by Kantar Health. The most recent figures from this market research were for the time period 26th June 2015 to 4th August 2015. There were 345 people with mCRPC receiving 1st line therapy. Abiraterone and enzalutamide together accounted for 66% of these therapies, with docetaxel comprising 31%.

For the purposes of their submission, the company assumed that use of mitoxantrone was equivalent to BSC. In the previous submission to the NICE for cabazitaxel (TA255), this assumption was deemed by the ERG to have clinical validity as mitoxantrone does not provide a proven extension to life for people with mCRPC.[15] For this submission, based on the advice provided by the clinical advisors to the ERG, the ERG believes this assumption to be reasonable.

Figure 1: Clinical pathways of care for mCRPC (reproduced from Figure 3, p40, CS)[a]



[a] The CS does not provide a footnote for '*' in the figure

The ERG is satisfied with the company's argument that sequential use of abiraterone and enzalutamide would not occur in clinical practice. However, there are a number of concerns with the company's description of existing NHS care pathways. These concerns are described below.

Is use of abiraterone and enzalutamide in the pre-chemotherapy setting standard NHS practice?

The company use the results of market research, which shows that 66% of patients receive either abiraterone or enzalutamide in the pre-chemotherapy setting, to justify denoting this as standard NHS practice. However, the ERG does not believe that this evidence represents suitable justification for the purposes of this appraisal.

This appraisal is concerned with potential clinical pathways that include the use of cabazitaxel. The market research provided by the company does not include evidence about the number of people treated with first-line abiraterone or enzalutamide who are also eligible to receive docetaxel and then cabazitaxel. In other words, an unknown proportion of the people receiving first line therapy with

abiraterone or enzalutamide will be receiving these because they are unsuitable for chemotherapeutic treatment.

The ERG also notes that there are ongoing NICE appraisals of both abiraterone and enzalutamide in the pre-docetaxel setting. The results of these appraisals may influence which of the two pathways described in the CS becomes NHS standard practice in the future.

Would patients be treated with cabazitaxel before they are treated with abiraterone or enzalutamide?
When abiraterone or enzalutamide are used in the post-chemotherapy setting, the company suggests that these are potential treatment alternatives to cabazitaxel. However, clinical advisors to the ERG, along with the expert submission submitted by Dr Andrew Goddard on behalf of the NCRI/RCP/RCR/ACP suggested that, for the majority of patients, cabazitaxel would only be considered following treatment with one of the advanced hormonal therapies.[16] This view is also supported by the recommendations of the St Gallen Advanced Prostate Cancer Consensus Conference.[17]

However, the ERG also acknowledges that whilst use of either advanced hormonal therapy may result in fewer side effects (and so be preferred to cabazitaxel), there is uncertainty with regards to whether abiraterone and enzalutamide are more clinically effective and more cost-effective than cabazitaxel. These considerations of effectiveness and cost-effectiveness are discussed further in sections 4.3 and 5.2 respectively.

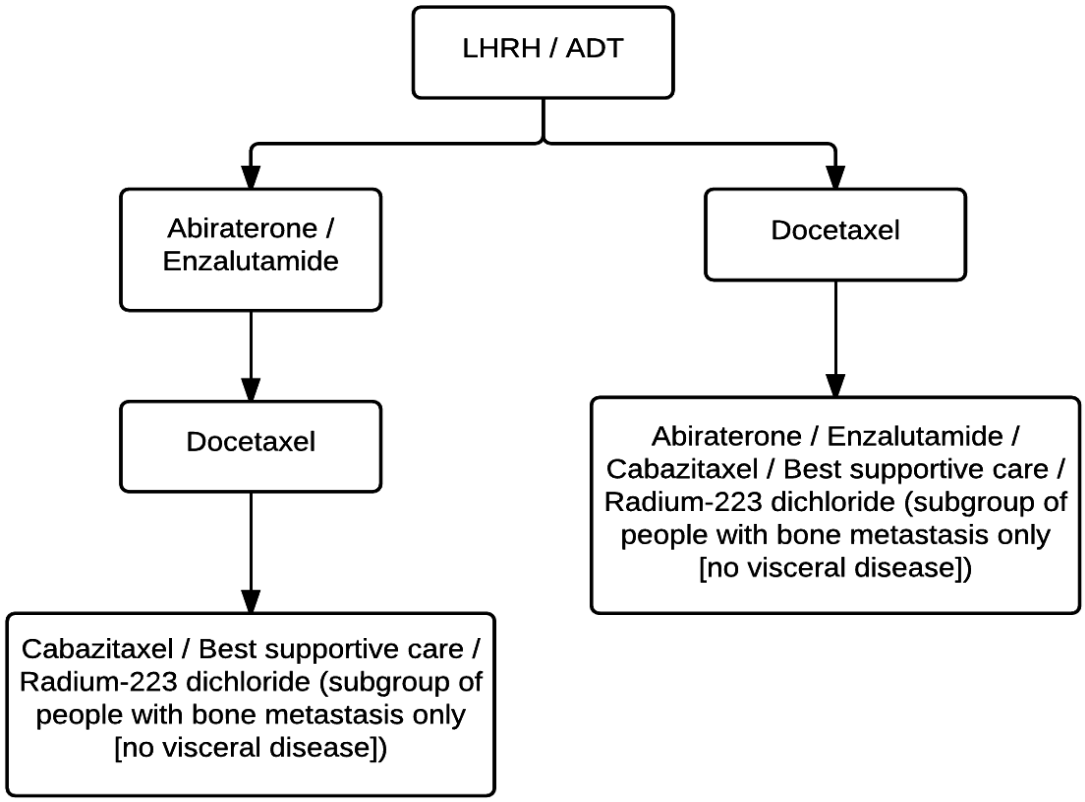
What is the role of radium-223 dichloride?
The company did not include radium-223 dichloride in their clinical pathways of care, nor did it include it in their economic evaluation. However, radium-223 dichloride was included in the final scope issued by NICE as a comparator. Radium-223 dichloride has European Union approval for people with mCRPC with symptomatic bone metastases and no known visceral metastases. An analysis for this subgroup was also included in the final scope, conditional on the available evidence. Clinical advisors to the ERG, along with the expert submission submitted by Dr Andrew Goddard on behalf of the NCRI/RCP/RCR/ACP suggested that radium-223 dichloride is a valid treatment option for people with mCRPC who had previously received docetaxel.[16]

In response to clarification question A1, the company defended their decision to exclude radium-223 dichloride on the basis that there was not sufficient evidence to perform a comparison. This is discussed in further detail in Section 3.3. However, irrespective of whether or not there is available evidence to conduct a meaningful comparison with radium-223 dichloride, this technology represents

a valid treatment option for people with mCRPC, and should have been included in the company's overview of current service provision.

Given the above considerations, an alternative overview of current clinical care pathways provided by clinical input is depicted in Figure 2. The ERG believes that there is insufficient available evidence to denote which use of the advanced hormonal agents (either pre-chemotherapy or post-chemotherapy) represents standard NHS practice. Further, whilst cabazitaxel is likely to be currently used after either of abiraterone or enzalutamide (in the post-chemotherapy setting) due to its worse side-effect profile, the clinical effectiveness and cost-effectiveness of this pathway need to be established.

Figure 2: Simplified clinical pathway of care illustrating the comparators for cabazitaxel



ADT: androgen deprivation therapy. LHRH: Luteinising hormone-releasing hormone

It is noted that treatment for mCRPC is an area of active research, and so the current clinical pathways may change in the future. For example, clinical advisors to the ERG noted that results from the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial had been presented at a recent conference, with results suggesting that use of docetaxel (in addition to current standards of care) should become routine amongst men with newly-diagnosed metastatic prostate cancer.[18]

3 CRITIQUE OF THE COMPANY'S DEFINITION OF DECISION PROBLEM

Table 1 summarises the population, intervention, comparators and outcomes specified within the company's decision problem. These are discussed and critiqued in the following sections.

Table 1: The company's decision problem (based on Table 5, p23-26, CS)

	Final scope issued by NICE	Decision problem addressed in the CS	ERG comments
Population	People with hormone-relapsed metastatic prostate cancer previously treated with a docetaxel-containing regimen.	People with hormone refractory relapsed metastatic prostate cancer previously treated with a docetaxel-containing regimen with or without prior treatment with abiraterone or enzalutamide.	The company included additional wording to emphasise that cabazitaxel has two different sets of comparators, depending on where in the clinical pathway of care abiraterone or enzalutamide are used. This is discussed further in Section 2.2 of the ERG report. There is also a potential difference between people with hormone refractory and castrate resistant prostate cancer, as discussed in Section 2.1 of the ERG report.
Intervention	Cabazitaxel in combination with prednisone or prednisolone	Cabazitaxel in combination with prednisolone (or prednisone) 10 mg/day up to a maximum of ten cycles	In the TROPIC trial[11], which provides evidence on the effectiveness of cabazitaxel, cabazitaxel was limited to a maximum of ten cycles, for consistency with mitoxantrone. However, the licence for cabazitaxel does not restrict its use in clinical practice.
Comparators	• Abiraterone in combination with prednisone or prednisolone • Enzalutamide • Mitoxantrone in combination with	Best supportive care represented by mitoxantrone. Abiraterone and enzalutamide in	The company assumes that use of mitoxantrone may be considered as equivalent to best supportive care. The ERG believes that this claim has clinical validity.

	prednisolone (not licensed in the UK for this indication) • Best supportive care (this may include radiotherapy, radiopharmaceuticals [apart from radium-223 dichloride], analgesics, bisphosphonates, and corticosteroids) For people with bone metastasis only (no visceral metastasis) • Radium-223 dichloride (NICE guidance is in development, funded by the CDF in the interim)	the context where these agents were not used prior to docetaxel. This was deemed alternative practice in the NHS.	The company notes that abiraterone and enzalutamide are only valid when they are used in the post-chemotherapy setting. However, the ERG does not believe that there is sufficient evidence to justify labelling this as 'alternative practice'. The company did not consider radium-223 dichloride as a comparator for its indicated sub-group. This was primarily justified by a lack of comparative evidence. This is discussed further in Section 3.3 of the ERG report.
Outcomes	The outcome measures to be considered include: • Overall survival (OS) • Progression-free survival (PFS) • Response rate • Adverse effects of treatment • Health-related quality of life.	• Primary outcome: OS • Secondary outcomes: o PFS o Radiographic PFS (rPFS) o Adverse effects of treatment o Health-related quality of life o Response rate.	No comments
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.	As the final scope issued by NICE. The availability of a Patient Access Scheme (PAS) for cabazitaxel was included in the analysis.	The ERG provides analyses based on the PAS prices for abiraterone and enzalutamide in a confidential appendix. The ERG provides exploratory analyses comparing

	The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.	The scenario analysis including abiraterone and enzalutamide were based on NHS list prices, as requested by NICE, as the PAS arrangements are confidential.	cabazitaxel with radium-223 dichloride (at list price) in this report, and compared with radium-223 dichloride (at a PAS price in a confidential appendix).
Other considerations	If evidence allows the following subgroups will be considered. • People who have received abiraterone or enzalutamide • People with bone metastasis only (no visceral metastasis).	The subgroup of people who have received abiraterone or enzalutamide was considered by the company. The subgroup of people with bone metastasis only (no visceral metastasis) was not considered by the company.	For the subgroup of people with bone metastasis only (no visceral metastasis) one of the relevant comparators is radium-223 dichloride. The exclusion of this comparator is discussed further in Section 3.3 of the ERG report. Exploratory analyses consider the cost-effectiveness of cabazitaxel compared with radium-223 dichloride.

3.1 Population

The patient population described in the final scope[19] is "People with hormone-relapsed metastatic prostate cancer previously treated with a docetaxel-containing regimen". The main source of clinical evidence used by the company is the TROPIC trial.[11] A sub-population of this trial is considered in the CS with people who received an insufficient prior dose of docetaxel (less than 225mg/m^2) or who had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 were excluded. These exclusions were justified by the company on the basis that the sub-population better reflects patients who are likely to be treated in clinical practice. The ERG believes that this is an appropriate population, although it is noted that data from the company's UK Early Access Programme (EAP) indicate that a small proportion of people who receive cabazitaxel had a PS of 2 (7/112; 6.3%).

3.2 Intervention

The intervention under consideration in the CS is cabazitaxel, which matches the intervention described in the final scope. Cabazitaxel is licensed within the EU for use in combination with prednisone or prednisolone for the treatment of patients with mHRPC previously treated with a docetaxel-containing regimen.[20]

It is marketed in the UK by Sanofi under the trade name Jevtana® and supplied as a pack containing one 1.5 ml vial of liquid cabazitaxel concentrate (60mg of cabazitaxel diluted in polysorbate 80 and citric acid), and one vial containing 4.5 ml of solvent. Dosing is by body surface area (BSA); the recommended dose is 25 mg/m^2, and some patients may require more than one pack per cycle of treatment. Unopened vials of cabazitaxel have a shelf-life of two years but, after opening, the concentrate and solvent should be used immediately.

Cabazitaxel is administered as a 60-minute intravenous infusion every three weeks. Patients should be observed closely for infusion-related hypersensitivity reactions, especially during the first and second infusions. Dose modifications should be made if patients experience specified adverse reactions, and treatment should be discontinued if the patient continues to experience any of those reactions at a dose of 20 mg/m^2 (for details, see

Table 2).

Table 2: Recommended dose modifications for adverse reactions in patients treated with cabazitaxel[20]

Adverse reaction	Dose modification
Prolonged (longer than 1 week) grade ≥3 neutropenia despite appropriate treatment including Granulocyte-Colony Stimulating Factors	Delay treatment until neutrophil count is >1,500 cells/mm^3, then reduce cabazitaxel dose from 25 mg/m^2 to 20 mg/m^2
Febrile neutropenia or neutropenic infection	Delay treatment until improvement or resolution, and until neutrophil count is >1,500 cells/mm^3, then reduce cabazitaxel dose from 25 mg/m^2 to 20 mg/m^2
Grade ≥3 diarrhoea or persisting diarrhoea despite appropriate treatment, including fluid and electrolytes replacement	Delay treatment until improvement or resolution, then reduce cabazitaxel dose from 25 mg/m^2 to 20 mg/m^2
Grade ≥2 peripheral neuropathy	Delay treatment until improvement, then reduce cabazitaxel dose from 25 mg/m^2 to 20 mg/m^2

To minimise the risk and severity of infusion-related hypersensitivity reactions, the following premedication regimen should be administered at least 30 minutes prior to each dose of cabazitaxel:

- antihistamine (dexchlorpheniramine 5 mg or diphenhydramine 25 mg or equivalent)
- corticosteroid (dexamethasone 8 mg or equivalent)
- H_2 antagonist (ranitidine or equivalent).

To minimise the risk of neutropenia and its complications, complete blood counts should be monitored on a weekly basis during the first cycle of cabazitaxel, and before each subsequent cycle, so that if necessary the dose can be adjusted.

Anti-emetic prophylaxis is recommended and can be given orally or intravenously as needed. Primary prophylaxis with Granulocyte-Colony Stimulating Factors (G-CSF) should be considered in patients with clinical features which put them at high risk of increased complications from prolonged neutropenia (these include being older than 65 years, poor PS, previous episodes of febrile neutropenia, extensive prior radiation ports, poor nutritional status, or other serious comorbidities).

Cabazitaxel should not be given to patients with hepatic impairment. Patients with moderate or severe renal impairment or end stage renal disease should be treated with caution and monitored carefully

during treatment. Co-administration with strong CYP3A inhibitors or strong CYP3A inducers should be avoided.

Oral prednisone or prednisolone, at a dose of 10 mg/day, should be taken throughout the course of treatment with cabazitaxel. Prednisone is a synthetic corticosteroid which is converted in the liver into the corticosteroid prednisolone. In the UK, prednisone is only licensed for use in moderate to severe rheumatoid arthritis, whereas prednisolone is licensed for use in a range of conditions. Patients who are medically castrated may also require ongoing therapy with LHRH agonists.

The licensed indication states that the use of cabazitaxel should be limited to units specialised in the administration of cytotoxic drugs, and that it should only be administered under the supervision of a qualified physician experienced in the use of anti-cancer chemotherapy and with facilities and equipment available to treat serious hypersensitivity reactions.

3.3 Comparators

The NICE final scope[19] listed five comparators for cabazitaxel in combination with prednisone or prednisolone. These were:

- Abiraterone in combination with prednisone or prednisolone
- Enzalutamide
- Mitoxantrone in combination with prednisolone
- Best supportive care (this may include radiotherapy, radiopharmaceuticals [apart from radium-223 dichloride], analgesics, bisphosphonates, and corticosteroids)
- Radium-223 dichloride for people with bone metastasis only (no visceral metastasis)

Of these comparators, mitoxantrone is not licensed in the UK for this indication, whilst NICE guidance is in development for radium-223 dichloride.

Within their submission the company argued that mitoxantrone could be considered equivalent to BSC, as there is no available evidence that it has any additional impact on survival. The ERG's clinical advisors concurred with this view.

The company did not consider radium-223 dichloride to be a valid comparator, and hence excluded it from their economic evaluation (nor did they discuss its clinical effectiveness). In response to clarification question A1, the company defended their decision to exclude radium-223 dichloride on the basis that there was not sufficient evidence to perform a comparison. The reasons provided by the

company for not being able to compare the pivotal trials for cabazitaxel and radium-223 dichloride (TROPIC[11] and ALSYMPCA[14], respectively) were:

- The two trials considered different patient populations: of the 755 people in the TROPIC trial 16% did not have bone-metastases, 25% had visceral metastases and 11% had liver metastases, for which radium-223 dichloride is contraindicated (these numbers are not mutually exclusive).
- It was not possible to derive a measure of progression-free survival from the ALSYMPCA trial that was consistent with the measures used in the pivotal trials for abiraterone and enzalutamide.

However, the ERG notes that these limitations would not have stopped the company performing a separate comparison between cabazitaxel and radium-223 dichloride, using data from the relevant sub-group of the TROPIC randomised controlled trial (RCT). In response to clarification question A1, the company did provide summary statistics from the ALSYMPCA trial for OS in the cohort of patients with previous docetaxel use. The potential impact of including radium-223 dichloride in the economic evaluation is discussed in Section 6.

3.4 Outcomes

The outcomes considered in the CS match those described in the final scope. The outcomes are discussed in turn.

- *Overall survival (OS)*

OS is taken as the primary outcome measure. The pivotal trials for cabazitaxel[11], abiraterone[12], enzalutamide[13] and radium-223 dichloride[14] all defined OS as the time from the date of randomisation to death from any cause. Data on OS were censored at the last date the patient was known to be alive, or at the data cut-off date, whichever was earlier.

- *Progression-free survival (PFS)*

There was no standard definition of PFS employed across the pivotal trials for cabazitaxel, abiraterone and enzalutamide. Within the TROPIC study[11] PFS was defined as the time from randomisation to the first occurrence of: tumour progression (based on Response Evaluation Criteria in Solid Tumours (RECIST) criteria); prostate specific antigen (PSA) progression; pain progression; or death due to any cause. Median time to progression using this definition was 1.4 months for mitoxantrone and 2.8 months for cabazitaxel. Treatment was discontinued following the identification of disease progression.

To allow for inclusion in a network meta-analysis (NMA) (also termed an indirect treatment comparison (ITC) by the company), an alternative definition of PFS, radiographic PFS (rPFS) was used. This was defined as the time from randomisation to the first occurrence of: tumour progression (based on RECIST criteria) or death due to any cause. Median time to progression using this definition was 5.9 months for mitoxantrone and 8.8 months for cabazitaxel.

Progression-free survival was not measured in the radium-223 dichloride study.[14] However, time to PSA progression was measured. Both the abiraterone and enzalutamide trials[12, 13] defined progression-free survival as the time from randomisation to the first occurrence of: tumour progression (based on RECIST criteria), bone scans showing two or more new lesions not consistent with tumour flare, or death.

- *Tumour response rate (assessed only in patients with measurable disease at baseline)*

Tumour response rate was only assessed in patients with measurable disease at baseline, and based on RECIST criteria.[21] These criteria define measurable disease as the presence of at least one lesion which can be accurately measured and whose longest dimension is $\geq$20 mm using conventional techniques or $\geq$10 mm using spiral CT scan. The RECIST criteria define tumour responses as follows:

  - Complete response: disappearance of all target lesions
  - Partial response : decrease of at least 30% in the sum of the longest diameter of target lesions
  - Progressive disease: increase of at least 20% in the sum of the longest diameter of target lesions
  - Stable disease: neither sufficient decrease to qualify as partial response nor sufficient increase to qualify as progressive disease.

- *Health-related quality of life (HRQoL)*

The TROPIC study did not collect data relating to HRQoL. For this outcome, the CS therefore utilised interim UK results from the EAP for cabazitaxel, a global study which includes nine active sites in the UK. In the UK sites only, Euro-QoL 5 Dimension (EQ-5D) questionnaires were administered to all patients at baseline, cycle 2, cycle 4, cycle 6, cycle 8, cycle 10, and 30 days after withdrawal from or completion of treatment; utility was also assessed using a visual analogue scale. Utility data from the EAP are limited by not being comparative (utility values for patients receiving mitoxantrone or BSC are not collected), and by not being blinded, which may cause some bias due the subjective nature of the EQ-5D questionnaire.

HRQoL values for abiraterone and enzalutamide were collected in their respective pivotal trials, using the Functional Assessment of Cancer Therapy – Prostate (FACT-P) tool. These were not considered

in the CS, as they contend that EQ-5D data from the EAP are of greater relevance. The radium-223 dichloride trial collected EQ-5D data; however details on this are not available in the public domain. In the AFFIRM study comparing enzalutamide with placebo, EQ-5D data were collected at some sites but only for a limited number of patients.[22] In the STA submission for enzalutamide EQ-5D data were used; in the abiraterone submission FACT-P data were mapped to EQ-5D However, these data were commonly redacted.

- *Adverse effects of treatment*

Adverse events (AEs) in TROPIC were recorded in patients who had received at least one dose of study drug. Grading of AEs was based on National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. These criteria classify severe AEs as grade 3, life-threatening or disabling AEs as grade 4, while grade 5 is used for deaths related to AEs.[23] If patients experienced multiple AEs within a treatment cycle then the worst (highest) NCI grade was used.

Rates of AEs may be based on either laboratory test results or be investigator reported. The former are reported in the key publication for TROPIC[11] with both being reported in the CS.

3.5 Other relevant factors

Cabazitaxel, abiraterone, enzalutamide and radium-223 dichloride are all subject to confidential Patient Access Schemes (PASs). In addition, abiraterone and enzalutamide are subject to ongoing NICE appraisals, which may affect their PASs. Mitoxantrone is available as a generic drug, and so is not subject to a PAS.

Within their submission, the company argued that cabazitaxel fulfilled the NICE criteria for a life-extending, end-of-life treatment. These NICE criteria are that:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional three months, compared to current NHS treatment, and;
- The treatment is licensed or otherwise indicated, for small patient populations.

The company's justification for why they believe that cabazitaxel fulfils these criteria, along with the ERG's critique of this, are described in Section 7.

In the CS (section 3.8, p50-51) it was noted that the prevalence of prostate cancer varied with ethnicity, with an estimated 29% of black men being diagnosed with prostate cancer during their

lifetime compared to 13.3% for white men and 7.9% for Asian men. The company further noted that black men are more likely to die from prostate cancer.

4 CLINICAL EFFECTIVENESS

This chapter presents a review of evidence relating to the clinical effectiveness of cabazitaxel in combination with prednisone or prednisolone for the treatment of patients with mCRPC previously treated with a docetaxel-containing regimen. Section 4.1 presents a critique of the company's systematic review and Section 4.2 provides a summary of the clinical effectiveness results (efficacy and safety) and critique of included cabazitaxel trials. Sections 4.3 and 4.4 provide a critique of the trials within the NMA and of the NMA respectively. Section 4.5 presents additional work on clinical effectiveness undertaken by the ERG. Finally, Section 4.6 provides the conclusions of the clinical effectiveness section.

4.1 Critique of the methods of review(s)

As part of the original submission, which informed TA255 for cabazitaxel in 2011,[15] the company performed three systematic searches with the following aims and objectives (which also apply to the current submission):

1. To identify all studies of cabazitaxel versus any comparator, in order to identify the complete evidence base for cabazitaxel.
2. To identify all RCTs in the second-line treatment of patients with mCRPC which had progressed after first-line docetaxel, in order to identify any RCT evidence that would allow indirect comparisons with the comparators specified in the NICE final scope[19] which had not been directly compared with cabazitaxel.
3. To identify all non-randomised studies of second-line therapy in patients with mCRPC which had progressed after first-line docetaxel, in order to identify any non-randomised evidence for cabazitaxel or its comparators which might potentially be relevant to the decision problem.

All searches were initially undertaken between September to November 2010 (as part of the original submission which informed TA255)[15] with updated searches undertaken in February 2015.

For the current submission, the company adopted a slightly different approach to that of the original submission in that two broad clinical effectiveness searches were undertaken to identify all RCT and non-RCT evidence on the use of cabazitaxel or its comparators in the context of mCRPC previously treated with docetaxel instead of separate searches for each of the reviews. However, the presentation of these sections in the CS is made somewhat confusing due to extensive cross-referencing between the main document and appendices.

In brief, for the original search of cabazitaxel versus any comparator and for RCTs of second-line therapy in mCRPC, several electronic bibliographic databases (including MEDLINE, MEDLINE in

Process, EMBASE, and the Cochrane Library) and research registers (ClinicalTrials.gov and the International Clinical Trials Platform) were searched covering the period from January 2000 to August/September 2010. Supplementary searches such as scanning of bibliographies of included studies, clinical study reports, regulatory agency websites and various conference proceedings were also undertaken. For the update searches, similar sources appear to have been searched and covered the period from January 2010 to February 2015. However, it is unclear why the Health Technology Assessment database and the Cochrane Database of Systematic reviews and the Database of Abstracts of Reviews of Effects, which forms part of the Cochrane Library, were not searched, as additional studies may have been identified from the reviews of primary studies. Nevertheless, the ERG considers the chosen electronic databases and internet sources to be appropriate. The company's second set of systematic searches were undertaken to identify all non-randomised studies in second-line therapy in mCRPC. In the original searches undertaken for NICE TA255,[15] three electronic bibliographic databases (MEDLINE, MEDLINE in Process, and EMBASE) and several conference proceedings were searched from January 2000 to March 2010. No additional searches, such as searches of company databases, were undertaken. For the update searches, similar sources appear to have been searched from January 2010 to February 2015.

In general, all searches in the CS were conducted in a systematic fashion and to a clear protocol based on an explicit PICOS question. However, Tables 8-10 (p35-39) and 15-16 (p49-51) of the appendices in the CS do not include numbers of results. This, combined with the fact that the ERG do not have access to the Embase.com platform for MEDLINE and EMBASE, made it difficult to recreate the searches exactly as the company had run them to verify the numbers of results against those given in the PRISMA flowchart.[24] In a systematic literature search it is customary to search each database separately in order (a) to indicate how many records were returned from each, and (b) to allow for the optimisation of the search strategy for each database by choosing the most appropriate subject headings, field codes and limits. Every database has a different thesaurus and indexing hierarchy (although there is some overlap between those of MEDLINE (MeSH) and EMBASE (Emtree)). Records imported from MEDLINE into EMBASE are automatically re-indexed to Emtree but the process is unmediated and can result in sub-headings losing their original context and treated as free-standing subject headings. For this reason, the ERG believes that searching EMBASE and MEDLINE together is not optimal.

When attempting to replicate the company's search on the OVID platform, numerous error messages were encountered due to the inclusion of subject headings which were not recognised by one or both of the databases being searched. Similarly, there is some redundant explosion of subject headings where this has no effect (e.g. Placebo/). The records of the searches are also confused by referring to PubMed as "MEDLINE In Process" in the tables of searches but as "MEDLINE" in the PRISMA

flowcharts. PubMed does indeed have the advantage of including "Pre-MEDLINE" (records to be added to Medline but not yet indexed with subject headings) and "Publisher supplied" records (see https://www.nlm.nih.gov/pubs/techbull/jf99/jf99_subset.html for more details) but the searches have not been restricted to these subsets and therefore there is likely to be substantial duplication with the EMBASE/MEDLINE searches.

There appears to be some errors in the subject headings chosen for the RCT search - for example, the correct Emtree heading is "Prostate tumor" (not "tumour", as used in the RCT search (Appendix 4, Table 8, CS) – though the ERG notes that this error was corrected for the non-RCT and cost-effectiveness searches) and the equivalent MeSH term is "Prostatic Neoplasms" (which in fact has a narrower heading, "Prostatic Neoplasms, Castration Resistant"). However, since free text searches for spelling variations have been included, the ERG is confident all relevant results will have been found.

Finally, the ERG also noticed a logic error in the combination of terms in the EMBASE/MEDLINE search: due to the way line 17 has been combined with the other search strings, it is likely to retrieve results related to other types of hormone-refractory cancer (not just prostate). However, since this error increases rather than reduces the sensitivity of the search, the only effect will have been to increase the number of articles requiring screening.

Despite the noted limitations, the ERG considers all the search strategies to be sufficiently comprehensive to retrieve important citations relating to all eligible studies of which the ERG and its clinical advisors are aware. No relevant published studies are likely to have been missed.

4.1.2 Inclusion criteria

The CS describes appropriate methods of identifying and screening references for inclusion in the systematic reviews of clinical effectiveness. Two independent reviewers applied pre-specified inclusion and exclusion criteria (via a two-stage sifting process) to citations identified by the searches. Any differences in selection were resolved through discussion between reviewers or consultation with a third reviewer (p58 and p90-91, CS). A summary of the inclusion and exclusion criteria, as reported in the CS (p56-58 and p88-90; data re-tabulated and adapted in a consistent and more transparent format), for each of the systematic reviews is summarised in Table 3.

Table 3: Inclusion/exclusion criteria used to select studies in the reviews conducted by the company (p56-58 and p88-90, CS)

Criteria	Review type		
	1. Systematic review of RCTs of cabazitaxel	**2. Systematic review of all RCTs in second-line for mCRPC**	**3. Systematic review of non-randomised studies in second-line for mCRPC**
	Inclusion criteria		
Population	• mCRPC patients • Age: Adults (≥18 years) • Race: Any • Line of therapy: Second-line or later • Prior therapy: Previously treated with docetaxel-based regimen	• As per review 1	• As per review 1
Interventions	The following treatments for mCRPC used in the second line or later [a]: • Jevtana (cabazitaxel) • Zytiga (abiraterone) • Xtandi (enzalutamide) • Novantrone (mitoxantrone) • Yervoy (ipilimumab) • Xofigo (radium-223 dichloride) • Provenge (sipuleucel-T) • Emcyt (estramustine)	• As per review 1	• As per review 1
Comparator	• Any (e.g. placebo, any chemotherapy, surgery, radiotherapy and/or best supportive care)	• As per review 1	• As per review 1
Outcomes	• Overall survival • 1-year survival • Progression-free survival • Time to disease progression • Complete response • Partial response • Overall response • Skeletal-related events	• As per review 1	• As per review 1

	• Prostate-specific antigen (PSA) response • Time to PSA progression • Time to opiate use • Time to pain progression • Safety and adverse events • Health-related quality of life • Resource utilisation		
Study design	• RCTs with any blinding status in phases beyond Phase I	• As per review 1	• Non - RCTs • Single-arm interventional studies/uncontrolled trials • Observational studies, including: o Cohort studies/longitudinal studies (prospective or retrospective) o Case-control studies o Cross-sectional study/survey o Hospital records and database studies
Publication timeframe	• From January 2010 to February 2015 as earlier studies would have been identified in a previous systematic review which informed TA255 for cabazitaxel in 2011[15]	• As per review 1	• As per review 1
Publication status	• Published, unpublished and grey literature (e.g. conference abstracts)	• As per review 1	• As per review 1
Language restrictions	• None	• As per review 1	• As per review 1
	Exclusion criteria		
General	• Studies with no subgroup data for the disease (mCRPC), disease stage (metastatic or unclear), and prior treatment (docetaxel-treated or unclear) were not included to avoid introducing heterogeneity • Study population aged <18 years • Study does not examine an intervention of	• As per review 1	• As per review 1

	interest • Study does not include any outcomes of interest • For review 1 and 2 the following study designs were excluded: Phase I RCTs, non RCTs single-arm studies/uncontrolled trials, observational studies, letters and case reports as these were considered as poor quality evidence • For review 3 the following study designs were excluded: RCTs as these were included in review 1 and 2 and non-randomised evidence including case studies/series/reports as these were considered as poor quality evidence. • Studies published before 2010 as earlier studies would have been identified in a previous systematic review which informed TA255 for cabazitaxel in 2011[15]		

mCRPC, metastatic castration-resistant prostate cancer; RCT, randomised controlled trial

[a] The list was limited to interventions that have been approved in the European Union, are currently seeking approval, or are otherwise known to be used in the European Union in clinical practice within this patient population

The specified inclusion and exclusion criteria were appropriate and generally reflect the information given in the decision problem; however, there appeared to be some irregularities in the CS.

Firstly, the statement of the decision problem proposed that the following treatments be considered as comparators: abiraterone (in combination with prednisone or prednisolone), enzalutamide, mitoxantrone in combination with prednisolone, BSC and radium-223 dichloride (for people with bone metastasis only). Initially, it was unclear to the ERG why other comparators such ipilimumab, sipuleucel-T, estramustine and other mitoxantrone containing regimens were included in the systematic reviews conducted by the company as no explicit details were provided in the CS. [25] Following a clarification response to question A9 (p10-12), the company noted that it initially considered a wider remit to capture the entire evidence base as part of the inclusion criteria (a summary table of all potential included studies was provided in the CS (Table 17, p59-61) and clarification response (Table 4, p11-12)), but then focused the systematic reviews to those studies directly relevant to the decision problem. As a result, the systematic reviews of RCT evidence (review 1 and 2) excluded interventions that were not listed in the decision problem after the study selection stage and thus were not discussed further in the CS.

Secondly, the company did not consider radium-223 dichloride to be a valid comparator as it is only licensed for use in a sub-population of adults who have mCRPC with symptomatic bone metastases and no known visceral metastases. It is also contra-indicated in people with liver metastases. Nevertheless, the ERG's clinical advisors and the expert submissions submitted by Dr Andrew Goddard on behalf of the NCRI/RCP/RCR/ACP[16] and Dr Amit Bahl on behalf of the British Uro-Oncology Group[26] indicate that radium-223 dichloride is a viable treatment option in some people with symptomatic bone-only disease. Moreover, preliminary NICE guidance recommends[27] radium-223 dichloride as an option for treating adults with hormone-relapsed prostate cancer, symptomatic bone metastases and no known visceral metastases, only if: they have had treatment with docetaxel, and the company provides radium-223 dichloride with the discount agreed in the confidential patient access scheme. Following an ERG request (company's clarification response to question A1, p1-2), the company re-expressed their concerns about the applicability and feasibility of including radium-223 dichloride as a comparator but provided a summary of the efficacy results for OS in the cohort of patients with previous docetaxel use from the ALSYMPCA study.[14] However, the company provided no further analysis (further details are provided in Section 4.3).

For the systematic review of non-randomised and non-controlled evidence, the company undertook a similar approach and initially identified all relevant studies (a summary of all potential included studies was provided in Appendix 6 of the CS), but focused the systematic review in the CS to those studies directly relevant to the decision problem, that is, on the safety of cabazitaxel in clinical

practice and the efficacy of cabazitaxel in sequence with abiraterone or enzalutamide (p93, CS). Three sequences were determined: (1) all-hormonal sequences such as abiraterone followed by enzalutamide, or enzalutamide followed by abiraterone; (2) cabazitaxel-hormonal such as cabazitaxel followed by abiraterone or enzalutamide; and (3) hormonal- cabazitaxel such as abiraterone or enzalutamide followed by cabazitaxel.

Whilst these approaches seem acceptable to the ERG, ideally, systematic reviews should have clearly focused research questions and inclusion/exclusion criteria at the outset.

4.1.3 Critique of data extraction

The data extracted and presented in the clinical Section of the CS appear appropriate and comprehensive. As noted in the CS (p58, 90-91) all relevant data for each of the reviews was extracted by two independent reviewers into a pre-defined data extraction table. All extractions were then checked for accuracy by a third independent reviewer.

4.1.4 Quality assessment

The validity assessment tools used to appraise the relevant included studies in the CS differed between the reviews undertaken. For the systematic review of cabazitaxel (review 1), the validity assessment tool was based on the quality assessment criteria for RCTs, as suggested in the NICE guideline template for evidence submissions by a company.[28] For the review of second-line therapies in mCRPC (review 2), the same template was used; however, no explicit consideration was given on how closely the included RCTs reflected routine clinical practice in England. For the review of non-randomised studies in second-line treatments for mCRPC (review 3) the National Institutes of Health National Heart, Lung, and Blood Institute Quality Assessment Tool for Cross-Sectional Studies[29] was used. As noted in the company's clarification response to question A12, methodological quality assessment of included studies for each of the reviews was performed by one researcher and checked independently by a second. The ERG considers the validity assessment tools used in the CS to be appropriate.

4.1.5 Evidence synthesis

The company undertook a narrative synthesis of the evidence for cabazitaxel; however, no explicit details were provided in the CS on how this approach was undertaken.[25] Ideally, a narrative synthesis approach should be justified, rigorous (i.e. describe results without being selective or emphasising some findings over others) and transparent to reduce potential bias.[30,31] Despite the lack of transparency regarding the methods adopted, the ERG acknowledges that the narrative synthesis approach undertaken by the company was acceptable. In the absence of any direct head-to-head RCTs comparing cabazitaxel and other second-line agents such as abiraterone or enzalutamide for the

treatment of mCRPC post-docetaxel, the company conducted a NMA. Further details on the studies included and a critique of the NMA can be found in Sections 4.3 and 4.4 respectively.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Studies included in/excluded from the submission

The company's Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram relating to the literature searches does not conform exactly to the PRISMA statement flow diagram (http://www.prisma-statement.org/). Despite this, the flow diagrams presented by the company represent the identification and selection of all relevant RCTs (see the company's clarification response to question A8, p9) and non-randomised studies (see CS, p92) of second-line therapies in mHRPC/ mCRPC post-docetaxel and appear to be an adequate record of the literature searching and screening process. However, for clarity, a separate PRISMA flow diagram for each of the reviews would have been beneficial (including details of the final set of studies that were included in the CS which were directly relevant to the decision problem) as it would aid the transparency of the identification and selection processes for each of the reviews.

The company's systematic review of RCTs of cabazitaxel identified and included only one relevant study. This was the TROPIC study,[11, 32] which compared cabazitaxel plus prednisone or prednisolone with mitoxantrone plus prednisone or prednisolone in patients with mHRPC which had progressed during or after previous treatment with docetaxel. Further details of the TROPIC study are provided in this section.

The company's broader systematic review of RCTs of all second-line agents in mHRPC/ mCRPC post-docetaxel (which was conducted to allow a NMA to be conducted with the comparator interventions listed in the decision problem i.e. abiraterone (in combination with prednisone or prednisolone), enzalutamide, mitoxantrone in combination with prednisolone, BSC and radium-223 dichloride (for people with bone metastasis only)) initially identified 13 potential studies (see company's clarification response to question A9, Table 4, p11). Of these, only two studies (the AFFIRM trial[13] which compared enzalutamide with placebo and the COU-AA-301 trial[12,33] which compared abiraterone acetate plus prednisone with placebo plus prednisone) in addition to the TROPIC study[11,32] were considered to be relevant to the decision problem. Further details of the AFFIRM[13] and COU-AA-301[12,33] trials are presented in Section 4.3. As noted in Section 4.1.2, the company did not consider radium-223 dichloride (as investigated in the ALSYMPCA study)[14] to be a valid comparator, whereas the remaining studies investigated other treatments that (isiltuximab,[34] cetuximab,[35] etoposide or vinorelbine,[36] ipilimumab,[37, 38] rilotumumab,[39] custirsen,[40] cixutumumab,[41]

cabozantinib[42] or sipuleucel-T[43] [which has been withdrawn from use in the EU]) either do not hold licenses for the treatment of mCRPC post-docetaxel use or are not used in UK clinical practice.

The company's systematic review of non-randomised and non-controlled evidence initially identified 103 studies from 107 citations (see p92 and Appendix A6, CS). However, despite minor discrepancies between the main text and appendices of the CS, it was not explicitly clear to the ERG how many studies (non-randomised and non-controlled) were included in the systematic review that directly provided evidence relevant to the decision problem. Nevertheless, it appears that 12 studies[44-55] from the Compassionate Use Programme (CUP) and EAPs for cabazitaxel provided data on the safety of cabazitaxel in post-docetaxel treatment for mCRPC in clinical practice (p93-95 and Appendix A6, CS).

For the efficacy sequencing review, 12 studies (3 studies on enzalutamide[33,56,57] and 9 studies on abiraterone)[13,58-65] provided data on cross-resistance in mCRPC patients who were treated with third line advanced hormonal therapies (enzalutamide or abiraterone) after having previously received docetaxel and another advanced hormonal therapy compared with studies of no prior hormonal therapy. In addition, 17 studies (7 full papers[66-72] and 10 abstracts[73-82] (the CS suggests that 11 abstracts were identified; however, one abstract[83] was recently published and included as a full paper[72]) provided data on the efficacy of cabazitaxel in sequence with abiraterone or enzalutamide post-docetaxel (p106-110 and Appendix A20, CS). The CS also provided brief details of a recent systematic review[84] on sequencing of abiraterone, enzalutamide and cabazitaxel after docetaxel) in patients with mCRPC, which was published just prior to the CS to NICE. Further details of the systematic review of non-randomised and non-controlled evidence are presented in Section 4.2.4.3.

- The main evidence (pivotal study: TROPIC trial)[11,32]

The CS (p64-74) included one phase III, manufacturer-sponsored, randomised, open-label, active-controlled, multicentre (146 centres in 26 countries including the UK) study designed to evaluate the efficacy and safety of cabazitaxel (plus prednisone or prednisolone) in 755 men aged over 18 years (median age 68 years and 84% were Caucasian) with mHRPC whose disease had progressed during (about 30% of patients) or after (about 70% of patients) treatment with a docetaxel-containing regimen. Eligible patients needed to have an ECOG PS score of 0 or 1 (n=694, 92%) or 2 (n=61, 8%) and documented disease progression according to the RECIST criteria[21] (measurable disease) with ≥1 visceral or soft-tissue metastatic lesion or based on a rising PSA level or the appearance of new lesions (non-measurable disease). A summary of the study design and population characteristics is provided in Table 4.

Table 4: Characteristics of the TROPIC study (see CS, p64-74 and de Bono *et al.*[11, 32])

Study	Location (sites)	Design	Population	Interventions	Comparator	Primary outcome measures	Duration
TROPIC (NCT 00417079)[11, 32]	146 centres in 26 countries (including 6 sites [n=37, 5%] in the UK)	Phase III, randomised, open-label, active drug controlled trial	Men aged ≥18 years with mHRPC post-docetaxel (n=755)	Cabazitaxel 25 mg/m^2 intravenously over 1 hour on day 1 of each 21-day cycle plus oral prednisone 10 mg/day or similar doses of prednisolone in countries in which prednisone was unavailable[a] (n=378)	Mitoxantrone 12 mg/m^2 intravenously over 15-30 minutes on day 1 of each 21-day cycle plus oral prednisone 10 mg/day or similar doses of prednisolone where prednisone was unavailable[b] (n=377)	Overall survival (calculated from date of randomisation to death)	Until death or the cut-off date for analysis (25 September 2009 [median follow-up was 12.8 months] and in the extension period to 10 March 2010 [median follow up was 20.5 months])

mHRPC, metastatic hormone-refractory prostate cancer

[a] Premedication, consisting of single intravenous doses of an antihistamine, corticosteroid (dexamethasone 8 mg or equivalent), and histamine H2-antagonist (except cimetidine) was administered 30 minutes or more before cabazitaxel

[b] Premedication with an anti-emetic only, with other premedication at the physician's discretion

The key exclusion criteria included active grade 2 or higher peripheral neuropathy or stomatitis, other serious illness (including secondary cancer) or a history of hypersensitivity to polysorbate 80-containing drugs and prednisone. In addition, a protocol amendment mandated that study subjects who received a cumulative dose of docetaxel less than 225 mg/m^2 (n=59, 8%) were excluded from the study. This amendment was made in light of guidelines suggesting that docetaxel treatment be maintained for a period of at least three cycles prior to instituting any change in order to obtain a true 'docetaxel-refractory' population.

All patients received oral prednisone 10mg daily (or prednisolone where prednisone was unavailable) and were randomised to receive cabazitaxel 25mg/m^2 intravenously over 1 hour (n=378) or mitoxantrone 12mg/m^2 intravenously over 15 to 30 minutes (n=377). Treatments were given on day 1 of each 21-day cycle and could be given for a maximum of ten cycles to minimise risk of mitoxantrone-induced cardiac toxicity. As noted in the company's clarification response to question A4, the license for cabazitaxel does not limit its usage to 10 cycles. Treatment delays up to two weeks were permitted, with one dose reduction per patient permitted if the initial dose was not tolerated: cabazitaxel from 25 to 20mg/m^2; and mitoxantrone from 12 to 10mg/m^2. The ERG notes that in the European Medicines Agency assessment report for cabazitaxel[1] it states that 'No dose escalation is mentioned in the protocol.' Prophylactic treatment with G-CSFs was not allowed during the first cycle, but thereafter was allowed at the physician's discretion and was mandated for patients with neutropenia lasting longer than seven days or neutropenia complicated by fever or infection. Patients in the cabazitaxel arm were given premedication consisting of antihistamine, corticosteroid and histamine-2 antagonists to reduce the risk of hypersensitivity reactions. Anti-emetic prophylaxis and other supportive care were given at the physician's discretion.

Exposure to the study treatment varied between the groups. In the cabazitaxel group, patients completed a median of six cycles of treatment, of which 10% of cycles required a dose reduction, with a median relative dose intensity of 96.1%. In contrast, patients in the mitoxantrone group completed a median of four cycles of treatment, of which 5% of cycles required a dose reduction, with a median relative dose intensity of 97.3%. The protocol prohibited crossover to cabazitaxel for patients randomised to the mitoxantrone group, although 44 (12%) patients in this group received treatment with tubulin-binding drugs at the time of disease progression.

The primary efficacy endpoint was OS (defined as the time from date of randomisation to death due to any cause or the study cut-off date, whichever came first) and the main secondary endpoint was PFS (a composite endpoint defined as the time between randomisation and the first date of progression as measured by a: rise in PSA levels; tumour progression; pain progression; or death, whichever

occurred first). Other secondary endpoints included: time to tumour progression; overall response rate; PSA progression; pain response measures; and safety.

- *Ongoing studies of cabazitaxel for mCRPC post-docetaxel*

Several ongoing studies on the use of cabazitaxel in patients with mCRPC after docetaxel-based therapy were noted in the CS; however, full and clear explicit details on study characteristics including expected completion dates were lacking (see Appendix 7, CS for further details). A summary of two key studies (PROSELICA, a phase III study comparing the efficacy and tolerability of cabazitaxel 25 mg/m^2 with cabazitaxel 20 mg/m^2 and ECLIPSE, an observational retrospective study on treatment sequencing of anti-cancer agents in mCRPC) that may provide evidence within the timeframe of this submission is provided in Table 5. In addition, the CS (p122) also notes that the FIRSTANA (NCT01308567) study may also provide preliminary outputs within the timeframe of this appraisal; however, this study is in mCRPC patients who are chemotherapy naïve and so falls outside the indication discussed in this submission.

Table 5: List of key ongoing studies of cabazitaxel for mCRPC post-docetaxel (p127 and Appendix 20, CS)

Criteria	PROSELICA study	ECLIPSE study
Title	Randomized, open label multi-centre study comparing cabazitaxel at 20 mg/m² and at 25 mg/m² every 3 weeks in combination with prednisone for the treatment of mCRPC previously treated with a docetaxel-containing regimen	Real Life treatment sequences and survival of men with mCRPC receiving cabazitaxel in UK clinical practice
Study ID number	Sanofi internal: XRP6258-EFC11785 Clincinaltrials.gov: NCT01308580	Sanofi internal: CABAZL07485
Primary objective	To demonstrate the non-inferiority in terms of overall survival of cabazitaxel 20 mg/m² (Arm A) versus cabazitaxel 25 mg/m² (Arm B) in combination with prednisone in patients with mCRPC previously treated with a docetaxel-containing regimen.	To describe anti-cancer treatment sequences and treatment outcomes in patients receiving cabazitaxel in England.
Secondary objectives	• To evaluate safety in the 2 treatment arms and to assess if cabazitaxel 20 mg/m² is better tolerated than cabazitaxel 25 mg/m² • To compare efficacy of cabazitaxel at 20 mg/m² and 25 mg/m² for: o Progression Free Survival o Prostate-Specific Antigen (PSA)-	• To describe the clinical outcomes of patients who have received cabazitaxel following prior docetaxel treatment (according to the treatment sequencing received post-docetaxel) • To describe the characteristics of patients receiving cabazitaxel treatment

	Progression o Pain progression o Tumour response in patients with measurable disease o PSA response o Pain response in patients with stable pain at baseline • To compare Health-related Quality of Life using the FACT-P tool • To assess the pharmacokinetics and pharmacogenomics of cabazitaxel	• To describe side effects associated with cabazitaxel use
Study design	Phase III, randomised, open-label, multi-centre, multinational study comparing cabazitaxel 20 mg/m² plus prednisone (Arm A) and cabazitaxel 25 mg/m² plus prednisone (Arm B) in patients with mCRPC post-docetaxel.	A multi-centre, observational, retrospective research study of patients with mCRPC who have received cabazitaxel in England.
Study location	Multinational, multicentre. Planned recruitment is from approximately 200 sites within 60 months.	5 centres in England
Study population	Expected 1200 mCRPC patients with similar baseline characteristics to the TROPIC population	115 patients with mCRPC treated with cabazitaxel following docetaxel failure and who started cabazitaxel treatment ≥1 year before data collection.
Study duration	Cabazitaxel administered every 3 weeks. Patients treated until progressive disease, unacceptable toxicity, patient's refusal of further study treatment or for a maximum of 10 cycles. After study treatment discontinuation patients followed until death or cut-off date, whichever comes first. In patients that progressed the follow up was performed every 12 weeks, in patient not progressed the follow up was performed every 6 weeks for the first 6 months and then every 12 weeks.	Data relating to patients' demographic and clinical characteristics and cancer treatment pathways (including life-prolonging anti-cancer treatments and clinical outcomes) were collected from electronic and paper-based hospital records between March 2015 and August 2015.
Expected completion date	August / September 2015 with full results expected within the next 12 months	Not reported but interim results available in Appendix A20, CS (p127-130)

4.2.2 Details of relevant studies not included in the submission

The ERG is confident that all relevant studies were included in the CS and details of ongoing trials that are likely to be reporting additional evidence within 12 months were reported.

4.2.3 Summary and critique of the company's analysis of validity assessment

The company provided a formal appraisal of the validity of the included cabazitaxel RCT using standard and appropriate criteria. The completed validity assessment tool for the TROPIC trial, as reported in the CS, is reproduced (with minor changes) in Table 6.

Table 6: Quality assessment results for the TROPIC study as assessed by the company

Quality assessment criteria	**Trial**	
	TROPIC	
	How addressed in the study	**Adequate or not**
Internal validity		
Was randomisation carried out appropriately?	Computer-generated random number sequence; stratified by pre-specified criteria.	Yes
Was the concealment of treatment allocation adequate?	Central randomisation was performed using an interactive voice response system.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Baseline demographic, disease and previous treatment characteristics were balanced.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Providers, participants and outcome assessors were not blind to treatment allocation; unlikely to bias assessment of overall survival, progression free survival or objective assessments of tumour response; potential for ascertainment bias in the subjective assessment of present pain intensity and clinical (not laboratory) assessment of adverse events.	No, but unlikely to impact on the main outcomes. Outcome assessors should probably have been blinded to avoid the possibility of bias. (See text for ERG comment on this)
Were there any unexpected imbalances in dropouts between groups?	No - only two patients, both in the mitoxantrone group, were lost to follow-up; a similar number of	Yes

	patients in each group (n=10 cabazitaxel, n=7 mitoxantrone) discontinued treatment due to events other than disease progression or adverse events; only one patient, in the cabazitaxel group, discontinued due to poor protocol compliance.	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	There is no suggestion information was omitted	Yes
Was follow-up adequate?	Patients were followed until death or the cut-off date for analysis.	Yes
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The primary outcome was analysed by intention to treat. Missing data were accounted for appropriately according to censoring rules for survival data.	Yes
External validity		
Was the RCT conducted in the UK, or were one or more centres of a multinational RCT located in the UK	International multicentre trial; 5% (37/755) of participants were recruited in the UK, 53% (402/755) in Europe.	Yes
How do the participants included in the RCT compare with patients who are likely to receive the intervention in the UK?	Demographics, disease and prior treatment are likely to be similar	Yes, data from the UK Early Access Programme[50] is available and this shows cabazitaxel use in a very similar patient population to the TROPIC study[11, 32] with improved adverse event profiles.
What dosage regimens were used in the RCT? Are they within those detailed in the summary of product characteristics?	Cabazitaxel 25 mg/m^2 one-hour intravenous infusion every three weeks (as in the summary of product characteristics)	Yes

	Mitoxantrone 12 mg/m^2 one-hour intravenous infusion every three weeks; recommended dosage for HRPC 12–14 mg/m² intravenous every three weeks. Mitoxantrone is not licensed for this indication in the UK but is licensed in the USA.	
ERG, Evidence Review Group; HRPC, hormone refractory prostate cancer; RCT, randomised controlled trial		

The CS considered the TROPIC study to be adequate in relation to all of these criteria with the exception of the criterion relating to the blinding of patients, care providers, and outcome assessors. The CS considered that the fact that the trial was open-label was unlikely to have introduced bias into the assessment of OS (primary outcome), or into objective assessments of tumour response or biochemical measurements such as PSA, but recognised that it might have introduced bias into the subjective assessment of pain and symptom deterioration (both of which were included in the definition of PFS) and of clinical (although not laboratory) assessment of AEs. In the guidance issued by NICE for cabazitaxel in 2011,[15] the Appraisal Committee accepted that, 'as an open-label study, TROPIC was susceptible to bias in the subjective outcomes included in progression-free survival, such as pain and deterioration in symptoms'. In addition, whilst a clear reason for the study being open label was lacking in the CS, NICE TA255[15] notes that 'The Committee heard from the manufacturer that blinding was not possible because of differences in the rate of infusion and colour of the drugs being compared'. Nevertheless, the ERG notes that there appears to be no reason why outcome assessors should not have been blinded to treatment allocation.

The CS states that the investigators used appropriate methods to generate the random allocation sequence and ensure allocation concealment, using a dynamic allocation method – a form of minimisation – to avoid extreme imbalance of treatment allocation within each study centre. However, it should be noted that such allocation is not truly random, and can potentially be subverted because of difficulties in concealing the allocation sequence. It is therefore theoretically possible that some patients may have been deliberately allocated to one or other treatment group on the basis of prognostic factors; however, the ERG has no reason to believe that this was the case.

The CS considered all the external validity criteria to be adequately met. However, the ERG notes that only 5% (37/755) of participants were recruited from the UK. Nevertheless, in NICE TA255,[15] the Appraisal Committee concluded that the results from the TROPIC trial would be generalisable to

clinical practice in the UK. Moreover, recent data presented in the CS (p124 and Appendix 20) from the UK EAP (n=112)[50] and the unpublished data from the ongoing UK ECLIPSE study (n=115) suggest that patients treated in clinical practice with cabazitaxel in the UK are of similar age to the TROPIC population (UK EAP[26]: median age 67.0 years (IQR: 63 – 72.5); ECLIPSE: mean age 69.4 years (standard deviation [SD]: 6.69); TROPIC:[11] median age 68 years (IQR: 62 – 73)) with a median of six cycles of treatment, with mean dose intensity of 97.82%.[50]

4.2.4 Summary and critique of results

This section presents the results (as reported by the company) from the TROPIC trial,[11,32] which forms the pivotal evidence in the CS for the efficacy and safety of cabazitaxel (plus prednisone or prednisolone) in people with mHRPC whose disease had progressed during or after treatment with a docetaxel-containing regimen. In the original TROPIC study, final analyses had been planned after 511 death events had occurred using the intention to treat (ITT) principle. The results for the whole trial population were first published by de Bono *et al*. in 2010[11] after a median follow-up of 12.8 months (study cut-off date: 25 September 2009), at which point 513 deaths had occurred. Although a summary of these data is not reported in Section 4.7 of the CS (p77-81), the ERG reports this data for completeness in Appendix 1. The CS does provide data from an updated analysis (OS data published by Bahl *et al*. in 2013)[32] after a median follow-up of 20.5 months (study cut-off date: 10 March 2010), at which point 585 deaths (77.5%) had occurred. All efficacy analyses were by ITT and estimates of the hazard ratio (HR) and corresponding 95% confidence intervals (CI) were provided using a Cox proportional hazard model stratified by factors specified at randomisation. Additional information, not reported in the CS, was provided by the company in their response to the clarification questions raised by the ERG. Where applicable, data have been re-tabulated by the ERG to provide further clarity.

4.2.4.1 Efficacy

- *OS*

In an updated analysis, with a median follow-up of 20.5 months, 277 (73.3%) deaths had occurred in the cabazitaxel group compared with 308 (81.7%) in the mitoxantrone group. Median survival values (HR for death 0.72, 95% CI: 0.61 to 0.84, p<0.0001) were similar to the 'final efficacy analysis' (HR for death 0.70, 95% CI: 0.59 to 0.83, p<0.0001), with a median gain of 2.3 months. As noted in the CS (p79), the mean OS was estimated using individual patient level data from the TROPIC trial. For the ITT population, based on Weibull extrapolations, OS was estimated to be 18.55 months in the cabazitaxel group compared with 14.53 months in the mitoxantrone group, with a mean survival gain of 4.02 months. A summary of the OS results are provided in Table 7.

Table 7: Summary of OS in the TROPIC study - updated efficacy analysis

	Cabazitaxel (n=378)	Mitoxantrone (n=377)	Hazard ratio (95% CI)	p value
Analysis at 10.3.10 (updated efficacy analysis) (p77-79, CS and Bahl *et al.*)[32]				
Total deaths, ITT population	277 (73.3%)	308 (81.7%)	NR	NR
Number of patients censored	101 (26.7%)	69 (18.3%)	NR	NR
Median overall survival, months (95% CI) [a]	15.08 (13.96 to 16.49)	12.78 (11.53 to 13.73)	0.72 [c] (0.61 to 0.84)	<0.0001 [c]
Estimated mean overall survival (extrapolated), months (95% CI) [b]	18.55 (NR)	14.53 (NR)	NR	NR
Additional data from CS (p77-78) and Bahl *et al.*[32]				
Patients alive at 12 months (95% CI)	64% (NR)	53% (NR)	NR	NR
Patients alive ≥ 24 months (95% CI)	27% (23 to 32)	16% (12 to 20)	NR	NR

CI, confidence interval; ITT, intention-to-treat; NR, not reported

[a] Median difference in overall survival, 2.3 months

[b] Mean difference in overall survival, 4.02 months (estimated using Weibull extrapolations to the Kaplan-Meier data from the TROPIC trial)

[c] Data discrepancy in CS: Table 2 (p18, CS) reports corresponding data as follows: HR 0.72, 95%CI: 0.61 to 0.85; p=0.0002 and Table 22 (p78, CS) reports corresponding data as follows: HR 0.72, 95%CI: 0.61 to 0.84; p=0.000

- *PFS*

Despite the lack of clarity and minor data discrepancies, the ERG assumes that the PFS data reported in the CS (Section 4.7, p79-81) are based on the updated analysis as the CS (p144) states that 'The key clinical data used to populate this model were informed by the updated cut-off data TROPIC trial. These data include PFS and OS of cabazitaxel and mitoxantrone, along with the risk of AEs associated with each treatment.'

In an updated analysis, cabazitaxel was associated with a statistically significant improvement in median PFS (a composite endpoint defined as the time between randomisation and first date of progression as measured by PSA progression, tumour progression, pain progression or death). PFS was 2.76 months in the cabazitaxel group and 1.41 months in the mitoxantrone group (HR 0.75, 95% CI: 0.65 to 0.87, p=0.0002) corresponding to a 25% reduction in the risk of progression. These results appear to be very similar to the final efficacy analysis data reported by de Bono *et al.*[11] (HR 0.74, 95%

CI: 0.64 to 0.86, p<0.0001). As discussed in the CS (p80) the observed PFS duration was somewhat shorter than other cancer types and other trials in this setting. A contributing factor to this difference was the conservative definition of PFS, including biochemical (PSA progression), which frequently precedes symptomatic or radiologic progression. The CS states that '40-50% of progression events were due to PSA progression, with symptom deterioration recorded in only 2-4% of patients. Patients were withdrawn from study treatment on first sign of progression, including confirmed PSA progression. Hence, the relatively short PFS duration.' A summary of the PFS results are provided in Table 8.

Table 8: Progression-free survival in the TROPIC study - updated efficacy analysis

	Cabazitaxel (n=378)	**Mitoxantrone (n=377)**	**Hazard ratio (95% CI)**	**p value**
Analysis at 10.3.10 (updated efficacy analysis as reported in CS, p79-81)				
Number of patients with progression-free survival events (%)	367 (97.1%) [a]	370 (98.1%) [a]	NR	NR
Median progression-free survival (months)	2.76 (2.43 to 3.12)	1.41 (1.35 to 1.77)	0.75 (0.65 to 0.87) [b]	0.0002
Death	41 (10.8%)	33 (8.8%)	NR	NR
Tumour progression	67 (17.7%)	68 (18.0%)	NR	NR
PSA progression	163 (43.1%)	186 (49.3%)	NR	NR
Pain progression	86 (22.8%)	69 (18.3%)	NR	NR
Symptom deterioration	10 (2.6%)	14 (3.7%)	NR	NR
Censored (calculated by the ERG)	11 (2.9%)	7 (1.9%)	NR	NR

CI, confidence interval; ITT, intention-to-treat; NR, not reported; PSA, prostate specific antigen

[a] Data discrepancy in CS: Table 23 (p80, CS) reports corresponding data as follows: cabazitaxel, n=364 (96.30%); mitoxantrone, n=366 (97.08) - this appears to be similar to the data reported for the final efficacy analysis

[b] Data discrepancy in CS: Table 2 (p18, CS) reports corresponding data as follows: 0.76 (0.65 to 0.89) - this appears to be the data reported for the subgroup analysis

- *Other secondary outcomes*

The CS did not report any results for the following secondary outcomes and no explanations were provided: tumour response; time to tumour progression; PSA response; PSA progression; pain response; and pain progression. In brief, the published final efficacy analysis results reported by de Bono *et al*.[11] found that cabazitaxel was associated with statistically significant improvements in: PSA response (p=0.0002); time to PSA progression (p=0.001); objective tumour response (p=0.0005); and

time to tumour progression (p<0.0001). However, it was not associated with statistically significant differences in pain response (p=0.63) or pain progression (p=0.52). A comprehensive summary and evaluation of the results is reported in NICE TA255.[15] Moreover, data on HRQoL were not collected in the TROPIC study.

- *Subgroup analyses*

A post-hoc subgroup analysis was performed in mCRPC patients previously treated with a docetaxel containing regimen (at least 225 mg/m^2) with an ECOG performance score of 0 or 1 (representing 83.7% [632/755] of the TROPIC trial population). In NICE TA255[15] the Appraisal Committee considered this group of people to be the most appropriate population to receive cabazitaxel in UK clinical practice as patients with an ECOG performance score of 2 would not be fit enough to tolerate further chemotherapy and patients would need to receive at least 225 mg/m^2 of docetaxel to gain the full benefit of first-line treatment before going on to second-line treatment with cabazitaxel.

In the subgroup of mCRPC patients with an ECOG performance score of 0 or 1 and who had received at least 225 mg/m^2 of prior docetaxel, the median OS was 15.61 months in the cabazitaxel group and 13.37 months in the mitoxantrone group and the HR was 0.69 (95% CI 0.57 to 0.82, p<0.001) corresponding to a 31% reduction in the risk of death. Thus, cabazitaxel plus prednisone/prednisolone was associated with a median survival gain of 2.24 months relative to mitoxantrone plus prednisone/prednisolone. A statistically significant improvement in median PFS was also observed. PFS was 2.76 months in the cabazitaxel group and 1.41 months in the mitoxantrone group (HR 0.76, 95% CI: 0.65 to 0.89, p=0.001) corresponding to a 24% reduction in the risk of progression. A summary of the OS and PFS results are provided in Table 9.

Table 9: Summary of the OS and PFS in patients with ECOG performance score of 0 or 1 and who had received >225mg/m^2 of docetaxel

	Cabazitaxel (n=319)	Mitoxantrone (n=313)	Hazard ratio (95% CI)	p value
Analysis at 10.3.10 (updated efficacy analysis as reported in CS, p83-84)				
Overall survival				
Number of patients with deaths [a]	228 (71.47 %)	253 (80.83%)	NR	NR
Number of patients censored	91 (28.53 %)	60 (19.17 %)	NR	NR
Median overall survival, months (95% CI)	15.61 (13.96 to 17.28)	13.37 (11.99 to 14.52)	0.69 (0.57 to 0.82)	<0.001
Progression-free survival				
Number of patients with progression-free survival events (%)	305 (95.61%)	304 (97.12%)	NR	NR
Median progression-free survival,[b] months (95% CI)	2.76 (2.43 to 3.12)	1.41 (1.35 to 1.84)	0.76 (0.65 to 0.89)	0.001

CI, confidence interval; NR, not reported; PSA, prostate specific antigen

[a] These figures were incorrectly presented in the CS Table 26 as number of patients censored, rather than number of deaths

[b] Progression-free survival was defined as a composite endpoint evaluated from the date of randomisation to the date of tumour progression, PSA progression, pain progression, or death due to any cause, whichever occurred first

4.2.4.2 Safety and tolerability

This section provides the main safety evidence for the use of cabazitaxel (plus prednisone or prednisolone) in people with mCRPC whose disease had progressed during or after treatment with a docetaxel-containing regimen from the TROPIC trial.[11] The CS (including the company's clarification response) also provided supplementary evidence based on a systematic review of non-randomised studies, on the safety of cabazitaxel in routine clinical practice. Further details of this review are provided in the supplementary evidence section.

In the TROPIC trial,[11] the median number of treatment cycles administered, and the number of patients completing the planned 10 cycles of treatment, were both higher in the cabazitaxel group than in the mitoxantrone group. Disease progression was the most common reason for discontinuation of study treatment, and was more common in the mitoxantrone group than in patients receiving cabazitaxel, whereas discontinuations because of unacceptable adverse effects or patient request were both more common in the cabazitaxel group. In addition, more patients in the

cabazitaxel group than in the mitoxantrone group required dose reductions and treatment delays, suggesting that cabazitaxel was less well tolerated than mitoxantrone. A summary of the treatments received and reasons for discontinuation (no statistical comparisons were reported in the CS for any of these outcomes) are provided in

Table 10.

Table 10: Treatment received and reasons for discontinuation in the TROPIC study[11]

	Cabazitaxel (n=378)	Mitoxantrone (n=377)
Patients who received study treatment,	371 (98%)	371 (98%)
Median number of treatment cycles (IQR)	6 (3 to 10)	4 (2 to 7)
Number of patients completing planned 10 cycles of study treatment	105 (28%)	46 (12%)
Median relative dose intensity (IQR)	96.1% (90.1 to 98.9) [a,b]	97.3% (92.0 to 99.3) [a,b]
Discontinuation of study treatment	266 (70%)	325 (86%)
Reasons for discontinuation of study treatment		
Disease progression	180 (48%)	267 (71%)
Adverse event	67 (18%)	32 (8%)
Non-compliance with protocol	1 (<1%)	0
Lost to follow-up	0	2 (1%)
Patient request	8 (2%)	17 (5%)
Other	10 (3%)	7 (2%)
Dose reductions		
Number of patients [c]	45 (12%)	15 (4%)
Number of cycles [d]	221 (9.8%)	88 (5.1%)
Treatment delays		
Number of patients [e]	104 (28%)	56 (15%)
Number of cycles [d]		
≥4 days	NR (9.3%)	NR (7.9%)
≤9 days	157 (7.0%)	110 (6.3%)
>9 days	51 (2.2%)	28 (1.6%)

IQR, interquartile range

[a] Data discrepancy in CS - p111 (CS) suggest a range (unit not specified) of 49.0% to 108.2% for cabazitaxel and 42.5% to 106% for mitoxantrone

[b] Data from de Bono *et al.*[11] and CS (p77, Table 26)

[c] One dose reduction was allowed per patient, 20 mg/m^2 for cabazitaxel or 10 mg/m^2 mitoxantrone

[d] Percentages are of total number of treatment cycles: 2251 for cabazitaxel and 1736 for mitoxantrone

[e] Delays of ≤2 weeks were allowed

All AEs in the TROPIC trial[11] were recorded from the time of first dose until 30 days after the cycle of treatment. General and serious AEs were assessed and graded according to National Cancer Institute Common Terminology Criteria for AE, version 3.[23] and were followed until resolution. Treatment emergent AEs of grade ≥3 occurred in 213/371 (57.4%) patients in the cabazitaxel group and 146/371 (39.4%) patients in the mitoxantrone group. Serious treatment emergent AEs were reported in 145 (39.1%) patients in the cabazitaxel group and 77 (20.8%) patients in the mitoxantrone group. The proportion of patients withdrawing from study treatment permanently due to any treatment emergent AE (including disease progression reported as a treatment emergent AE) was 18.3% (68/371) in the cabazitaxel group compared with 8.4% (31/371) in the mitoxantrone group. The most common treatment emergent AEs leading to treatment discontinuation in the cabazitaxel group compared with the mitoxantrone group were neutropenia (2.4% versus 0%), renal failure including acute renal failure (1.9% versus 0%) haematuria (1.3% versus 0.3%), sepsis including neutropenic sepsis, pneumococcal sepsis and septic shock (1.3%% versus 0.3%), diarrhoea (1.1% versus 0.3%), fatigue (1.1% versus 0.3%), and abdominal pain (0.8% versus 0%) and febrile neutropenia (0.8% versus 0%), respectively.[85]

The most common AEs in the TROPIC trial[11] (≥ grade 3 occurring in ≥5% of patients in either treatment group) were: neutropenia and its complications (febrile neutropenia and infections); asthenic conditions (asthenia and fatigue); and gastrointestinal toxicity (diarrhoea, nausea and vomiting), which were noticeably higher in the cabazitaxel group than in the mitoxantrone group. As stated in the company's clarification response to question A5 (p5-6), 'regulatory authorities require an assessment of both clinical and subclinical changes to body systems and physiological processes. Whilst abnormal laboratory findings are important to their assessment, in real practice such departures may not be observed…For example in TROPIC if both laboratory and symptomatic events ('patient felt') are included neutropenia (grade 3 and above) was observed in 82% of people in the cabazitaxel arm. However the proportion of people experiencing events that required intervention of some kind was far less at 21%.' The clinical advisors to the ERG agreed with the company's response and commented that high levels of monitoring in a trial setting would result in abnormal laboratory measurements being recorded as AEs despite the fact that these may not cause any problems for the patient. Whilst a detailed summary of all AEs from the TROPIC study is provided in Section 4.5 (so that a comparison can be made with studies included in the NMA), Table 11provides a brief summary of AEs requiring medical intervention (e.g. dose reduction, dose modifications, use of supportive treatment or treatment discontinuation) in all patients who received at least part of one dose of study drug (safety analysis) in the TROPIC trial and in the subgroup of mCRPC patients previously treated with a docetaxel containing regimen (at least 225 mg/m^2) with an ECOG performance score of 0 or 1. This was considered by the company to be the most appropriate information to include in the economic model.

Table 11: AEs requiring medical intervention[a] (≥ grade 3 occurring in ≥5% of patients in either treatment group) in the TROPIC trial (reproduced with minor changes; p19 and 113, CS)

Adverse Event	Proportion of patients			
	Safety analysis (all patients who received study drug)		Subgroup with ECOG PS 0-1 with 225mg/m^2 prior docetaxel	
	Cabazitaxel	Mitoxantrone	Cabazitaxel	Mitoxantrone
Haematological				
Neutropenia	0.210	0.073	0.201	0.081
Febrile neutropenia	0.073	0.016	0.080	0.019
Anaemia	0.035	0.013	0.032	0.006
Thrombocytopenia	0.024	0.003	0.022	0.000
Non-Haematological				
Diarrhoea	0.062	0.003	0.064	0.003
Fatigue	0.049	0.030	0.051	0.023
Asthenia	0.046	0.024	0.042	0.019
Leukopenia	0.038	0.013	0.032	0.013
Back pain	0.038	0.030	0.038	0.032
Pulmonary embolism	0.019	0.022	0.019	0.026
Dehydration	0.022	0.008	0.016	0.006
Nausea	0.019	0.003	0.019	0.003
Bone pain	0.008	0.024	0.010	0.026
Deep vein thrombosis	0.019	0.008	0.016	0.010
Neuropathy	0.005	0.003	0.006	0.003

[a] AEs reported by the investigator and do not include abnormal laboratory values

The number of deaths reported within 30 days of the last dose of study drug (n=27) are summarised in Table 12. Such deaths were more common with cabazitaxel than with mitoxantrone. Neutropenia was the most common cause of such death in patients receiving cabazitaxel, compared with disease progression in those receiving mitoxantrone. A FDA medical review of cabazitaxel[85] considered five of the 18 deaths in the cabazitaxel group to be due to infections; 80% of these deaths occurred after a single dose of cabazitaxel, and none of the five patients had been given prophylactic G-CSF. As noted in the CS (p112), neutropenia is to be expected when treating with taxane-based chemotherapy and is not necessarily difficult to manage for experienced centres. Similarly, in TA255,[15] the Appraisal Committee noted that the incidence of neutropenia was lower among participants recruited

at European centres than other centres and 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. Recent evidence from the UK EAP study suggests that cabazitaxel can be used safely in UK practice with manageable toxicity. As noted by Bahl *et al*.[50] (the authors of the UK EAP study) lower rates of neutropenia and sepsis were observed in the UK EAP cohort where primary prophylactic G-CSF use was common, whereas this was not permitted during the first cycle in the original TROPIC study[11] but was allowed (at physicians discretion) after first occurrence of either neutropenia lasting ≥7 days or neutropenia complicated by fever or infection.

Table 12: Deaths occurring within 30 days of last dose of study drug in the TROPIC trial[11]

	Cabazitaxel (n=371)	**Mitoxantrone (n=371)**
Deaths within 30 days of last dose of study drug	18 (5%)	9 (2%)
Causes of deaths within 30 days of last dose of study drug		
Disease progression	0	6 (2%)
Neutropenia & clinical consequences/sepsis	7 (2%)	1 (<1%)
Cardiac	5 (1%)[a]	0
Dyspnoea (apparently related to disease progression)	0	1 (<1%)
Dehydration/electrolyte imbalance	1 (<1%)	0
Renal failure	3 (1%)[b]	0
Cerebral haemorrhage	1 (<1%)	0
Unknown cause	1 (<1%)	0
Motor accident	0	1 (<1%)

[a] Cardiac arrest (n=3), sudden death (n=1) and ventricular fibrillation (n=1). None of these events were regarded as being related to the study drug.[86]

[b] Data discrepancy: FDA reviewers attributed 4 deaths to renal failure,[85] rather than the 3 reported by de Bono *et al*.[11]

Moreover, none of the cardiac deaths in the TROPIC study were considered by the study investigators to be treatment related[86] and additional evidence provided in the company's clarification response to question A15, p16-19 (i.e. results of studies evaluating cardiac toxicity associated with cabazitaxel, the conclusions of a review by an expert panel of renal events observed with cabazitaxel and post-marketing safety data) suggest there are no safety concerns related to cardiac or renal toxicity. In TA255,[15] the Appraisal Committee also concluded that '…there is no evidence of additional risk other than that included in the SPC.'

4.2.4.3. Supplementary evidence

The CS included a review based on a systematic search of non-randomised and uncontrolled evidence considered relevant to the decision problem (further details are provided in Section 4.1). The stated aim of the review was to identify evidence related to:

- Safety of cabazitaxel in clinical practice
- Efficacy of cabazitaxel used in sequence with abiraterone or enzalutamide. These sequences formed three broad categories: (1) all-hormonal sequences such as abiraterone followed by enzalutamide, or enzalutamide followed by abiraterone; (2) cabazitaxel-hormonal such as cabazitaxel followed by abiraterone or enzalutamide; and (3) hormonal- cabazitaxel such as abiraterone or enzalutamide followed by cabazitaxel.

In brief, only studies of patients with mCRPC previously treated with a docetaxel-based regimen were eligible for inclusion but there was no limitation on comparators and broad inclusion criteria for outcomes and study designs. Case series and case reports were excluded but studies published only as conference abstracts were eligible for inclusion.

The methods used for study selection and data extraction were adequate. However, the company stated that 107 studies met the inclusion criteria (51 full papers and 56 conference abstracts) but only a small proportion of these were used in the analysis. The selective inclusion of part of the evidence base should be kept in mind when interpreting the findings.

Evidence on the safety of cabazitaxel in clinical practice was derived from the CUP and the EAPs in various countries and regions (see Table 13 for details of published reports). Seven published reports[44-50] and five conference abstracts[51-55] were included. As noted in the company's clarification response, there is overlap in some of the European data from the CUP/EAPs, however, the extent of overlap is not explicitly clear within the CS. All the studies were uncontrolled, open label observational studies. Patients received cabazitaxel 25 mg/m^2 intravenously every three weeks in combination with prednisone or prednisolone 10 mg daily. Treatment was stopped in the event of disease progression, unacceptable toxicity, investigator's decision or after 10 cycles. The CUP/EAP studies were primarily designed to assess safety, although efficacy data were collected in some countries.

The CS only included a quality (risk of bias) assessment for one of the included studies, namely the UK EAP.[50] The assessment used the National Institutes of Health National Heart, Lung and Blood Institute Quality assessment Tool for Cross-Sectional Studies.[29] Following a clarification response to question A18 (p21) the company noted that a quality assessment of the other CUP/EAP studies would be provided; however, these were not received prior to the completion of the ERG report. The

limitations identified for the UK EAP study were lack of a sample size justification or power calculation; that the study did not examine effects of different levels of exposure to the study drug; lack of blinding and lack of adjustment for confounders. In addition, the participation rate of eligible patients was unclear and loss to follow-up was not reported. These limitations were in line with what would be expected for an uncontrolled observational study. It is likely that CUP/EAP studies from other countries would have the same limitations. The CS commented that studies of this kind are inherently susceptible to selection bias. Demographic details of the participants are summarised in Table 13, which also includes the cabazitaxel arm of the TROPIC study[11] for comparison purposes. There were no dramatic differences between the trial and the CUP/EAP populations, although some characteristics, for example baseline PSA level, varied between countries in the CUP/EAP studies. The Korean study had a higher proportion of patients with an ECOG PS of 2 and a lower proportion with bone metastases compared with the other national studies.

Table 14 summarises the efficacy and safety results from the TROPIC trial (cabazitaxel arm) and the fully published CUP/EAP reports. The CS noted that in the EAP reports, neutropenia was only recorded when it represented a clinical AE, whereas in the TROPIC study, data for haematological AEs were based on laboratory assessments. This would explain why levels of neutropenia recorded in cabazitaxel-treated patients in the TROPIC study were markedly higher than those reported from CUP/EAP settings. For example, neutropenia was recorded for 94% of patients in the TROPIC cabazitaxel arm (82% at grade 3 or above)[11] compared with 12.5% (9.8% grade 3 or above) in the UK EAP observational study.[50] Febrile neutropenia occurred in 8% of patients in the TROPIC cabazitaxel arm[11] compared with 1.8% in the UK EAP.[50] In addition, seven patients (6.3%) experienced neutropenic sepsis during treatment in the UK EAP, however, none of these patients had received prophylactic G-CSF. Clinical advisors to the ERG considered the data from the UK EAP[50] to be a reasonable reflection of the situation in clinical practice.

Table 13: Patient characteristics in TROPIC study and selected EAP/CUP reports (reproduced from CS, Table 33, p98)

Baseline characteristic	Country							
	TROPIC trial: (cabazitaxel arm: multiple countries)[11]	European EAP[44]	Korea[45]	Germany[46]	Italy[47]	Netherlands[48]	Spain[49]	UK[50]
Number of patients	378	746	26	111	218	49	153	112
Median age, in years	68	Mean 67.7 (SD ±7.5)	66.5	67.9	70	64.6	70.0	67
Age range	62 – 73	NR	53 - 82	49 – 81	49 – 87	59 – 70	65 – 75	63 – 72.5
Eastern Cooperative Oncology Group performance status (%)								
0	0 – 1: 93%	38.7	12	45	67.4	6.1	30.7	42.0
1		50.9	69	49.5	31.2	71.4	58.2	51.8
2		10.5	19	5.5	1.4	24.5	11.1	6.3
Sites of metastases (%)								
Bone	80	91.7	42	91	88.0	95.9	94.1	92.0
Lung	NR	NR	19	10.8	22.6	12.2	9.2	14.3
Liver	NR	NR	19	10.8	13.8	14.3	13.1	8.0
Regional lymph	NR	31.6	NR	42.3	33.6	34.7	26.1	41.1
Distant lymph	NR	30.1	NR	31.5	44.7	49.0	22.9	27.7
Visceral	25	25.3	31	NR	NR	NR	26.8	NR
Baseline Prostate Specific Antigen, ng/mL, median (IQR)	143.9 (51.1 − 416.0)	NR	95.3 (9.1 – 297.7)	733.3 (56.2 – 7679)	NR	355.5 (123.0 - 1515.4)	NR	NR
Time from last docetaxel dose to inclusion, months (IQR unless otherwise stated)	6.2 (SD ±6.7)	5.3 (2.4 – 10.6)	6.6 (0.6 – 44.4)	4.07 (2.04 – 8.67	NR	3.22 (1.36 – 6.87)	6.5 (2.5 - 12.1)	33% (within 3 months post docetaxel)

EAP, Early Access Programme; IQR, interquartile range; NR, not reported; SD, standard deviation

Table 14: Efficacy and safety outcomes in TROPIC study and selected EAP/CUP reports (reproduced, with minor changes from CS, Table 36, p104-105)

Country	Cabazitaxel cycles (median and IQR)	Overall survival, months (95% CI)	Progression-free survival,[a] months (95% CI)	Deaths n, (%)	Percentage of patients with adverse events. All grades (≥3)						
					Any	Neutro-penia	Febrile neutro-penia	Anaemia	Diarrhoea	Nausea	Fatigue
TROPIC study: multiple countries[11]	6 (3–10)	Median:15.1 (14.0 – 16.5)	Median: 2.8 (2.4-3.0)	277 (61)	95.7	94 (82)[b]	8 (8)	97 (11)	47 (6)	34 (2)	37 (5)
UK[50]	6 (3 – 10)	NR	NR	4 (3.6)	NR (NR)	12.5 (9.8)	1.8 (1.8)	NR	64.3 (4.5)	46.4 (1.8)	54.5 (13.4)
Europe (20 countries)[44]	4.0 (1–16)	NR	NR	16 (21.5)	<70 years: 88 (47) 70–74 years: 90.5 (50) ≥75 years: 88.3 (56.6)	19.8 (17.0)	5.5 (5.4)	21.6 (4.7)	34.6 (2.8)	22.1 (0.8)	25.2 (4.2)
Germany[46]	6 (3 – 10)	Mean: 13.9 (0.7–35.8)	Mean: 3.78 (0.7–31.47)	6 (5.4)	64 (46.8)	NR (7.2)	NR (2)	NR (4.5)	NR (0.9)	NR	NR
Italy[47]	6 (NR)	NR	NR	4 (1.8)	NR (NR)	NR (33.9)	NR (5.0)	NR (6.0)	NR (2.8)	NR (NR)	NR (3.7)
Netherlands[48]	6 (1 – 21)	Median: 8.7 (6.0 – 15.9)	Median: 2.8 (1.7 – 4.9)	NR	100 (51)	6.1 (4.1)	4.1 (4.1)	28.6 (4.1)	40.8 (2.0)	44.9 (2.0)	61.2 (10.2)
Spain[49]	6 (4 – 8)	NR	Median: 4.4 (2.7 –6.1)	5 (3.3)	93.5 (43.1)	22.2 (16.3)	5.2 (5.2)	37.9 (5.9)	45.8 (5.2)	22.2 (1.3)	4.6 (1.3)
Korea[45]	5 (1 –23)	Median: 16.5 (12.1 –20.9)	Median: 8.5 (3.0 –13.1)	3 (12)	96 (77)	31 (31)	31 (31)	35 (4)	42 (0)	31 (0)	35 (4)

CI, confidence interval; IQR, interquartile range; NR, not reported; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen

[a] Mean or Median time to composite progression as stated in the publication (defined as the time between randomisation and the first date of progression as measured by PSA progression, tumour progression, pain progression or death).

[b] In the EAP, neutropenia was based on adverse event declaration, whereas in TROPIC, data for haematological adverse events were based on laboratory assessments. Routine full blood count was performed prior to every cycle; for cycle 1 further full blood counts were performed in weeks 2 and 3.

The CS argued that differences in levels of neutropenia and febrile neutropenia between TROPIC and the CUP/EAP studies may partially reflect more rigorous application of guidance regarding prophylaxis with G-CSFs in clinical practice (Section 4.12.3, p114, CS). No direct evidence was presented to support this statement but it was noted that prophylactic G-CSF treatment was not permitted for the first cabazitaxel cycle in TROPIC but was allowed from the first cycle in the European CUP/EAP programme. The CS also noted that other AEs associated with cabazitaxel (for example, fatigue, diarrhoea, nausea and vomiting) are predictable and can be managed in practice by medication and patient education.

The CS (p117-119) also included two other sources of evidence on AEs: safety results from a prospective product registry in Belgium and a summary of a Periodic Benefit Risk Evaluation (PBRE) report compiled by Sanofi. These both appear to be unpublished sources of data (results from the Belgian registry are designated academic in confidence) and their relationship to the systematic search and study selection process is unclear.

The Belgian registry (HRQLana: Registry Number CABAZL06515) included 93 patients eligible for cabazitaxel treatment for mCRPC according to Belgian reimbursement criteria. The mean age was 69.4 (SD 8.8) years and ECOG PS was 0 for 25 patients (26.9%) and 1 for 68 (73.1%). Treatment-emergent AEs were reported for 81 patients (87.1%) and 43 patients (46.2%) had AEs of grade 3 or above. The most frequent AEs of grade 3 or above were: febrile neutropenia (8 patients, 8.6%); neutropenia (7 patients, 7.5%); anaemia (5 patients, 5.4%); and fatigue (3 patients, 3.2%). The CS (p118) noted that the population in this registry was more heterogeneous than the TROPIC trial population in terms of disease characteristics and had followed different therapeutic pathways so the two groups were not directly comparable. Furthermore, the time period of data collection was not reported for this registry. However, the results provide further uncontrolled evidence that the safety profile seen in the CUP/EAP studies is broadly representative of outcomes seen in clinical practice.

The CS provided a brief summary of the PBRE report, with no detailed results (p118-119, CS). The latest issue of the report covers the period from the 17th of June 2013 to the 17th of June 2014. The company stated that approximately 36,550 patients have been exposed to cabazitaxel worldwide, including 11,800 patients during the period covered by this report; approximately 4500 patients were exposed to cabazitaxel in clinical trials up to June 2014. The company stated that the PBRE findings are consistent with the known safety profile of cabazitaxel and that this is comparable with that of other products in this therapeutic class.

The ERG considers that despite the limitations of the evidence review process and the evidence itself, the CS provides a reasonable summary of the safety profile of cabazitaxel and of possible differences

between the results seen in the TROPIC study[11] and those seen in centres providing high-quality care in clinical practice.

The CS also presented a section (4.11.12) entitled 'Efficacy of cabazitaxel in the post abiraterone or enzalutamide setting. Resistance to advanced hormonal therapies'. This section included studies identified by the systematic search for non-randomised and non-controlled evidence together with other studies published since the date of that search. The section also draws on a systematic review by Maines *et al*.[84]

The first part of Section 4.11.12 of the submission (p106-108) comprises two tables. Table 38 of the CS (p106) compares patients treated with abiraterone with and without prior enzalutamide while Table 39 of the CS (p106) compares patients treated with enzalutamide with and without prior abiraterone (the legends to these tables appear to be incorrect). In both of these tables the 'no prior treatment' data are taken from randomised trials (COU-AA-301[33] and AFFIRM,[13] respectively) and these are compared with data from what appear to be retrospective cohort studies. These tables in the CS appear to show shorter PFS and fewer patients with a ≥50% decline in PSA in the studies of patients with prior treatment with another hormonal agent. No data on OS were reported. Table 15 summarises these data. Dates of the references by Schrader *et al*. and Thomsen *et al*. were reported as 2013 in the CS but the ERG believes 2014 to be correct. The CS identified one further study[65] but this apparently did not report any data on PFS or decline in PSA.

Table 15: Studies examining cross resistance between abiraterone and enzalutamide (reproduced, with minor changes, from CS Tables 38 and 39, p 106)

Reference	n	Median abiraterone duration	Patients with ≥50% PSA decline	Median PFS
No prior enzalutamide				
De Bono 2011[33]	797	8 months	29%	5.6 months
Prior enzalutamide				
Loriot 2013[56]	38	3 months	8%	2.7 months
Noonan 2013[57]	30	3 months	3%	3.6 months
Reference	**n**	**Median enzalutamide duration**	**Patients with ≥50% PSA decline**	**Median PFS**
No prior abiraterone				
Scher 2012[13]	800	8.3 months	54%	8.3 months
Prior abiraterone				
Schrader 2014[58]	35	4.9 months	29%	2.8 months
Thomsen 2014[59]	24	4.0 months	17%	2.8 months
Badrising 2014[60]	61	3.0 months	21%	2.8 months
Bianchini 2014[61]	39	2.9 months	23%	3.1 months
Schmid 2014[62]	35	2.8 months	10%	4.6 months
Azad 2015[63]	68	4.1 months	22%	NR
Brasso 2014[64]	137	3.2 months	18%	NR

PFS, progression-free survival; PSA, prostate-specific antigen; NR, not reported

The CS also included details of studies supporting the continuing efficacy of cabazitaxel after treatment with enzalutamide or abiraterone. Although seven full papers[66-69, 71, 72, 87] and 10 conference abstracts[73-82] were identified (Table 40, p108-110 and Appendix A20 of the CS), these were simply listed with no additional analyses undertaken.

The ERG notes that in the absence of further details, it is unclear whether the included studies were designed, as stated, to examine cross resistance between abiraterone and enzalutamide and / or treatment sequencing. In addition, the criteria for inclusion in the review of non-randomised and non-controlled evidence (based on those reported in Tables 29 and 30 on p88-90 of the CS) were broad and no explicit details were provided on how studies were selected and included in section 4.11.12 (p106-110) of the CS. Although a list of relevant studies were provided, no details of study or patient

characteristics were reported, no quality assessment was undertaken, data synthesis was limited and the discussion of the findings including the strength and weaknesses of the findings was lacking.

The CS (p107) also identified a systematic review by Maines *et al.*[84] on the sequential use of agents (cabazitaxel, abiraterone and enzalutamide) after docetaxel treatment in patients with mCRPC. However, no further details were provided in the CS. The CS states that '…a review by Maines of all the available evidence on the use of cabazitaxel, abiraterone and enzalutamide in the post docetaxel setting was published just prior to this submission'. For completeness, a brief summary of the systematic review is provided by the ERG. This systematic review undertook comprehensive searches of two electronic databases (MEDLINE and EMBASE) to identify all published studies between January 2012 and March 2015 (in the English language) reporting monthly OS rates of mCRPC patients receiving third-line new agents after having previously received docetaxel and another new agent. Searches were supplemented by searching key conference websites. For the descriptive analysis, the treatments were merged into three groups: (1) all-hormonal sequences i.e. abiraterone followed by enzalutamide, or enzalutamide followed by abiraterone; (2) cabazitaxel-hormonal i.e. cabazitaxel followed by abiraterone or enzalutamide; and (3) hormonal- cabazitaxel i.e. abiraterone or enzalutamide followed by cabazitaxel. No quality assessment was undertaken. The cumulative monthly OS rates in each group were determined using a weighted-average approach. OS was considered to be the most reliable measure of clinical outcome as endpoints such as biochemical or objective response rates and PFS can be greatly influenced by different definitions and/or timings of follow-up between studies. The review included thirteen retrospective studies[56, 57, 60, 62, 63, 66, 68, 69, 72, 73, 88-90] including 1016 patients who received the following sequences (some were multi-arm studies): all-hormonal sequences (n=397 [72 patients were excluded from the analysis because they were chemo-naïve]), cabazitaxel-hormonal (n=229) and hormonal-cabazitaxel (n=318). The 6-month OS rates were 65.4%, 94.8%, and 85.8%, whereas the 12-month OS rates were 28.5%, 76.4%, and 61.3%, respectively. There were no statistically significant differences in terms of known prognostic factors (median age, ECOG PS 0-1 and ≥2, Gleason score ≥8, and the rate of bone, lymph nodes and visceral metastases). The authors concluded that 'The retrospective nature of included studies, the limited cohort size, the short follow-up of most of them as well as the heterogeneity of patient population across studies and the inevitable selection and methodological biases require caution in the interpretation of the results. Our analysis does not allow any definite conclusions to be drawn, and the suggestion that sequences including CABA [Cabazitaxel] may lead to better disease control needs to be prospectively validated in larger series, ideally head-to-head comparison trials…'

4.3 Critique of trials identified and included in NMA

In the absence of any direct head-to-head RCTs comparing cabazitaxel and other second-line agents (abiraterone and enzalutamide) for the treatment of mCRPC, the company conducted an NMA. This is

an extension of the conventional pairwise meta-analysis, combining direct and indirect evidence from RCTs. This approach allows simultaneous comparisons of multiple treatments from trials comparing different sets of treatments (providing there is a connected network) and ensures that the estimates produced between the pairwise comparators are not discrepant. It is typically performed in a Bayesian manner to allow for all sources of uncertainty and to allow probabilistic statements to be made about population parameters.

The company conducted a systematic review (review 2) to collate the clinical evidence from published RCTs which assess the efficacy of second-line agents for the treatment of mCRPC which had progressed after first-line docetaxel. Full details of the inclusion and exclusion criteria of the systematic reviews are provided in Section 4.1.2. In brief, the population of interest was adults with mCRPC who had been previously treated with docetaxel based regimens where the relevant study was an RCT and the outcomes included efficacy. The interventions of interest (relevant to the decision problem) were: cabazitaxel; abiraterone; enzalutamide; mitoxantrone; and BSC. It is noteworthy that radium-223 dichloride was listed in the final scope as a comparator for the subgroup of patients with bone metastasis only (no visceral metastasis). However, as discussed in Section 4.1.2, the company expressed their concerns about the applicability and feasibility of including radium-223 dichloride as a comparator. As noted in the company's clarification response to question A1 (p1-2), the company states that 'Given these anticipated issues with the different RCT populations, study endpoints coupled with the characteristics of patients in whom the different drugs are likely to be used, it remains a concern that inclusion of ALSYMPCA in the existing NMA is problematic and we have not done this analysis.' Nevertheless, the company did provide a summary of the efficacy results for OS in the cohort of patients with previous docetaxel use from the ALSYMPCA study[14] and the TROPIC study[11] (Table 16) but with no further analysis.

Table 16: Overall survival for the TROPIC and ALSYMPCA (previous docetaxel use) populations

Trial	Active therapy (cabazitaxel, radium-223 dichloride)	Placebo (mitoxantrone for cabazitaxel)	Difference	Hazard ratio
TROPIC (ITT)[11]	15.1 (14.0 – 16.5)	12.8 (11.5 – 13.7)	2.3 months	0.72 (0.61 - 0.85)
ALSYMPCA[14] (patients with previous docetaxel use)	14.4 months (12.5 – 15.5)	11.3 months (10.0 – 12.9)	3.1 months	0.70 (0.56 – 0.88)

The systematic review methods undertaken for the NMA (e.g. literature searching, study selection, data extraction and quality assessment) were similar to those undertaken for the cabazitaxel systematic review. As noted in Section 4.1, adequate methods were undertaken to identify, select and quality assess all relevant RCT studies.

Although numerous studies were initially identified, only three studies (which were considered relevant to the decision problem by the company) were included in the NMA. The TROPIC study[11] compared cabazitaxel plus prednisone with mitoxantrone plus prednisone; the AFFIRM study[13] compared enzalutamide plus placebo with placebo with or without prednisone; and the COU-AA-301 study[12] compared abiraterone plus prednisone with prednisone plus placebo. A summary of the key design and study characteristics, as reported in the CS, is provided in Table 17. Inclusion and exclusion criteria were similar for all three studies.

Table 17: Characteristics of trials included in the NMA (adapted from Section 4.3 and appendices B (tables 1 and 2) of the CS)

	TROPIC[11]	AFFIRM[13]	COU-AA-301[12, 33]
Location	146 sites in 26 countries (6 UK sites)	156 sites in 15 countries (12 UK sites)	130 sites in 13 countries (12 UK sites)
Design	Phase III RCT	Phase III RCT	Phase III RCT
Duration	Treatment to disease progression or unacceptable toxicity or maximum of ten cycles; follow-up to death or study cut-off	24 months	Treatment to disease progression
Randomisation	By interactive voice response system stratification by measurability of disease and ECOG PS	By interactive voice response system; stratification by ECOG PS and pain score	By interactive web response system; stratification by baseline ECOG PS; presence or absence of pain; 1 vs. 2 previous chemotherapy regimens; and type of disease progression at study entry
Blinding	Patients and treating physicians not blinded	Patients, investigators, site personnel and sponsor's staff involved in the study were blinded to study drug	Patients and investigators blinded to study drug
Intervention(s) and comparator(s)	Cabazitaxel plus prednisone (n=378) Mitoxantrone plus prednisone (n=377)	Enzalutamide (n=800) Placebo (n=399) Use of prednisone or other glucocorticoids was permitted but not required	Abiraterone acetate plus prednisone/prednisolone (n=797) Placebo plus prednisone/prednisolone (n=398)
Primary outcomes	OS: defined as time from randomisation to death from any	OS: time from randomisation to death from any cause	OS: time from randomisation to death from any cause

	cause		
Secondary outcomes	PFS; tumour response rate; time to tumour progression; PSA progression; PSA response; pain progression; pain response; adverse events in patients who had received at least one dose of study drug	Time to PSA progression; radiographic PFS; time to first skeletal-related event; FACT-P response rate; rate of pain palliation at week 13	Time to PSA progression; PSA response rate
Other endpoints		PSA response rate; best overall radiographic response; EQ-5D; ECOG PS; pain progression rate; time to pain progression; change from baseline in pain severity and pain interference; change from baseline in QoL	Modified PFS; objective tumour response rate; pain palliation; time to pain progression; fatigue palliation and time to fatigue progression; functional status measured by FACT-P; AEs and clinical laboratory tests for safety; medical resource utilisation information
Duration of follow-up	Median 12.8 months in publication, 20.5 months in updated analysis included in CS	Median 14.4 months at interim analysis and 15 months at database lock	Up to 60 months

AEs, adverse events; ECOG, Eastern Co-operative Oncology Group; EQ-5D, EuroQoL-5D quality of life instrument; FACT, Functional Assessment of Cancer Therapy-Prostate; OS, overall survival; PFS, progression-free survival; PS, performance status; PSA' prostate-specific antigen; QoL, quality of life; RCT, randomised controlled trial; UK, United Kingdom

Despite stating that 'the populations are comparable between the trials' included in the NMA (Appendices B, p6, CS), the CS also presented data indicating that 'patients entering the studies had different disease characteristics' (Appendices B, p9, CS). Firstly, the CS stated that 'in the COU-AA-310 trial, only 30% of patients were refractory to docetaxel whilst 70% in TROPIC had progressed whilst on docetaxel or within three months of receiving it'. The ERG was unable to verify the statement about COU-AA-301 from the publication cited.[12] Secondly, the CS stated that in AFFIRM 'the mean time to start of enzalutamide therapy from last docetaxel exposure was 9 months' (Appendices B, p9, CS). No reference was provided and the ERG was unable to verify the statement in the main AFFIRM trial publication[13] (including supplementary appendices). For comparison, Table 3 of the COU-AA-301 study publication[12] indicates that 339/1195 patients (28%) started treatment in the trial within three months of their last dose of docetaxel. No mean or median value for time since the last dose of docetaxel was reported. In TROPIC, the median time from last docetaxel dose to disease progression (before entering the trial) was 0.7 months in the control group and 0.8 months in the cabazitaxel group.[11]

Data indicating possible differences in disease status between trial populations need to be interpreted in the context of the generally similar patient characteristics presented in Table 18. Clinical advisors to the ERG indicated that while the TROPIC trial may involve patients with more advanced disease than the other two trials, the best measure for this and hence the significance of any differences was unclear. The ERG noted that when groups are compared for a large number of variables, it is possible that some potentially significant differences will be identified by chance.

Table 18: Characteristics of patients enrolled in the trials included in the NMA (reproduced from CS, Appendices B, Table 5)

Baseline Characteristics	TROPIC[11]		AFFIRM[13]		COU-AA-301[12, 33]	
	Cabazitaxel (n=378)	Mitoxantrone (n=377)	Enzalutamide (n=800)	Placebo (n=399)	Abiraterone + Prednisone (n=797)	Placebo + Prednisone (n=398)
Age (years)						
Median (range)	68 (62−73)	67 (61−72)	69 (41, 92)	69 (49, 89)	69 (42, 95)	69 (39, 90)
≥75 years	69 (18%)	70 (19%)	199 (24.9%)	104 (26.1%)	220/797 (28%)	111/397 (28%)
Ethnicity	White: 83.5% Asian: 7.5% Black: 5% Other: 3.5%		White: 93.1% Asian: 1.7% Black: 3.6% Other: 1.6%		White: 92.6% Asian: 1.1% Black: 4.0% Other: 2.2%	
Time since diagnosis (months) Mean ± SD	NR	NR	86.1 ± 54.83	81.9 ± 50.89	85.8 ± 53.6	82.5 ± 56.3
Eastern Cooperative Oncology Group performance status						
0-1	350 (93%)	344 (91%)	730 (91.3%)	367 (92.0%)	715/797 (90%)	353/398 (89%)
2			70 (8.8%)	32 (8.0%)	82/797 (10%)	45/398 (11%)
Prostate Specific Antigen (ng/ml)						
Median	143·9	127·5	107.7	128.3	128.8	137.7
Gleason score at initial diagnosis						
≤7	NR	NR	355/726 (49%)	175/368 (48%)	341/697 (49%)	161/350 (46%)
≥8	NR	NR	366/726 (50%)	193/368 (52%)	356/697 (51%)	189/350 (54%)
Number of previous cytotoxic chemotherapy regimens						
1	260 (69%)	268 (71%)	579 (72.4%)	296 (74.2%)	558/797 (70%)	275/398 (69%)
2	94 (25%)	79 (21%)	196 (24.5%)	95 (23.8%)	239/797 (30%)	123/398 (31%)
3			25 (3.1%)	8 (2.0%)	0	0
>2	24 (6%)	30 (8%)				
Disease location						
Bone	NR	NR	730 (92.2%)	364 (91.5%)	709/797 (89%)	357/397 (90%)
Node	NR	NR	92 (11.6%)	34 (8.5%)	361/797 (45%)	164/397 (41%)

Baseline Characteristics	TROPIC[11]		AFFIRM[13]		COU-AA-301[12, 33]	
Liver	NR	NR	442 (55.8%)	219 (55.0%)	90/797 (11%)	30/397 (8%)
Previous cancer therapy						
Surgery	198 (52%)	205 (54%)	531 (66.4%)	243 (60.9%)	429/797 (54%)	193/398 (49%)
Radiotherapy	232 (61%)	222 (59%)	571 (71.4%)	287 (71.9%)	570/797 (72%)	285/398 (72%)
Hormonal	375 (99%)	375 (99%)	800 (100%)	399 (100%)	796 (100%)	396 (100%)
Number of previous docetaxel regimens						
1	316 (84%)	327 (87%)	NR	NR	NR	NR
2	53 (14%)	43 (11%)	NR	NR	NR	NR
>2	9 (2%)	7 (2%)	NR	NR	NR	NR

NR, not reported; SD, standard deviation

The NMA presented by the company links cabazitaxel with abiraterone and enzalutamide via a comparator defined as 'BSC' (Figure 3). The actual interventions received by patients in the control group differed between trials: mitoxantrone + prednisone in TROPIC; placebo with or without prednisone in AFFIRM; and prednisone + placebo in COU-AA-301. In the appraisal of enzalutamide (TA316), it was accepted that the three control groups could be considered equivalent for the purposes of indirect comparison of OS.[25] This was based on evidence that:

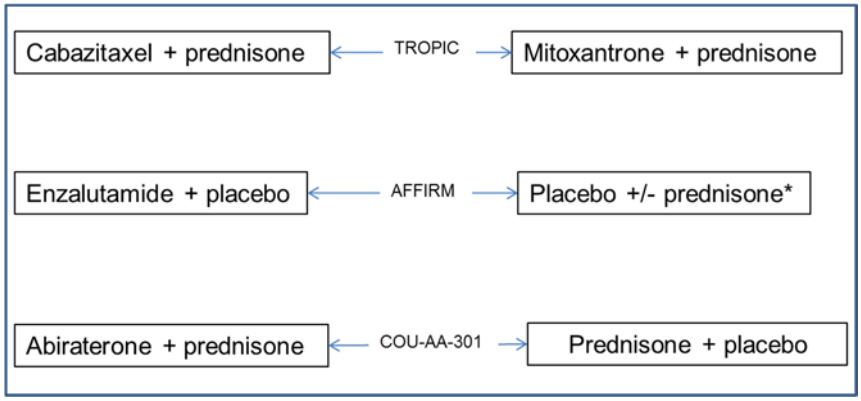
- prednisone was unlikely to affect overall or progression-free survival given that patients would have already received steroids and progressed on this treatment earlier in the course of the disease (ERG report TA316,[22] p82)
- median times for OS in the control groups were similar across the three trials (12.7 months in TROPIC, 11.7 months in COU-AA-301 and 13.6 months in AFFIRM (ERG report TA316,[22] Table 4.27, p86)).

In the CS for the current appraisal (Appendices B, p1), additional evidence is presented to support the claim that mitoxantrone does not improve survival and therefore a regimen comprising mitoxantrone plus prednisone together with BSC can be considered equivalent to BSC alone. A recent study[91] analysed data from the control arms of TROPIC[11] and SUN1120.[92] In the latter trial control group patients received prednisone plus placebo. Both trials enrolled men with mCRPC whose disease had progressed after docetaxel treatment. Propensity score matching was used to balance patient characteristics across the two trials, based on age and key prognostic variables for survival. The study found that median survival was similar between mitoxantrone plus prednisone and prednisone alone (385 vs. 336 days). Although this study had limitations associated with combining data from two different trials, taken together with other evidence it seems reasonable to consider the control arm of TROPIC as equivalent to BSC for the purposes of the NMA of OS. The ERG notes that if mitoxantrone does confer an advantage (to either OS or PFS) over BSC, then this would be unfavourable to cabazitaxel in indirect comparisons.

The other outcome analysed in the NMA was rPFS. The CS (p86-87) pointed out that the three trials included in the NMA used different definitions of PFS (see

Table 19). TROPIC[11] used a composite definition of progression so a patient's disease was considered to have progressed if they met criteria for: PSA progression; tumour progression; pain progression; or death. By contrast, AFFIRM[13] and COU-AA-301[12] used a definition based solely on tumour progression. However, rPFS was reported in the AFFIRM and COU-AA-301 trials. To facilitate comparison across the trials rPFS was derived from the patient level data from TROPIC, with the aim of reflecting the endpoint that was reported in the AFFIRM and COU-AA-301 trials.

Figure 3: Network diagrams for the included trials



* 45.6% of patients were exposed to prednisone in the placebo arm of AFFIRM

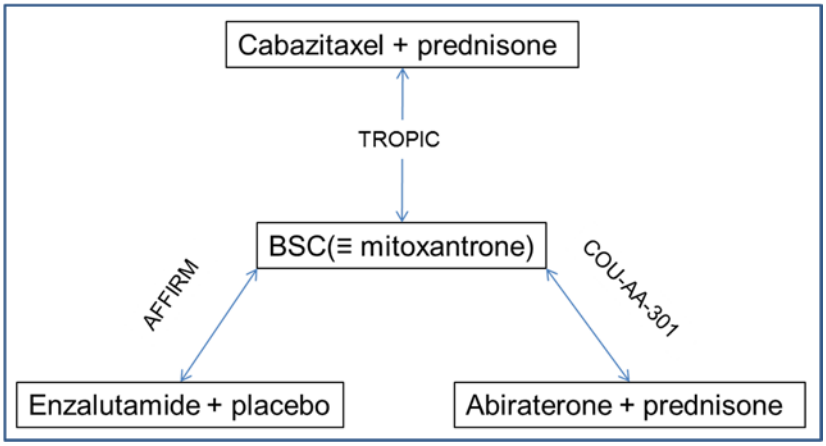


Table 19: Definitions of progression-free survival in trials included in the NMA

Study	Definition of progression-free survival	Type of endpoint	Comments
TROPIC[11]	Time from randomisation to first date of progression as measured by PSA progression, tumour progression, pain progression or death	Secondary	For use in the NMA, a modified definition was used: time from randomisation to the first occurrence of: tumour progression (based on RECIST criteria) or death
AFFIRM[13]	Time to progression of soft-tissue disease according to RECIST version 1.1; progression of osseous disease according to bone scans showing two or more new lesions per PCWG2; or death from any cause	Secondary	Confirmed by CT or MRI imaging of soft tissue or radionuclide bone scanning
COU-AA-301[12]	Time to radiographic progression defined as soft-tissue disease progression by modified RECIST criteria or progression according to bone scans showing two or more new lesions not consistent with tumour flare	Secondary	Also had PSA progression as an endpoint

CT, computed tomography; MRI, magnetic resonance imaging; PCWG2, Prostate Cancer Working Group 2; PSA, prostate-specific antigen; RECIST, response evaluation criteria in solid tumours

The analysis of rPFS revealed that there were differences in this outcome between the control groups of the three trials. Specifically, the control group in TROPIC had a longer median rPFS (5.9 months, 95% CI: 5.1 to 7.0) compared with the control groups in AFFIRM (2.9 months, 95% CI: 2.8 to 3.4) and COU-AA-301 (3.6 months, 95% CI: 2.9 to 5.5). It is noteworthy that despite the different point estimates there was some overlap in the 95% CI for median rPFS between TROPIC and COU-AA-301. The company argued that:

> The relatively poor performance of the control arms [in] the AFFIRM and COU-AA-301 trial[s], compared to the almost double median rPFS for mitoxantrone in the TROPIC trial raises questions about the comparability of the control arms for the indirect comparison. Hazard ratios for rPFS from both AFFIRM and COU-AA-301 are lower compared to those

from TROPIC, and as such bias against cabazitaxel when combined in the indirect comparison (Appendices B, p9, CS).

The ERG accepts that it is questionable whether outcomes of PFS can be synthesised in a NMA when the definitions of the outcome are different; however, assuming that the derived measure of rPFS is adequate, then this concern can be considered to have been addressed in the presented analysis. Therefore, use of rPFS was appropriate to allow a comparison across trials. This issue is discussed in Section 4.4. Furthermore, the ERG notes that for the company's economic evaluation, increased values of rPFS lead to worse estimates of cost-effectiveness. Hence the company's argument that the results of the NMA bias against the clinical effectiveness of cabazitaxel may result in a bias in favour of the cost-effectiveness of cabazitaxel.

Risk of bias was assessed for the three RCTs in the CS (TROPIC in Section 4.6.2 and the other RCTs in appendices B, Tables 3 and 4). The results are summarised in Table 20.

Table 20: Quality (risk of bias) assessment for trials included in the NMA (based on data in the CS)

	TROPIC[11]	AFFIRM[13]	COU-AA-301[12]
Was randomisation carried out appropriately?	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes
Were the groups similar at baseline in terms of prognostic factors?	Yes	Yes	Yes
Were care providers, participants and outcome assessors blind to treatment allocation?	No	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	Not clear	Not clear
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Yes	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes/Yes	Yes/Not clear	Yes/Yes

The CS concluded that there was no evidence of risk of bias in the AFFIRM and COU-AA-301 trials. The question about selective reporting bias was answered 'yes' for AFFIRM because EQ-5D data

have not been reported but this does not suggest a major problem with selective reporting of study outcomes. The major potential risk of bias in trials used for the NMA arises from the lack of blinding of care providers, participants and outcome assessors in TROPIC. The company acknowledged this as a limitation of the trial but argued that it was unlikely to impact on the main outcomes. In the previous appraisal of cabazitaxel, the ERG agreed that OS (the primary outcome) and tumour response were unlikely to have been affected by bias. However, there was some risk of bias in the assessment of subjective outcomes such as pain and symptomatic disease progression. PFS, a composite endpoint incorporating some subjective outcomes, was therefore potentially susceptible to bias.

4.4 Critique of the NMA

4.4.1 Efficacy

A NMA was performed to compare treatment effects of cabazitaxel, enzalutamide, abiraterone and BSC for the outcomes of OS and rPFS using data from the following trials: TROPIC;[11] AFFIRM;[13] and COU-AA-301.[12] Separate NMAs were undertaken for each outcome. The results of the NMA are relevant for the scenario analysis (alternative treatment practice) presented in Section 5.2.9.2.

It is assumed that the respective control-arms of the trials namely, mitoxantrone + prednisone (TROPIC), placebo + prednisone (COU-AA-301) and prednisone alone (AFFIRM) can all be considered equivalent to BSC. Under this assumption, the studies provide a connected network, as presented in Figure 3.

Despite conducting the NMA, as required by the scope, the CS (p85-87) raises concerns over the validity of the indirect comparisons due to differences between i) patient populations and trial design ii) control-arm treatments and iii) definition of PFS. The described differences have been discussed in Section 4.3 and the effect that these have on the validity of the NMA are discussed below.

Heterogeneity between studies is to be expected, but will only result in biased estimates of treatment effects if there is an imbalance in treatment effect modifiers across studies comparing different pairs of treatments. Although the CS (p87) notes concerns relating to differences in patient characteristics there is no discussion of whether the treatment effects are modified by these characteristics. Previous reports have considered potential treatment effect modifiers. For the TROPIC study[11] the results indicated “no significant interactions between the prognostic factors of interest and treatment response”.[15] For the AFFIRM[13] study it was stated that “The overall survival benefit was consistent across all subgroups, including… type of disease progression at entry”.[13] The COU-AA-301[12] trial found “the test for heterogeneity of treatment effect between subgroups showed no significant finding”, although they note small sample sizes for some subgroups.

Based on the derived estimate of median rPFS for the TROPIC[11] trial and the reported rPFS outcomes for the AFFIRM[13] and COU-AA-30[12] trials, the control arms of the three trials are described by the CS (p87) to be "substantially different, indicating that for the purposes of the NMA they should not be considered equivalent". The ERG notes that variation in control effects between studies are to be expected, reflecting differences in patient characteristics. In an NMA it is the treatment effects (in this case the HR) that are assumed to be combinable across studies. The CS (p87) states that "Hazard ratios for rPFS from both AFFIRM and COU-AA-301 are lower compared to those from TROPIC, and as such bias against cabazitaxel when combined in the indirect comparison." The ERG notes that the reasoning provided in the CS does not in itself imply that the resulting treatment effects will be biased. The treatment effects may be biased if there is an imbalance in treatment effect modifiers between the studies; however, no evidence has been provided to suggest that this is the case. Validity of the NMAs for both OS and rPFS are dependent on the assumption that the control treatments of the three included trials can be considered exchangeable, and therefore provide a connected evidence network. If this is not the case (i.e. the control treatments are not exchangeable) then we may expect considerable heterogeneity. In the presence of between study heterogeneity a fixed effect model is not appropriate, and the ERG considers that a random effect model should be used for the analysis (as discussed in further detail below).

The results of the company's NMA are presented in

Table **21** in terms of HR for cabazitaxel versus each treatment (BSC, enzalutamide, abiraterone). The results are based on a fixed effects model, with results from a random effects model also provided in the appendix (although this has not been implemented correctly in the absence of sufficient sample data and the results are therefore not valid). Following a request for clarification (question A20), the company failed to provide updated results using a weakly informative prior to inform the random effects meta-analysis. When there are too few studies to estimate the between-study SD from the sample data alone and a fixed effect model is used, this can be viewed as asserting that the between study SD is zero. Although prior distributions should not be used without reasonable justification, the ERG considers that the assumption of zero between-study variation should also be treated with caution given the clear case that has been made to suggest heterogeneity. In the absence of further information on which to base the choice of prior, use of a half-normal prior as described in the NICE Technical Support Document (TSD)[93] is recommended. Furthermore, in the presence of heterogeneity, the predictive distribution, rather than the distribution of the mean treatment effect, would better represent uncertainty about the treatment effect in a future study.[93] In a Bayesian setting, the predictive distribution can be obtained by generating samples from a normal distribution with mean equal to the estimated mean treatment effect, and variance given by the estimated between-trial heterogeneity.

Based on results from the fixed effects NMA, the CS (Section 8: Appendices B pg22-23) concludes that treatment effects for cabazitaxel, abiraterone and enzalutamide are broadly similar for OS. With regards to rPFS the results of the fixed effects NMA indicate that the disease appears to progress slower when patients are treated with enzalutamide rather than when patients are treated with cabazitaxel or abiraterone. The ERG considers the NMA results should be interpreted with caution since they were based on an assumption of no between-study variance (using a fixed effects model), despite the stated concerns in terms of differences between patient populations and exchangeability of control treatments. Results from an amended random effects model (Section 4.5) confirm this finding of broadly similar treatment effects for OS but, contrasting to the results presented in the CS, also indicate that no active treatments are significantly more effective than other active treatments for rPFS.

The ERG also notes that HRs have been used for the synthesis. HRs are averaged estimates of treatment effect, ignoring any potential treatment by time interaction, and use of HR in the NMA will only be appropriate if the hazards are proportional.[94] Alternative methods that allow the relative treatment effects to vary over time have been proposed, including the use of fractional polynomials[95] which could be implemented in this case using individual patient data from the trials where available, and reconstructed individual patient data from Kaplan-Meir curves otherwise. The company state in their clarification response to question A19 that they are “aware that the Fizazzi *et al.* comment that

the hazard ratios are not proportional in the updated COU-AA-301study for abiraterone vs. placebo and inspection of the KM data (from Figure 2 in Fizzazi 2012) shows that the placebo OS line crosses the abiraterone line at 24 months." Despite this, they state that use of HR can be "seen as a reasonable approach given the limitations with the data and the comparisons in general." The ERG consider that the results of the NMA can be used as an indication of the treatment effects between relevant comparators, but should be treated with caution due to the described uncertainty in the suitability of the effect measure, in addition the other stated concerns in terms of implementation of the NMA.

Table 21: Key results from the fixed effects NMA – ITT population, (reproduced, with minor changes, pg87, CS.)

	Overall survival			Radiographic progression free survival		
	HR	Credible intervals		HR	Credible intervals	
Cabazitaxel vs BSC[a]	0.72	0.61	0.85	0.75	0.65	0.88
Cabazitaxel vs abiraterone	0.97	0.78	1.21	0.97	0.76	1.22
Cabazitaxel vs enzalutamide	1.14	0.90	1.45	1.88	1.54	2.29

HR, Hazard Ratio; BSC, Best Supportive Care

[a] mitoxantrone assumed equivalent to BSC

4.4.2 Safety

Following a clarification response to question B10, the company provided details of AEs from the TROPIC, COU-AA-301 and AFFIRM trials. A summary is provided in Table 22. It should be noted that this table only includes AEs of grade 3 or above (see Appendix 2 for all grade AE). The source of some of these data were unclear as only frequently occurring AEs were reported in the AFFIRM trial publication cited by the company.[13] It should also be noted that the 2012 publication of the COU-AA-301 trial[12] reported three cases of febrile neutropenia (grade 4) in the abiraterone group rather than zero as reported in Table 22. Data from the ALSYMPCA trial of radium-223 dichloride[14] have been added given that radium-223 dichloride was identified as a relevant comparator in the NICE final scope.[19] These data are for patients previously treated with docetaxel who received radium-223 dichloride in the ALSYMPCA study, and were provided in the company's response to clarification (question A18).

Comparison across trials is limited by differences in reporting. While TROPIC and COU-AA-301 reported fully on AEs during treatment, the AFFIRM publication only reported events that occurred in more than 10% of patients in the enzalutamide group and whose rate was at least 2 percentage points higher with enzalutamide compared with placebo. The ALSYMPCA publication reported haematological AEs that occurred in at least 5% of patients in either treatment group and non-haematological events that occurred in at least 10% of patients.[14]

Differences in AEs across the four trials reflect the different mechanisms of action of the agents involved. Cabazitaxel, which acts by blocking cell division, would be expected to have a different AE profile to the advanced hormonal agents abiraterone and enzalutamide. Table 22 shows that high rates of haematological AEs such as anaemia and neutropenia were observed in patients treated with

cabazitaxel plus prednisone. However, clinical advisors to the ERG commented that high levels of monitoring in a trial setting would result in abnormal laboratory measurements being recorded as AEs despite the fact that these may not cause any problems for the patient. The ERG's clinicians agreed with the view expressed in the CS that rates of haematological AEs reported in the CUP and EAPs were likely to be more reflective of clinical practice. This evidence is discussed in Section 4.2.

Among non-haematological AEs, the most common in cabazitaxel-treated patients in TROPIC[11] were diarrhoea (47%), fatigue (37%), nausea (34%) and vomiting (23%). The most common AEs in patients receiving abiraterone in COU-AA-301[12] were fatigue (44%), nausea (30%), back pain (30%) and arthralgia (27%). Comparison with the enzalutamide group of the AFFIRM trial[13] was only possible for diarrhoea (21%) and fatigue (34%). The most common AEs in ALSYMPCA[14] in the relevant patient subgroup (those who had previously received docetaxel) were bone pain (53%), nausea (40%) and fatigue (27%).

Table 22: Table of adverse event data used in the company's economic model (based on company clarification response, Table 17)

	TROPIC[11]		COU-AA-301[12]		AFFIRM[13]		ALSYMPCA (subgroup with previous docetaxel use)[14]	
Grade ≥3	Cabazitaxel (n=371)	Mitoxantrone (n=371)	Abiraterone (n=791)	Placebo plus prednisone (n=394)	Enzalutamide (n=800)	Placebo (n=399)	Radium-223 dichloride (n=347)	Placebo (n=171)
Haematological								
Neutropenia	303 (82%)	215 (58%)	1 (<1%)	1 (<1%)	NR	NR	11 (3%)	1 (<1%)
Febrile neutropenia	28 (8%)	5 (1%)	0 (0%)	0 (0%)	NR	NR	NR	NR
Leukopenia	253 (68%)	157 (42%)	NR	NR	NR	NR	5 (1%)	1 (<1%)
Anaemia	39 (11%)	18 (5%)	62 (8%)	32 (8%)	62 (8%)	38 (10%)	50 (14%)	25 (15%)
Thrombocytopenia	15 (4%)	6 (2%)	11 (1%)	2 (<1%)	8 (1%)	3 (<1%)	31 (9%)	5 (3%)
Non-haematological								
Diarrhoea	23 (6%)	1 (<1%)	9 (1%)	5 (1%)	9 (1%)	1 (<1%)	2 (<1%)	4 (2%)
Fatigue	18 (5%)	11 (3%)	72 (9%)	41 (10%)	50 (6%)	29 (7%)	16 (5%)	10 (6%)
Asthenia	17 (5%)	9 (2%)	26 (3%)	8 (2%)	20 (2.5%)	10 (2.5%)	NR	NR
Back pain	14 (4%)	11 (3%)	56 (7%)	40 (10%)	40 (5%)	16 (4%)	NR	NR
Nausea	7 (2%)	1 (<1%)	17 (2%)	11 (3%)	12 (1.5%)	13 (3%)	8 (2%)	3 (2%)
Vomiting	7 (2%)	0 (0%)	21 (3%)	12 (3%)	9 (1%)	10 (2.5%)	9 (3%)	5 (3%)
Haematuria	7 (2%)	2 (1%)	12 (2%)	9 (2%)	12 (1.5%)	4 (1%)	NR	NR
Abdominal pain	7 (2%)	0 (0%)	18 (2%)	8 (2%)	NR	NR	NR	NR
Pain in extremity	6 (2%)	4 (1%)	24 (3%)	20 (5%)	14 (2%)	14 (3.5%)	NR	NR

Dyspnoea	5 (1%)	3 (1%)	14 (2%)	9 (2%)	5 (<1%)	6 (1.5%)	NR	NR
Constipation	4 (1%)	2 (1%)	10(1%)	4 (1%)	6 (<1%)	5 (1%)	3 (1%)	1 (<1%)
Pyrexia	4 (1%)	1 (<1%)	3 (<1%)	5 (1%)	NR	NR	NR	NR
Arthralgia	4 (1%)	4 (1%)	40 (5%)	17 (4%)	20 (2.5%)	7 (2%)	NR	NR
Urinary-tract infection	4 (1%)	3 (1%)	12 (2%)	3 (<1%)	10 (1%)	3 (<1%)	3 (1%)	4 (2%)
Pain	4 (1%)	7 (2%)	7 (1%)	8 (2%)	NR	NR	NR	NR
Bone pain	3 (1%)	9 (2%)	51 (6%)	31 (8%)	18 (2%)	13 (3%)	74 (21%)	53 (31%)
Other								
Cardiac disorders	7 (2%)	3 (1%)	41 (5%)	9 (2%)	7 (1%)	8 (2%)	NR	NR
Abnormalities in liver function tests	NR	NR	30 (4%)	14 (4%)	3 (<1%)	3 (<1%)	NR	NR
Hypertension	1 (<1%)	1 (<1%)	10 (1%)	1 (<1%)	16 (2%)	5 (1%)	NR	NR
Hypokalaemia	2 (<1%)	0 (0%)	35 (4%)	3 (<1%)	NR	NR	NR	NR
Fluid retention or oedema	2 (<1%)	1 (<1%)	20 (3%)	4 (1%)	8 (1%)	3 (<1%)	6 (2%)	2 (2%)
Seizure	1 (<1%)	0 (0%)	NR	NR	5 (<1%)	0 (0%)	NR	NR
Weight decrease	NR	NR	NR	NR	NR	NR	4 (1%)	5 (3%)
Anorexia	NR	NR	NR	NR	NR	NR	4 (1%)	2 (1%)

NR, not reported

Rates of withdrawal due to AEs were higher in patients treated with cabazitaxel in TROPIC[11] than in the abiraterone and enzalutamide arms of COU-AA-301[12] and AFFIRM,[13] respectively. Rates of AEs leading to death were higher in COU-AA0301 than the other two trials, although it should be noted that the rates of events leading to withdrawal and those leading to death were reported as identical for the abiraterone group in this trial. Table 23 summarises these data. For comparison, in the ALSYMPCA trial of radium-223 dichloride, withdrawals due to AEs occurred in 99/600 (17%) patients in the radium-223 dichloride group and 62/301 (21%) in the placebo group.[14] The breakdown of withdrawals between patients previously treated with docetaxel or untreated was not reported, which limits the relevance of the data to this appraisal.

Clinical advisors to the ERG stated that enzalutamide or abiraterone would normally be given to patients with mCRPC before cabazitaxel because of the lower toxicity of the hormonal agents. However, the advisors recognised that this may not be the approach adopted by all clinicians.

Table 23: Adverse events leading to withdrawal or death in trials included in the NMA

	TROPIC[11]		AFFIRM[13]		COU-AA-301[12]	
	Cabazitaxel	Mitoxantrone	Enzalutamide	Placebo	Abiraterone + prednisolone	Placebo + prednisolone
AEs leading to withdrawal	67/378 (18%)	32/377 (8%)	61/800 (8%)	39/399 (10%)	105/791 (13%)	71/394 (18%)
AEs leading to death	18/378 (5%)	2/377 (<1%)	23/800 (3%)	14/399 (4%)	105/791 (13%)	61/394 (16%)

AEs, adverse events

In the clarification response, the company also reported results of the fixed effects NMA for AEs across the TROPIC, AFFIRM and COU-AA-301 trials (Tables 18–27, question B10). These data were used in the economic model but were not reported in the discussion of the NMA in the CS. The ERG believes that odds ratios were used and not HRs as reported in the table headings. There were also discrepancies in labelling of some of the tables, making it unclear to which AEs the table referred. Key results from the NMAs are summarised for each AE in Table 24. For anaemia and nausea, the estimated treatment effects indicate a statistically significantly increase AE for cabazitaxel compared with BSC, abiraterone and enzalutamide. For diarrhoea there is a statistically significantly increase in AEs for cabazitaxel compared with BSC and abiraterone, and for neutropenia there is a

statistically significant increase in AEs for cabazitaxel compared with BSC. As with the NMA of clinical effectiveness, the ERG considers results from the NMA for AEs should be interpreted with caution since they were based on an assumption of no between-study variance (using a fixed effects model), despite the previously stated concerns in terms of differences between patient populations, and an assumption that control treatments were exchangeable. The uncertainty in treatment effects is therefore likely to be underestimated.

Table 24: Key results from fixed effects NMAs of adverse events (summarised from Tables 18-27, company's clarification response to question B10)

Adverse event	Cabazitaxel vs		
	BSC [a]	Abiraterone	Enzalutamide
Neutropenia	**3.24(2.33,4.53)**	6.54 (0.16,251)	-
Anaemia	**2.33 (1.31.4.29)**	**2.42 (1.16,5.09)**	**2.91 (1.42,6.14)**
Thrombocytopenia[b]	2.66 (1.04,7.74)	0.85 (0.1,4.91)	1.83 (0.29,9.82)
Diarrhoea	**33.4 (5.66,1070)**	**36.7 (4.16,1370)**	5.59 (0.12,306)
Fatigue	1.7 (0.79,3.82)	1.96 (0.83,4.86)	1.98 (0.8,5.08)
Asthenia[c]	1.98 (0.88,4.74)	2.28 (0.93,5.99)	1.94 (0.61,6.15)
Back pain	1.29 (0.57,3.01)	1.92 (0.77,4.89)	1.01 (0.36,2.81)
Nausea	**9.69 (1.47,252)**	**12.6 (1.6,355)**	**22 (2.74,618)**
Bone pain	0.3 (0.06,1.07)	0.37 (0.07,1.43)	0.43 (0.08,1.89)

BSC, Best Supportive Care

All comparisons are reported as odds ratios (OR) and 95% credible intervals

Statistically significant OR are shown in bold

[a] Mitoxantrone assumed equivalent to BSC

[b] Note: original table labelled as anaemia rather than thrombocytopenia

[c] Note: original table labelled as fatigue rather than asthenia

4.5 Additional work on clinical effectiveness undertaken by the ERG

The NMA reported in Table 28 (p87) of the CS were based on a fixed effects model with the assumption of no between study variance. To assess the impact of incorporating between study heterogeneity, the ERG conducted additional analyses using a random effects model. Since there were too few studies to estimate the between-study SD from the sample data alone, and in the absence of further information on which to base the choice of prior, a weakly informative half-normal prior with variance 0.32^2 was used. Choice of this prior is discussed in more detail in the NICE TSD.[93] Under this prior, the between-study SD has a mean of 0.26. NMA results based on this prior were used by the ERG when estimating the ERG base-case cost-effectiveness results, as detailed in Section 6. In order to demonstrate the effect of choice of prior on the sensitivity of the results, additional analyses were conducted with a prior that suggests a more conservative amount of between-study

heterogeneity; a half-normal prior with variance 0.22^2. Under this prior, the between-study SD has a mean of 0.17.

Results of the random effects NMA are summarised in Table 25 and Table 26. The median HRs are consistent with the results presented in Table 28 of the CS (p87), but with wider credible intervals, suggesting that there is no statistically significant difference between the three interventions for either OS or rPFS.

Table 25: Results of NMA using random effects model, half-normal prior with variance 0.32^2

	Overall survival				Radiographic progression free survival			
	HR				HR			
Cabazitaxel vs	**median**	**mean**	**95% CrI**	**95% PrI**	**median**	**mean**	**95% CrI**	**95% PrI**
BSC	0.72	0.77	(0.35,1.47)	(0.26,1.99)	0.75	0.80	(0.36,1.53)	(0.28,2.07)
Abiraterone	0.97	1.10	(0.35,2.74)	(0.24,4.16)	0.96	1.09	(0.34,2.71)	(0.23,4.12)
Enzalutamide	1.14	1.29	(0.41,3.19)	(0.27,4.73)	1.87	2.12	(0.66,5.22)	(0.45,7.70)

HR, Hazard Ratio; CrI, Credible Interval; PrI, Predictive Interval; BSC, Best Supportive Care

[a] mitoxantrone assumed equivalent to BSC

Table 26: Results of NMA using random effects model, half-normal prior with variance 0.22^2

	Overall survival				Radiographic progression free survival			
	HR				HR			
Cabazitaxel vs	**median**	**mean**	**95% CrI**	**95% PrI**	**median**	**mean**	**95% CrI**	**95% PrI**
BSC	0.72	0.74	(0.44,1.17)	(0.37,1.44)	0.75	0.77	(0.46,1.22)	(0.38,1.50)
Abiraterone	0.97	1.03	(0.49,1.97)	(0.37,2.57)	0.96	1.02	(0.48,1.96)	(0.37,2.54)
Enzalutamide	1.14	1.20	(0.55,2.28)	(0.42,2.94)	1.87	1.97	(0.91,3.70)	(0.69,4.81)

HR, Hazard Ratio; CrI, Credible Interval; PrI, Predictive Interval; BSC, Best Supportive Care

[a] mitoxantrone assumed equivalent to BSC

4.6 Conclusions of the clinical effectiveness section

4.6.1 Completeness of the CS with regard to relevant clinical studies and relevant data within those studies

The clinical evidence in the CS is based on a systematic review of cabazitaxel in combination with prednisone or prednisolone for the treatment of patients with mCRPC previously treated with a docetaxel-containing regimen. The ERG is content that all relevant studies (published and unpublished) of cabazitaxel were included in the CS, including data from ongoing/planned studies. The ERG is also confident that no published comparator studies of abiraterone and enzalutamide are likely to have been missed. However, whilst the ERG acknowledges the exclusion of radium-223 dichloride from the NMA due to differences in patient populations and variations in the definitions of PFS used, it should have been considered as a relevant comparator as it was specified in the NICE final scope.[19]

4.6.2 Interpretation of treatment effects reported in the CS in relation to relevant population, interventions, comparator and outcomes

A key issue that may limit the robustness of the efficacy and safety data reported in the CS relates to lack of blinding of patients, care providers, and outcome assessors in the TROPIC study. For objective outcomes, such as OS (which was primary outcome), unblinded assessment is unlikely to bias the trial results. However, treatment effect estimates may be exaggerated for subjective outcomes such as pain and symptom deterioration (both of which were included in the definition of PFS) and of clinical (although not laboratory) assessment of AEs, when outcome assessors are not blinded.[96, 97] Another issue that may limit the robustness of the efficacy evidence relates to the post-hoc subgroup analyses of participants from the TROPIC trial that had mCRPC with an ECOG performance score of 0 or 1 and who had received at least 225 mg/m^2 of prior docetaxel. The TROPIC study was not powered for this exploratory subgroup analysis and in addition to the known limitations of post-hoc subgroup analyses,[98] Sun et al.[99] also suggest that the credibility of subgroup effects, even when claims are strong, is usually low. Nevertheless, for NICE TA255[15] both the Appraisal Committee and clinical advisors to the ERG considered this group of people to be the most appropriate population to receive cabazitaxel in UK clinical practice.

The results of the NMA, modified by the ERG using a random effects model, indicate that there is no statistically significant difference between cabazitaxel, abiraterone and enzalutamide in terms of OS or rPFS. However, the indirect comparisons between the treatments were considered subject to uncertainty due to potential imbalances in treatment effect modifiers, comparability of the control treatments and, in the case of rPFS, definition of the outcome. Since there was evidence of heterogeneity among the trials included in the NMA, the ERG considers a random effects model to be more appropriate so that this uncertainty is appropriately reflected in the estimated treatment effects.

However, due to the small number of studies in the network, and lack of replication within pairs of treatments, a weakly informative prior for the between-study heterogeneity was required in this analysis. Further evidence (i.e. implementation of further studies) would ideally provide more precise treatment estimates. The results of the NMA are further limited by the use of HRs to describe the treatment effects. HRs are averaged estimates of treatment effect that ignore any potential treatment by time interaction, and their use is only appropriate if the hazards are proportional. Evidence presented in the CS (including the clarification responses) suggests that the hazards are not proportional in the COU-AA-301 study reported by Fizazzi *et al*.[12]

4.6.3 Uncertainties surrounding the reliability of the clinical effectiveness

The main uncertainties in the clinical evidence primarily relate to the absence of any head-to-head RCTs comparing cabazitaxel with other second-line agents such as abiraterone or enzalutamide for the treatment of mCRPC following treatment with docetaxel. In addition, there is no high quality evidence from prospective controlled trials to guide optimum sequencing of these agents after docetaxel treatment in patients with mCRPC. Although there is uncertainty over the optimal dose and frequency of cabazitaxel administration in men with mCRPC, the ongoing PROSELICA trial is examining the dosage of cabazitaxel (either 25 or 20 mg/m^2) to optimise treatment benefits in relation to potential toxicity. This study was expected to achieve database lock in August/September 2015 with full results reported within the next 12 months.

5 COST EFFECTIVENESS

5.1 ERG comment on the company's review of cost-effectiveness evidence

5.1.1 The objective of cost effectiveness review

Within the submission for TA255[15] the company conducted a simple but highly sensitive search to identify the complete evidence base for cabazitaxel, looking for any instance of the drug name (or synonyms) across a wide range of databases including specialist databases such as the Health Economic Evaluations Database and the NHS Economic Evaluation Database. The ERG concluded in its report that this search, combined with the accompanying clinical effectiveness search, was sufficient to identify all relevant economic evaluations.

In 2015, a more structured approach has been employed to identify publications since 2010 (and conference presentations since 2012). Searches again encompassed an appropriate selection of databases, but this time included filters to identify economic studies. The ERG noted some minor errors in the filters and queried the fact that no sources were cited for these. During the clarification response to question A11 the company responded that all the filters used in their submission were based on those developed for the Scottish Intercollegiate Guidelines Network (SIGN) but that they had modified them slightly by introducing additional terms to increase sensitivity. Although SIGN filters are not necessarily validated prior to publication, the ERG recognises the reputation of the resource and considers the filters fit for purpose. While any modification to a published filter risks reducing its effectiveness, the ERG was content that on this occasion the company's modifications would not have adversely affected recall.

As with the clinical effectiveness searches, the ERG was unable to reproduce the company's search exactly as presented due to the different platform used (Embase.com); but since the numbers of results retrieved by each search string had been included on this occasion, it was possible to approximate their work and the ERG believes that all economic studies would have been identified.

HRQoL searches

Within the submission for TA255[15] the company followed the traditional process of searching a range of databases for studies reporting the HRQoL of mCRPC, noting that "Utilities papers may not be specific to a particular intervention; therefore, the search was structured to retrieve records mentioning prostate cancer in combination with utilities." In its report for TA255 the ERG noted that fewer synonyms for the condition had been used in the HRQoL review than in the clinical effectiveness review.[15]

For the 2015 submission the CS bases its quality of life review largely on another recent evidence submission from Bayer which had already reviewed the HRQoL evidence for mCRPC up to 22nd

February 2013.[100] For this reason, they did not conduct a full systematic update search of all sources but instead searched only PubMed (including Pre-MEDLINE, also known as MEDLINE In Process) from 2013-2015, once again using a shorter list of synonyms for the condition than were used for some of the other searches. While the ERG would ideally have preferred to see a more comprehensive search encompassing multiple databases, it recognises that PubMed is the most appropriate single source for a "pragmatic" update search of this nature.

5.1.2 The inclusion and exclusion criteria used in the study selection

The review of cost-effectiveness described in the CS considered economic evaluations (cost effectiveness analyses, cost-utility analyses and cost benefit analyses) and identified these using a recognised filter. Date limits were applied to consider published studies from 2010, when the coverage of the previous cabazitaxel submission to NICE (TA255) ended.[15] In order to identify more recent research which had not yet been published, additional searches were conducted of conference proceedings since 2012 (where searchable abstracts were available).

The review included studies of cabazitaxel or of comparators from a list of those used in second-line therapy (or later) for adult patients previously treated with a docetaxel-based regimen. No restrictions were placed on race, but studies were only included if they addressed a defined list of outcomes (see Table 48, p130 of the CS for further details). This resulted in the rejection of seven studies at the full-text review stage.

Searching and sifting have been reported in accordance with PRISMA guidelines.[24] The ERG believes that the inclusion and exclusion criteria used by the company in the submission were appropriate.

HRQoL searches

For the review of HRQoL evidence, as previously noted, the company had largely relied on the radium-223 dichloride submission,[100] updated from 2013-2015 with a brief PubMed search. As is typical for a HRQoL review, this search was designed to find any studies relating to utilities or quality of life for people with mCRPC, without restriction to any specific intervention(s).

Studies were excluded on the basis of:

- Publication status (letters, comments, systematic reviews of economic evaluations)
- Incorrect population (including where insufficient information was available about the nature of the disease)
- Outcomes not relevant to HRQoL
- Language (the review only included English language studies)

Searching and sifting have been reported in accordance with PRISMA guidelines.[24] The ERG believes that the inclusion and exclusion criteria used by the company in the submission were appropriate.

5.1.3 Findings and conclusions of the cost effectiveness review

The systematic literature review undertaken by the company identified 319 records after removal of duplicates. Of these records, 277 were excluded based on their title or abstract for the following reasons:

- Incorrect intervention: 83
- Incorrect study type: 77
- Outcomes not relevant: 65
- Incorrect patient population: 49
- Data superseded: 3

Of the remaining 42 records, 17 were excluded after a sift of their full text for the following reasons:

- Outcomes not relevant: 7
- Data superseded or duplicated: 5
- Incorrect patient population: 2
- Incorrect intervention: 2
- Full-text not available: 1

Of the 25 remaining papers (from 23 studies), five were full-text publications, and 20 were conference abstracts. Of these 25 papers, a summary of 17 was provided in the CS (Table 50, p134). This summary also included the ongoing assessment by NICE of radium-223 dichloride, which was not identified in the searches. It is unclear why the summary did not include all 23 studies. A separate hand search identified reports from the Scottish Medicines Consortium and the Irish National Center for Pharmacoeconomics; these are summarised in Table 51 (p138) of the CS. None of the identified records were formally assessed for quality.

No conclusion from the cost-effectiveness review was presented by the company, who argued that the results of the review were limited by the heterogeneous definitions of survival employed, differences in patient populations, and differences in the trial protocols. As such the company presented the cost-effectiveness results from an updated version of the *de novo* model developed for TA255 and described in Section 5.2 of this report.

5.2 ERG summary and critique of the company's submitted model and economic evaluation

5.2.1 NICE reference case

A summary of the key features of the company's *de novo* model is provided in Table 27.

Table 27: Key features of the company's *de novo* model

Population, intervention, comparators and outcomes.	See Table 1.
Time horizon	10 years
Cycle length	Three weeks
Half-cycle correction	Included
Measure of health effects	QALYs
Primary health economic outcome	Incremental cost per QALY gained
Discount of 3.5% for utilities and costs	Costs and benefits were discounted at 3.5%, using continuous discounting.
Perspective	The NHS in England.

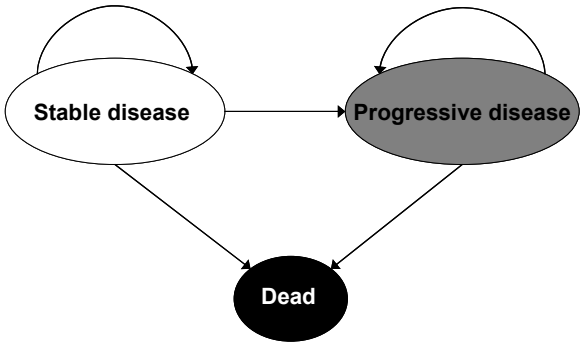
The ERG is satisfied that these are consistent with the NICE reference case.

5.2.2 Model structure

The model structure employed by the company was the same as that used in the previous submission, TA255:[15] a cohort Markov model constructed in Microsoft Excel©. Three health states were modelled, representing: stable disease; progressive disease; and dead. All patients begin in stable disease; during each model cycle they may either remain in this state, transition to progressive disease, or die. Following progression it was assumed that patients could not revert to stable disease, but would instead remain in the progressed state until death. Time-varying transition probabilities were used, as described in Section 5.2.6. A model schematic is presented in

Figure 4, taken from the CS (p142).

Figure 4: Model schematic



A cycle length of three weeks was employed in the model, to reflect the timing of treatment cycles for cabazitaxel. Serious AEs due to treatment were included by applying an additional (treatment-specific) cost and disutility to a proportion of the cohort in the stable disease state.

One-off transition costs were applied upon transitions to the progressive disease state (to account for post-second-line treatment) and transitions to the death state (to account for end of life costs). These are described in Section 5.2.8.

5.2.3 Population

For the comparison between cabazitaxel and mitoxantrone the company used the following population:

- Patients within TROPIC who received ≥ 225mg/m^2 of first-line docetaxel and with an ECOG PS of 0 or 1

In a scenario analysis the entire intention-to-treat TROPIC population was considered.

The population used for this comparison (a sub-group of the TROPIC trial) is the same as that used by the ERG when calculating their most plausible incremental cost effectiveness ratio (ICER) for the appraisal of cabazitaxel (TA255), and was judged to have clinical validity. For this appraisal the ERG, following discussions with its clinical experts, believe that there are no strong reasons for changing this population.

When comparing cabazitaxel with abiraterone and enzalutamide, the entire ITT TROPIC population was used for cabazitaxel.

The company did not consider the sub-population of people with bone metastasis. The ERG believes that this sub-population was inappropriately omitted, for the reasons detailed in Section 3.3.

5.2.4 Interventions and comparators

The intervention modelled was cabazitaxel (25 mg/m^2) plus 10 mg per day of prednisolone given every three weeks for a maximum of ten cycles. Three comparators were considered by the company. These were:

- Mitoxantrone (12 mg/m^2) plus 10 mg per day of prednisolone given every three weeks.
- Abiraterone, 1.0 g daily in combination with 10 mg/day of prednisolone.
- Enzalutamide, 160 mg daily.

Of the comparators, mitoxantrone is a chemotherapeutic agent, whilst abiraterone and enzalutamide are both advanced hormonal agents. Amongst patients with stable disease, cabazitaxel and mitoxantrone may be taken for a maximum of ten cycles. In contrast, abiraterone and enzalutamide are taken until disease progression or death. The company noted that, due to cross-resistance, sequential use of abiraterone and enzalutamide was not permitted in the CDF.[8] Clinical advisors to the ERG also confirmed that these two hormonal agents would not be used sequentially. The submission made on behalf of the NCRI/RCP/RCR/ACP stated that mitoxantrone is rarely used in clinical practice, with BSC used instead.[16] However, the company asserted that comparison with mitoxantrone was expected to be similar to a comparison with BSC with regards to impact on OS; this assertion was supported by the ERG's clinical experts. The ERG notes that the restriction on cabazitaxel use to a maximum of ten cycles is consistent with the trial protocol for TROPIC[11], but that the license for cabazitaxel does not restrict its use to ten cycles.

Cabazitaxel was directly compared with mitoxantrone in the TROPIC trial.[32] No head-to-head comparisons were available for cabazitaxel and the two hormonal agents. Instead, the effectiveness of these hormonal agents (relative to cabazitaxel) was estimated by the company using an NMA, as described in Section 4.3.

The company did not include radium-223 dichloride in their economic evaluation, for the reasons provided in Section 3.3. However, radium-223 dichloride was in the final scope issued by NICE, and the ERG believes that it should have been included. Radium-223 dichloride (50 kBq/kg body weight) is administered by intravenous injection every four weeks, for six injections. The potential implications of including radium-223 dichloride in the economic evaluation are discussed in Section 6.

5.2.5 Perspective, time horizon and discounting

The perspective of the evaluation was appropriately that of the NHS and personal social services. A lifetime horizon was also appropriately used to capture differential mortality rates between the

intervention and the comparators. This was estimated using a time horizon of 10 years. After 10 years, the proportion of patients alive in the company's base case was 0.0001% for cabazitaxel and less than 0.0014% for each of the comparators.

The company used discount rates of 3.5% per year for both costs and benefits, in line with the NICE reference case.[101] It is noted that a continuous discount rate is used despite the fact that the model handles time as a discrete variable. However, this difference is of no material significance. A half-cycle correction was appropriately implemented.

5.2.6 Assumed treatment effectiveness

Within the health economic model, treatment effectiveness was modelled by including treatment-dependent transition probabilities for both OS (the probability of moving to the dead state from either of the other two states) and PFS (the probability of moving from the stable to the progressed health state).

Data on the effectiveness of cabazitaxel and mitoxantrone were taken from the TROPIC trial. For abiraterone and enzalutamide data were taken from the COU-AA-301 and AFFIRM trials respectively. For the purposes of conducting an NMA between cabazitaxel, abiraterone and enzalutamide it was assumed that effectiveness data for the control arm of the three trials was interchangeable. The appropriateness of this assumption is discussed in Section 4.4.

To extrapolate the effectiveness of cabazitaxel and mitoxantrone, parametric models were fitted to the observed data. Each parametric model was used to derive time-dependent transition probabilities for the cohort's entire lifetime (and was used in preference to the Kaplan Meier curves for the observed time period in the company's base case). For both OS and PFS the company considered five different parametric models: Exponential; Weibull; Gompertz; Log-logistic; and Log-Normal. To inform the choice of parametric model for extrapolation both Akaike's information criterion (AIC) and the Bayesian information criterion (BIC) were considered. The choice of curve was restricted so that the same parametric model was used for both cabazitaxel and mitoxantrone for a given effectiveness measure (but different parametric models could be used for OS and PFS). Because of this restriction the parametric model chosen was that which minimised the sum (combination) of the information criteria for the two treatments. It is commented that these goodness of fit tests do not indicate a definite selection of a curve since information criteria cannot be formally tested for significance. An overview of these values is provided in Table 28, with minimum values, which highlight the best model fit to the data, highlighted in bold.

Table 28: Goodness of fit data for the parametric models

	Combined values: overall survival		Combined values: progression-free survival	
	AIC	BIC	AIC	BIC
Exponential	1573.21	1580.71	1843.01	1850.48
Weibull	**1456.99**	**1472.00**	1840.86	1855.81
Gompertz	1498.41	1513.43	1834.93	1849.89
Log-logistic	1458.04	1473.06	1775.18	1790.14
Log-Normal	1494.51	1509.52	**1769.93**	**1785.49**

AIC: Akaike's information criteria. BIC: Bayesian information criteria

Use of either the AIC or BIC led to the same parametric model being chosen. It is unclear which measure the company would have preferred if the two suggested different models. The company did not consider fitting separate parametric models to the two treatment arms (for either type of survival). The company justified this approach by stating (p145) that:

"Ideally, the same parametric model type should be chosen for the two treatment arms unless there is a specific expectation that they should be different."

Based on the information criteria results, separate curves based on the Weibull model were fit to the two treatment arms to generate transition probabilities for death, and separate curves based on the Log-Normal model were used for transition probabilities to the progressed disease state. The use of separate curves based on separate parametric models (for each treatment) was considered by the ERG, as discussed in Section 5.3, with results in Section 6.

To generate transition probabilities for abiraterone and enzalutamide, estimated HRs (as detailed in Section 4.3) for these two comparators were applied to the parametric models for cabazitaxel. As the Log-Normal model (used to model PFS) is not a proportional hazards model, a Weibull model was instead used to model PFS. The justification for using a Weibull model is not stated, but it is noted that, of the three proportional hazards models (Exponential, Weibull and Gompertz), this provides the lowest AIC and BIC values when considering the cabazitaxel arm which is then adjusted using HRs for abiraterone and enzalutamide. To use proportional hazards models requires an assumption of proportional hazards. The appropriateness of this assumption is discussed in Section 4.4.

For both OS and PFS, the company considered the use of each of the four alternative parametric models in scenario analyses. The use of Kaplan Meier data for the observed time period was also explored in a scenario analysis. The results of these analyses are discussed in Section 5.2.10.

It was noted that in TA255 the NICE Appraisal Committee considered the use of piecewise curves to be the most appropriate approach.[15] However, this approach was not considered in the initial submission provided by the company. In response to clarification on this issue (question B1), the

company argued against using this approach for the NMA, stating that it would lead to "questionable derived curves for the comparator arms" and "add additional complexity and create excessive computational challenges of implementation". The company further do not use piecewise curves in the comparison between cabazitaxel and mitoxantrone, arguing for consistency with the modelling approach used in the NMA. However, the ERG notes that the company assesses the results from the NMA separately to the comparison between cabazitaxel and mitoxantrone, so it is unclear why the modelling approach for the two should be consistent. One of the main drivers for considering piecewise curves was the observation of early deaths from cabazitaxel-induced neutropenia, which may have affected subsequent extrapolations. To account for this, the company present the results of an analysis which used the observed Kaplan-Meier curve for cabazitaxel for the first 2.1 months, followed by a Weibull curve fit to the remaining trial data, and used for extrapolation. No change was made to the modelling of the mitoxantrone arm. Use of this hybrid model led to a slight decrease in the ICER comparing cabazitaxel to mitoxantrone, from £49,327 to £48,543. The ERG believes that, of the approaches to modelling OS presented by the company, this hybrid approach is likely to be the most appropriate. However, the company did not present details about the Weibull curve that was used, and so the ERG was not able to replicate this analysis.

Within the economic model base-case analysis a proportion of patients receiving cabazitaxel or mitoxantrone discontinued treatment but remained in the stable disease state. The ERG had three concerns with how this type of discontinuation was modelled. These concerns are discussed in turn.

1. It was assumed in the model that patients who discontinued did not incur drug costs during the cycle of discontinuation. The ERG believed that this would under-estimate drug costs, as patients would discontinue after receiving the drug.
2. It was assumed in the model that patients who discontinued would have the increased utility related to additional treatment cycles. The ERG believed that this would over-estimate utilities.
3. Within the model the proportion of drug costs that was removed due to discontinuation was not cumulative. In other words, for any given cycle, patients who discontinued during a previous cycle and remained with stable disease would incorrectly incur drug costs. The ERG believed that this would over-estimate drug costs.

In response to clarification question B6, the company stated that patients who were modelled as discontinuing actually did so during the previous cycle, and so it was appropriate to exclude drug costs for their current cycle. However, this is not how discontinuation has been implemented in the model (as patients can discontinue during cycle zero). Hence the ERG maintains that drug costs are under-estimated due to this. The company agreed with points 2 and 3, and provided the results of an analysis which assumed that patients who discontinued (but remained in the stable disease state) had a

utility equal to that of patients in the progressed disease health state, and which also removed a cumulative proportion of drug costs. The result of these changes had a minimal impact on the ICER.

People who received either abiraterone or enzalutamide were not modelled as being able to discontinue and remain in the stable disease state. This inconsistency of modelling approach may affect the validity of comparisons between cabazitaxel, abiraterone and enzalutamide.

The ERG noted that within the economic model, transition probabilities that exceeded one were sometimes used. This appears to be because the calculated probabilities for remaining in the stable disease health state and for dying are not mutually exclusive: transitions to death are included in both the estimates of OS and of PFS. Using transition probabilities that exceed one without adjustment in the economic model would lead to the sum of the proportions in each health state exceeding one. To remedy this, the company appear to have incorporated an adjustment that reduces the proportion of patients in the progressive disease health state with the effect of potentially underestimating the number of patients in the progressive disease health state. However, in response to clarification question B5 the company noted that the impact of this on the ICER was likely to be small. The ERG agreed with this.

5.2.7 Health related quality of life

HRQoL data were not collected in the TROPIC trial. Utility values for people receiving cabazitaxel measured using the EQ-5D were collected in the UK EAP,[50] and used in the health economic model. In addition, the company provided details about the results of a systematic search for data on HRQoL. The UK EAP is discussed first, followed by the systematic search results.

The UK EAP is an open-label, single-arm study of cabazitaxel and thus does not include mitoxantrone. Within the UK EAP, participants were asked to complete the EQ-5D questionnaire at baseline, prior to cycles 2, 4, 6, 8 and 10 of chemotherapy, and after completing treatment. The ERG notes that the EQ-5D questionnaire asks people about their HRQoL on the day of completing the questionnaire. Hence it would not capture to any effects of chemotherapy that lasted for less than six weeks (the time-frame between completing questionnaires).

Baseline data used in the health economic model were available for 103 participants, with a mean EQ-5D summary score of 0.682. The data used in the economic model are more up-to-date than that reported in Bahl *et al*.[50] Mean scores increased with each cycle of treatment (and the sample size decreased), with a mean score at cycle 10 of 0.819, based on 32 participants. The weighted mean EQ-5D summary score across all 10 cycles was 0.737. Results for the sub-group of participants who

completed all 10 cycles of treatment produced consistent results with the full sample, which suggest that the observed increase in utility may not be due to selection bias.

Within the UK EAP, 25 participants were identified as having both disease progression and an EQ-5D summary score recorded 30 days after their last treatment. The mean utility value of 0.627 for these participants was used within the economic model for progressed disease.

There were two components to the stable disease utility values used within the economic model. The first was the UK EAP values, which were assumed to reflect the utility of patients with stable disease regardless of the treatment that they received. Cycle-specific values were used for the first 10 cycles, after which the cycle 10 utility value (0.819) was used for all subsequent cycles. The second component was a treatment-specific disutility due to AEs. Fifteen AEs were considered: neutropenia; febrile neutropenia; diarrhoea; fatigue; asthenia; leukopenia; back pain; anaemia; thrombocytopenia; pulmonary embolism; dehydration; nausea; bone pain; deep vein thrombosis; and neuropathy. The duration of events, and their rate of occurrence for cabazitaxel and mitoxantrone were taken from the TROPIC trial.[11] Rates for abiraterone and enzalutamide were taken from their respective pivotal trials, as described in Section 4.5. Disutility values for the AEs were based on a literature review conducted for the submission in relation to TA255.[15] In the absence of evidence for people with prostate cancer, values for people with breast cancer or non-small cell lung cancer were used.

An overview of the utility values used in the economic model is provided in Table 29, whilst an overview of the adverse event data used is provided in Table 30.

Table 29: Utility values used in the economic model

	Utility
Stable disease (weighted average UK EAP values)	0.737
Disutility due to treatment with cabazitaxel	0.00033
Disutility due to treatment with mitoxantrone	0.00022
Disutility due to treatment with abiraterone	0.00007
Disutility due to treatment with enzalutamide	0.00005
Progressed disease	0.627

Table 30: Adverse event data used in the economic model

Adverse Event	Disutility	Duration (days)
Neutropenia	-0.090	1.9
Febrile neutropenia	-0.120	6.2
Diarrhoea	-0.047	8.0
Fatigue	-0.094	19.3
Asthenia	-0.094	13.3
Leukopenia	-0.090	11.1
Back pain	-0.069	7.2
Anaemia	-0.125	25.4
Thrombocytopenia	-0.090	23.8
Pulmonary embolism	-0.145	27.0
Dehydration	-0.151	3.8
Nausea	-0.076	6.2
Bone pain	-0.069	9.5
Deep vein thrombosis	-0.160	24.0
Neuropathy	-0.116	5.0

Because the UK-EAP only measured EQ-5D during even-numbered cycles, a method of interpolation was required to estimate utility values for odd-numbered cycles. The company applied a linear regression to estimate these values. Within the economic model the company used observed values for even-numbered cycles and estimated values for odd-numbered. The ERG notes that this approach leads to potential logical inconsistencies. For example, the modelled utility for cycle six is lower than that for cycle five. A more consistent approach (with regards to having monotonically increasing utility values) would have been to use the estimated values for all 10 cycles. The ERG also requested that the company provide an analysis using the mean of the UK EAP utility values for all 10 cycles. In response, the company provided two analyses: one which used the unweighted mean of the UK EAP, and one which used the mean value at cycle 6 of the UK EAP (which corresponds to the median number of cycles received). These changes did not have a material impact on the base-case ICER.

The ERG carried out additional analyses: (1) using values estimated from a linear regression for all 10 cycles, and (2) using the weighted mean of the UK EAP utility values for all 10 cycles. The results of these are discussed in Section 5.3, and show that the ICER is robust to these changes.

The company also assumed that people with progressive disease would have zero utility in their last three months of life. This assumption was used as a simplified means of incorporating any reductions in HRQoL as people approached the end of their life. This was incorporated within the model as a disutility. However, the calculation of the treatment-specific disutility was based upon all deaths, not upon deaths amongst people with progressive disease. In addition, this calculation assumed that

everybody had a zero utility for three months, even if they lived for less than three months. In response to clarification question B5 the company adjusted the disutility calculations so that people who died before three months contributed a reduced disutility. This amendment had a minimal impact on the ICER. However, the company did not alter the disutility calculations to be based on only people with progressive disease, stating that cycle-specific deaths from this health state were not tracked. However, the ERG notes that the company could have amended their model to track this. The ERG believes that applying a disutility based on all patients who die is of questionable validity.

The company's literature review identified nine studies that directly measured EQ-5D values. There were no studies that directly measured EQ-5D values amongst people receiving cabazitaxel. Instead, the company subjectively categorised the reported values as pertaining to patients with either stable or progressed disease. Utility values for stable disease ranged from 0.66 (patients with mCRPC undergoing chemotherapy)[102] to 0.85 (asymptomatic and minimally symptomatic, chemotherapy-naive patients with mCRPC).[103] Utility values for progressed disease ranged from 0.54 (people with prostate cancer in their last year of life)[104] to 0.66 (post-chemotherapy patients with mCRPC).[105] The company noted that these ranges were consistent with their UK EAP values, and used this as an additional justification for use of the observational data in their submission.

It has previously been noted that participants in the UK EAP may not be comparable with participants in the TROPIC[106], as participants in TROPIC had higher levels of previous chemotherapy use (31% had received at least two previous chemotherapy regimens compared to 11% in the UK EAP), and were more likely to have progressed during or within three months of finishing treatment with docetaxel (72% compared to 33%). This, in combination with the non-comparative non-blinded nature of the UK EAP limits the applicability of the data. However, in the absence of more robust data, the ERG believes that use of the UK EAP within the economic model is appropriate. It is further noted that the company's implementation of HRQoL values appropriately disadvantages cabazitaxel as this has the largest disutility due to being associated with the largest number of AEs.

5.2.8 Resources and costs

Data on unit costs were taken from standard national sources (The British National Formulary,[107] NHS reference costs[108] and Personal Social Services Research Unit [PSSRU][109]). The main sources for evidence on resource use were the TROPIC trial,[11] a UK clinical audit (as described in Appendix 14 of the CS), and expert opinion.

Stable disease

Cabazitaxel and mitoxantrone are both provided in vials with the required dosage dependent on BSA (25 mg/m^2 for cabazitaxel and 12 mg/m^2 for mitoxantrone). Within the submission the company assumed that the mean BSA was 1.9 (with a standard error of 0.21 used to estimate the average number of vials required per patient), with vial sharing for cabazitaxel but not for mitoxantrone. The value of 1.9 was based on the clinical opinion of UK experts; the mean BSA observed in the TROPIC (2.01) was used in a scenario analysis. The standard error of 0.21 was based on TROPIC data. The ERG queried why the TROPIC-derived BSA was used in the base-case for the original submission (TA255), but not for this submission. The company justified this change by stating that the value of 1.9 is more likely to reflect values observed in the UK. The ERG notes that, based on the company's economic model, the threshold for an increase in vials is a BSA of [redacted] for cabazitaxel and [redacted] for mitoxantrone.

The ERG queried why it was assumed that there was no vial wastage for cabazitaxel. The company responded with:

"Sanofi believe there will be no wastage of active ingredient because patient specific doses in the form of compounded IV bags of cabazitaxel can be supplied direct to NHS hospitals".

The ERG asked their clinical advisors if they believed that there would be vial wastage for cabazitaxel. The following reply was obtained from a pharmacist:

"As far as I am aware, most centres do not buy in compounded bags as this would add to the total cost of treatment as likewise they would need to add a compounding fee to treatment. Occasionally we have been able to "save" a vial where several patients are receiving treatment on one day and as a result vials can be 'campaigned worked' (i.e. shared). This can seldom be achieved however and certainly isn't generally the rule."

The ERG noted that in addition vial wastage may occur, if people did not attend their appointment. Hence there is uncertainty over the degree of vial wastage that would occur in clinical practice. The ERG further noted that in the company's base-case there appeared to be no wastage assumed for either cabazitaxel or mitoxantrone.

Treatment with abiraterone requires 1.0g daily whilst for enzalutamide 160mg is required daily.

Costs for cabazitaxel and all three comparators were taken from the BNF June 2015.[107] A pack of abiraterone contains 120 tablets of 250mg, whilst a pack of enzalutamide contains 112 tablets of 40mg. These costs, which do not include any Patient Access Scheme or any administration costs, are displayed in Table 31. With the exception of enzalutamide, all of the treatments are in combination with 10 mg/day of prednisolone, at a 3-week cycle cost of £1.94.

Table 31: Direct treatment costs

Treatment	Cost per unit	Details	Cost per 3-week cycle*
Mitoxantrone	£100.00	Cost per vial	£172.87
Cabazitaxel	£3696.00	Cost per vial	£3696.00
Abiraterone	£2930.00	Cost per 120-tab pack	£2,051.00
Enzalutamide	£2734.67	Cost per 112-cap pack	£2,051.00

*Mitoxantrone and cabazitaxel are estimated by the company to require 1.73 and 1.00 vials per cycle, respectively

It was assumed that all four treatments would require one visit to a clinical oncologist every three weeks, at a cost of £320 per visit.[27] Treatment with cabazitaxel and mitoxantrone incurred additional administration costs for pharmacist time. The hourly cost for pharmacist time used was £42,[109] it was assumed that mitoxantrone would require an hour of pharmacy time and cabazitaxel would require 15 minutes.

Pre-medication resource use for cabazitaxel and mitoxantrone were taken from the TROPIC, as detailed in Table 63 of the CS (p165-167). The main driver of pre-medication costs was the use of primary prophylaxis, with a unit cost of £175.67. This was received by 25% of patients in the cabazitaxel arm and 10% in the mitoxantrone arm. It was assumed that patients receiving either abiraterone or enzalutamide would have the same resource use as mitoxantrone, but with no primary prophylaxis. The resulting three-weekly pre-medication costs were £87.29 for cabazitaxel, £36.32 for mitoxantrone, and £7.52 for either abiraterone or enzalutamide.

For patients with stable disease, the direct treatment costs (as detailed in Table 31), along with administration costs and pre-medication costs were incurred for either the first ten cycles of treatment (for cabazitaxel and mitoxantrone) or until disease progression or death (for abiraterone and enzalutamide).

In addition, patients with stable disease also required treatment with an LHRH agonist, at a cost of £52.59 every three weeks. Additional costs relating to outpatient care, inpatient care, hospice care, imaging and laboratory tests were also incurred, at a cost of £303.65 every three weeks. These two additional costs were incurred by patients as long as they remained in the stable disease state.

The costs of treating AEs were incorporated into the economic model as an additional treatment-specific cost for patients with stable disease who are receiving treatment. The rates of occurrence of AEs as used in the economic model are described in Table 22. Costs for treating AEs were based on the cost of inpatient visits and drug costs. The company assumed that no additional outpatient costs would be required for treating AEs. Costs for inpatient visits, and the length of stay, were both taken from NHS reference costs.[27] These were weighted by the proportion of people experiencing the AEs

who required an inpatient stay. These proportions were based on TROPIC data[32] adjusted by expert opinion. The proportions applied were irrespective of treatment received. The drugs required to treat AEs were based on expert opinion, with unit costs from the BNF.[107]

The two most expensive AEs to treat were febrile neutropenia (£4,077.58) and pulmonary embolism (£2,517.72). All other AEs cost less than £900 to treat. The average cycle costs of treating AEs were £105.18 (cabazitaxel), £53.78 (mitoxantrone), £5.15 (abiraterone), and £5.05 (enzalutamide). The main cost contributions for cabazitaxel were febrile neutropenia (£64.44) and neutropenia (£13.02). For mitoxantrone these were febrile neutropenia (£20.62) and pulmonary embolism (£17.07).

The ERG noted that, based on the CS, some AEs received neither inpatient care nor drugs. In response to clarification question B19 the company provided a scenario analysis where the rates of drug use for all AEs were 100%. The ICER was robust to this extreme case, with an increase of 0.53% from the base-case value.

For the company's base-case analysis, the total cost of AEs during the first ten weeks of treatment were £546.44 (cabazitaxel), £207.19 (mitoxantrone), £41.36 (abiraterone), and £44.84 (enzalutamide). For cabazitaxel and mitoxantrone these are also the lifetime costs of AEs, as treatment cannot exceed ten weeks in the model. For abiraterone and enzalutamide the lifetime costs were £73.60 and £118.20 respectively.

Progressed disease

Sequencing of the four treatments was not considered by the company. Instead, if people progressed whilst on treatment, they received either a post-second line treatment mix or BSC. The proportion receiving post-second line treatment was independent of the previous treatment received, and was 56% in the company's base-case analysis: this proportion was taken from the TROPIC trial. An alternative estimate of 20% receiving post-second line treatment (and hence 80% receiving BSC), derived from a UK-based treatment audit, is used in a scenario analysis. Post-second line treatment costs had two components: the costs of chemotherapeutic drugs, and administration costs. There were three sources providing evidence on these costs: the two treatment arms (cabazitaxel and mitoxantrone) of the TROPIC trial,[32] and a UK clinical audit.[25] The costs of chemotherapeutic drugs derived from the TROPIC trial were £1192.81 for the cabazitaxel arm and £1767.02 for the mitoxantrone arm. The driver for the difference in these costs was the increased use of docetaxel in the mitoxantrone arm (17% of people, compared to 11%, increasing costs by £423.59). The drug cost derived from the UK clinical audit was between the middle of the two TROPIC estimates, at £1364.07. Costs relating to treatment administration were similar for the cabazitaxel (£1328.56) and mitoxantrone (£1255.26) treatment arms in TROPIC. Administration costs derived from the UK

clinical audit were almost half (£691.96) of the TROPIC estimates, due to an estimated shorter duration of treatment.

For the company's base-case analysis post-second line treatment costs for cabazitaxel and mitoxantrone were based on their respective TROPIC treatment arms. Costs for abiraterone and enzalutamide were based on the mitoxantrone arm. Post-second line treatment was incorporated within the economic model as a one-off cost upon transitioning from stable to progressed disease. The ERG queried why data from the TROPIC trial were used in preference to the UK clinical audit. The company's justification was that TROPIC data "was used to maintain consistency with what was done in the trial". This may be appropriate if the differences in post-second line treatment in TROPIC contributed to the observed differences in OS. However, if this is not the case then the ERG believes that the use of arm-specific post-second line treatment costs is inappropriate. The ERG notes that mitoxantrone has no known effect on OS, so it is unlikely that post-second line treatment will have an impact. Clinical advisors to the ERG agreed with this view. In addition, it is unclear why post-second line treatment costs for mitoxantrone (which are the most expensive of the three available estimates) are used for abiraterone and enzalutamide.

Following post-second line treatment, people received on-gong treatment with an LHRH agonist, at a cost of £52.59 every three weeks. A proportion of patients received additional treatment. This consisted of analgesics, steroids, palliative radiotherapy and bisphosphonate, with an overall cost of £41.68 every three weeks, in addition to the cost of an LHRH agonist. The company labelled this additional treatment as BSC. Using the base-case estimate that 44% of patients received BSC, the average cycle cost for progressed disease was £70.93, independent of the previous treatment received (ignoring the one-off cost for post-second line treatment). Using the alternative estimate of 80% receiving BSC, the cycle cost changes to £85.93.

Additional costs relating to outpatient care, inpatient care, hospice care, imaging and laboratory tests were also incurred, at a cost of £303.65 every three weeks for patients with progressed disease, irrespective of the previous treatment received.

End of life costs

End of life costs for treating prostate cancer were included within the CS. Evidence on the number of inpatient and outpatient hospitalisations was available from a UK clinical audit.[25] Evidence on home visits (from nurses and GPs) along with hospice home stays was based on expert opinion. End of life costs were included as a one-off cost upon transition to death, from either of the other two health states. The estimated cost was £1952.15, independent of the previous treatments received. The main

cost component was inpatient visits at an overall cost of £1374.72 (based on a unit cost of £537 per day and an average of 2.56 days). Costs relating to end of life drugs were not included.

An overview of the per-cycle costs that vary depending on the treatment received is displayed in Table 32.

Table 32: Additional treatment-dependent costs (base-case values per three weeks unless otherwise specified)

Treatment	Administration	Pre-medication	Post-second line chemotherapeutic drugs*	Post-second line administration*	Adverse events
Mitoxantrone	£362.50	£87.29	£1767.02	£1328.56	£105.18
Cabazitaxel	£330.50	£36.22	£1192.81	£1255.26	£53.78
Abiraterone	£320.50	£ 7.52	£1364.07	£691.96	£5.15
Enzalutamide	£320.50	£ 7.52	£1364.07	£691.96	£5.05

*Applied as a one-off cost and only received by a proportion of patients

The costs of generic drugs (which include the cost of mitoxantrone) were taken from the BNF for the company's base-case analysis. An alternative estimate of generic drug costs is available from the electronic market information tool (eMIT), made available by the Department of Health.[110] In response to clarification question B7 the company used eMIT prices in place of BNF prices. The eMIT prices used reflect the average price paid by English trusts for the period September 2014 to December 2014. The cost per unit for mitoxantrone is £100 based on the BNF (June 2015) and £29.37 based on the eMIT, resulting in a cost of £486 per cycle. Comparisons for the other generic drugs are provided in Table 11 of the company's response to clarification question B7. The impact of using these costs within the economic evaluation is discussed in Section 5.2.10.

5.2.9 Cost effectiveness results

5.2.9.1 Cabazitaxel compared to mitoxantrone

Within their initial submission,[25] the company presented an ICER for cabazitaxel compared to mitoxantrone. This ICER was based on a deterministic analysis, and is displayed in Table 33. An estimate of the ICER based on the results of the probabilistic sensitivity analysis was not presented. In response to clarification question B4 the company presented a probabilistic ICER of £50,659, which is reported in Table 33 of this report. The ERG notes that an ICER based on the results of a probabilistic sensitivity analysis is more appropriate than an ICER based on a deterministic analysis as the former incorporates any potential non-linear relationships between model inputs and model results.[111]

The probabilistic ICER included a slight amendment to the originally submitted model (the proportion of patients who received BSC as post second-line treatment was initially fixed but was subsequently included in the probabilistic sensitivity analysis). The company tested a number of alternative scenarios, and made model adjustments in response to clarification questions, as described in Section 5.2.10. However, in the updated model provided by the company in response to clarification questions, the only change that was incorporated was the afore-mentioned inclusion of the proportion of patients receiving BSC in the probabilistic sensitivity analysis. This suggests that the base-case deterministic results presented by the company did not change in response to clarification questions.

At a willingness to pay value of £50,000 per QALY, the probability of cabazitaxel being a cost-effective treatment when compared to mitoxantrone was 46.20%. At £40,000 this probability was 6.4% whilst at £30,000 it was less than 0.001%.

The economic model provided by the company did not record total costs and QALYs when saving the results of probabilistic sensitivity analyses. Hence for the probabilistic sensitivity analyses only the incremental values were reported. The mean values of the incremental costs and QALYs contained in the revised economic model submitted by the company following the clarification process are displayed in Table 33.

Table 33: Cost-effectiveness results comparing cabazitaxel with mitoxantrone

Treatment	Total values		Incremental values		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	
Deterministic results					
Mitoxantrone	[redacted]	[redacted]	-	-	-
Cabazitaxel	[redacted]	[redacted]	£11,450	0.232	£49,327
Probabilistic sensitivity analysis results					
Mitoxantrone	NR	NR	-	-	-
Cabazitaxel	NR	NR	£11,829	0.233	£50,682

ICER: Incremental cost-effectiveness ratio. NR: Not reported. QALYs: Quality adjusted life years

5.2.9.2 Cabazitaxel compared to abiraterone and enzalutamide

The company also reported the results of scenario analyses that compared cabazitaxel with abiraterone and enzalutamide (a fully incremental comparison including mitoxantrone was not undertaken). These results use the BNF list price of abiraterone and enzalutamide as the PAS for these interventions are commercial in confidence. The impact of using the confidential PAS prices on the cost-effectiveness results was explored in a confidential appendix prepared for the Appraisal Committee only.

The results of the company's analyses are not directly comparable with those displayed in Table 33 in Section 5.2.9.1 for three main reasons:

- A different parametric model is used for PFS because the parametric model used to compare mitoxantrone and cabazitaxel in 5.2.9.1 did not assume proportional hazards, and
- A different definition of PFS is employed (rPFS, as opposed to the broader definition used in the TROPIC trial), and
- The entire TROPIC population is used, as opposed to the sub-group who received at least 225 mg/m^2 of docetaxel and had an ECOG performance score of 0 or 1.

When comparing cabazitaxel with the two advanced hormonal therapies the company used the confidential PAS price for cabazitaxel, and the BNF list prices for both abiraterone and enzalutamide. The results of these comparisons were presented as scenario analyses. From the CS it is unclear if these results are based on a deterministic analysis or a probabilistic sensitivity analysis. These results are presented in

Table 34, with the results taken from the revised economic model submitted by the company following the clarification process. For the probabilistic sensitivity analysis 2,000 runs were performed, and only the incremental values were reported. As cost-effectiveness results for BSC derived from the NMA are not included in the company's economic model, these are not included and a fully incremental analysis is not presented. The ERG notes that the company used median hazard ratios when estimating the deterministic results. The ERG believes that use of means is more appropriate.

Table 34: Cost-effectiveness results comparing cabazitaxel with abiraterone and enzalutamide

Treatment	Total values		Incremental values compared to cabazitaxel		ICER compared to cabazitaxel (£)
	Costs (£)	QALYs	Costs (£)	QALYs	
Deterministic results					
Cabazitaxel	[redacted]	[redacted]	-	-	-
Abiraterone	[redacted]	[redacted]	25,310	-0.017	Dominated by cabazitaxel
Enzalutamide	[redacted]	[redacted]	20,504	0.085	241,968
Probabilistic sensitivity analysis results					
Cabazitaxel	NR	NR	-	-	-
Abiraterone	NR	NR	25,362	-0.018	Dominated by cabazitaxel
Enzalutamide	NR	NR	20,716	0.0816	253,956

ICER: Incremental cost-effectiveness ratio. NR: Not reported. QALYs: Quality adjusted life years.

5.2.10 Sensitivity analyses

The company performed a number of sensitivity analyses to test the robustness of the model to changes in the values of various input parameters. The results of these analyses are described in Tables 79 and 80 of the CS (p186-188). The key results from these analyses, along with the results of additional sensitivity analyses carried out by the company in response to clarification questions, are described in this section. All of the sensitivity analyses relate to a deterministic base-case comparison between cabazitaxel and mitoxantrone. An overview of the sensitivity analyses presented by the company, both in the CS and in response to clarification questions, is provided in Table 35.

Utility values

The base-case results were relatively robust to changes in the utility values for stable disease, with an increase or decrease by 20% changing the ICER by less than 10%. However, the ICER was more sensitive to changes in the modelled utility value for progressive disease. Decreasing the base-case value by 20% (from 0.627 to 0.522) increased the ICER by 13% (from £49,327 to £55,749), whilst an increase in the value of 20% (from 0.627 to 0.752) decreased the ICER by 13% (to £44,232). However, it is noted that under this latter sensitivity analysis the utility value for progressive disease is greater than the utility for the first four cycles with stable disease. The sensitivity of the ICER to the utility value for progressive disease is relevant given this value is estimated with a large degree of uncertainty as it is derived from 25 patients with an SD of 0.298. This provides a standard error of

0.060 and a 95% CI of 0.510 to 0.743 (based on the normal approximation). The CS did not vary the utility for progressive disease in the probabilistic sensitivity analysis, although this was only noted after the clarification process and therefore not amended in the model supplied post-clarification.

Methods for extrapolating trial evidence

Within the base-case analysis, OS and PFS were extrapolated using Weibull and log-normal curves (respectively) for both treatment arms. As described in Section 5.2.6, the company chose these curves as they minimised goodness-of-fit statistics when fitting to both curves simultaneously. Based on these statistics, the goodness of fit of the log-logistic curve to both observed OS and observed PFS is almost identical to the fit of the two curves used in the base-case (with maximum differences in information criteria of 1 [0.1%] and 5 [0.3%] units respectively – all of the alternative curves have differences of at least 38 [2.5%] units).

Use of the log-logistic curve for OS decreased the ICER from the base-case value of £49,327 to £41,875 (it is believed that there is a typographical error in the CS that reports this as £41,920). Use of the log-logistic curve for PFS produced an ICER of £47,921. The company justified the use of the Weibull curve for OS by noting that use of the log-logistic curve led to longer mean survival, which may be "unrealistic". The cabazitaxel treatment arm mean survival is 18.5 months using a Weibull curve and 21.8 months using a log-logistic curve, with mean survival gains over mitoxantrone of 4.1 and 5.4 months respectively. The ERG notes that there is little external data to inform estimates of long-term (and hence mean) survival for patients with mCRPC previously treated with docetaxel.

Other notable sensitivity analyses performed in the initial submission

The inclusion of discontinuation for reasons other than disease progression in the economic model has been critiqued in Section 5.2.6. Not including this type of discontinuation increased the ICER by 2.1% to £50,370.

Using the mean BSA from the TROPIC trial (in preference to the value obtained from UK clinical experts), increased the ICER by 3.4% to £50,985.

Use of the entire TROPIC population (as is used in the NMA) increased the ICER by 5.1% to £51,833.

Sensitivity analyses performed in response to clarification questions

Three sensitivity analyses were performed relating to utilities (two using alternative values for stable disease and one which modified the calculations for the disutility due to reduced HRQoL in the last

three months of life); the base-case results were not materially changed under any of these analyses. The analyses are described further in Section 5.2.7.

The company considered a change in how OS for cabazitaxel was modelled. Kaplan-Meier curves were used for the first 2.1 months, with a Weibull curve used for the remaining lifetime. This analysis was designed to account for early deaths due to cabazitaxel-induced neutropenia. Under this analysis the ICER reduced by 1.6% to £48,543.

In the company's base-case generic drugs were costed using the BNF. An alternative cost estimate is the eMIT (see Section 5.2.8 for further details). Using these costs increased the ICER by 4.8% to £51,675.

Finally, a sensitivity analysis was performed under which all AEs were treated with drugs – this did not materially change the base-case ICER.

Table 35: Overview of deterministic sensitivity analyses presented by the company

Scenario tested	Incremental costs	Incremental QALYs	Incremental cost-effectiveness ratio
Included within the company submission			
Base-case	£11,450	0.232	£49,327
Progressive disease utility +20%	£11,450	0.259	£44,232
Progressive disease utility -20%	£11,450	0.206	£55,749
Use of log-logistic curves for overall survival	£12,724	0.304	£41,920
Not including discontinuation for reasons other than disease progression	£11,693	0.232	£50,370
Mean BSA value taken from the TROPIC trial	£11,852	0.232	£50.985
Use of the entire TROPIC population	£11,141	0.215	£51,833
Performed in response to clarification questions*			
Use of Kaplan-Meier curves for the first 2.1 months of overall survival for cabazitaxel (B1).	£11,568	0.238	£48,543
Using eMIT for generic drug costs (B7).	£11,995	0.232	£51,675
Rates of drug use for all adverse events = 1 (B19).	£11,511	0.232	£49,587

*(numbers in brackets denote the clarification question).

QALYs: Quality-adjusted life years.

5.2.11 Model validation and face validity check

The company provided the following details with regards to model validation:

"The model was run under a variety of settings of the input parameters to see if the results appeared to be reasonable. The validation analyses included setting inputs to extreme values and verifying the results for logical consistency." No further details were provided. The ERG performed its own model validation checks when critiquing the company's submitted evidence. The main issues are summarised in Section 5.2.12.

5.2.12 Overview of the ERG's critique of the cost-effectiveness evidence

This section provides an overview of the critiques previously discussed, concentrating on the main areas of uncertainty or disagreement.

Exclusion of radium-223 dichloride as a comparator

Radium-223 dichloride was included in the final NICE scope,[19] but not in the company's economic evaluation. The ERG believes that radium-223 dichloride should have been included. A formal estimate of the cost effectiveness of radium-223 dichloride relative to cabazitaxel would have required the ERG to both conduct an NMA and adapt the company's model. This was not possible in the time-frame of the assessment. However, the potential impact of including radium-223 dichloride in the economic evaluation is discussed in Section 5.3.

Modelling of overall survival

For the company's base-case analysis, OS and PFS were modelled using separate Weibull and log-normal curves (respectively) for both treatment arms. In response to clarification question B1, which queried why piecewise curves were not used, the company presented the results using a hybrid method for estimating OS following cabazitaxel treatment with the mitoxantrone OS curve unchanged. This method used Kaplan-Meier curves for the first 2.1 months and a Weibull curve for the remaining lifetime for the cabazitaxel arm. Under this method the base-case ICER reduced by 1.6% to £48,543. The ERG believes that this hybrid method is likely to be more appropriate than the base-case method. However, it is noted that details regarding the Weibull curve used for the hybrid method were not provided, so the ERG was not able to replicate this analysis.

Utility values

Data from the UK EAP[50] were used by the company to derive utility values for patients with stable disease and progressive disease. The UK EAP data are more mature than when used for the TA255 submission[15]. While it is believed that the estimated values have face validity it is noted that the model results are sensitive to the utility value for progressive disease and that there is uncertainty over this value, as it is only based on data for 25 people. It is unclear what impact reducing uncertainty in the utility value for progressive disease would have on the ICER.

Resource use and costs

Two national sources are available for estimates of the costs of generic drugs: the BNF[107] and the eMIT.[112] The company used the BNF in its base-case analysis. However, the ERG feels that use of the eMIT is more appropriate, as this is based on the actual price paid by English trusts. Use of eMIT prices increased the ICER comparing cabazitaxel with mitoxantrone by 4.8% to £51,675.

Three different estimates of post-second line treatment costs are available. The most expensive estimate (£1767.02) is for the mitoxantrone arm of the TROPIC trial. The least expensive estimate (£1192.81) is for the cabazitaxel arm of the TROPIC trial. The third estimate was based on a UK clinical audit (£1364.07). Within the economic model the cabazitaxel arm estimate was used for

treatment following cabazitaxel, and the mitoxantrone arm estimate was used for treatment following any of mitoxantrone, abiraterone or enzalutamide. The ERG believes that differences in post-second line treatment were unlikely to have contributed to differences in OS for the TROPIC trial. Hence the ERG believes that the same post-second line treatment costs should be used for cabazitaxel and each of the comparators. The ERG performed an analysis which used the values from the UK clinical audit for cabazitaxel and all of the comparators. This increased the ICER comparing cabazitaxel with mitoxantrone by 2.3% to £50,444.

Within their base-case the company assumed that there would not be any wastage of cabazitaxel. As discussed in Section 5.2.8, the ERG believes that there is likely to be some vial wastage occurring in clinical practice, but there is uncertainty about how much vial wastage would occur. The ERG performed an analysis which assumed that a cycle of treatment with cabazitaxel (or mitoxantrone) would require the cost of a vial of cabazitaxel (or mitoxantrone). This increased the ICER by [redacted] to [redacted].

Modelling of discontinuation for reasons other than progression

For cabazitaxel and mitoxantrone the company modelled discontinuation for reasons other than disease progression. People who discontinued this way remained in the stable disease state. The ERG identified three potential issues with how this approach was implemented and it believes that only two of these were adequately addressed by the company in their response to clarification question B6 (see Section 5.2.6 for a fuller discussion). In addition, the ERG believes that it is inappropriate to include this type of discontinuation for cabazitaxel and mitoxantrone but not for the two advanced hormonal therapies. Not including this type of discontinuation in the economic model increased the ICER by 2.1% to £50,370.

Disutility during the end of life period

The company included a disutility in the QALY calculations to account for the assumed reduced quality of life experienced by people with progressive disease in their last three months of life. However, the ERG noted that this disutility was calculated based on all deaths observed, not deaths amongst people with progressive disease. This was not changed in response to clarification question B11. The ERG notes that as all patients are modelled until death, the effect of this disutility will cancel out except for differences in discounting due to the differential timing of deaths for the different treatments. The impact on the ICER of removing this disutility was tested by the ERG, as discussed in Section 5.3, was to increase the ICER by 0.74% to £364.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

The ERG undertook a number of additional sensitivity analyses using the economic model, and base-case settings, supplied by the company (these did not change following response to clarification questions). Due to the requirement of following the template for ERG reports the results produced from key analyses undertaken by the ERG are reported in Section 6 (Table 36).

The following exploratory analyses had a notable effect on the base-case ICER reported in the CS.

For the company's base-case it was assumed that wastage would not occur for either cabazitaxel or mitoxantrone. As discussed in Section 5.2.8, the ERG believes that wastage could still occur. Hence an analysis was conducted that allowed for wastage. This was implemented in the company's model by setting the cost for mitoxantrone and cabazitaxel to be the cost per vial (instead of the cost per mg).

The ERG changed the post-second line treatment mix so that it was no longer treatment-specific, with resource use estimates from a UK clinical audit used instead.[25] The rationale for this change is summarised in Section 5.2.12. The change was achieved by changing the drop-down box of cell 'Post2ndChemoMix' (sheet 'Resource input') from 'TROPIC (arm-specific)' to 'Country-specific (general)'.

The ERG examined how sensitive the model results were to including a dose-reduction for both cabazitaxel and mitoxantrone. These reductions were removed by setting cells Rel_dose_int_caba and Rel_dose_int_mitox both equal to one.

For the comparison between cabazitaxel and mitoxantrone, the choice of parametric curve for extrapolation was based on minimising the goodness of fit to both TROPIC arms. The ERG explored the impact on the ICER of minimising the goodness of fit to the TROPIC arms separately (hence allowing for different parametric models to be used for the two treatments). This led to modelling OS with the Weibull curve for cabazitaxel and the log-logistic curve for mitoxantrone. For PFS the log-logistic curve was used for cabazitaxel and the log-normal curve was used for mitoxantrone.

The ERG noted that, based on their goodness of fit to the observed data, the use of log-logistic curves for both OS and PFS was a plausible alternative to the curves used in the base-case, although the ERG notes the statements made in the CS (p187)[25] that these had less face validity regarding long-term projection of survival. The ERG enacted these changes using the options in the 'RUN MODEL' sheet.

The ERG explored the sensitivity of the model results to the choice of progressive disease. The value used in the base-case was 0.6266, based on data from the UK EAP. Based on the standard error of

0.060 derivable from the UK EAP data, a normal 95% CI for the utility value for progressive disease is 0.510 to 0.743. These values were used in the economic model by changing the cell 'utility_value_PD' to these values. It should be noted that when using the latter estimate, the modelled utility will increase for people who progressed after receiving less than four cycles of treatment. Hence these results should be viewed with caution.

The company did not consider radium-223 dichloride to be a valid comparator, and so did not include it within their NMA. The ERG believes that this exclusion was inappropriate, as discussed in Section 3.3. When queried about this exclusion (clarification question A1), the company did provide summary statistics comparing OS amongst the TROPIC population with OS amongst the ALSYMPCA population with previous docetaxel use. This comparison is reproduced in Table 16 (comparable measures of PFS were not reported by the two trials):

The ERG notes that the differences in OS (both absolute and relative) are similar for cabazitaxel and radium-223 dichloride. Hence, the cost-effectiveness of cabazitaxel in comparison with radium-223 dichloride is likely to be driven mainly by the costs of the two drugs. The list price for a course of radium-223 dichloride (£4040) is [redacted] the PAS price for a cycle of cabazitaxel [redacted]. Radium-223 dichloride is taken for a maximum of six courses, whereas in the company's economic model cabazitaxel is taken for a maximum of ten cycles. In clinical practice there is no restriction on the maximum number of cycles for which cabazitaxel may be taken, although the median number of treatment cycles observed in both the TROPIC trial[11] and the UK EAP[50] was six. Data on the median number of treatments for radium-223 dichloride is not available. [redacted]. A consideration of the effect of the PAS for radium-223 dichloride on cost-effectiveness is discussed in a confidential appendix.

The following analyses did not materially affect the company's reported base-case ICER.
The company included a disutility to HRQoL to reflect the potentially worsening HRQoL for people with progressive disease in their last three months of life. The ERG had concerns with how this was implemented in the economic model, as discussed in Section 5.2.12. Hence an analysis was performed that removed this disutility. This was achieved by setting cells B3 to B6 on sheet 'Utility death' each equal to zero.

The ERG performed three sensitivity analyses concerning the stable disease utility values. These were:

1. Use of the weighted mean utility from the UK EAP (0.737) for all cycles.

2. Use of the values estimated from the 'TREND' function for each of the 10 cycles (as opposed to just being used for odd cycles - see response to clarification question B21 for further details).
3. Estimating the values for odd cycles as a weighted mean of the adjacent values (for example, the cycle 3 value would be the mean of the values observed for cycles 2 and 4).

5.4 Conclusions of the cost effectiveness section

The report was generally well written and the model was transparent with relatively few errors identified. The clarification process was smooth and the company responded to all of the ERG's questions.

Within the CS (p39)[25] it was argued that there are two clinical pathways of care for mCRPC, depending on whether or not the advanced hormonal therapies (abiraterone and enzalutamide) are used in the pre-chemotherapy or post-chemotherapy setting. Their use in the pre-chemotherapy setting was considered by the company to represent standard NHS practice. For this setting, the CS included a comparison between cabazitaxel and mitoxantrone. For the alternative pathway (post-chemotherapy use of the advanced hormonal therapies) the CS included comparisons between cabazitaxel and abiraterone and between cabazitaxel and enzalutamide although there was not an intention to perform a fully incremental analysis and BSC was not considered. The ERG notes that the exclusion of radium-223 dichloride from both pathways will lead to uncertainty in the cost-effectiveness results. However, given the results in Table 16 it did not seem unreasonable to explore the potential cost-effectiveness of radium-223 dichloride and cabazitaxel assuming equal efficacy of the interventions. This is detailed in Section 5.3, whilst an analysis using the PAS prices for cabazitaxel and radium-223 dichloride is provided in a confidential appendix. The ERG does not believe that the company provided sufficient justification for denoting the use of abiraterone and enzalutamide in the pre-chemotherapy setting as standard NHS practice. It is noted that both of these advanced hormonal therapies have NICE approval in the post-chemotherapy setting, and both are subject to on-going NICE appraisals in the pre-chemotherapy setting.

There was uncertainty relating to the amount of vial wastage that would occur for cabazitaxel in clinical practice. The base-case analysis assumed no wastage. If wastage does occur, this would increase the ICER.

Additional uncertainties related to the estimate of utility for patients with progressive disease, and how effectiveness data should be extrapolated. It is unclear if resolving these uncertainties would increase or decrease the base-case ICER.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

An overview of the ERG changes to the company's model is displayed in Table 36, along with estimates from the ERG base-case. The results presented in Table 36 are for the comparison between cabazitaxel and mitoxantrone. As discussed in Section 5.2.12, the ERG believes that the hybrid method for modelling the effectiveness of cabazitaxel is more appropriate than the company's base-case method. However, the ERG was not able to replicate this hybrid method. Use of the hybrid method decreased the company's base-case ICER by 1.6%, hence including the hybrid method is likely to reduce the ERG base-case ICER. In addition, as discussed in Section 5.2.8 there is uncertainty about the extent to which vial wastage occurs in clinical practice. Hence, two ERG base-cases are presented: one for which cabazitaxel treatment is based on the vial price (assuming that there will be some wastage of the vial), and one which assumes no wastage, with the clinical advisors to the ERG believing the scenario with vial wastage to be more realistic. It is noted that there will be some unavoidable wastage if people fail to attend their appointments for treatment. All probabilistic sensitivity analyses used 2,000 iterations.

Table 36: Overview of ERG changes to the model

Individual changes made	Cabazitaxel		Mitoxantrone		Incremental values		ICER (£)
	Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	Costs (£)	QALYS	
Company deterministic base-case	[redacted]	[redacted]	[redacted]	[redacted]	11,450	0.232	49,327
Company probabilistic base-case	NR	NR	NR	NR	11,829	0.233	50,682
Changes made							
A1) Use eMIT prices*	[redacted]	[redacted]	[redacted]	[redacted]	11,994	0.232	51,667
A2) Discontinuation for reasons other than disease progression not modelled	[redacted]	[redacted]	[redacted]	[redacted]	11,693	0.232	50,370
A3) Reduced disutility in the last 3 months of progressive disease not modelled	[redacted]	[redacted]	[redacted]	[redacted]	11,450	0.230	49,691
A4) Post-second line treatment resource use from UK audit for all treatments.	[redacted]	[redacted]	[redacted]	[redacted]	11,710	0.232	50,444
A5) Network meta-analysis results using a weakly informative prior (does not affect the comparison with mitoxantrone).	[redacted]	[redacted]	[redacted]	[redacted]	11,450	0.232	49,327
A6) Cost of cabazitaxel and mitoxantrone based on vial cost (assuming wastage).	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.232	[redacted]
A7) Use of log-logistic curves for both overall and progression-free survival.	[redacted]	[redacted]	[redacted]	[redacted]	12,627	0.309	40,887
A8) Parametric curves for OS and PFS based on lowest AIC value (no requirement	[redacted]	[redacted]	[redacted]	[redacted]	9,347	0.137	68,168

for same parametric form for both arms)**							
A9) Use of the 95% low confidence interval value for progressive disease (0.510).	[redacted]	[redacted]	[redacted]	[redacted]	11,450	0.207	55,248
A10) Use of the 95% high confidence interval value for progressive disease (0.743).	[redacted]	[redacted]	[redacted]	[redacted]	11,450	0.257	44,560
ERG Deterministic base-case 1 (changes A1 to A6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.230	[redacted]
ERG Probabilistic base-case 1 (changes A1 to A6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.231	[redacted]
ERG Deterministic base-case 2 (changes A1 to A5)	[redacted]	[redacted]	[redacted]	[redacted]	12,218	0.230	53,021
ERG Probabilistic base-case 2 (changes A1 to A5)	[redacted]	[redacted]	[redacted]	[redacted]	12,654	0.234	54,126

ICER: Incremental cost-effectiveness ratio. NR: Not reported. OS: Overall survival. PFS: Progression-free survival. QALYS: Quality-adjusted life-years.

*Note: when the company used eMIT prices (in response to clarification question B7), the reported total costs for cabazitaxel and mitoxantrone were £28,902 and £16,906 respectively, resulting in an ICER of £51,675. The ERG was unable to replicate these values.

** For cabazitaxel the Weibull curve is used for OS and the log-logistic curve for PFS. For mitoxantrone the curves are the log-logistic and the log-normal, respectively.

Under the ERG base-cases (using the results of probabilistic sensitivity analyses), the ICER comparing cabazitaxel with mitoxantrone was [redacted] if vial wastage occurs and £54,126 in the absence of vial wastage. Clinical advice given to the ERG suggests that vial wastage would be likely. The sensitivity analyses performed (A7 to A10) showed that the ICER was also sensitive to the methods employed for extrapolating clinical effectiveness data, and the utility value used for progressive disease. In addition, the ERG noted that when choosing the parametric form to extrapolate OS (and allowing cabazitaxel and mitoxantrone to have different parametric forms), the difference in goodness of fit statistics were less than 0.2% for both treatments. The models with the lowest goodness of fit statistics provided estimated mean survival times of 1.54 and 1.36 years for cabazitaxel and mitoxantrone respectively (ICER: £73,592). The models with the second lowest goodness of fit statistics provided estimated mean survival times of 1.82 and 1.20 years for cabazitaxel and mitoxantrone respectively (ICER: £35,947).

Based on the ERG base-cases, the cost-effectiveness of cabazitaxel when compared with abiraterone, enzalutamide or BSC is displayed in Table 37 (assuming vial wastage) and Table 38 (with no vial wastage). The company's model was amended to include BSC as a comparator. It was assumed that BSC was represented by mitoxantrone with respect to per-cycle costs and utility values. The effectiveness of BSC was modelled in the same manner as for abiraterone and enzalutamide by using HRs for BSC derived from the NMA as updated by the ERG (see Section 4.5 for more details).

Table 37: Cost-effectiveness results comparing cabazitaxel with BSC, abiraterone and enzalutamide (ERG base-case assuming vial wastage)

Treatment	Total values		Incremental cost-effectiveness ratio (£)
	Costs (£)	QALYs	
Deterministic results			
BSC	[redacted]	[redacted]	-
Cabazitaxel	[redacted]	[redacted]	£112,800 compared with best-supportive care
Abiraterone	[redacted]	[redacted]	Extendedly dominated by enzalutamide
Enzalutamide	[redacted]	[redacted]	£134,326 compared with cabazitaxel
Probabilistic sensitivity analysis results			
BSC	[redacted]	[redacted]	-
Cabazitaxel	[redacted]	[redacted]	£109,325 compared with best-supportive care
Abiraterone	[redacted]	[redacted]	Extendedly dominated by enzalutamide
Enzalutamide	[redacted]	[redacted]	£141,363 compared with cabazitaxel

BSC: Best supportive care. QALYs: Quality adjusted life years.

Table 38: Cost-effectiveness results comparing cabazitaxel with BSC, abiraterone and enzalutamide (ERG base-case assuming no vial wastage)

Treatment	Total values		Incremental cost-effectiveness ratio (£)
	Costs (£)	QALYs	
Deterministic results			
BSC	[redacted]	[redacted]	-
Cabazitaxel	[redacted]	[redacted]	£87,191 compared with best-supportive care
Abiraterone	[redacted]	[redacted]	Extendedly dominated by enzalutamide
Enzalutamide	[redacted]	[redacted]	£150,338 compared with cabazitaxel
Probabilistic sensitivity analysis results			
BSC	[redacted]	[redacted]	-
Cabazitaxel	[redacted]	[redacted]	£88,766 compared with best-supportive care
Abiraterone	[redacted]	[redacted]	Extendedly dominated by enzalutamide
Enzalutamide	[redacted]	[redacted]	£155,014 compared with cabazitaxel

BSC: Best supportive care. QALYs: Quality adjusted life years.

Based on the ERG base-case assumptions (using the results of probabilistic sensitivity analyses) the ICER for cabazitaxel compared with BSC is estimated to be £109,325 with vial wastage and £88,766 without vial wastage.. Abiraterone does not lie on the efficiency frontier, as the ICER comparing abiraterone with cabazitaxel is greater than that comparing enzalutamide with abiraterone regardless of the assumption made concerning vial wastage, and hence abiraterone is extendedly dominated by enzalutamide. Compared with cabazitaxel, the ICER for enzalutamide is £141,363 with vial wastage and £155,014 without vial wastage.

It should be noted that the ICERs comparing cabazitaxel with BSC are substantively greater than those comparing cabazitaxel with mitoxantrone, as reported in Table 35. This shows that the estimated cost-effectiveness results are sensitive to the modelling approach employed for extrapolating clinical effectiveness data. For the NMA results (which are used when comparing cabazitaxel with BSC and the two advanced hormonal therapies), an assumption of proportional hazards is required. The ERG has already noted that this assumption is questionable, and that the NMA results should be treated with caution, as discussed in Section 4.4.

Sensitivity analyses for the comparison between cabazitaxel, BSC, abiraterone and enzalutamide were not performed as the list prices used for abiraterone and enzalutamide do not reflect the true cost to the NHS. Cost-effectiveness results and sensitivity analysis based on the PAS for abiraterone and enzalutamide are reported in a confidential appendix.

There are two important uncertainties that are not captured within the ERG base-case. Firstly, it is noted that clinical use is not restricted to a maximum of ten cycles. However, this restriction was used in the TROPIC trial, to enable comparison with mitoxantrone, which is restricted to ten cycles of use. The TROPIC trial provides estimates for the effectiveness of cabazitaxel as used in the economic model. Using cabazitaxel for more than ten cycles would increase the lifetime costs associated with cabazitaxel, although it would be anticipated that this could also increase OS and utility and thus the impact on the ICER is unknown. In response to clarification question A4 the company stated that:
"The economic evaluation evaluates up to 10 cycles of treatment in order to be consistent with the trial evidence base, however based on UK experience (UK EAP and the number of cycles recorded on the CDF), it is reasonable to assume most patients will receive less than 10 cycles." Data from the UK EAP[50] show that 30.4% (34/112) of people received ten or more cycles of cabazitaxel. The maximum number of cycles received was 16, experienced by one person. It is further unclear what impact receiving more than ten cycles of cabazitaxel would have on HRQoL. Data from the UK EAP are only provided for the first ten cycles. They show that HRQoL improves as more cycles of cabazitaxel are received, although this improvement is not statistically significant. It is unclear if this improvement would be maintained beyond ten cycles.

The second important uncertainty relates to the results of the NMA. Both the ERG and the company believe that the results should be treated with caution. In addition, the ERG notes the uncertainty in using rPFS, which the company believes may bias against cabazitaxel when compared with abiraterone or enzalutamide. Within the economic model lower estimates of rPFS compared with a constant OS are associated with improved cost-effectiveness, as less drug costs are incurred, which may produce a favourable ICER for cabazitaxel.

The company did not consider the cost-effectiveness of cabazitaxel when compared to radium-223 dichloride. Whilst it was not possible within the timescales of the STA to include radium-223 dichloride within the existing cost-effectiveness analyses, a discussion of the potential consequences of including radium-223 dichloride as a comparator (for the sub-group for which it is indicated) is provided in both Section 5.3 and a confidential appendix.

7 END OF LIFE

To satisfy the NICE criteria for a life-extending, end-of-life treatment, three separate criteria must be met. These criteria, along with the company's justification for why they are met and the ERG's critique of this justification, are discussed in turn. It is noted that the decision of whether cabazitaxel meets end of life criteria may depend on the treatments to which it is being compared. These treatments may be BSC (including mitoxantrone), or an active comparator (abiraterone, enzalutamide and radium-223 dichloride), which do have a proven impact on OS when compared with BSC.

1. The treatment is indicated for patients with a short life expectancy, normally less than 24 months.

The company refer to a recent review of the literature by West *et al*,[10] who showed that median OS for patients treated first-line with docetaxel was 19 months. As cabazitaxel has marketing authorisation for treatment following prior adequate treatment with docetaxel, it is expected that OS in this group will be less than 19 months. The company also note that median OS for the control arms of the pivotal trials for cabazitaxel, abiraterone, enzalutamide and radium-223 dichloride varied from 11.2 months to 13.6 months. The ERG notes that OS for the active treatment arms (not including cabazitaxel) were 15.8 months (abiraterone), 18.4 months (enzalutamide) and 14.4 months (radium-223 dichloride).

2. There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional three months, compared to current NHS treatment, and;

When compared to mitoxantrone, cabazitaxel offered an estimated extension to median OS of 2.4 months (based on the full TROPIC population), and an estimated extension to mean OS of 4.1 months (based on the company's base-case analysis where OS is modelled using Weibull curves). In Section 5.2.10 the ERG noted that the fit to the observed data using log-logistic curves was similar to the fit produced using Weibull curves. Use of log-logistic curves led to an estimated mean extension to OS of 5.4 months.

The company did not consider if cabazitaxel met this criteria when compared to other treatments. The ERG notes that within the company's NMA, no statistically significant difference was found in OS between cabazitaxel and either abiraterone or enzalutamide. This lack of difference is based on the 95% credible interval for the estimated HR including one in both comparisons, based on the results from a fixed effects model. The ERG further notes that use of a random effects model would be likely to lead to an increase in the width of the 95% credible interval (and so still include one). A comparison with radium-223 dichloride was not performed. However, as discussed in Section 5.3, the

available evidence suggests that cabazitaxel and radium-223 dichloride potentially have similar effects on OS.

3. The treatment is licensed or otherwise indicated, for small patient populations.

The company provided details of a calculation which estimated that 1,690 people would be eligible for cabazitaxel. The ERG believes that this estimate is appropriate, although it is noted that there is uncertainty in the values used to derive this estimate. Further details are provided in Section 2.1. The ERG notes that the CSs for abiraterone and enzalutamide estimated that the number of patients eligible for treatment following docetaxel would be 3,300 and 2,977 respectively.

8 OVERALL CONCLUSIONS

The ERG did not identify any issues relating to the company's systematic review which appeared likely to influence the size of the ICER, with the possible exception of the subgroup analyses which are discussed below.

The company reported the results of an NMA using a fixed effects model. The ERG believes that by not using a random effects model the uncertainty in the effectiveness of treatments will be underestimated. The ERG updated the NMA results using a random effects model. The findings confirmed that there were broadly similar treatment effects for OS. They also indicate that no active treatments are significantly more effective than any of the other active treatments for rPFS. However, there is uncertainty in the results of the NMA due to concerns over differences between patient populations and exchangeability of control treatments. In addition, the relative treatment effects are assumed to be constant over time, which may not be realistic.

Within the CS a probabilistic base-case ICER of £50,682 comparing cabazitaxel with mitoxantrone was presented. In scenario analyses the company presented cost-effectiveness results, based on their NMA, to suggest that use of cabazitaxel dominated use of abiraterone (being associated with both reduced lifetime costs and improved overall HRQoL), and was cheaper but less effective than enzalutamide with an ICER of £212,038 for enzalutamide compared with cabazitaxel.

The company noted that there were two clinical pathways of care for people with mCRPC. Use of abiraterone or enzalutamide in the pre-chemotherapy setting was taken by the company to represent standard NHS practice, whilst use of abiraterone or enzalutamide in the post-chemotherapy setting was taken to be alternative practice. For standard NHS practice the company presented a probabilistic base-case ICER of £50,682 comparing cabazitaxel with mitoxantrone. For alternative practice the company presented cost-effectiveness results, using results from their NMA, to suggest that use of cabazitaxel dominated use of abiraterone (being associated with both reduced lifetime costs and improved overall health-related quality of life), and was cheaper but less effective than enzalutamide with enzalutamide having an ICER of £253,956 per QALY gained compared with cabazitaxel. The comparisons against abiraterone and enzalutamide were both undertaken using the list price of these drugs.

The ERG does not believe that there is sufficient justification for denoting either clinical pathway as standard NHS practice. It is noted that both of these advanced hormonal therapies have NICE approval in the post-chemotherapy setting, and both are subject to on-going NICE appraisals in the pre-chemotherapy setting. For the sub-group of people with symptomatic bone metastases and no

known visceral metastases radium-223 dichloride is a comparator in the NICE final scope, so excluding it will lead to uncertainty in the cost-effectiveness of cabazitaxel for both clinical pathways. In addition, not including BSC in the alternative practice pathway also leads to uncertainty about the cost-effectiveness of cabazitaxel.

The ERG's estimate of the ICER comparing cabazitaxel with mitoxantrone was [redacted] when modelling vial wastage and £54,126 when this was not modelled. The ERG also considered the cost-effectiveness of cabazitaxel when compared with BSC, abiraterone and enzalutamide. Effectiveness data were taken from the NMA adjusted by the ERG. The ICER comparing cabazitaxel with BSC was £109,325 when vial wastage was modelled and £88,766 when it was not modelled. Abiraterone was extendedly dominated by enzalutamide irrespective of how vial wastage was modelled. The ICER comparing enzalutamide with cabazitaxel was £141,363 when vial wastage was modelled and £155,014 when it was not modelled.

8.1 Implications for research

There are no direct comparisons of the clinical and cost effectiveness of cabazitaxel and any of abiraterone, enzalutamide or radium-223 dichloride. Hence there is a need for RCTs that directly compare these treatments, collects sufficient evidence on resource use and costs, and is powered to detect clinically meaningful changes in both OS and PFS. Trials comparing different sequences of treatment involving cabazitaxel and the advanced hormonal agents would also be beneficial.

Further research into the utility of people with mCRPC, particularly for people with progressed disease and how this utility varies over time, would help to reduce the uncertainty in the cost-effectiveness results. Uncertainty would also be reduced if longer-term data concerning the effectiveness of cabazitaxel (and each of the comparators) were available.

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10 APPENDICES

Appendix 1: Summary of TROPIC results (final analyses) as published by de Bono *et al.*[11]

In the TROPIC study, final efficacy analyses were planned after 511 death events had occurred using the ITT principle. The results for the whole trial population were first published by de Bono *et al*. in 2010[11] after a median follow-up of 12.8 months (study cut-off date: 25 September 2009), at which point 513 deaths had occurred. All efficacy analysis were by ITT and estimates of the HR and corresponding 95% CI were provided using a Cox proportional hazard model stratified by factors specified at randomisation. A brief summary of the key results is provided below.

- *OS*

Following a median follow-up of 12.8 months, 234 patients in the cabazitaxel group and 279 patients in the mitoxantrone group had died. Median OS (calculated using Kaplan-Meier methodology) was 15.1 months in the cabazitaxel group and 12.7 months in the mitoxantrone group and the HR was 0.70 (95% CI 0.59 to 0.83, p<0.0001, Table 39). Thus, cabazitaxel plus prednisone/prednisolone was associated with an estimated median survival gain of 2.4 months relative to mitoxantrone plus prednisone/prednisolone. The estimated modelled mean survival gain, reported in NICE TA255,[15] was 4.2 months.

Table 39: Summary of OS in the TROPIC study – final efficacy analysis

	Cabazitaxel (n=378)	Mitoxantrone (n=377)	Hazard ratio (95% CI)	p value
Analysis at 25.9.2009 (final efficacy analysis)[11]				
Total deaths, ITT population	234 (61.9%)	279 (74.0%)	NR	NR
Number of patients censored	144	98	NR	NR
Median overall survival, months (95% CI) [a]	15.1 (14.1 to 16.3)	12.7 (11.6 to 13.7)	0.70 (0.59 to 0.83)	<0.0001

CI, confidence interval; ITT, intention-to-treat

[a] Median difference in overall survival, 2.4 months

- *PFS*

In the final analysis, as reported by de Bono *et al*.[11] cabazitaxel was associated with a statistically significant improvement in median PFS (a composite endpoint defined as the time between randomisation and first date of progression as measured by PSA progression, tumour progression, pain progression or death). Median PFS was 2.8 months in the cabazitaxel group and 1.4 months in the mitoxantrone group (HR: 0.74, 95% CI 0.64 to 0.86, p<0.0001). Additional data from a FDA

reviewers' report[85] indicated that the majority (43-49%) of progression events were related to PSA progression. A summary of the PFS results are provided in Table 40.

Table 40: Progression-free survival in the TROPIC study – final efficacy analysis

	Cabazitaxel (n=378)	Mitoxantrone (n=377)	Hazard ratio (95% CI)	p value
Analysis at 25.9.2009 (final efficacy analysis)				
Number of patients with progression-free survival events (%)[85]	364 (96.3%)	367 (97.3%)	NR	NR
Median progression-free survival, months (95% CI)[11]	2.8 (2.4 to 3.0)	1.4 (1.4 to 1.7)	0.74 (0.64 to 0.86)	<0.0001
Death	38 (10.1%)	29 (7.7%)	NR	NR
Tumour progression	67 (17.7%)	68 (18.0%)	NR	NR
PSA progression	163 (43.1%)	186 (49.3%)	NR	NR
Pain progression	86 (22.8%)	70 (18.6%) [a]	NR	NR
Symptom deterioration	10 (2.6%)	14 (3.7%)	NR	NR
Censored	14 (3.7%)	10 (2.7%)	NR	NR

CI, confidence interval

[a] Data discrepancy in CS: updated efficacy analysis had fewer number of patients (n=69)

- *Other secondary outcomes*

In general, as reported by de Bono *et al.*[11] cabazitaxel was associated with statistically significant improvements in PSA response ($p = 0.0002$), time to PSA progression ($p = 0.001$), objective tumour response ($p = 0.0005$) and time to tumour progression $p < 0.0001$. However, it was not associated with statistically significant differences in pain response ($p=0.63$) or pain progression ($p = 0.52$). Data on HRQoL were not collected in the TROPIC study.

Appendix 2: Additional data on adverse events

A comparison of the adverse events observed in the trials included in the NMA are provided in Table 41.

Table 41: Comparison of adverse events in trials included in the NMA

	TROPIC (cabazitaxel + prednisone arm, n=371)[11]		AFFIRM (enzalutamide arm, n=800)[13]		COU-AA-301 (abiraterone + prednisone arm, n=791)[12]		ALSYMPCA (radium-223 dichloride arm with previous docetaxel use, n=347)[14]	
	All grades	Grades ≥ 3	All grades	Grades ≥ 3	All grades	Grades ≥ 3	All grades	Grades ≥ 3
Haematological								
Anaemia	361 (97%)	39 (11%)	NR	NR	178 (23%)	59 (7%)	120 (35%)	50 (14%)
Thrombocytopenia	176 (47%)	15 (4%)	NR	NR	28 (4%)	11 (1%)	53 (15%)	31 (9%)
Leukopenia	355 (96%)	253 (68%)	NR	NR			21 (6%)	5 (1%)
Neutropenia	347 (94%)	303 (82%)	NR	NR	7 (1%)	1 (<1%)	24 (7%)	11 (3%)
Febrile neutropenia		28 (8%)	NR	NR	0 (0%)	0 (0%)	NR	NR
Non-haematological								
Abdominal pain	43 (12%)	7 (2%)	NR	NR	95 (12%)	16 (2%)	NR	NR
Anorexia	NR	NR	NR	NR	NR	NR	58 (17%)	4 (1%)
Arthralgia	39 (11%)	4 (1%)	NR	NR	215 (27%)	33 (4%)	NR	NR
Asthenia	76 (20%)	17 (5%)	NR	NR	104 (13%)	18 (2%)	NR	NR
Back pain	60 (16%)	14 (4%)	NR	NR	233 (30%)	47 (6%)	NR	NR
Bone pain	19 (5%)	3 (1%)	NR	NR	194 (25%)	44 (6%)	185 (53%)	74 (21%)
Cardiac disorder	NR	NR	49 (6%)	7(1%)	106 (13%)	33(4%)	NR	NR
Constipation	76 (20%)	4 (1%)	NR	NR	206 (26%)	8 (1%)	62 (18%)	3 (1%)

Diarrhoea	173 (47%)	23 (6%)	171 (21%)	9 (1%)	139 (18%)	5 (<1%)	85 (25%)	2 (1%)
Dyspnoea	44 (12%)	5 (1%)	NR	NR	102 (13%)	10 (1%)	NR	NR
Fatigue	136 (37%)	18 (5%)	269 (34%)	50 (6%)	346 (44%)	66 (8%)	94 (27%)	16 (5%)
Fluid retention and oedema	NR	NR	NR	NR	241 (31%)	18 (2%)	39 (11%)	6 (2%)
Haematuria	62 (17%)	7 (2%)	NR	NR	65 (8%)	11 (1%)	NR	NR
Headache	NR	NR	93 (12%)	6 (<1%)	NR	NR	NR	NR
Hot flash	NR	NR	162 (20%)	0	NR	NR	NR	NR
Hypertension	NR	NR	NR	NR	77 (10%)	10 (1%)	NR	NR
Hypokalaemia	NR	NR	NR	NR	135 (17%)	30 (4%)	NR	NR
Liver function abnormality	NR	NR	8 (1%)	3 (<1%)	81 (10%)	27 (3%)	NR	NR
Musculoskeletal pain	NR	NR	109 (14%)	8 (1%)	NR	NR	NR	NR
Nausea	127 (34%)	7 (2%)	NR	NR	233 (30%)	13 (2%)	137 (40%)	8 (2%)
Pain	20 (5%)	4(1%)	NR	NR	13 (2%)	5 (1%)	NR	NR
Pain in extremity	30 (8%)	6 (2%)	NR	NR	134 (17%)	19 (2%)	NR	NR
Pyrexia	45 (12%)	4 (1%)	NR	NR	71 (9%)	3 (<1%)	NR	NR
Seizure	NR	NR	5 (<1%)	5 (<1%)	NR	NR	NR	NR
Urinary tract infection	27 (7%)	4 (1%)	NR	NR	91 (12%)	17 (2%)	26 (8%)	3 (1%)
Vomiting	84 (23%)	7 (2%)	NR	NR	168 (21%)	14 (2%)	83 (24%)	9 (3%)
Weight loss	NR	NR	NR	NR	NR	NR	48 (14%)	4 (1%)

NR, not reported