Committee Papers

Cabazitaxel for treating hormone-relapsed metastatic prostate cancer after a docetaxel-containing regimen (review of TA255) [ID889]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Cabazitaxel for treating hormone-relapsed metastatic prostate cancer after a docetaxel-containing regimen (review of TA255) [ID889]

Appraisal Committee Meeting – Wednesday 6 January 2016

The following documents are made available to Consultees and Commentators:

1. **Pre-Meeting Briefing (PMB)**

2. **Final Scope and Final Matrix**

3. **Company submission** from Sanofi

4. **Clarification letters**
   - NICE request to the company for clarification on their submission
   - Company response to NICE's request for clarification

5. **Patient group, professional group and NHS organisation submission** from:
   - Prostate Cancer UK
   - TACKLE
   - British Uro-Oncology Group
   - NCRI RCP RCR ACP

6. **Expert personal perspectives** from:
   - Dr Amit Bahl – clinical expert, nominated by British Uro-Oncology Group
   - Dr Zafar Malik – clinical expert, nominated by Sanofi
   - Hugh Gunn – patient expert, nominated by TACKLE
   - Allan Higgins – patient expert, nominated by Prostate Cancer UK

7. **Evidence Review Group report** prepared by School of Health and Related Research (ScHARR)
   - Evidence Review Group report
   - Errata

8. **Evidence Review Group report – factual accuracy check**

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Premeeting briefing

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

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Key issues for consideration

Decision problem

- What are the relevant comparators: A) for people who had abiraterone or enzalutamide and then docetaxel; B) for people who did not have abiraterone or enzalutamide before docetaxel?
- Is radium-223 dichloride a relevant comparator?

Clinical effectiveness

- The patients in the TROPIC trial did not have abiraterone or enzalutamide before docetaxel. Are the results of TROPIC generalisable to the population of NHS patients who have had this treatment sequence?
- The company's preferred analyses come from the subgroup in TROPIC with ECOG performance status of 0 or 1 who previously had at least 225 mg/m^2

docetaxel. Is this subgroup representative of the patients who would be treated with cabazitaxel in the NHS?

- Is a fixed effects indirect treatment comparison appropriate considering the heterogeneity between the trial outcomes?
- Is it appropriate to use hazard ratios to inform the indirect treatment comparison when the proportional hazards assumption does not hold for 1 trial?

Cost effectiveness

- The company stated that 'compounded IV bags of cabazitaxel can be supplied direct to NHS hospitals'. Is it appropriate to assume no wastage of cabazitaxel in the model? Is this assumption appropriate?

- Both the company and the ERG consider the indirect treatment comparison to be uncertain. Is the ERG's fully incremental cost-effectiveness analysis, which is informed by the indirect treatment comparison, suitable for decision-making?

- Does cabazitaxel meet the end-of-life criteria: A) for people who had abiraterone or enzalutamide and then docetaxel; B) for people who did not have abiraterone or enzalutamide before docetaxel?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was to appraise the clinical and cost effectiveness of cabazitaxel within its marketing authorisation for treating hormone-relapsed metastatic prostate cancer previously treated with a docetaxel-containing regimen.

1.2 Cabazitaxel was previously appraised in NICE technology appraisal 255 (Cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen), 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. Following a review it was agreed to reappraise cabazitaxel because more mature data

from the trial had been published and a patient access scheme was proposed by the company.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed by company in the submission	Comments from the company	Comments from the ERG
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 additional wording was included to accommodate treatment with abiraterone or enzalutamide pre- or post-docetaxel.	The ERG noted that this is an appropriate population.
Intervention	Cabazitaxel in combination with prednisone or prednisolone	Cabazitaxel in combination with prednisolone (or prednisone) 10 mg per day up to a maximum of 10 cycles (each cycle is 3 weeks).	None.	None.
Comparison	Abiraterone in combination with prednisone or prednisolone Enzalutamide Mitoxantrone in combination with 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)	Comparator in base case: best supportive care represented by mitoxantrone. Comparators in scenario analyses: abiraterone and enzalutamide. A comparison with radium-223 was not presented.	The company considers mitoxantrone to be equivalent to best supportive care. The company considered that it is established NHS practice to have abiraterone or enzalutamide and then docetaxel. Thus, the company considered the main comparator to be best supportive care (see section 2.2). Radium-223 is not considered to be a comparator due to differences in trial patient populations and resulting marketing authorisations (nor is	The ERG's clinical advisors acknowledged that best supportive care can be represented by mitoxantrone. The ERG noted that the company could have performed

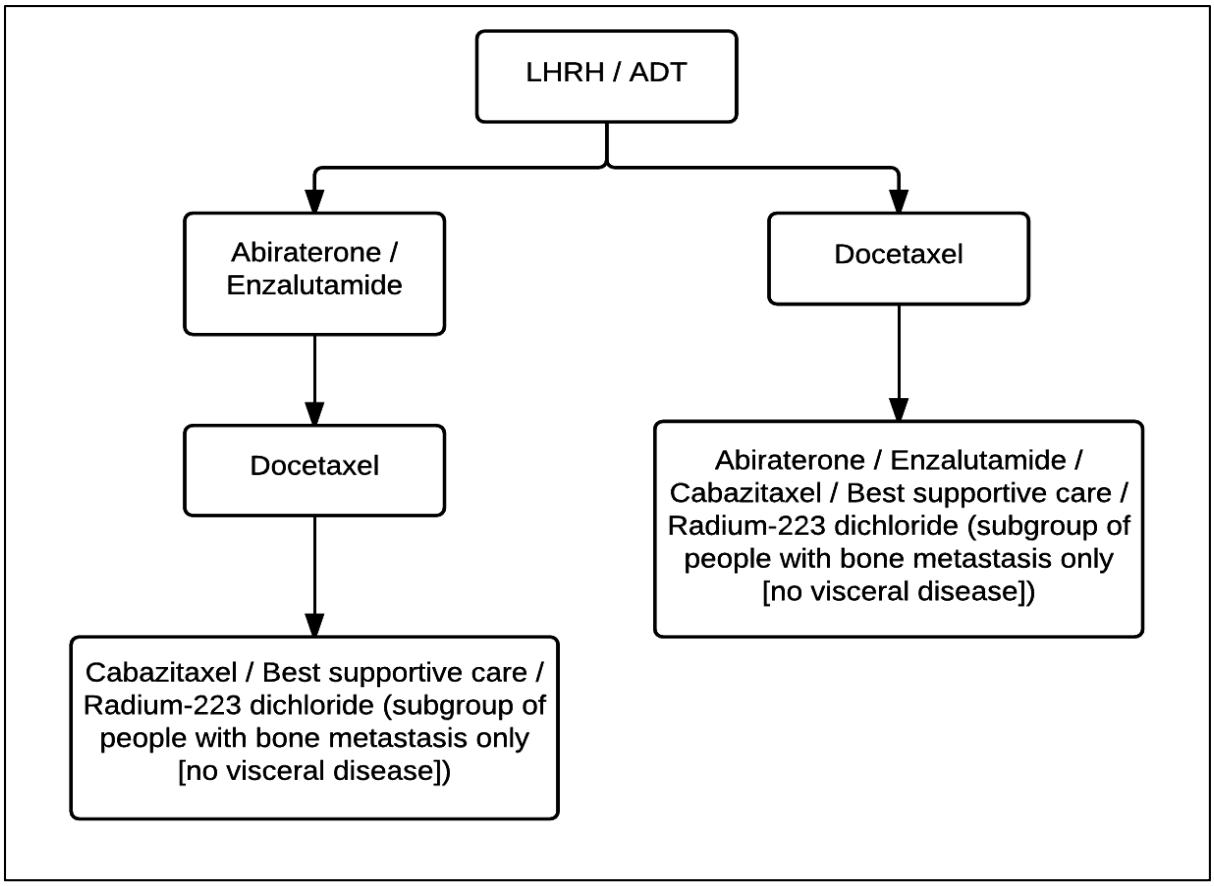
			cabazitaxel considered to be a comparator in the ongoing NICE appraisal for Radium-223 dichloride). Further the company note that its use is currently not established in the UK.	a separate comparison between cabazitaxel and radium-223 dichloride, using data from the relevant sub-group of the TROPIC trial.
Outcomes	The outcome measures to be considered include: overall survival progression-free survival (PFS) response rate adverse effects of treatment health-related quality of life.	Primary outcome: overall survival Secondary outcomes: Progression-free survival (PFS) Adverse effects of treatment Health-related quality of life.	No comments.	No comments.

2 The technology and the treatment pathway

2.1 Cabazitaxel (Jevtana, Sanofi) is an anticancer drug known as a taxane. It disrupts the microtubular network and inhibits cell division and cell death. It is administered by intravenous infusion.

2.2 NICE clinical guideline 175 recommends that people are offered the following treatments for metastatic prostate cancer: orchidectomy (surgical removal of the testes, also known as surgical castration) or luteinising hormone-releasing agonists (known as medical castration). If the cancer becomes refractory to treatment NICE technology appraisal guidance 101 recommends docetaxel as a treatment option for those with metastatic hormone-refractory disease who have a Karnofsky performance-status score of 60% or more (a higher percentage reflects better function). NICE technology appraisal guidance 259 and 316 recommend abiraterone or enzalutamide, as options for treating metastatic hormone-relapsed prostate cancer that has progressed during or after docetaxel-containing chemotherapy. Abiraterone and enzalutamide also have marketing authorisations for use before docetaxel and are available to people through the Cancer Drugs Fund. NICE technology appraisal guidance for abiraterone and enzalutamide in the pre-chemotherapy setting is under development. A NICE final appraisal determination recommends enzalutamide as an option for treating metastatic hormone-relapsed prostate cancer in people who have no or mild symptoms after androgen deprivation therapy has failed, and before chemotherapy is indicated, only when the company provides it with the discount agreed in the patient access scheme. A NICE final appraisal determination recommends radium-223 dichloride as an option for treating adults with hormone-relapsed prostate cancer with 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 patient access scheme.

Figure 1 Clinical pathway for cabazitaxel (figure 1, page 22 of ERG report)



Key: LHRA/ADH; luteinizing hormone-releasing hormone agonists/androgen deprivation therapy

Table 2 Technology

	Intervention	Comparators			
	Cabazitaxel	**Mitoxantrone**	**Abiraterone**	**Enzalutamide**	**Radium-223 dichloride**
Marketing authorisation	Cabazitaxel in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen	Mitoxantrone is indicated for the treatment of metastatic breast cancer, non-Hodgkin's lymphoma and adult acute non-lymphocytic leukaemia.	Abiraterone is indicated with prednisone or prednisolone for: • the treatment of metastatic castration resistant prostate cancer in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen • the treatment of metastatic castration resistant prostate cancer in adult men who are asymptomatic or mildly symptomatic after failure of androgen	Enzalutamide is indicated for: • the treatment of adult men with metastatic castration-resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated • the treatment of adult men with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel	Radium-223 is indicated for the treatment of adults with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases.

			deprivation therapy in whom chemotherapy is not yet clinically indicated.	therapy.	
Administration method	25 mg/m^2 administered as a 1 hour intravenous infusion every 3 weeks in combination with oral prednisolone 10 mg administered daily.	14 mg/m^2 administered as a single intravenous dose which may be repeated at 21-day intervals.	1,000 mg (4 x 250 mg tablets) as a single daily dose.	160 mg (4 x 40 mg capsules) as a single oral daily dose.	The dose regimen of radium-223 is an activity of 50 kBq (kilobecquerel) per kg body weight, given at 4 week intervals for 6 injections.
Cost	List price £3696 per vial, equivalent to £61.60 per mg [BNF 2015]. A patient access scheme discount of [redacted] has been approved. This reduces the price of cabazitaxel to [redacted] per vial, or [redacted] per mg.	£30.36 per 20mg/10ml solution for infusion (Drugs and pharmaceutical electronic market information [eMit]).	List price £2930.00 per 120-tab pack (250 mg). A confidential patient access scheme discount has been approved (see confidential appendix for details).	List price £2734.67 per 112-cap pack (40 mg). A confidential patient access scheme discount has been approved (see confidential appendix for details).	Radium 223 is available at a radioactivity of 6 MBq in a 6 ml vial at a net price of £4040 (excluding VAT). A confidential patient access scheme discount has been approved (see confidential appendix for details).

3 Comments from consultees

3.1 A professional group commented on the treatment options available for people with hormone-relapsed metastatic prostate cancer. It was advised that in England, people are offered treatment with either abiraterone or enzalutamide. If the disease does not respond to these treatments, people may be offered docetaxel (if not previously taken), radium-223 dichloride (if they have symptomatic disease with metastasis in bone only) or cabazitaxel (if they previously had docetaxel). The professional group advised that mitoxantrone does not have a UK marketing authorisation for treating prostate cancer; it is used only rarely, as part of best supportive care, for people with symptomatic disease who have no other treatment options.

3.2 A patient group advised that the symptoms experienced by people with advanced prostate cancer include significant pain and fatigue which leave people unable to perform day-to-day activities. Other signs and symptoms associated with advanced disease include hypercalcaemia, urinary problems, swollen lymph nodes and occasionally, and spinal cord compression. In addition to physical symptoms people with advanced prostate cancer can experience anxiety and depression.

3.3 A patient group commented that radium-223 dichloride is contraindicated in people with liver metastases. The group noted that cabazitaxel is possibly the only treatment option available for people whose prostate cancer has metastasised to the liver following treatment with docetaxel or enzalutamide/abiraterone.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company identified 1 phase III randomised open label multi-centre trial (TROPIC) which compared cabazitaxel with mitoxantrone in men with

metastatic castration-resistant prostate cancer previously treated with a docetaxel-containing regimen. Patients aged 18 years or older were randomised 1:1 to have either:

- 25 mg/m^2 of cabazitaxel intravenously every 3 weeks in combination with 10 mg prednisone (or prednisolone) for a maximum of 10 cycles or
- 12 mg/m^2 of mitoxantrone every 3 weeks with 10 mg prednisone (or prednisolone) for a maximum of 10 cycles

(The investigators capped the treatment at a maximum of ten cycles to minimise the risk of mitoxantrone induced cardiac toxicity).

4.2 The trial included patients whose disease had progressed 6 months or less following treatment with a docetaxel containing regimen and who had an orchidectomy or treatment with a luteinising hormone-releasing hormone (LHRH) agonist. The trial excluded people previously treated with mitoxantrone. For a full list of trial inclusion and exclusion criteria, please see page 64-66 of the company submission.

ERG comments

4.3 The ERG noted that the company's systematic review process, including the inclusion and exclusion criteria, was appropriate and reflected the decision problem. The submission included all relevant studies of cabazitaxel in combination with prednisone or prednisolone (including data from ongoing or planned studies) but excluded studies of radium-223 dichloride.

Design of the clinical trial

Outcomes

4.4 The primary outcome measure in TROPIC was overall survival, defined as the time from the date of randomisation to death from any cause. In the absence of confirmation of death, the survival time was censored at the last date the patient was known to be alive or at the data cut-off date. Secondary outcomes included progression free survival defined as the

time from randomisation to tumour progression, prostate specific antigen progression, pain progression (pain progression supported by clinical evidence and or radiological evidence of disease progression), or death due to any cause. For further details of secondary outcomes see page 69 of the company submission.

Statistical analysis

4.5 The company noted that in the original TROPIC study, final analyses had been planned after 511 deaths had occurred using the intention to treat principle. The results for the whole trial population were first published after a median follow-up of 12.8 months (study cut-off date: 25 September 2009), at which point 513 deaths had occurred. The updated analysis was published 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 used the intention to treat and estimates of the hazard ratio and corresponding 95% confidence intervals were provided using a Cox proportional hazard model stratified by factors specified at randomisation.

4.6 The trial included 2 analyses: intention to treat and per protocol. The intention to treat analysis included all randomised patients (n=755) and the per protocol analysis included only those patients who had received at least 1 dose of the study treatment (n=742).

4.7 A post-hoc subgroup analysis was conducted for patients in TROPIC with an ECOG performance status of 0-1 who had received at least 225 mg/m^2 docetaxel. See section 4.11.

Baseline characteristics

4.8 In the intention-to-treat analysis, 378 patients were randomised to receive cabazitaxel and 377 patients were randomised to receive mitoxantrone. The median age of patients in the cabazitaxel group was 68 years and in the mitoxantrone group, 67 years. In the cabazitaxel group 92.6% of patients had an ECOG performance status of 0 or 1; this was 91.2% in the

mitoxantrone group. In the cabazitaxel group 71% of patients were previously treated with chemotherapy; this was 69% in the mitoxantrone group. No patients were previously treated with enzalutamide or abiraterone. For further details on patient characteristics see table 19 on page 73 of the company submission.

ERG comments

4.9 The ERG noted that a lack of blinding of patients, care providers, and outcome assessors in the TROPIC study could bias the results. The ERG noted that for objective outcomes, such as overall survival un-blinded assessment is unlikely to bias the trial results. However, estimates of treatment effect for subjective outcomes such as pain and symptom deterioration (both of which were included in the definition of progression free survival) may be biased by unblinding.

Results of TROPIC

4.10 In the intention-to-treat analysis, median survival was 15.1 months in the cabazitaxel group and 12.8 months in the mitoxantrone group. The difference was statistically significant (p = 0.0002). The hazard ratio (HR) was 0.72 (95% confidence interval [CI]: 0.61 to 0.84).

Table 3 TROPIC overall survival results (table 22, page 78 of company submission)

Outcome	**TROPIC**	
	Cabazitaxel + prednisone (n=378)	**Mitoxantrone + prednisone (n=377)**
Median survival in months (95% CI)	15.08 (13.96-16.49)	12.78 (11.53-13.73)
Hazard ratio	0.72 (0.61 - 0.84)	
p value	<0.001	

Subgroup analysis

4.11 The company presented a post hoc sub group analysis for patients in TROPIC with an ECOG performance status of 0-1 (a lower ECOG score

reflects better function) who had received at least 225 mg/m^2 docetaxel[1]. The company highlighted that in NICE technology appraisal guidance 255 the Committee had considered that this subgroup was representative of clinical practice in England because people who had an ECOG performance score of 2 or more were not suitable for treatment with chemotherapy and therefore unlikely to be treated with cabazitaxel.

4.12 The subgroup analysis was conducted on the updated TROPIC dataset (see section 4.5) and represented 632 (83.7%) patients out of the intention to treat population of 755.

Baseline characteristics in the subgroup

4.13 The median age of patients in the cabazitaxel group was 68 years and in the mitoxantrone group 66 years. For further details of baseline characteristics see table 25, page 82 of the company submission.

Results of the subgroup

4.14 The company included 632 patients in the subgroup analysis; 319 in the cabazitaxel group and 313 in the mitoxantrone group. Median overall survival was 15.6 (95% CI 13.96 - 17.28) months in the cabazitaxel group and 13.4 (95% CI 11.99 - 14.52) months in the mitoxantrone group. The difference was statistically significant (p <0.001). The hazard ratio was 0.69 (0.57 - 0.82).

Table 4 Overall survival in the subgroup of patients with ECOG performance score of 0 -1 who have received at least 225 mg/m^2 docetaxel (table 26, page 83 of company submission)

	Cabazitaxel + prednisone (n=319)	Mitoxantrone + prednisone (n=313)
Median overall survival in months (95% CI)	15.61 (13.96-17.28)	13.37 (11.99-14.52)
Hazard ratio (95% CI)	0.69 (0.57-0.82)	
P value	<0.001	
Key: CI = confidence interval		

[1] The company noted that patients would need to receive at least 225 mg/m2 of docetaxel to gain the full benefit of first-line treatment before going on to second-line treatment with cabazitaxel (see page 54 of the ERG report).

4.15 Median progression free survival in the subgroup was 2.76 (95% CI 2.43-3.12) months in the cabazitaxel group and 1.41 (95% CI 1.35-1.84) months in the mitoxantrone group. The difference was statistically significant (p = 0.001). The hazard ratio was 0.76 (95% CI 0.65-0.89).

Table 5 Progression free survival in the subgroup of patients with ECOG performance score of 0 -1 who have received at least 225 mg/m^2 docetaxel (table 27, page 84 of company submission)

	Cabazitaxel + prednisone (n=319)	Mitoxantrone + prednisone (n=313)
Number of patients with PFS events (%)	305 (95.61)	304 (97.12)
Median PFS in months (95%CI)	2.76 (2.43-3.12)	1.41 (1.35-1.84)
Hazard ratio (95% CI)	0.76 (0.65-0.89)	
p value	0.001	

Key: CI = confidence interval; PFS = progression-free survival
PFS 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 Source

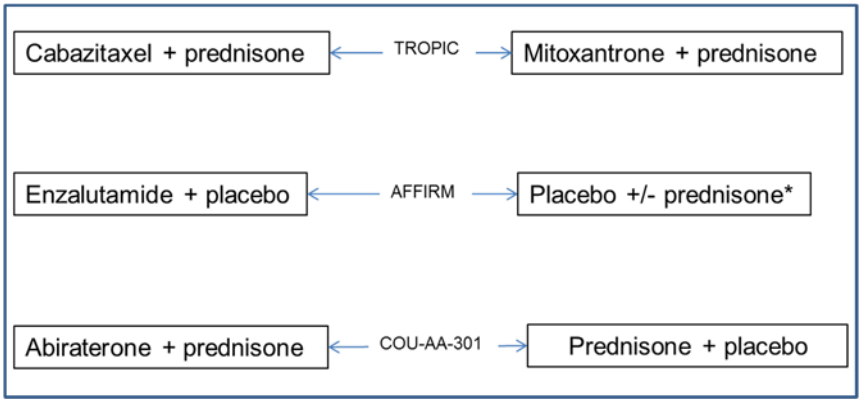
Indirect treatment comparison

Overview

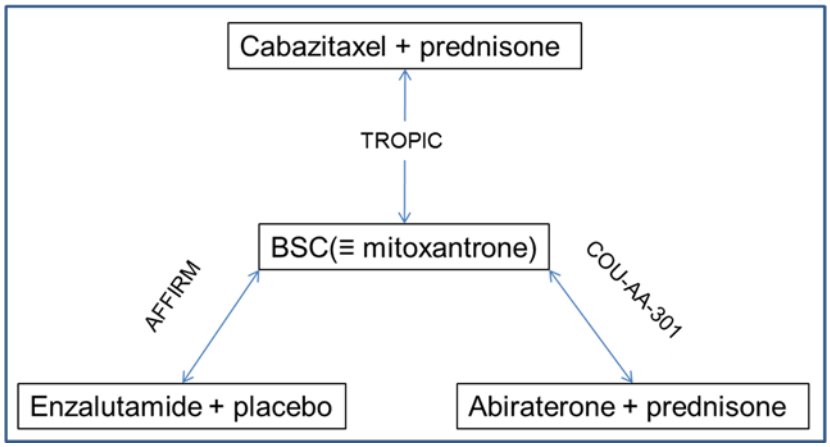
4.16 The company performed an indirect treatment comparison comparing cabazitaxel with abiraterone and enzalutamide. It identified the COU-AA-301 (abiraterone) trial and the AFFIRM (enzalutamide) trial from its systematic literature review. The AFFIRM study compared enzalutamide with placebo. The COU-AA-301 study compared abiraterone plus prednisone with prednisone plus placebo (see section 4.1 page 52 of company submission for further details) (Figure 2).

Network diagram

Figure 2 Company's network diagrams for the included trials (figure 11, page 86 of company submission)



* The NICE technical team suggests that there is a typographical error for the intervention group of the AFFIRM trial, which should read 'Enzalutamide + prednisone and not placebo.



Outcomes

4.17 The company noted that the definition of progression in TROPIC is different to the definition in COU-AA-301 and AFFIRM because it used a multiple-component endpoint. Therefore, to compare the trials, the company chose radiographic progression free survival to inform its indirect treatment comparison which it defined as the time from randomisation to the first occurrence of tumour progression (based on the response evaluation criteria in solid tumours [RECIST] criteria) or death due to any cause.

4.18 The company estimated the median radiographic progression free survival for the intention to treat population in TROPIC. This was 8.8 months (95% CI 7.6 - 9.7) in the cabazitaxel group and 5.9 months (95% CI 5.1 - 7.0) in the mitoxantrone group (p = 0.003 [HR 0.75; 95% CI, 0.65–0.88]). For further details of the methods informing this analysis see pages 11-13 of appendix B in the company submission.

Table 6 Overview of the clinical trials included in the indirect treatment comparison in the intention to treat populations (adapted from table 8, page 14 of appendix b in the company submission)

	TROPIC (cabazitaxel)	COU-AA-301 (abiraterone)	AFFIRM (enzalutamide)
Intervention	Cabazitaxel + prednisone/prednisolone (n=371)	Abiraterone Acetate + prednisone/prednisolone (n=797)	Enzalutamide (n=800)
Comparator	Mitoxantrone + prednisone/prednisolone (n=377)	Placebo + prednisone/prednisolone (n=398)	Placebo (n=399)
rPFS HR (95%CI)	0.75 (0.65-0.88)	0.78 (0.65-0.88)	0.4 (0.35-0.45)
Key: ITC, indirect treatment comparison; rPFS, radiographic progression free survival HR: hazard ratio			

Results

4.19 The results of the fixed effects indirect treatment comparison showed a nonsignificant decrease in overall survival between cabazitaxel and abiraterone and a nonsignificant increase in overall survival for enzalutamide (see Table 7). For radiographic progression free survival there was a nonsignificant decrease in risk of progression between cabazitaxel and abiraterone and a statistically significant difference between cabazitaxel and enzalutamide (in favour of enzalutamide) HR 1.88 (credibility interval 1.54, 2.29). See Table 7 for details.

4.20 The company's indirect treatment comparison assumed that the control treatments in all 3 trials had similar efficacy and a similar safety profile, but the company stated that these assumptions may not hold true. Specifically, radiographic progression free survival was longer in the

control group of TROPIC (median 5.9 months) than in the control groups of AFFIRM and COU-AA-301 (median 2.9 and 3.6 months respectively). Accordingly, the company advised that the results from the indirect treatment comparison should be treated with caution. See page 86-87 of the company submission for further details.

Table 7 Results from the mixed treatment comparisons (table 28, page 87 of company submission)

	Overall survival			Radiographic progression free survival		
	HR	Credible intervals		HR	Credible intervals	
Cabazitaxel compared with BSC[a]	0.72	0.61	0.85	0.75	0.65	0.88
Cabazitaxel compared with abiraterone	0.97	0.78	1.21	0.97	0.76	1.22
Cabazitaxel compared with enzalutamide	1.14	0.90	1.45	1.88	1.54	2.29
[a] mitoxantrone assumed equivalent to BSC. Key: HR: Hazard Ratio; BSC: Best Supportive Care.						

ERG comments

4.21 The ERG acknowledged the company's concerns about the validity of its indirect comparisons (see section 4.20). It noted that the validity of the analysis for both overall survival and radiographic progression free survival are dependent on the assumption that the control treatments of the 3 included trials can be considered exchangeable. If this is not the case (the control treatments are not exchangeable) then there will be considerable heterogeneity. In the presence of between-study heterogeneity a fixed effects model is not appropriate, so the ERG advised that a random effects model should have been used.

4.22 The ERG also noted that the company's use of hazard ratios for the analysis may not have been appropriate because this analysis assumes that the difference in the risk of death between treatment groups within a trial is constant over time (the proportional hazards assumption). In the

COU-AA-301 study for abiraterone compared with placebo, the placebo overall survival curve crosses the abiraterone curve at 24 months, which means that the proportional hazards assumption may not hold. Accordingly, the ERG advised that the results of the indirect treatment comparison should be treated with caution.

ERG exploratory analyses

4.23 To assess the impact of differences between-trials, the ERG conducted additional analyses using a random effects model. In the absence of information on which to base the choice of a prior probability, the ERG used a weakly informative half-normal prior with variance 0.32^2 (see Table 8). The results showed no significant difference in overall survival or radiographic progression free survival between the 3 interventions.

Table 8 Results of NMA using random effects model, half-normal prior with variance 0.32^2

	Overall survival			Radiographic progression free survival		
	HR (mean)	Credible intervals		HR	Credible intervals	
Cabazitaxel compared with BSC[a]	0.77	0.35	1.47	0.80	0.36	1.53
Cabazitaxel compared with abiraterone	1.10	0.35	2.74	1.09	0.34	2.74
Cabazitaxel compared with enzalutamide	1.29	0.41	3.19	2.12	0.66	5.22

[a] mitoxantrone assumed equivalent to BSC.
Key: HR: Hazard Ratio; BSC: Best Supportive Care.
A hazard ratio (HR) less than 1 indicates a lower risk of death or disease progression with cabazitaxel.

Adverse effects of treatment

4.24 In the intention-to-treat population of TROPIC, adverse events associated with treatment of grade ≥3 occurred in 57.4% of patients in the cabazitaxel group and 39.4% of patients in the mitoxantrone group. The proportion of patients withdrawing from study treatment because of a 'treatment emergent' adverse event (including disease progression) was 18.3% in

the cabazitaxel group compared with 8.4% in the mitoxantrone group. The incidence of treatment emergent adverse events (not coded as disease progression) leading to death was 4.9% in the cabazitaxel group and 1.9% in the mitoxantrone group.

Table 9. 5 most common adverse events grade 3 and above reported in patients in TROPIC (adapted from table 42, page 113 of company submission).

	Proportion of patients – Subgroup (ECOG-PS 0-1 with 225mg/m^2 prior docetaxel)		Proportion of Patients - ITT	
Adverse Event	**Cabazitaxel**	**Mitoxantrone**	**Cabazitaxel**	**Mitoxantrone**
Neutropenia	0.201	0.081	0.210	0.073
Febrile neutropenia	0.080	0.019	0.073	0.016
Diarrhoea	0.064	0.003	0.062	0.003
Fatigue	0.051	0.023	0.049	0.030
Asthenia	0.042	0.019	0.046	0.024
Key: ITT, intention to treat				

5 Cost-effectiveness evidence

Overview

5.1 The company produced a Markov model to assess the cost effectiveness of cabazitaxel compared with mitoxantrone. This was an updated version of the model presented for NICE technology appraisal guidance 255. In the base case the modelled population was the subgroup of patients in TROPIC (see section 4.12) who had:

- An ECOG performance status of 0-1; and
- Previously had at least 225 mg/m^2 of docetaxel.

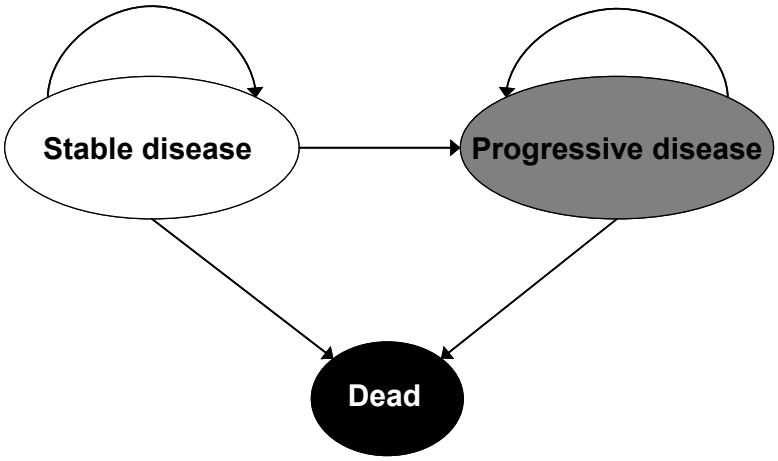
5.2 The company considered it standard NHS practice to treat metastatic castrate resistant prostate cancer with either abiraterone or enzalutamide in the pre-chemotherapy setting, that is, before docetaxel. Thus, in its main analyses, the company compared cabazitaxel with best supportive care (represented by mitoxantrone). However, for the alternative pathway (using abiraterone or enzalutamide after docetaxel) the company

compared cabazitaxel with abiraterone and cabazitaxel with enzalutamide (see 5.17).

Model structure

5.3 The company developed a transition Markov model with 3 states to represent disease progression from stable disease through to progressive disease and death (see Figure 3). The model included a 10-year time horizon, 3-week cycle lengths and discounting of costs and health benefits at 3.5%. The company included the costs incurred by the NHS and personal and social services (see table 52, page 142 of company submission for further details).

Figure 3 Company's model structure (Figure 15, page 142 of company submission)



Model details

5.4 The base-case model compared 2 treatments:

- Mitoxantrone, 12 mg/m^2 every 3 weeks in combination with 10 mg/day of prednisolone
- Cabazitaxel, 25 mg/m^2 every 3 weeks in combination with 10 mg/day of prednisolone.

5.5 In the base case, the company assumed that only patients in the stable disease health state received treatment with cabazitaxel or mitoxantrone. Patients in the model continued treatment from the start of the model until 1 of the following events occurred: disease progression, death or treatment up to a maximum of 10 cycles of chemotherapy.

5.6 In TROPIC, 23% of patients in the cabazitaxel group and 16% in the mitoxantrone group stopped treatment for reasons other than progression. To reflect this, the company included a rate of discontinuation in the model. Based on the proportion of patients who discontinue treatment, the company derived a discontinuation rate over 10 cycles and applied it to patients on treatment: 2.6% over 10 cycles in the cabazitaxel arm and 1.7% over 10 cycles in the mitoxantrone arm. In a sensitivity analysis, the company excluded these rates.

Clinical parameters

5.7 To model time to progression and survival times, the company applied several parametric distributions to the subgroup data from TROPIC (that is, patients with an ECOG performance status of 0-1 and previously treated with at least 225 mg/m^2 of docetaxel). It chose the distribution that had the best fit to the trial data, based on Akaike's information criterion and the Bayesian information criterion. The company chose to use the same parametric distribution for both the cabazitaxel and mitoxantrone arms of the model. In its base case, the company used a Weibull curve to model survival times and a log-normal curve to model time to disease progression (see tables 53 and 54, page 146–148 of company submission for further details).

Figure 4 Weibull model for overall survival (figure 17, page 146 of company submission)

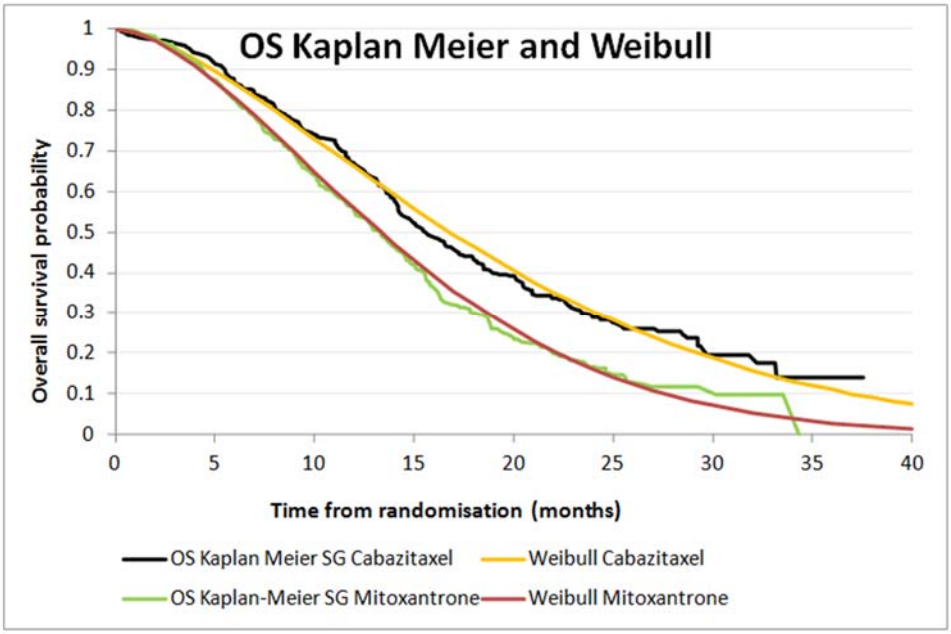
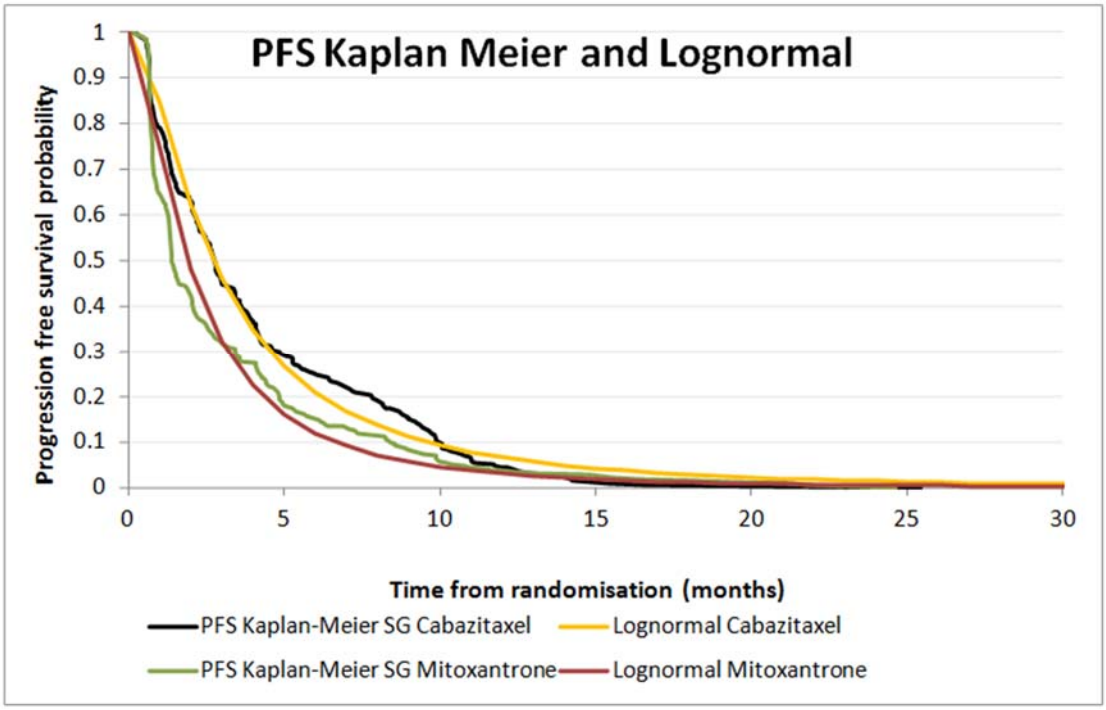


Figure 5 Log-normal model for progression-free survival (figure 19, page 148 of company submission).



Key; SG, subgroup; OS, overall survival. PFS, progression-free survival.

Health-related quality of life

5.8 The company did not collect data on health-related quality of life in TROPIC, so it took utility values from the UK Early Access Programme (EAP) for cabazitaxel. The programme measured the health-related quality of life (using the EQ-5D) of men who had been treated with cabazitaxel after docetaxel (see Table 10).

Table 10 utility values used in company model (table 61, page 161 of company submission)

State	Utility value		Reference in submission	Justification
Stable disease	Drug Cycle	Stable Disease	UK EAP	The company used the same utility values for patients having cabazitaxel and for patients having mitoxantrone, because it did not expect health-related quality of life to differ between treatment groups.
	1	0.704		
	2	0.728		
	3	0.728		
	4	0.750		
	5	0.753		
	6	0.752		
	7	0.778		
	8	0.789		
	9	0.803		
	10 and thereafter	0.819		
Progressive disease	0.6266 until last 3 months of life which are set to 0		UK EAP	This utility value was measured 30 days after the last cycle of treatment with cabazitaxel for people with disease progression. This was the last measure of health-related quality of life in the trial.

5.9 Disutility values for adverse events were not collected in either the UK EAP or in TROPIC. The company derived disutility values associated with experiencing each adverse event from a literature review that was conducted for NICE technology appraisal guidance 255. These studies were of breast and lung cancer, not prostate cancer. See section 4.4.6 pages 156-157 of the company submission for further details.

Treatment related adverse events

5.10 The company modelled 15 adverse events using the rates of adverse events in TROPIC and included all grade ≥3 which occurred in 2% or more of patients in any treatment group of TROPIC. In addition, the company included deep vein thrombosis and neuropathy, as they were classified as important based on clinical expert opinion (see section 4.24).

Resource use

5.11 The company estimated resource use based on data from TROPIC, a UK clinical audit and expert opinion. It estimated costs using the British national formulary (BNF), NHS reference costs and data from the Personal Social Services Research Unit.

5.12 In the stable disease state, the company included drug acquisition costs (for active treatment, pre-medications and concomitant medications), costs of chemotherapy administration, costs of disease management including hospitalisations and testing, and adverse event costs. Costs for active treatment, pre-medications and chemotherapy administration were applied for up to 10 cycles for cabazitaxel and mitoxantrone (the maximum number allowed in TROPIC). Cabazitaxel and mitoxantrone are both provided in vials with the required dosage dependent on body surface area. The company assumed that the mean body surface area was 1.9 m^2 (based on clinical opinion; the mean body surface area observed in TROPIC was 2.01 m^2) with vial sharing for cabazitaxel and mitoxantrone. After clarification, the company explained that it believes there will be no wastage of cabazitaxel because 'patient specific doses in the form of compounded IV bags of cabazitaxel can be supplied direct to NHS hospitals'.

5.13 In the progressed disease state, the company included acquisition costs for post-progression chemotherapy and best supportive care, costs of chemotherapy administration, and cost of disease management including

hospitalisations and testing. For further details on costs see section 5.5 (from page 162 onwards) of company submission.

Table 11 Unit costs used in company model (table 62, page 164 of company submission)

Item	Cabazitaxel	Mitoxantrone	Abiraterone	Enzalutamide
Drug cost	[redacted] per vial according to PAS discount	£100 per vial	£2930.00 per 120 tablet pack (list price)	£2734.67 per 112 capsule pack (list price)
Administration cost per cycle	[redacted]	[redacted]	n.a.	n.a.
Pre- & Concomitant medication per cycle	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event management costs	£105.18	£53.78	£5.15	£5.05
Progressive disease: active treatment per cycle	[redacted]	[redacted]	[redacted]	[redacted]
Progressive disease: best supportive care treatment cost per cycle	[redacted]	[redacted]	n.a.	n.a.
End of life cost – one off cost applied when patients transition to the dead state	£1952.15	£1952.15	£1952.15	£1952.15

Company's base-case results and sensitivity analyses

5.14 The company's base case analysis (Table 12) showed that cabazitaxel (with PAS discount) compared with mitoxantrone resulted in a deterministic incremental cost-effectiveness ratio (ICER) of £49,327 per quality adjusted life year (QALY) gained (incremental costs £11,450, incremental QALYs 0.232). The probabilistic ICER was £50,682 per QALY gained (incremental costs £11,829; incremental QALYs 0.233).

Table 12 Deterministic base-case results: cabazitaxel (with PAS) compared with mitoxantrone

Treatment	Total cost	Total QALY	Inc. cost	Inc. QALY	ICER

Mitoxantrone	[redacted]	[redacted]			
Cabazitaxel	[redacted]	[redacted]	£11,450	0.232	£49,327
Abbreviations: Inc., incremental; QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio					

5.15 Following the factual accuracy check, the company noted that its original base case assumed no drug wastage of mitoxantrone. This was an error, so the company submitted a new scenario assuming mitoxantrone wastage. The deterministic ICER reduced from £49,327 to £48,256 per QALY gained.

5.16 The company's deterministic sensitivity analyses varied the utility values, time horizon, discount rates, method for extrapolating overall survival data, and the percentage of patients having best supportive care after disease progression. The company stated that the model was most sensitive to variations in the utility value for the progressive disease health state (see table 79, page 186 of company submission for further details).

Company's scenario analyses

5.17 The company's scenario analyses compared cabazitaxel (including PAS discount) with enzalutamide (at list price) and, separately, abiraterone (at list price). These analyses used the intention-to-treat population of TROPIC (see page 188, section 5.8.4 of the company submission for further details). The company assumed that enzalutamide and abiraterone were taken until disease progression or death, whereas cabazitaxel was taken for up to 10 cycles.

5.18 Hazard ratios for abiraterone and enzalutamide were taken from the company's indirect treatment comparison and applied to the parametric distributions modelling overall survival and progression-free survival with cabazitaxel. The company used a Weibull curve to model progression-free survival because the log-normal distribution (used in the base case) is not a proportional hazards model.

5.19 Both enzalutamide and abiraterone have confidential PASs. Accordingly, the ERG re-calculated the company's scenario analyses using the PAS discounts for enzalutamide and abiraterone (table 19 of the confidential appendix). The company did not report a fully incremental analysis.

ERG comments and exploratory analysis

Clinical parameters

5.20 Regarding the extrapolation of overall survival data, the ERG queried why the company had not used piecewise curves. Piecewise methods use the Kaplan-Meier curve from the trial to calculate transition probabilities for a period of time at the start of the model, then after a cut-off point use a parametric distribution. The ERG noted that, in NICE technology appraisal guidance 255, the Committee preferred the piecewise approach over the other methods presented by the company for that appraisal. This was because there were some early deaths due to neutropenia in the cabazitaxel group, which may have affected the predicted survival times from a single extrapolation curve. During clarification, the company presented results using a piecewise curve for the cabazitaxel arm (specifically, using the Kaplan-Meier curve for the first 2.1 months and a Weibull curve thereafter). The company did not alter the base-case methods for modelling the mitoxantrone arm. This scenario reduced the company's base-case ICER by 1.6% to £48,543 per QALY gained (question B1, page 24 of clarification responses). The ERG advised that the piecewise curve for overall survival with cabazitaxel is likely to be more appropriate than the single Weibull curve the company used in its base case. However, a piecewise curve was not used in the ERG's base case because the company had not provided full details of this analysis. Following the factual accuracy check, the company updated the ERG's base case exploratory analysis (see section 5.27) using the piecewise curves it submitted during clarification. The results reduced the ERG's ICER (assuming no vial wastage) from £51,308 to £50,195 per QALY gained. The ERG has not had an opportunity to critique this analysis.

5.21 The ERG identified issues in the company's methods for modelling stopping treatment. The company's model assumed that patients who stopped treatment did not incur drug costs during the cycle when they stopped. The ERG stated that this would underestimate drug costs, as patients would stop only after receiving the drug. The company also assumed that patients who stop treatment would have increased utility related to additional treatment cycles. The ERG stated that this would overestimate utilities. Finally, the ERG noted that for any cycle, patients who had stopped treatment during a previous cycle and remained with stable disease would incorrectly incur drug costs. The ERG noted that this would overestimate drug costs. Correcting these issues by removing treatment discontinuation for any reason other than disease progression increased the ICER by 2.1% to £50,370 per QALY gained.

Health-related quality of life

5.22 The ERG noted that the data on utility from the UK EAP are more mature than those in the company's submission for NICE technology appraisal guidance 255. The ERG further noted that the model results are sensitive to the utility value for progressive disease, which is uncertain because it is based on data for 25 people. The ERG explored this uncertainty in sensitivity analyses (see Table 13).

5.23 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 3 months of life. The ERG noted that this disutility was calculated based on all deaths observed, not deaths amongst people with progressive disease. Removing this disutility increased the ICER by 0.74% to £49,691 per QALY gained.

Resource use

5.24 The ERG advised that for generic drugs it is more appropriate to use prices from the electronic market information tool (eMIT) than the British National Formulary (BNF) because eMIT is based on the price paid by

English hospitals. Using eMIT prices increased the ICER comparing cabazitaxel with mitoxantrone by 4.8% to £51,675 per QALY gained.

5.25 The ERG highlighted that 3 different estimates were available for the costs of treatment in the progressed disease health state. The most expensive estimate (£1767.02) was for the mitoxantrone group in the TROPIC trial. The least expensive estimate (£1192.81) was for the cabazitaxel group in the TROPIC trial. The third estimate was from a UK clinical audit (£1364.07). The company's model used the estimate from the cabazitaxel group in TROPIC for the costs of treatment after cabazitaxel, and the estimate from the mitoxantrone group in TROPIC for the costs of treatment after mitoxantrone, abiraterone or enzalutamide. The ERG noted that differences in post-progression treatment were unlikely to have contributed to differences in overall survival for the TROPIC trial. Therefore, in the ERG's opinion the company should have used the same post-progression treatment costs for cabazitaxel and each of the comparators. The ERG performed an analysis which used the UK clinical audit to estimate the post-progression treatment costs for cabazitaxel and all of the comparators. This reduced the ICER comparing cabazitaxel with mitoxantrone to £48,908 per QALY gained.

5.26 The ERG noted that the company assumed no wastage of cabazitaxel. During NICE technology appraisal guidance 255, clinical experts advised that there is likely to be some wastage of cabazitaxel in NHS clinical practice, but there was uncertainty about how much wastage would occur. The ERG performed an analysis which assumed that a cycle of treatment with cabazitaxel would require the cost of a vial of cabazitaxel. This increased the ICER by [redacted] per QALY gained.

ERG exploratory analyses

Cabazitaxel compared with mitoxantrone

5.27 The ERG's exploratory base case included the following assumptions:

- Use eMIT prices for generic drugs

- Do not model stopping treatment for reasons other than disease progression
- Use UK clinical audit data to model costs of post-progression treatment resource use and the proportion of patients having best supportive care
- Do not model a reduced utility value for the last 3 months of progressive disease.

5.28 The ERG presented 2 exploratory base cases (Table 13). When vial wastage was assumed (the ERG's preferred assumption), the deterministic ICER for cabazitaxel compared with mitoxantrone was [redacted] per QALY gained. When there was no vial wastage, the deterministic ICER reduced to £51,308 per QALY gained. Under both assumptions, the probabilistic ICER was slightly higher than the deterministic ICER. Of all the changes to the model made by the ERG, assuming drug wastage had the biggest impact on the ICER.

5.29 In addition, the ERG performed deterministic sensitivity analyses (ERG analysis numbers A7 to A10) which showed that the ERG's ICER was sensitive to the method for extrapolating clinical effectiveness data and the utility value used for progressive disease.

Table 13 ERG exploratory analyses for cabazitaxel (with PAS) compared to mitoxantrone in the TROPIC subgroup of patients with ECOG performance score of 0 -1 who have received at least 225 mg/m^2 docetaxel (table 36, page 123 of the ERG report erratum)

Scenario	Incremental cost (£)	Incremental QALY	ICER (£)
Company's base case	11,450	0.232	49,327
Company probabilistic base-case	11,829	0.233	50,682
A1) Use eMIT prices	11,994	0.232	51,667
A2) Discontinuation for reasons other than disease progression **not** modelled	11,693	0.232	50,370
A3) Reduced disutility in the last 3 months of progressive disease not modelled	11,450	0.230	49,691
A4) Post-progression treatment resource and proportion receiving BSC both from UK audit for all treatments.	11,353	0.232	48,908
A5) Indirect treatment comparison results using a weakly informative prior (does not affect the comparison with mitoxantrone).	11,450	0.232	49,327
A6) Cost of cabazitaxel and mitoxantrone based on vial cost (assuming wastage).	[redacted]	0.232	[redacted]
ERG Deterministic base-case 1 (changes A1 to A6)	[redacted]	0.230	[redacted]
ERG Probabilistic base-case 1 (changes A1 to A6)	[redacted]	0.231	[redacted]
ERG Deterministic base-case 2 (changes A1 to A5)	11,823	0.230	51,308
ERG Probabilistic base-case 2 (changes A1 to A5)	12,133	0.234	51,849
ERG sensitivity analyses			
A7) Use of log-logistic curves for both overall and progression-free survival.	12,627	0.309	40,887
A8) Parametric curves for OS and PFS based on lowest AIC value (no requirement for same parametric form for both arms)*	9,347	0.137	68,168
A9) Use of the 95% low confidence interval value for progressive disease utility (0.510).	11,450	0.207	55,248
A10) Use of the 95% high confidence interval value for progressive disease utility (0.743).	11,450	0.257	44,560

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

* 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.

Cabazitaxel compared with enzalutamide, abiraterone and best supportive care

5.30 The ERG presented a fully incremental analysis comparing cabazitaxel with enzalutamide, abiraterone and best supportive care. The ERG used the assumptions in section 5.27 and it also used a weakly informative prior for the indirect treatment comparison. The ERG used the PAS price discounts for each drug so the results are presented in a confidential appendix. The ERG also conducted a one-way sensitivity analyses using estimates from the limits (low and high) of the confidence interval for utility of progressed disease and using the median hazard ratios from the company's indirect treatment comparison.

5.31 The ICERs for cabazitaxel compared with best supportive care were substantially higher in the ERG's fully incremental analysis than in the ERG's base-case pairwise comparison with mitoxantrone (see confidential appendix to the PMB). The incremental analysis used the indirect treatment comparison results to estimate the effectiveness of each treatment, whereas the pairwise comparison used data from the TROPIC trial. The ERG advised that the indirect treatment comparison assumes proportional hazards, but the data may not meet this assumption. Both the ERG and the company stated that the results of the indirect treatment comparison should be treated with caution (see section 4.22).

5.32 The ERG noted 2 further areas of uncertainty in the company's model. The first was that the model restricted cabazitaxel use to a maximum of 10 cycles (to reflect the TROPIC trial) but the marketing authorisation for cabazitaxel does not restrict treatment duration. The ERG advised that using cabazitaxel for more than 10 cycles would increase the lifetime costs associated with cabazitaxel but it could also increase overall survival and quality of life. Therefore, the ERG stated that the impact of longer treatment on the ICER is unknown.

5.33 The second area of uncertainty relates to the results of the indirect treatment comparison. Both the ERG and the company advised that the

results should be treated with caution (see 5.31). In addition, the ERG noted the uncertainty in using radiographic progression free survival. The company noted that because radiographic progression free survival was lower in the enzalutamide and abiraterone trials compared to TROPIC it could bias against cabazitaxel in the indirect treatment comparison (see 4.18). Within the company's economic model however, lower estimates of radiographic progression free survival are associated with improved cost-effectiveness because less drug costs are incurred. The ERG notes that this may produce a favourable ICER for cabazitaxel.

5.34 The ERG noted that the company did not compare cabazitaxel with radium 223-dichloride. Following clarification (question A1, page 2 of the clarification responses), the company provided results from the ALSMYPCA trial which compared radium-223 dichloride with placebo. In ALSYMPCA, the subgroup of patients treated with radium-223 and who had previously had docetaxel had a median overall survival of 14.4 months (95% CI 12.5 to 15.5 months). For comparison, patients in the cabazitaxel group of TROPIC (intention-to-population) had median overall survival of 15.1 months (95% CI 14.0 to 16.5 months). The ERG noted that both overall survival and progression-free survival with radium-223 dichloride appeared to be similar to that with cabazitaxel and that if the cost effectiveness of these 2 drugs was compared, drug costs would likely be a key driver. As the company's model did not compare the cost-effectiveness of cabazitaxel and radium-223, the ERG presented a cost-minimisation comparison of the price of these 2 drugs. This informal comparison is included in a confidential appendix to the PMB.

6 End-of-life considerations

Table 14 End-of-life considerations (see page 20 of company submission for further details).

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	The company presented a literature review of life expectancy in castrate-resistant prostate cancer. In the 11 treatment groups identified that were treated with first-line docetaxel, median overall survival was 19 months. Survival was shorter in the post-docetaxel setting (see page 20 of company submission). NICE guidance recommends abiraterone or enzalutamide after docetaxel. The ERG noted that, in the trials of abiraterone and enzalutamide after docetaxel, patients in the intervention group lived for a median of 15.8 and 18.4 months respectively.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	In the intention-to-treat population of TROPIC, cabazitaxel increased median overall survival by 2.3 months compared with mitoxantrone. The company's base-case model showed that cabazitaxel increased survival by a mean of 4.02 months (95% CI 2.17, 5.91; derived from the probabilistic sensitivity analysis) compared with mitoxantrone. The ERG noted that the company did not assess the extension of life with cabazitaxel compared with abiraterone, enzalutamide or radium-223. The ERG observed that the indirect treatment comparison found no statistically significant difference in overall survival between cabazitaxel, abiraterone and enzalutamide. The ERG also noted that survival times appear to be similar with cabazitaxel and radium-223 (see section 7, page 128 of ERG report).
The treatment is licensed or otherwise indicated for small patient populations	According to the company, data from the CDF for the year 2013/14 showed that approximately 600 patients were receiving cabazitaxel. The company estimated that the total eligible population is 1690 people in England. The ERG advised that this estimate was appropriate.

7 Equality issues

7.1 No equality issues were identified during scoping or in the patient expert submissions. During the development of NICE technology appraisal guidance 255, the Committee understood that people who have proposed, started or completed male to female gender reassignment can develop prostate cancer. The Committee therefore concluded that this appraisal should refer to people rather than to men.

8 Authors

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Appendix A: Clinical efficacy section of the draft European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002018/WC500104766.pdf

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

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

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of cabazitaxel within its marketing authorisation for treating hormone-relapsed metastatic prostate cancer previously treated with a docetaxel-containing regimen.[1]

Background

Prostate cancer is a condition in which tumours develop in the prostate, a gland in the male reproductive system. Its cause is thought to be multifactorial, involving both environmental and genetic factors. The incidence of prostate cancer increases with age and is higher in people of black African or black Caribbean family origin. In England, approximately 35,600 people were diagnosed with prostate cancer in 2011, and over 9000 people died from prostate cancer in 2012 (Cancer Research UK, 2014).

Around 55–65% of people with prostate cancer develop metastatic disease (in which cancer spreads to other parts of the body). Over 90% of people with metastatic prostate cancer initially respond to hormonal therapy but eventually become resistant to it. This clinical condition is known as hormone-relapsed prostate cancer (but the terms 'castration-resistant prostate cancer', 'androgen-independent prostate cancer' and' hormone-refractory prostate cancer' are also used).

For metastatic hormone-relapsed prostate cancer, NICE clinical guideline 175 'Prostate cancer: Diagnosis and treatment' and NICE technology appraisal guidance 101 recommend docetaxel as a treatment option for men with metastatic hormone-refractory disease who have a Karnofsky performance-status score of 60% or more. NICE technology appraisals 259 and 316 recommend abiraterone and enzalutamide , respectively, as options for treating metastatic hormone-relapsed prostate cancer that has progressed during or after docetaxel-containing chemotherapy. Abiraterone and enzalutamide also have marketing authorisations to be used before chemotherapy, and are available through the Cancer Drugs Fund. NICE guidance for abiraterone and enzalutamide in the pre-chemotherapy setting

[1] The remit for this appraisal was formally referred to NICE in 2010 and described the condition as hormone refractory, metastatic prostate cancer. In January 2013, NICE and the Department of Health agreed that, following feedback received from stakeholders during scoping and appraisal consultations, the condition should be referred to as 'hormone-relapsed prostate cancer' (HRPC). The remit has therefore been reworded with the consent of the Department of Health.

are under development. Radium-223 dichloride has a marketing authorisation for the treatment of adults with hormone-relapsed prostate cancer, symptomatic bone metastases and no known visceral metastases, and is funded by the Cancer Drug Fund whilst NICE guidance is in development .

NICE technology appraisal 255 did not recommend cabazitaxel for hormone-relapsed metastatic prostate cancer previously treated with a docetaxel-containing regimen. NICE recommendations for abiraterone and enzalutamide have since resulted in a change in clinical practice. In addition, more evidence on the effect of cabazitaxel on survival, progression free survival and health-related quality of life is now available which may address some of the key uncertainties identified during NICE technology appraisal 255. Therefore, the clinical and cost effectiveness of cabazitaxel will be reviewed and compared with the relevant technologies.

The technology

Cabazitaxel (Jevtana, Sanofi) belongs to a class of anticancer drugs known as taxanes. It works by disrupting the microtubular network and causes inhibition of cell division and cell death. It is administered by intravenous infusion.

Cabazitaxel has a UK marketing authorisation 'in combination with prednisone or prednisolone for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen'.

Intervention(s)	Cabazitaxel in combination with prednisone or prednisolone
Population(s)	People with hormone-relapsed metastatic prostate cancer previously treated with a docetaxel-containing regimen

Comparators	• Abiraterone in combination with prednisone or prednisolone • Enzalutamide • Mitoxantrone in combination with 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)
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life.
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. 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.

Other considerations	If the evidence allows the following subgroups will be considered. • People who have received abiraterone or enzalutamide • People with bone metastasis only (no visceral metastasis) Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: 'Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen' (July 2014) NICE Technology Appraisal 316 Review date TBC 'Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen' (June 2012) NICE Technology Appraisal 259 Review date TBC 'Cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen' (May 2012) NICE Technology Appraisal 255 Docetaxel for the treatment of hormone-refractory metastatic prostate cancer' (June 2006) NICE Technology Appraisal 101 Guidance on static list. Appraisals in development 'Radium-223 dichloride for treating metastatic hormone-relapsed prostate cancer with bone metastases' NICE technology appraisals guidance [ID576] Publication expected January 2016 'Abiraterone for treating metastatic hormone-relapsed prostate cancer not previously treated with chemotherapy' NICE technology appraisals guidance [ID503] Publication expected TBC 'Enzalutamide for metastatic hormone-relapsed prostate cancer when chemotherapy is not yet clinically indicated' NICE technology appraisals guidance [ID683] Publication expected TBC Related Guidelines:

	'Prostate cancer: diagnosis and treatment' (January 2014) NICE guideline 175 Review date March 2016 Related Quality Standards: 'Prostate cancer' (June 2015) NICE Quality standard 91] Related NICE Pathways: 'Prostate Cancer' (2015) NICE pathway http://pathways.nice.org.uk/pathways/prostate-cancer
Related National Policy	NHS England, January 2014, 'Manual for prescribed specialised services 2013/14', Chapter 105: Specialist cancer services (adults). National Service Frameworks, Cancer Department of Health, 2013, 'NHS Outcomes Framework 2014-2015'. Department of Health, 2011, 'Improving outcomes: a strategy for cancer'. Department of Health, 2009, 'Cancer commissioning guidance'. Department of Health, 2007, 'Cancer reform strategy'. Department of Health, 2011, The national cancer strategy: stakeholder engagement report – Annex H: Prostate Cancer. Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013. Domains 1 and 2. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Cabazitaxel for hormone-relapsed metastatic prostate cancer previously treated with a docetaxel-containing regimen (review of TA255) [ID889]

Final matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
Company • Sanofi (cabazitaxel) Patient/carer groups • Black Health Agency • Bob Champion Cancer Trust • Cancer Black Care • Cancer Equality • Equalities National Council • Everyman • HAWC • Helen Rollason Cancer Charity • Independent Cancer Patient's Voice • Macmillan Cancer Support • Maggie's Centres • Marie Curie Cancer Care • Muslim Council of Britain • Orchid • Prostate Cancer UK • Prostate Help Association • South Asian Health Foundation • Specialised Healthcare Alliance • Tackle Prostate Cancer • Tenovus Professional groups • Association of Cancer Physicians • British Association of Urological Nurses • British Association of Urological Surgeons • British Geriatrics Society • British Institute of Radiology • British Prostate Group • British Psychosocial Oncology Society • British Society of Urogenital Radiology • British Uro-Oncology Group	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Possible comparator companies • Accord (mitoxantrone) • Astellas Pharma (enzalutamide) • Bayer (radium-223 dichloride) • Baxter (mitoxantrone) • Hospira (mitoxantrone) • Janssen (abiraterone) Relevant research groups • Cochrane Prostate Diseases and Urologic Cancers Group • Institute of Cancer Research • MRC Clinical Trials Unit • National Cancer Research Institute • National Cancer Research Network • National Institute for Health Research • Ovarian and Prostate Cancer Research Trust • Pro Cancer Research Fund

Consultees	**Commentators (no right to submit or appeal)**
• Cancer Research UK • Pelican Cancer Foundation • Prostate Cancer Advisory Group • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal College of Radiologists • Royal College of Surgeons • Royal Pharmaceutical Society • Royal Society of Medicine • Society and College of Radiographers • UK Clinical Pharmacy Association • UK Health Forum • UK Oncology Nursing Society • Urology Foundation <u>Others</u> • Department of Health • NHS England • NHS North East Essex CCG • NHS Wigan Borough CCG • Welsh Government	• Prostate Cancer Research Centre <u>Evidence Review Group</u> • School of Health and Related Research (ScHARR) • National Institute for Health Research Health Technology Assessment Programme <u>Associated Guideline groups</u> • National Collaborating Centre for Cancer <u>Associated Public Health groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies;
Healthcare Improvement Scotland; the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines); other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the *British National Formulary*.

All non-company commentators are invited to nominate clinical specialists or patient experts.

Evidence Review Group (ERG)

An independent academic group commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA Programme) to assist the Appraisal Committee in reviewing the company evidence submission to the Institute.

[1]Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

(Review of TA255)

Company evidence submission

October 2015

File name	Version	Contains confidential information	Date
Cabazitaxel	Final_updated_redacted	No	02_12_15

Table of Contents

List of figures 7
List of Appendices 8
Abbreviations 9
1. Executive summary 11
Background 12
Changes in the patient pathway since TA255[4] 14
Conclusions 22
2. The technology 27
2.1 Description of the technology 27
2.1.1. Brand name, UK approved name, the therapeutic class and a brief overview of the mechanism of action. 27
2.2 Marketing authorization /CE marking and Health Technology Assessment 28
2.2.1. UK marketing authorisation status. 28
2.2.2. Indication 28
2.2.3. Summary of restrictions or contraindications in the summary of product characteristics (SmPC). 28
2.2.4. Summary of Product characteristics 28
2.2.5 European Public Assessment Report[3] 28
2.2.6. Summary of the main issues discussed by the regulatory authorities. 28
2.3 Administration and costs of the technology 30
2.3.1. Costs of the technology being appraised 30
2.3.2. Patient Access Scheme 33
2.3.3. For devices, provide the list price and average selling price. 33
2.4 Changes in service provision and management 34
2.4.1. Additional tests, investigations or particular administration requirements for the technology 34
2.4.2. Estimated NHS resource use 34
2.4.3. Additional infrastructure requirements for the NHS. 34
2.4.4. Effect on patient monitoring compared with established clinical practice. 34
2.4.5. Concomitant therapies administered with the technology. 35
2.5 Innovation 36
3. Health condition and position of the technology in the treatment pathway 37
3.1. Brief overview of metastatic Castration Resistant Prostate Cancer mCRPC 37
3.2. Effect of mCRPC on patients, carers and society. 38
3.3. Clinical pathway of care contextualising the established use of cabazitaxel. 39
3.4. Life expectancy of people with mCRPC in England including the number of people with mCRPC for which cabazitaxel is being appraised. 41
3.5 Details of NICE guidance, pathways and commissioning guides related to mCRPC for which cabazitaxel is being used. 42
3.6 Other clinical guidelines and national policies. 46
3.7 Describe any issues relating to current clinical practice, including any variations or uncertainty about established practice. 50
3.8 Equity and equality 50
4. Clinical effectiveness 52
4.1 Identification and selection of relevant studies 52
4.1.1. Search strategy developed to identify relevant studies for cabazitaxel. 55
4.1.2 Description of the search strategies used to retrieve relevant clinical data. 55
4.1.3 Inclusion and exclusion selection criteria, language restrictions and the study selection process. 56
4.1.4. Flow diagram of the numbers of studies included and excluded at each stage. 59

4.1.5. Data sources for the trials considered in the analysis. 61
4.1.6. Reference list for excluded studies. 62
4.2 List of relevant randomised controlled trials 62
4.2.1. List of relevant RCTs comparing cabazitaxel with other therapies (including placebo) in the mCRPC patients. 62
4.2.2 Justification for the exclusion of other RCT data. 63
4.3 Summary of methodology of the relevant randomised controlled trials 64
4.3.2. Comparative summary of the methodology of the RCTs. 70
4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials 70
4.4.1 Trial populations[8] 70
4.4.2 Statistical analysis 70
4.5 Participant flow in the relevant randomised controlled trials 72
4.5.1. Patient numbers in TROPIC 72
4.5.2. Baseline patient demographics. 73
4.6 Quality assessment of the relevant randomised controlled trials 74
4.6.1. Critical appraisal of TROPIC 74
4.6.2. Methods used for assessing risk of bias and generalizability. 75
4.6.3 If there is more than 1 RCT, tabulate a summary of the responses applied to each of the quality assessment criteria. 77
4.7 Clinical effectiveness results of the relevant randomised controlled trials 77
4.8 Subgroup analysis 81
4.8.1 Details for the subgroup of patients with ECOG PS 0 -1 and having received at least 225 mg/m^2 docetaxel 81
4.8.2 Characteristics of the participants in the subgroup. 82
4.8.3 Details of the statistical tests used in the primary analysis of the subgroups, including any tests for interaction. 82
4.8.4 Summary of the results for the subgroup: patients with ECOG PS 0 -1 who have received at least 225 mg/m^2 docetaxel 83
4.9 Meta-analysis 85
4.10 Indirect and mixed treatment comparisons 85
4.11 Non-randomised and non-controlled evidence 88
4.11.1 Results from the non-randomised and non-controlled evidence literature survey. 92
4.11.2 Provide a comparative summary of the methodology of the studies in a table. 95
4.11.3 Potential biases in the non-randomised evidence. 96
4.11.4 Description of the characteristics of the participants at baseline for each of the studies by country. 98
4.11.5 The quality assessment for the EAP 99
4.11.6 Assessment of the risk of bias in the UK EAP. 100
4.11.7 If there is more than 1 non-randomised or non-controlled study, tabulate a summary of the responses applied to each of the quality assessment criteria. 102
4.11.8 Quality assessment for each study should be included. 102
4.11.9 Data from trial analyses should be presented whenever possible and a definition of the included participants provided. 103
4.11.10 The information may be presented graphically to supplement text and tabulated data. 103
4.11.11 Evidence from the CUP/EAP and other studies 103
4.12 Adverse reactions 111
4.12.1 Evidence from sources other than TROPIC. 111
4.12.2. Summary of adverse reactions. 111
4.12.3 Details of the additional studies that report additional adverse reactions. 113
4.12.4 Overview of the safety of the technology in relation to the decision problem. 121

4.13 Interpretation of clinical effectiveness and safety evidence 122
4.13.1 A statement of principal findings from the clinical evidence highlighting the clinical benefits and harms of the technology. 122
4.13.2 Discussion of the strengths, limitations, validity and relevance of the clinical evidence base for the technology. 122
4.14 Ongoing studies 125
5. Cost effectiveness 128
5.1 Published cost-effectiveness studies 128
5.1.1. Description of the strategies used to retrieve cost-effectiveness studies relevant to decision-making in England. 128
5.1.2. Overview of the included reports 132
5.1.3. Provide a complete quality assessment for each relevant cost-effectiveness study identified. 139
5.2 De novo analysis 140
5.2.1 Patient groups are included in the economic evaluation. 140
5.2.2 Model structure. 140
5.2.3. Features of the de novo analysis. 141
5.2.4. Implementation of cabazitaxel and comparators in the model. 142
5.2.5 Treatment continuation and discontinuation rules 143
5.3 Clinical parameters and variables 143
5.3.1. Description of how the clinical data were incorporated into the model. 143
5.3.2. Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix and describe the details of the transformation of clinical outcomes or any other relevant details here. 149
5.3.3. If there is evidence that (transition) probabilities may change over time for the treatment effect, condition or disease, confirm whether this has been included in the evaluation. 149
5.3.4. Assessment of the applicability of the clinical parameters or approximations. 149
5.4 Measurement and valuation of health effects 149
5.4.1 Health-related quality-of-life (HRQL) data collected in the clinical trials 149
5.4.2. Mapping of HRQL data 149
5.4.3. Description of the systematic searches for HRQL data. 151
5.4.4. Details of the included studies in which HRQL was measured. 154
5.4.5 Highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials. 154
5.4.6. The effect of adverse reactions on HRQL 155
5.4.7 Patient experience of HRQL in the health states described by the model 157
5.4.8 Clarify whether HRQL is assumed to be constant over time in the cost-effectiveness analysis. If not, provide details of how HRQL changes over the course of the disease or condition. 158
5.4.9 Describe whether the baseline HRQL assumed in the cost-effectiveness analysis is different from the utility values used for each of the health states. State whether quality-of-life events were taken from this baseline. 159
5.4.10 Adjustment of the health state utility values 159
5.4.11 Health effects found in the literature or clinical trials that were excluded from the cost effectiveness analysis 159
5.4.12 Summary of the utility values for the disease states in the model. 159
5.5 Cost and healthcare resource use identification, measurement and valuation 161
5.5.1 All parameters used to estimate cost effectiveness should be presented clearly in a table with details of data sources. 161
5.5.2 Describe how relevant cost and healthcare resource use data for England were identified. 161

5.5.3 When describing how relevant unit costs were identified, comment on whether NHS reference costs or payment-by-results (PbR) tariffs are appropriate for costing the intervention being appraised. 162
5.5.4 Clinical expert assessment of the applicability of the cost and healthcare resource use values 162
5.5.5. Summary of the cost and associated healthcare resource use of each treatment. .. 162
5.5.6 Summary of the costs included in each health state. 164
5.5.7 Summary of adverse reaction unit costs and resource use included in the de novo cost-effectiveness analysis. 174
5.5.8 Additional costs and healthcare resource not been covered elsewhere. 177
5.6 Summary of base-case de novo analysis inputs and assumptions 177
5.6.1 Summary of base-case de novo analysis inputs 177
5.7 Base-case results 181
5.7.1 Base-case incremental cost effectiveness analysis results 181
5.7.2 Disaggregated results of the base-case incremental cost effectiveness analysis 182
5.7.3 Summary of costs by health state 182
5.8 Sensitivity analyses 183
5.8.1 Probabilistic sensitivity analysis 183
5.8.2 Deterministic sensitivity analysis 184
5.8.3 Scenario analysis – cabazitaxel versus mitoxantrone 185
5.9 Subgroup analysis 188
5.10 Validation 188
5.11 Interpretation and conclusions of economic evidence 189
6. Assessment of factors relevant to the NHS and other parties 192

List of tables

Table 1. Technology being appraised 13
Table 2. OS and PFS – ITT population 18
Table 3. Key adverse events (≥ grade 3) observed in the TROPIC study. 19
Table 4 Base-case incremental cost-effectiveness results 22
Table 5. The decision problem 23
Table 6. Previous UK Health Technology Assessments of cabazitaxel 30
Table 7. Costs of the technology being appraised 31
Table 8 Dose adjustments* 32
Table 9. Current list price and PAS discount. 33
Table 10. Calculation of second line chemotherapy eligible patients in England 41
Table 11. Related NICE Health Technology Assessments 43
Table 12. National CDF listing 46
Table 13. Key European guidelines for the treatment of mCRPC 48
Table 14. RCTs identified in the original literature review carried out for TA255 in second-line mCRPC (post-docetaxel). 54
Table 15. Inclusion criteria (PICOS framework) used in search strategies 56
Table 16. Exclusion criteria checklist 58
Table 17. List of articles retained for full text review with reason for exclusion if applicable. 59
Table 18. List of relevant RCTs 62
Table 19. Characteristics of participants in the studies across treatment groups in the TROPIC trial. 73
Table 20. Quality assessment of the TROPIC study.[8] 75
Table 21. Treatment received in the TROPIC trial[8] 77

Table 22. Overall survival – ITT population 78
Table 23. Progression-free survival – ITT population 80
Table 24. Descriptive analysis of progression-free events – ITT population 80
Table 25. Characteristics of participants in the subgroup with ECOG PS 0 -1 and who have received at least 225 mg/m^2 docetaxel across treatment groups in the TROPIC trial. 82
Table 26. Overall survival in the subgroup of patients with ECOG PS 0 -1 who have received at least 225 mg/m^2 docetaxel. 83
Table 27. Progression-free survival in the subgroup with ECOG PS 0 -1 who have received at least 225 mg/m^2 docetaxel. 84
Table 28. Key results from the mixed treatment comparisons – ITT population 87
Table 29. Inclusion criteria (PICOS framework) used in the search strategies 88
Table 30. Exclusion criteria checklist 90
Table 31. Published evidence from the CUP/EAP 93
Table 32. Additional CUP/EAP studies presented at conferences. 94
Table 33. Selected baseline patient characteristics for the CUP/EAP studies reported in full publications. 98
Table 34. Selected baseline patient characteristics for the CUP/EAP studies reported in conferences abstracts. 99
Table 35. Quality assessment of the UK EAP study entitled: Final quality of life and safety data for patients with metastatic castration-resistant prostate cancer treated with cabazitaxel in the UK Early Access Programme (EAP) (NCT01254279).[12] 100
Table 36. Summary of the safety and efficacy results from the full publications for the CUP/EAPs for cabazitaxel 104
Table 37. Summary of the safety results from the conference abstracts for the CUP/EAPs for cabazitaxel 105
Table 38. Studies examining the cross resistance in the sequence abiraterone : enzalutamide. 106
Table 39. Studies examining the cross resistance in the sequence enzalutamide: abiraterone. 106
Table 40. Studies with evidence on the effect of pre-treatment with abiraterone or enzalutamide on cabazitaxel efficacy. 108
Table 41. Deaths reported in the TROPIC trial – ITT population. 113
Table 42. Adverse events grade 3 or above reported in patients in TROPIC who received at least one dose of study treatment*. Subgroup ECOG-PS 0-1 with 225mg/m^2 prior docetaxel exposure and ITT populations. 113
Table 43. Conference abstracts with safety information 116
Table 44. Baseline patient characteristics for the patients enrolled in HRQLANA 117
Table 45. Phase III cabazitaxel RCTs listed on clinicaltrials.gov (23/07/2015). 120
Table 46 End-of-life criteria. 125
Table 47. PROSELICA study description. 126
Table 48. PICOS Framework 129
Table 49. List of published articles retained for full text review with reasons for exclusion 132
Table 50. Cost-effectiveness evidence from economic analyses of post-docetaxel treatments for mHRPC and mCRPC (ICER per QALY gained) 133
Table 51. Additional summary of HTA reports in mCRPC in Scotland and Ireland. 136
Table 52. Features of the de novo analysis 141
Table 53. AICs and BICs for different parametric models for overall survival probability extrapolation 145
Table 54. AICs and BICs for different parametric models for progression-free probability extrapolation 147
Table 55. Utility results from EAP 150
Table 56. PubMed search terms for HRQL in mCRPC 151

Table 57. Inclusion and exclusion criteria applied to the search results from the HRQL PubMed search. 152
Table 58. List of articles retained for full text review from the PubMed search with reasons for exclusion 153
Table 59. Utility values from the literature for the stable and progressive disease states .. 154
Table 60. Disutility due to treatment related adverse events used in the model* 156
Table 61. Summary of utility values for cost-effectiveness analysis 160
Table 62. Unit costs associated with the technology in the economic model 163
Table 63. Resource use estimates for stable disease state 164
Table 64. Unit cost inputs for stable disease state 166
Table 65. Frequency of post-second-line chemo for the base-case population 170
Table 66. The treatments that constitute the UK-specific post-second-line treatment mix[42] 171
Table 67. Resource use estimates for progressive disease state 172
Table 68. Unit costs for progressive disease cost items 173
Table 69. Cost for drugs used to treat AEs* 174
Table 70. Costs of adverse events 175
Table 71. Hospitalisation rates by severe adverse event (Grade ≥3) 176
Table 72. Best fit Parametric Functions used in the CEA vs mitoxantrone 178
Table 73. Summary of key variables applied in the economic model 179
Table 74. Assumptions used in the modelling. 180
Table 75. Base-case results: cabazitaxel vs. mitoxantrone - SG: ECOG PS 0-1, tottax ≥225. 181
Table 76. Summary of QALY gain by health state for the comparison versus mitoxantrone - SG: ECOG PS 0-1, tottax≥225. 182
Table 77. Summary of costs by health state for the comparison versus mitoxantrone - SG: ECOG PS 0-1, tottax≥225. 182
Table 78. One-way sensitivity analyses implemented in the model 184
Table 79. One-way sensitivity analyses for the comparison versus mitoxantrone - SG: ECOG PS 0-1, tottax≥225. 185
Table 80. Additional Sensitivity analyses for the comparison versus mitoxantrone 186
Table 81 Scenario results vs abiraterone 188
Table 82 Scenario results vs enzalutamide 188
Table 83. Estimation of mCPRC patients eligible for second-line chemotherapy in England 192
Table 84. Estimated number of patients receiving cabazitaxel 192
Table 85. Estimated pharmacy cost of cabazitaxel. 193

List of figures

Figure 1. Summary of utility results from the UK EAP.[12] 20
Figure 2. Cabazitaxel: molecular structure 27
Figure 3. mCRPC: current disease management and existing place in therapy for cabazitaxel. 40
Figure 4. PRISMA flow diagram for the systematic literature review. 59
Figure 5. TROPIC trial: study design 64
Figure 6. CONSORT participant flow diagram 72
Figure 7. Overall survival and number of patients at risk by study month (ITT population) .. 79
Figure 8. Kaplan–Meier curves of PFS and number of patients at risk by study month (ITT population) 81
Figure 9. Kaplan–Meier curves of overall survival in the subgroup with ECOG PS 0 -1 who have received at least 225 mg/m^2 docetaxel. 84

Figure 10. Kaplan–Meier curves of PFS survival in the subgroup with ECOG PS 0 -1 who have received at least 225 mg/m^2 docetaxel. 85
Figure 11. Network diagrams for the included trials..... 86
Figure 12. PRISMA flow diagram for the literature review of non-randomised evidence..... 92
Figure 13. Graphical representation of the PROSELICA study design..... 127
Figure 14. PRISMA figure for the cost effectiveness searches..... 131
Figure 15. Schematic model structure 141
Figure 16 Kaplan-Meier estimates of overall survival probability in TROPIC (subgroup population) 144
Figure 17. Weibull model for overall survival – subgroup population (compared to the TROPIC Kaplan-Meier data)..... 145
Figure 18. Kaplan-Meier estimates of progression-free survival in TROPIC (subgroup population) 146
Figure 19. Lognormal model for progression-free survival - subgroup population (compared to the TROPIC Kaplan-Meier data)..... 147
Figure 20. Flow diagram of the included studies from the PubMed search 153
Figure 21. Cost-effectiveness plane based on 2000 probabilistic simulations..... 183
Figure 22. Cost-effectiveness Acceptability Curve (CEAC) 184

List of Appendices

Appendicies A

Appendix 1	Summary of product characteristics
Appendix 2	European public assessment report
Appendix 3	Details of the original literature search for the identification of studies from TA255
Appendix 4	Updated literature review for studies in mHRPC and mCRPC
Appendix 5	Systematic review of non-randomised and non-controlled evidence in mHRPC carried out for TA255
Appendix 6	Update to the systematic review of non-randomised and non-controlled evidence
Appendix 7	Completed and ongoing studies
Appendix 8	Inclusion and exclusion criteria for PROSELICA
Appendix 9	Original literature searches for cost effectiveness studies in TA255
Appendix 10	Updated search for cost-effectiveness reports
Appendix 12	Description of the original search carried out for TA255 for studies reporting HRQL.
Appendix 13	Update to the search for studies reporting HRQL.
Appendix 14	Resource identification, measurement and valuation.
Appendix 15	Resource utilization captured in the literature review.
Appendix 16	Details of the included studies in which HRQL was measured.
Appendix 17	Quotes from clinicians to support the quality of life benefit of cabazitaxel
Appendix 18	Survival analysis
Appendix 19	Stochastic sensitivity analysis

Appendices B Indirect treatment comparsions with abiraterone and enzlautamide

Abbreviations

ACD	Appraisal Committee Determination
AE	Adverse event
ASCO	American Society of Clinical Oncology
AWMSG	All Wales Medicines Strategy Group
BSC	Best Supportive Care
CEAC	Cost Effectiveness Acceptability Curve
CG	Clinical Guideline
CHMP	Committee for Human Medicinal Products
CR	Castration resistant
Cr. Int.	Credible Interval
CRUK	Cancer Research UK
CT	computed tomography
CUP	Compassionate Use Programme
EAP	Early Access Programme
EAU	European Association of Urology
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
EoL	End Of Life
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European Assessment Report
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
FACT-P	Functional Assessment of Cancer Therapy – Prostate
FDA	(United States) Food and Drug Administration
G-CSF	Granulite-Stimulating Colony Factor
HR	Hazard Ratio
HRQL	Health-Related Quality of Life
ICER	Incremental Cost Effectiveness Ratio
IDMC	Independent Data Monitoring Committee
ITT	Intention to Treat
IV	Intravenous
LHRHa	Luteinising hormone-releasing hormone agonist
mCRPC	Metastatic castration resistant prostate cancer
MDT	Multidisciplinary Team
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mHRPC	Metastatic Hormone Resistant Prostate Cancer
ml	Milliliter
MRI	Magnetic resonance imaging
nCDF	National Cancer Drugs Fund

NICE	National Institute for Health and Clinical Excellence
NMA	Network Meta-Analysis
ONS	Office for National Statistics
OS	Overall Survival
PAS	Patient Access Scheme
PASLU	Patient Access Scheme Liaison Unit
PC	Prostate cancer
PD	Progressive Disease
PFS	Progression Free Survival
PSA	Prostate Specific Antigen
QALY	Quality Adjusted Life Year
QOL	Quality of Life
RCT	Randomised Controlled Trial
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious Adverse Events
SD	Stable Disease
SG	Sub-Group
SI	International system of units
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
TA	Technology Appraisal
TTP	Time To Tumour Progression
UK	United Kingdom
US	United States

1. Executive summary

- Prostate cancer is the most common cancer amongst men in England and currently affects ~40,000 people, around 6,000 of whom suffer from metastatic disease.
- Docetaxel was the first agent to show survival benefit in metastatic Hormone Resistant Prostate Cancer (mHRPC) and has for many years been the mainstay of treatment.
- Patients with metastatic disease post-docetaxel typically have a poor prognosis with a life expectancy of less than 24 months.
- Cabazitaxel was developed and licensed to address docetaxel resistance. Prior to this, no active licensed option was available so mitoxantrone chemotherapy was used off-label.
- Cabazitaxel has become well established in NHS clinical practice as second-line chemotherapy after early progression on docetaxel. Use has largely displaced mitoxantrone which offers palliative benefits but no proven survival advantage over best supportive care (BSC).
- Cabazitaxel has been approved for use through the CDF on the basis of its clinical effectiveness, and is now used to treat ~600 patients per year.
- More recently, pathways have evolved which include the newer advanced hormonal agents (abiraterone and enzalutamide); although approved by NICE in the post-docetaxel setting, these agents are predominantly used by the NHS ahead of docetaxel, and funded by the Cancer Drug Fund (CDF).
- Clinical guidelines state the use of one of the advanced hormonal therapies precludes the subsequent use of the other due to cross resistance.
- The Phase III TROPIC study demonstrated that cabazitaxel has a significant mean overall survival benefit (4 months vs. mitoxantrone) even in those patients with aggressive disease who have progressed during or rapidly after docetaxel treatment and therefore may not be appropriate for advanced hormone therapy.
- Disease heterogeneity and the emergence of hormone refractory tumours over time mean that patients need tailored treatment options to extend overall survival.
- A simple Patient Access Scheme has been offered to enable NICE to reconsider the cost-effectiveness of cabazitaxel, a treatment with demonstrated survival benefit, in a small population of patients with particular treatment needs.

Background

Prostate cancer is the most common cancer amongst men in the England and currently affects ~40,000 people around 6,000 of whom suffer from metastatic disease. Overall patients with metastatic disease have a life expectancy of less than 24 months and a poor prognosis.

Docetaxel was the first agent to show survival benefit in metastatic Hormone Refractory Prostate Cancer (mHRPC) and since approval by NICE in 2006 (TA101) has for many years been the mainstay of treatment.

Cabazitaxel was developed specifically because of its activity in docetaxel resistant cell lines.[1] The clinical benefit of cabazitaxel has been clearly demonstrated in the pivotal TROPIC study which was the first to show a survival advantage for a treatment in the post-docetaxel setting. Prior to cabazitaxel authorisation, no active licensed option was available so mitoxantrone chemotherapy was used off-label for palliation. Mitoxantrone has not demonstrated any significant overall survival benefit over BSC.[2]

The manufacturer's submission to support the review of TA255 presented here is based on:

- The use of the updated Phase III pivotal trial data throughout.
- The inclusion of a simple Patient Access Scheme (PAS).
- Updated Health Related Quality of Life (HRQL) evidence.
- Improved understanding of prostate cancer and the importance of non-hormonal systemic therapies in improving outcomes
- Consideration of the changes to the treatment pathway on the availability of new life-extending hormonal agents in the metastatic Castrate Resistant Prostate Cancer (mCRPC) setting.

Sanofi reached agreement with NHS England to allow continued access for patients to cabazitaxel following delisting from the CDF, as an interim measure pending NICE re-review.

Description of the cabazitaxel marketing authorisation.

Table 1. Technology being appraised

UK approved name and brand name	• Approved name: cabazitaxel • Brand name: Jevtana®
Marketing authorisation/CE mark status	Marketing authorisation for cabazitaxel was granted by the European Commission on 17th March 2011.[3]
Indications and any restriction(s) as described in the summary of product characteristics	**Indication:** • Cabazitaxel in combination with prednisone or prednisolone is indicated for the treatment of patients with Metastatic Castrate Resistant Prostate Cancer (mCRPC) previously treated with a docetaxel-containing regimen. • Patients with mild hepatic impairment (total bilirubin > 1 to ≤1.5 x Upper Limit of Normal (ULN) or AST >1.5 x ULN) should have their dose reduced to 20 mg/m^2 and should be closely monitored during treatment. • For patients with moderate hepatic impairment (total bilirubin >1.5 to ≤ 3.0 x ULN) dose should not exceed 15 mg/m^2. **Contraindications** • Hypersensitivity to cabazitaxel, to other taxanes, or to any excipients of the formulation including polysorbate 80. • Neutrophil counts less than 1,500/mm^3. • Concomitant vaccination with yellow fever vaccine. • Severe hepatic impairment (total bilirubin >3 x ULN)
Method of administration and dosage	• The recommended dose of cabazitaxel is 25 mg/m^2 administered as a 1 hour intravenous infusion every 3 weeks in combination with oral prednisone or prednisolone 10 mg administered daily throughout treatment. (Note: prednisone and prednisolone are considered to be equivalent; only prednisolone is available in the UK). • Dose modifications by down titration to 20 mg/m^2 should be made if patients experience the adverse reactions tabulated in section 2.3.1: Table 8 or if they are experiencing hepatic impairment.

Cabazitaxel was appraised by NICE in 2010 (TA255).[4] In this review the clinical benefit of cabazitaxel was acknowledged and the Committee agreed that it qualified for consideration under the End of Life (EoL) criteria. Nonetheless, negative guidance was received on the basis that the technology was considered not cost-effective at the submitted price (TA255).[4] Cabazitaxel was subsequently made available via the CDF because of its clinical effectiveness and has become standard of care post-docetaxel in patients appropriate for cytotoxic therapy, displacing mitoxantrone use in the NHS.

Changes in the patient pathway since TA255[4]

The availability of advanced hormonal agents abiraterone and enzalutamide in the pre- and post-docetaxel setting have increased the options for patients, resulting in tailoring of the treatment pathway. NHS England does not fund sequential use of the advanced hormonal agents because there is significant observational and pre-clinical evidence of cross resistance between abiraterone and enzalutamide. As a result two pathways tend to be followed with the advanced hormone therapies used either pre- (NHS standard practice) or post- (alternative practice) docetaxel.

The use of the advanced hormone agents in the pre-docetaxel setting is the typical treatment pathway in England today with over two-thirds of patients following this treatment paradigm.[5] Patients following this pathway initially tend to have less aggressive, asymptomatic or mildly symptomatic disease (unlikely to be resistant to further hormone therapy). These patients only become eligible for cabazitaxel following docetaxel. No alternative active treatment to cabazitaxel is available in this position in the pathway (left hand side).

Younger, fitter patients with aggressive, symptomatic disease tend to follow alternative practice (right hand side) and depending upon the response to docetaxel, the next step in the pathway would be determined by disease assessment and patient choice.

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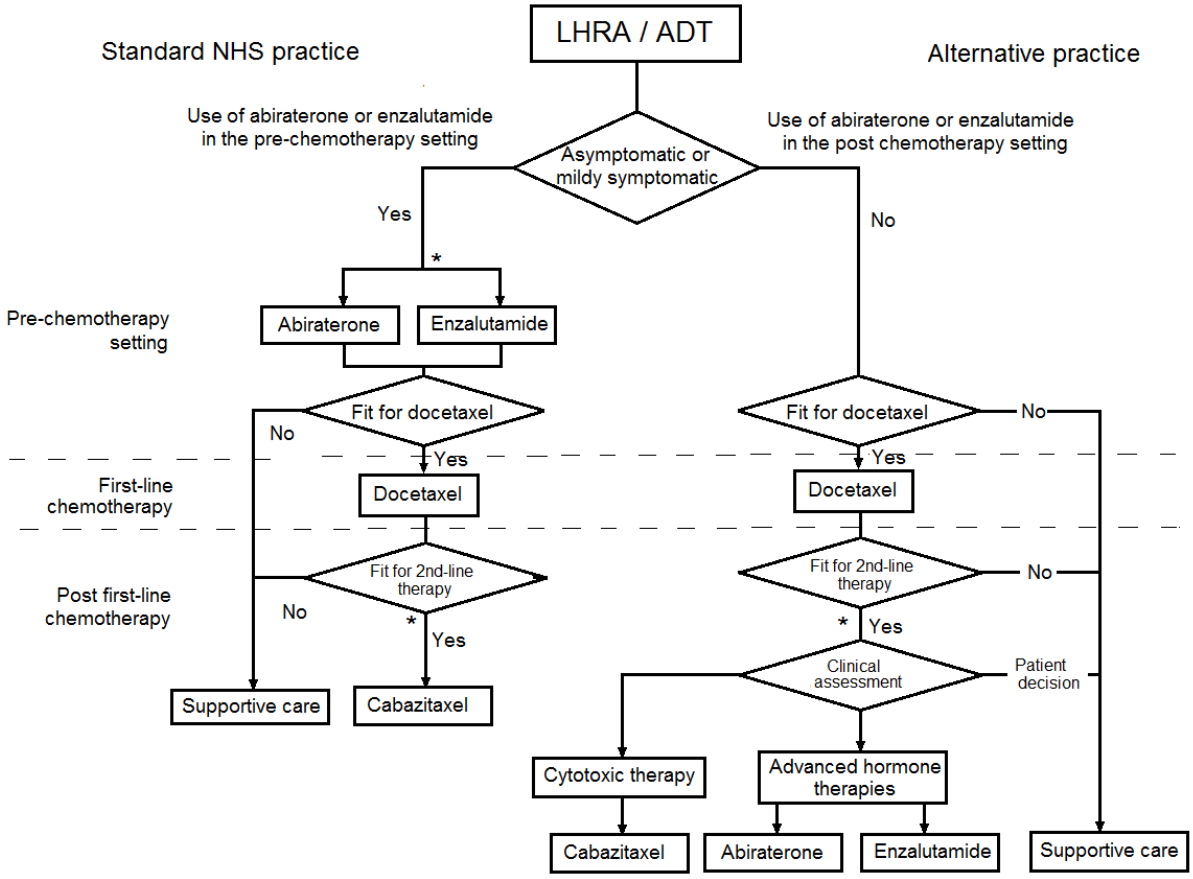


* Radium-223 is licenced for patients with two or more bone metastases but no visceral metastases

The marketing authorisations for the advanced hormonal agents[6, 7] are in metastatic Castrate Resistant Prostate Cancer (mCRPC) whilst the cabazitaxel authorisation is for metastatic Hormone Refractory Prostate Cancer (mHRPC). Whilst often used interchangeably, mHRPC and mCRPC have an important distinction in definition. Abiraterone and enzalutamide interrupt the production of testosterone (by the tumour) which means they work only on tumours with some sensitivity to hormones. Cabazitaxel has a different mechanism of action. It blocks tumour cell division and thus disrupts many pathways, related or not to androgen receptors. This means it not only works on tumour sensitive cell lines, but it also works on the aggressive clones which do not respond to advanced hormonal agents.

Therefore, the disease characteristics of patients appropriate for chemotherapy will not be the same as those appropriate for hormone therapy at this stage in the

treatment pathway. This is reflected by the patient's response to docetaxel within Phase III clinical trials.

Understanding of disease heterogeneity and resistance

Prostate cancer used to be perceived as a homogeneous disease resulting from malignant androgen dependent clonal tissue. It has become evident that prostate cancer tumours are in fact heterogeneous as they contain cells with a variety of malignant genetic changes.

The majority of late-stage prostate cancers harbour mutations in the androgen receptor that convey resistance to currently available medicines targeting androgen signalling (i.e. the advanced hormonal agents). In addition, evidence suggests that sequential treatment with advanced hormonal agents is not beneficial due to acquired resistance. As a result, CDF guidance explicitly excludes sequential treatment with advanced hormonal therapy.

It is therefore important that an effective second-line cytotoxic agent is available for treating prostate cancer, as a significant proportion of post-docetaxel patients with aggressive disease, who have progressed during or rapidly after docetaxel treatment may not be suitable for the advanced hormonal agents abiraterone or enzalutamide.

Summary of the base-case analysis

Base-case analysis – standard NHS practice

The pivotal Phase III trial compares cabazitaxel to mitoxantrone as this was the comparator required by the regulator at the time. Mitoxantrone is unlicensed in this indication and is now rarely used in the UK since the introduction of cabazitaxel. Mitoxantrone, despite having palliative benefit, has not demonstrated any survival advantage over best supportive care[2] so in the context of this decision problem is considered as at least equivalent to BSC.

Scenario analysis – alternative practice

In line with the scope, analysis is also provided for patients who have not followed current standard practice and therefore could still receive abiraterone and enzalutamide in the post-docetaxel setting. However, based on the increased characterisation of the mechanisms of resistance to hormone therapy, it is not often considered as an alternative for patients eligible to receive cabazitaxel. Therefore we consider this analysis is of limited relevance to the decision problem.

Clinical effectiveness

The pivotal registration clinical trial (see Section 4.7) was the TROPIC study (EFC6193, NCT00417079).[8] This was a large randomised, open-label, international, multi-centre, Phase III study in which 755 patients were randomised to receive either cabazitaxel 25 mg/m^2 intravenously every 3 weeks for a maximum of 10 cycles with prednisone or prednisolone 10 mg orally daily (n=378), or to receive mitoxantrone 12 mg/m^2 intravenously every 3 weeks for a maximum of 10 cycles with prednisone or prednisolone 10 mg orally daily (n=377).[8, 9]

The median study follow-up was 20.5 months. A 28% reduction in the risk of death was observed for cabazitaxel compared to mitoxantrone (p=0.0002 HR=0.72 (95%CI, 0.61-0.85)).[9] Overall survival (OS) in the ITT population is presented in Table 2. Median OS was significantly longer with cabazitaxel compared to mitoxantrone (15.1 versus 12.7 months respectively). The base-case estimate of the mean OS extrapolated using the Weibull distribution was (18.55 versus 14.53 months; difference of 4.02 months). (See Section 5.6).

Progression-free survival (PFS) defined as the earliest progression in tumour growth, PSA increase, pain or death was also statistically significantly longer in the cabazitaxel group compared to the mitoxantrone group (p<0.0001, HR = 0.74 (95%CI, 0.64 - 0.86)). Median progression-free survival was 2.8 months versus 1.4 months. Median Radiologic PFS (rPFS) was estimated using time to progression (TTP) plus mortality as it was not reported in the trial as a pre-specified end point although is common in other trials in mCRPC. Median rPFS was 8.8 months versus 5.9 months, (p=0.0003, HR = 0.75 (95% CI: 0.65 - 0.88). The key results are presented in Table 2.

Table 2. OS and PFS – ITT population

	Mitoxantrone + prednisone (n=377)	Cabazitaxel + prednisone (n=378)	Difference (months)
Median Overall Survival[8]			
OS, months (95%CI)	12.8 (11.5 – 13.7)	15.1 (14.0 – 16.5)	2.3
Hazard ratio (95% CI)*	0.72 (0.61 - 0.85)		
P value†	0.0002		
Estimated mean Overall Survival (extrapolated)			
OS, months (95%CI)	14.53	18.55	4.02
Median Progression-free survival (PFS)[8]			
PFS, months (95%CI)	1.4 (1.4 – 1.8)	2.8 (2.4 – 3.1)	1.4
Hazard ratio (95% CI)	0.76 (0.65 - 0.89)		
p value	0.0002		
Median progression free survival (r(PFS)) (analysed for the purposes of ITC)			
Number of patients with rPFS, n (%)	337 (89.4)	318 (84.1)	-
rPFS, months (95%CI)	5.9 (5.1 - 7.0)	8.8 (7.6 - 9.7)	2.2
Hazard ratio (95% CI)	0.75 (0.65 – 0.88)		
p value	0.0003		
Key: CI = confidence interval. * P value from stratified log rank test, stratifying for ECOG performance status and measurable disease at baseline. † Hazard ratio is estimated using a Cox proportional hazards regression model, HR <1 indicates a lower risk with cabazitaxel plus prednisone with respect to mitoxantrone plus prednisone.			

Safety and tolerability

In TROPIC the most common haematological adverse reactions were neutropenia and febrile neutropenia. However these can be managed effectively in clinical practice with primary G-CSF prophylaxis according to EORTC guidelines or careful monitoring and typically rates of neutropenia are lower in the real-world than observed in the trial. Patients currently treated by the NHS receive six cycles on average, consistent with TROPIC and this demonstrates tolerability in the real-world setting.

Table 3. Key adverse events (≥ grade 3) observed in the TROPIC study.

Adverse event*	Mitoxantrone (n=371)	Cabazitaxel (n=371)
Neutropenia	27 (7.3%)	78 (21%)
Febrile neutropenia	6 (1.6%)	27 (7.3%)
Leukopenia	5 (1.6%)	14 (3.7%)
Anaemia	5 (1.6%)	13 (3.5%)
Thrombocytopenia	1 (0.3%)	9 (2.4%)
Diarrhoea	1 (0.3%)	23 (6.2%)
Fatigue	11 (3.0%)	18 (4.9%)

*Rates for AEs requiring clinical intervention.

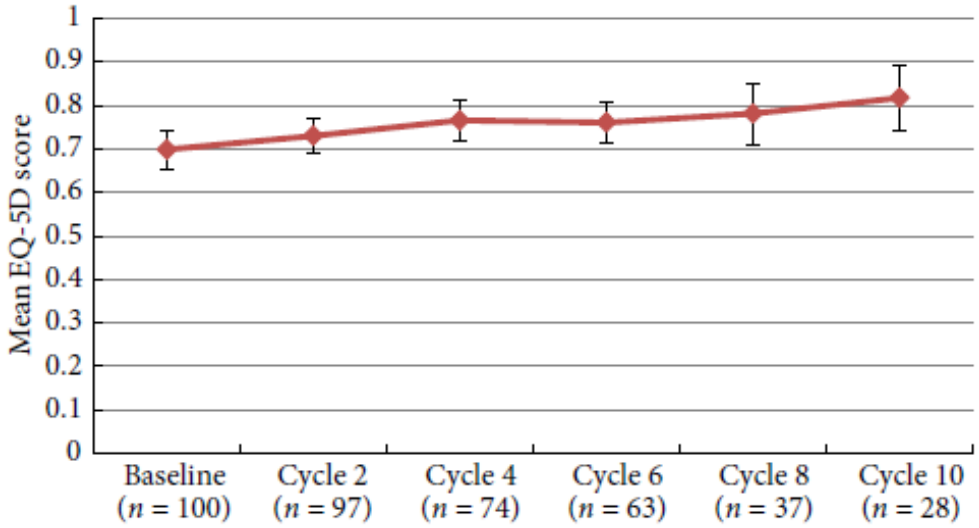
In response to the scope, and only relevant to an examination of the alternative treatment practice (right-hand-side in Figure 1), Indirect Treatment Comparisons (ITC) were carried out to evaluate the relative effectiveness of cabazitaxel in comparison with abiraterone and enzalutamide. The ITCs were based on the outcomes reported in the TROPIC,[9] AFFIRM[10] and COU-AA-301[11] trials.

The evidence from the ITC indicates that cabazitaxel and the advanced hormonal therapies offer broadly similar treatment effects for OS. The ITC is subject to uncertainty due to differences in patient populations and reported end points in the pivotal Phase III trials.

Health Related Quality of Life

Health Related Quality of Life (HRQL) data was not collected in TROPIC. However, EQ-5D data was collected in the UK arm of the international Early Access Programme (EAP) for cabazitaxel (NCT01254279).[12] This study evaluated a similar population to TROPIC and provides the baseline utility values for the economic evaluation outlined in Section 5. A summary of the results for treatment cycles 1 to 10 is provided in Figure 1 below and indicates that patients progressing on earlier lines of therapy (baseline) experience increases to their initial HRQL and maintain this over time whilst on cabazitaxel treatment in the stable disease.

Figure 1. Summary of utility results from the UK EAP.[12]



End of Life criteria

We consider that the End of Life (EoL) criteria continue to apply to cabazitaxel as was the case in the original NICE technology appraisal (TA255).[4]

Despite newer agents becoming available, the life expectancy of patients with prostate cancer remains limited. A recent literature review examined, life expectancy with castrate resistant prostate cancer (CRPC)[13] In the 11 treatment groups identified that were treated with first-line docetaxel, median OS was 19 months (IQR: 17–20). In the post-docetaxel setting survival was shorter. For example in the four main RCTs with results in the post-docetaxel setting the observed median OS results for patients in the control arms were: TROPIC, 12.7 months, COU-AA-301 (abiraterone): 11.2 months, AFFIRM (enzalutamide): 13.6 months and ALSYMPCA (Radium-223): 11.3 months. These results suggest that typical life expectancy of patients suitable for cabazitaxel is considerably less than 24 months regardless of previous therapeutic interventions.

Data from the CDF for the year 2013/14 showed that around 600 patients were receiving cabazitaxel.[14] This number is below the ceiling of 7,000 patients required to meet End of Life (EoL) criteria. The total eligible population is estimated to be 1690 patients in England.

Incremental mean OS (assessed by the best fit (Weibull) parameterisation of the TROPIC data: 4.02 months) is likely to be greater than 3 months (Table 2) with cabazitaxel versus mitoxantrone. Incremental OS using other parameterisations ranges between 3.6 and 8.1 months. This is consistent with the ERG estimates in the original NICE technology appraisal.

For patients previously treated with the advanced hormonal agents, or for those no-longer suitable for them, cabazitaxel represents an life-extending EoL therapy.

Summary of the cost-effectiveness analysis

A simple Patient Access Scheme (PAS) has been offered to enable NICE to reconsider the cost-effectiveness of cabazitaxel.

A Markov model was used to represent the progressive nature of the disease for the economic evaluation. Patients start in the stable disease state at the first cycle of treatment. Once patients progress, they move to the 'progressive disease' state. Patients can die from all causes, and at any time. The cycle length in the model was three weeks, reflecting the timing of treatment cycles in both TROPIC and usual clinical practice. The time horizon was limited to ten years and discounting was applied at the usual rate of 3.5%.

Given that current established use of cabazitaxel is almost entirely in patients who have already received either abiraterone or enzalutamide, we believe the most appropriate comparison for cabazitaxel remains mitoxantrone, as pivotal trial comparator and as a proxy for BSC and this is presented as the base-case analysis.

The cost-effectiveness analysis presented here which incorporates the PAS has shown that cabazitaxel is associated with a base case ICER of £49,327/QALY. This arises from an average incremental increase in life years of 0.338 and an incremental QALY gain of 0.232, set against an increased lifetime cost of £11,450 of which a sizable cost (~18%) is incurred through additional survival gained in the high-cost progressive disease state. These results have been tested in one-way sensitivity analysis and were found not to vary greatly.

Table 4 Base-case incremental cost-effectiveness results

	Cabazitaxel	Mitoxantrone/BSC
Total costs	*Commercial in confidence information removed.*	
Total life years		
Total QALYs		
Incremental costs: cabazitaxel vs. mitoxantrone	£11,450	-
Incremental life years: cabazitaxel vs. mitoxantrone	0.338	-
Incremental QALYs: cabazitaxel vs. mitoxantrone	0.232	-
ICER	£49,327	-
Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALY = quality-adjusted life-year. *Includes administration, premedication and concomitant medication.		

Supplementary analysis for alternative practice

We have carried out a scenario analysis of cost-effectiveness analysis for cabazitaxel versus abiraterone or enzalutamide. As requested by NICE, this analysis is not based upon the net prices available through the patient access schemes for abiraterone and enzalutamide as they are confidential. Results from this analysis can be found in appendices B.

Conclusions

Disease heterogeneity and the emergence of hormone refractory tumours over time mean that patients need tailored treatment options to extend overall survival in mCRPC. Cabazitaxel is an established life-extending chemotherapy for a group of patients with poor prognosis and few remaining treatment options. As such it has a critical role in the armamentarium to tackle prostate cancer.

Statement of the decision problem

Table 5. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
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 addition of wording to accommodate treatment with advanced hormonal agents pre- or post-docetaxel reflects the influence of these agents in driving the two alternative pathways for metastatic Castrate-Resistant Prostate Cancer (mCRPC) patients discussed below.
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	N/A
Comparator (s)	• Abiraterone in combination with prednisone or prednisolone • Enzalutamide • Mitoxantrone in combination with 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)	Best supportive care represented by mitoxantrone and relevant to standard NHS practice and alternative practice. Abiraterone and enzalutamide in the context of alternative practice.	In line with the scope, mitoxantrone is considered to be a valid comparator and can be considered to be equivalent to best supportive care for OS. This is the base-case analysis. A scenario analysis is provided comparing cabazitaxel to abiraterone or enzalutamide. However, it is not considered that patients eligible for chemotherapy in this setting would also be appropriate for hormone therapy due to disease heterogeneity and treatment resistance (see Section 4)

	For people with bone metastasis only (no visceral metastasis) • Radium-223 dichloride (NICE guidance is in development, funded by the CDF in the interim)		Radium-223 is not considered to be a comparator (nor is cabazitaxel considered to be a comparator in the ongoing NICE appraisal or EPAR for Radium-223) due to differences in trial patient populations and resulting marketing authorisations. Use is currently not established in the UK.
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival (PFS) • response rate • adverse effects of treatment • health-related quality of life.	• Primary outcome: OS • Secondary outcomes: o Radiographic PFS (rPFS) o Adverse effects of treatment o Health-related quality of life.	
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. 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	The cost-effectiveness of cabazitaxel is expressed as an incremental cost per QALY. The time horizon in the base-case is the patient's lifetime and constrained to a maximum of 10 years Costs are considered from an NHS and PSS perspective The availability of a Patient Access Scheme (PAS) for cabazitaxel is included in the analysis. The scenario analysis including abiraterone and enzalutamide are based	

	schemes for the intervention or comparator technologies should be taken into account.	on NHS list prices, as requested by NICE, as the PAS arrangements are confidential.	
Subgroups to be considered	If evidence allows the subgroups indicated in the 'comparators' section will be considered. People for whom abiraterone or enzalutamide are not suitable include people in whom • abiraterone or enzalutamide are not expected to be effective • the disease has progressed after abiraterone or enzalutamide Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	The base-case will be the population in TROPIC with Eastern Cooperative Oncology Group performance status (ECOG PS) 0 -1 and who have previously received ≥ 225 mg/m^2 of docetaxel Sensitivity analysis will be conducted using the ITT population from the TROPIC study.	In line with previous NICE opinion and the use of cabazitaxel in clinical practice, patients with lower performance score (ECOG PS ≥ 2) and limited exposure to docetaxel are excluded from the base-case population, as they are typically less likely to be fit enough to receive further lines of chemotherapy. This base-case population makes up the large majority of patients in the TROPIC study (84%) and is the patient population that is expected to receive cabazitaxel in clinical practice.. The licence for cabazitaxel is in the post docetaxel indication. No other subgroups are examined.
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has	No additional issues relating to equity or equality were identified by Sanofi or the commentators to the draft scope. It is expected that EoL considerations will apply to the population identified in standard NHS practice and alternative	As agreed at the decision-problem meeting, NICE will look at the application of EoL criteria on a case-by-case basis and that it is appropriate to recognise where this applies given the new treatment pathway

	underpinned the marketing authorisation granted by the regulator.	practice pathways.	

2. The technology

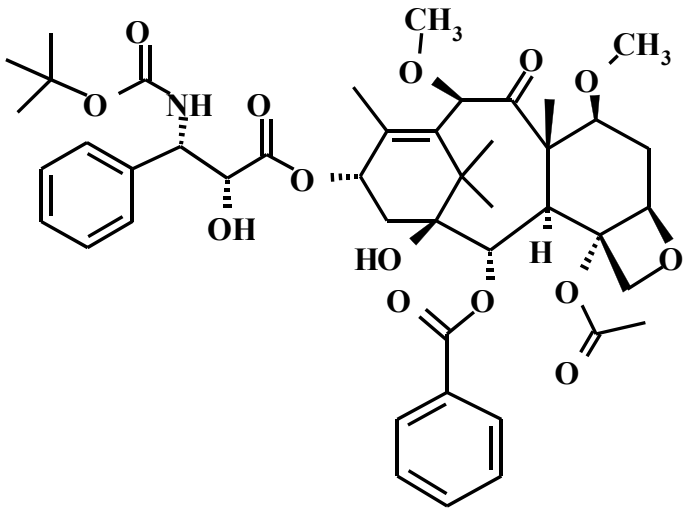
2.1 Description of the technology

2.1.1. Brand name, UK approved name, the therapeutic class and a brief overview of the mechanism of action.

- Brand name: Jevtana®
- Approved name: cabazitaxel
- Therapeutic class: taxane

Cabazitaxel (XRP6258) (Figure 2) is a semi-synthetic taxane derived from 10-deacetylbaccatin III, the natural taxane extracted from European Yew tree needles. It has been developed for the treatment of prostate cancer because it has shown anti-tumour activity in docetaxel-resistant and docetaxel-sensitive cell lines and tumour models in preclinical studies.[1, 15]

Figure 2. Cabazitaxel: molecular structure



Microtubules play a critical role in cell division, intracellular transport and the development and maintenance of cell shape. Cabazitaxel inhibits microtubule disassembly.[16] inhibiting mitotic and interphase cellular functions, leading to tumour cell cytotoxicity.

Taxanes represent a well-established class of chemotherapy agents; however, efficacy is limited by intrinsic or acquired resistance. Cabazitaxel was selected from over 450 candidates based on characteristics critical to overcoming taxane resistance.

In vitro, cabazitaxel stabilized microtubules as effectively as docetaxel but was 10-fold more potent than docetaxel in cell lines resistant to taxanes or other chemotherapeutic agents such as doxorubicin, vincristine, or vinblastine[1] The greater potency of cabazitaxel in

docetaxel-resistant tumours is attributed to a stronger suppression of microtubule dynamics, faster drug uptake, and better intracellular retention compared to docetaxel.[17]

In vivo, cabazitaxel demonstrated excellent antitumor activity in a broad spectrum of docetaxel-sensitive tumour xenografts, including a castration-resistant prostate tumor xenograft, HID28, where cabazitaxel exhibited greater efficacy than docetaxel. Importantly, cabazitaxel was also active against tumours with innate or acquired resistance to docetaxel, suggesting therapeutic potential for patients progressing following taxane treatment and those with docetaxel-refractory tumours.

2.2 Marketing authorization /CE marking and Health Technology Assessment

2.2.1. UK marketing authorisation status.

Marketing authorisation was granted by the European Medicines Agency (EMA) on 17th March 2011.[3]

2.2.2. Indication

Cabazitaxel in combination with prednisone or prednisolone is indicated for the treatment of patients with metastatic hormone-refractory prostate cancer previously treated with a docetaxel-containing regimen.[15]

2.2.3. Summary of restrictions or contraindications in the summary of product characteristics (SmPC).

- Hypersensitivity to cabazitaxel, to other taxanes, or to any excipients of the formulation including polysorbate 80.
- Neutrophil counts less than 1,500/mm^3.
- Hepatic impairment (bilirubin ≥1 x ULN, or AST and/or ALT≥1.5 × ULN).
- Concomitant vaccination with yellow fever vaccine.

2.2.4. Summary of Product characteristics

The summary of product characteristics (SmPC) is provided in Appendix 1.

2.2.5 European Public Assessment Report[3]

The European Assessment Report (EPAR) is provided in a separate annex.

2.2.6. Summary of the main issues discussed by the regulatory authorities.

Cabazitaxel has a full marketing authorisation, but should be confined to units specialised in the administration of cytotoxics and it should only be administered under the supervision of a physician experienced in the use of anticancer chemotherapy. Facilities and equipment for

the treatment of serious hypersensitivity reactions like hypotension and bronchospasm must be available.

The EMA considered that the principal adverse effects of cabazitaxel observed in the non-clinical safety studies were consistent with the pharmacological (anti-mitotic) activity of a taxoid–type antineoplastic compound and resemble those reported for other taxoid anticancer drugs. In view of its therapeutic indication of the treatment of patients with mCRPC previously treated with a docetaxel containing regimen there were no major objections or other concerns raised about the results from these studies.

The regulator recognised that the efficacy of cabazitaxel in combination with prednisone or prednisolone for the treatment of patients with mCRPC previously treated with a docetaxel containing regimen was established in the TROPIC study.

However uncertainty in the efficacy for patients that had received less than <225 mg/m^2 cumulative dose of docetaxel was highlighted. A sub-group of 59 patients received prior cumulative dose of docetaxel <225 mg/m² (29 patients in cabazitaxel arm, 30 patients in mitoxantrone arm) and there was no significant difference in overall survival in this group of patients (HR (95%CI) 0.96 (0.49-1.86)). This observation may be due to a lower efficacy in this subgroup due to different patient or disease characteristics, however the low number of patients in this subgroup may also explain the lack of a clear effect. Thus, although there is insufficient evidence to conclude that the benefits are lacking in this subgroup, this information has been included in the SmPC to help make an informed treatment choice.

The side effect profile for the < 25mg/m² dose was generally more favourable when compared to the ≥25mg/m² dose in the Phase II study submitted as part of the evidence package, in patients with taxane and/or anthracycline-resistant metastatic breast cancer (ARD6191). The EPAR states that it is unclear whether the <25mg/m² dose would have similar activity to the ≥25mg/m² dose but with a more acceptable safety profile. The PROSELICA study comparing cabazitaxel at 20 mg/m² and at 25 mg/m² in second line mCRPC patients will address this issue and is discussed in Section 4.14.

The European regulatory submission, as described in the European Public Assessment Report (EPAR), concluded that cabazitaxel had a positive risk-benefit profile, with clinically meaningful benefits, and no requirement for a special risk-minimisation plan.[3]

2.2.7. Date of availability in the UK.

Cabazitaxel was made commercially available in the UK from 20th May 2011.

2.2.8. State whether the technology has regulatory approval outside the UK. If so, please provide details.

In June 2010, the US FDA approved cabazitaxel (Jevtana®) for use in combination with prednisone or prednisolone for the treatment of patients with mCRPC previously treated with a docetaxel-containing regimen.

The European Commission granted marketing authorization in all 27 countries of the European Union (EU) 17 March 2011.

Cabazitaxel is approved in more than 85 countries worldwide.

2.2.9 State whether the technology is subject to any other Health Technology Assessment in the UK. If so, give the timescale for completion.

Summaries of previous UK Health Technology Assessments of cabazitaxel are presented in Table 6.

Table 6. Previous UK Health Technology Assessments of cabazitaxel

Agency	Ref.	Indication	Status and date
NICE	TA255	Cabazitaxel for hormone-refractory metastatic prostate cancer (mCRPC) previously treated with a docetaxel-containing regimen	Not recommended May 2012
SMC	Drug ID: 735/11	Cabazitaxel for the treatment of patients with metastatic hormone refractory prostate cancer (mCRPC) previously treated with a docetaxel-containing regimen	Not Recommended 07/11/2011. Resubmission planned for Q4 2015 with PAS.
AWMSG	Ref. No. 775	Cabazitaxel in combination with prednisone or prednisolone for the treatment of patients with hormone refractory metastatic prostate cancer (mCRPC) previously treated with a docetaxel-containing regimen	Excluded due to NICE appraisal 13/10/2011
NICE: National Institute for Health and Care Excellence; SMC: Scottish Medicines Consortium; AWMSG: All Wales Medicines Strategy Group; mCRPC: metastatic hormone refractory prostate cancer			

2.3 Administration and costs of the technology

2.3.1. Costs of the technology being appraised

Relevant costs are presented in Table 7 overleaf

Table 7. Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	Cabazitaxel 60 mg/1.5 ml concentrate and solvent for infusion is supplied as a kit consisting of the following: • One single vial of cabazitaxel concentrate 60 mg/1.5 ml (contains 60 mg cabazitaxel in 1.5 ml polysorbate 80) • One single vial of diluent for cabazitaxel injection 60 mg/1.5 ml (contains approximately 5.7 ml of 13% (w/w) ethanol in water for injection). Both items are in a blister pack in one carton.	
Acquisition cost (excluding VAT) *	£3696 per vial, £61.60 per mg The PAS adjusted cost will be *Commercial in confidence information removed* per vial, *Commercial in confidence information removed* per mg Cabazitaxel is given in combination with daily oral prednisolone 10 mg for the duration of treatment = £0.01 / mg (Non-proprietary: 5 mg, 28-tab pack = £1.29) Intravenous premedication : • Antihistamine (dexchlorpheniramine 5 mg or diphenhydramine 25 mg or equivalent) = £0.45 / mg. (Based on cost for chlorphenamine maleate, 10 mg/mL, 1-mL ampule = £4.47) • Corticosteroid (dexamethasone 8 mg or equivalent), £0.52 / mg. (Based on cost for dexamethasone, 1-mL vial containing 3.8 mg/mL = £1.99). • H_2 antagonist (ranitidine or equivalent) = £0.01 /mg. (Based on cost for ranitidine, 25 mg/mL, 2-mL ampule = 54p)	List prices: BNF Sept. 2015[18]
Method of administration	Intravenous infusion over 60 minutes	SmPC[15]
Doses	The recommended dose in the SmPC is 25 mg/m^2 with the option to down-titrate to 20 mg/m^2 if adverse events are experienced.† For patients with mild and moderate hepatic impairment 20 mg/m^2 and 15 mg/m^2 doses	SmPC[15]

	Cost	Source
	are recommended.	
Dosing frequency	Intravenous infusion every three weeks, and prednisolone 10 mg orally given daily (Note: prednisone and prednisolone are considered to be equivalent; only prednisolone is available in the UK).	SmPC[15]
Average length of a course of treatment	In TROPIC (see Section 4.7), the median number of cycles received was six. (The maximum number of permitted cycles is ten). In the UK Early Access Programme (EAP) (See SECTION 5.4.2), patients also received a median of six cycles of cabazitaxel.	De Bono, 2011[8] Bahl, 2015[12]
Average cost of a course of treatment	*Commercial in confidence information removed* including administration, pre and concomitant medications. Based on a patient of 1.9m^2 surface area).	Estimated from the economic model
Anticipated average interval between courses of treatments	Only one course of cabazitaxel recommended according to the SmPC	SmPC[15]
Anticipated number of repeat courses of treatments	No repeat courses will be given.	
Dose adjustments†	See Table 8†	SmPC[15]
Anticipated care setting	Secondary care setting in units specialising in the administration of cytotoxics.	SmPC[15]
* Indicate whether this acquisition cost is list price or includes an approved Patient Access Scheme. When the marketing authorisation or anticipated marketing authorisation recommends the intervention in combination with other treatments, the acquisition cost of each intervention should be presented.		

†Dose modifications should be made if patients experience the following adverse reactions (Grades refer to Common Terminology Criteria for Adverse Events (CTCAE 4.0)):

Table 8 Dose adjustments*

Adverse reactions	Dose modification
Prolonged grade ≥3 neutropenia (longer than 1 week) despite appropriate treatment including G-CSF	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.

Adverse reactions	Dose modification
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.

* The treatment should be discontinued if a patient continues to experience any of these reactions at 20 mg/m^2. Taken from the SmPC.[15]

2.3.2. Patient Access Scheme

A simple, confidential discount Patient Access Scheme (PAS) was submitted to the Department of Health on 10th of April.

The list price and details of the proposed scheme are provided in Table 9 below.

Table 9. Current list price and PAS discount.

	List price and discount
Current UK list price(s) for all relevant brand names and preparations of the product	Cabazitaxel 60 mg / 1.5 ml concentrate and solvent for infusion: £3696 per vial, £61.60 per mg.[18]
Proposed discount (if appropriate, specify by brand name and preparation)	The Patient Access Scheme will be a simple confidential reduction off the list price at the point of invoice. The PAS adjusted cost will be *Commercial in confidence information removed* per vial, *Commercial in confidence information removed* per mg.

As this is a simple scheme, Sanofi will not collect any clinical or outcomes data.

2.3.3. For devices, provide the list price and average selling price.

No device is associated with cabazitaxel.

2.4 Changes in service provision and management

2.4.1. Additional tests, investigations or particular administration requirements for the technology.

There are no additional tests or investigations needed for selection of patients for treatment. However prognostic factors which may prompt clinicians to consider cabazitaxel include: suspected hormonal independence, (especially in those patients with a more aggressive potential; Gleason ≥ 8), rapid progression to mCRPC with primary ADT and patients who are clearly refractory to docetaxel (particularly if progression has occurred during treatment with this drug). Prior treatment with ketoconazole and baseline serum levels of adrenal androgens may also be taken into account.[19]

Cabazitaxel is an intravenously administered chemotherapy drug. As such, cabazitaxel requires specialist administration by a qualified physician experienced in the use of anti-neoplastic medicinal products similar to other intravenous (IV) chemotherapies. Facilities and equipment for the treatment of serious hypersensitivity reactions like hypotension and bronchospasm must be available.

2.4.2. Estimated NHS resource use

Similar costs of administration are incurred by other IV chemotherapies used in the first- and second-line treatment of mCRPC. Cabazitaxel, as established standard of care post-docetaxel, has been used in chemotherapy units to treat mCRPC patients for the last 4 years and its continued use is not anticipated to add a major resource burden. There are no implications for primary care resources.

Cabazitaxel should be administered under the supervision of a qualified physician experienced in the use of anti-neoplastic medicinal products, in a unit with facilities suitable for administering IV chemotherapy. The infusion time is 60 minutes and, provided there are no AEs, patients can usually be discharged immediately after their infusion. The cost estimated for administration of chemotherapy in a day-case setting is estimated as £320 per administration according to NHS reference costs.[20]

2.4.3. Additional infrastructure requirements for the NHS.

No additional NHS infrastructure is required beyond that found in existing units specialising in the administration of cytotoxics.

2.4.4. Effect on patient monitoring compared with established clinical practice.

Cabazitaxel is an established therapy with over 36,500 patients worldwide having received it to date [Periodic safety review] and the safety and adverse event profile are well understood. The response to the scope provided by Tackle Prostate cancer stated that '…*After talking with patients who have received this* treatment, it has been shown to be well tolerated with fewer side effects that expected.' Today clinicians are experienced in monitoring patients

requiring interventions during cytotoxic treatment and there are several guidelines which have contributed to established clinical practice (Table 13).

For cabazitaxel, monitoring is required for infusion-related hypersensitivity reactions (common with all infusion-administered drugs) and neutropenic complications, which are common to the taxanes as a class. There are no other reasons for special monitoring of cabazitaxel patients.

Infusion reactions can lead to temporary interruption or withdrawal of treatment. To mitigate the risk and severity of hypersensitivity, a premedication regimen consisting of an antihistamine, an H_2 antagonist and a corticosteroid is recommended for all patients prior to the initiation of the infusion of cabazitaxel.[15] Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions.

Established clinical practice according to EORTC guidelines[21] during the administration of cytotoxic drugs to minimise the risk of neutropenia and its complications requires monitoring of complete blood counts on a weekly basis during cycle 1 and before each treatment cycle thereafter. If necessary the dose can be adjusted or secondary prophylaxis with granulocyte-colony stimulating factors (G-CSF) administered to reduce the risks of neutropenic complications. Primary G-CSF prophylaxis is used to reduce the haematological side effects in high risk patients (whilst this is variable, around 20 – 25% of patients are managed in this way in clinical practice). Lower risk patients are monitored and neutropenia is managed quickly and effectively with G-CSF as the need arises.

2.4.5. Concomitant therapies administered with the technology.

- Cabazitaxel is given in combination with OD 10 mg of oral prednisolone for the duration of treatment.
- Premedication is recommended at least 30 minutes prior to each administration of cabazitaxel to mitigate the risk and severity of hypersensitivity:
    - antihistamine (dexchlorpheniramine 5 mg or diphenhydramine 25 mg or equivalent)
    - corticosteroid (dexamethasone 8 mg or equivalent)
    - H_2 antagonist (ranitidine or equivalent)
- Antiemetic prophylaxis is recommended and can be given orally or intravenously as needed. Throughout the treatment, adequate hydration of the patient needs to be ensured, in order to prevent complications like renal failure.
- G-CSF may be given at clinical discretion as primary prophylaxis to patients considered being at increased risk of neutropenia, and as secondary prophylaxis to prevent recurrent neutropenic complications.
- It is expected that luteinising hormone-releasing hormone (LHRH) agonists would be given in parallel as part of standard care to patients who are not surgically castrated.

2.5 Innovation

Taxanes have formed the bedrock of management of mHRPC, since the pivotal TAX327 trial of docetaxel,[22] which was the first study to demonstrate a survival benefit in patients progressing on androgen-based therapies. The full benefit of docetaxel is still being explored, with results from the recent CHAARTED trial demonstrating a 13.6 month OS benefit when docetaxel was used earlier, in metastatic, hormone-sensitive disease. This reflects the nature of oncology drug development whereby drugs are initially investigated in later-stage oncology (for ethical reasons), but frequently show much greater benefits when they are used earlier in the treatment pathway.

One of the key limitations of docetaxel is the development of resistance. Cabazitaxel was specifically designed to overcome this resistance and was the first agent to demonstrate a significant survival benefit in patients with mCRPC that has progressed on or after a docetaxel-containing regimen.

Late-stage prostate cancer treatment has improved significantly over the last two to three years with the introduction of new agents including cabazitaxel and the advanced hormone therapies abiraterone and enzalutamide.

There is clear evidence for cross-resistance between the hormonal agents, and reflecting this, the NHS does not allow sequential use of abiraterone and enzalutamide. Emerging evidence suggests that some patients, particularly those with aggressive disease and those who responded poorly to initial ADT, do not respond well to further hormonal therapy with abiraterone and enzalutamide.

In patients with innate and acquired resistance to hormonal agents, there are few or no alternatives and in these patients cabazitaxel is an important innovation to extend survival and progression-free survival at the end of life.

Late-stage prostate cancer is an area of active research and it is likely that our understanding of the disease and optimal sequencing of available agents will continue to evolve. It is important that UK clinicians and patients have access to all of the best available treatments at the right time in order to provide the greatest benefit for UK patients.

3. Health condition and position of the technology in the treatment pathway

- Prostate cancer is a complex and heterogeneous disease
- Heterogeneity is seen in the variation the cancer's behaviour between patients and also in how the disease metastasises as it spreads through an individual patient.
- Use of the newer hormonal therapies at different stages in disease progression has led to the evolution of pathways, characterised by use of these agents either pre- or post-docetaxel.
- The eventual development of the tumour's resistance to various different types of hormonal therapy is now becoming better understood.
- Second-line chemotherapy is the only active option for many patients in those with acquired or innate resistance to hormonal therapies or for some patients with more aggressive disease.
- Multiple treatment options are sought at each stage of the disease to address tumour variability, prognosis, and opportunities for sequencing of therapies is important.

3.1. Brief overview of metastatic Castration Resistant Prostate Cancer mCRPC.

Prostate cancer can develop when cells in the prostate start to grow in an uncontrolled way. Prostate cancer is the most common form of cancer among men in the UK and in England there are around 40,000 patients with prostate cancer.[23] It is estimated that one patient dies every hour from the disease in England.[24]The main risk factors for prostate cancer are age, ethnicity, family history, diet and hormone metabolism. Prostate cancer mainly affects men over 50 years and risk increases with age. The average age for men to be diagnosed with prostate cancer is between 70 and 74 years.[24]Today the prognosis for early stage prostate cancer is good but, left untreated, it becomes significantly worse as the disease progresses and 5 year survival in patients with metastatic disease is less than 30%.[19]

There is considerable variation in prostate cancer behaviour between patients but also significant variability in how the disease metastasises as it spreads through an individual patient. During disease progression multiple chromosomal changes occur which explains why the response to Prostate Cancer specific drugs is heterogeneous and changes over time indicating that a single treatment plan would not be suitable for all patients with Prostate Cancer. Disease progression is also quite heterogeneous clinically; including patients who

are asymptomatic or mildly symptomatic, to patients with multiple bone and visceral metastases, pain and poor functional status.

mCRPC develops when advanced prostate cancers treated with any form of androgen deprivation therapy begin to progress and tumours spread outside of the prostate. The mechanisms of progression to castration resistance have been extensively studied and may be classified in two main categories: (1) mechanisms allowing AR-positive tumour cells to adapt to a low testosterone environment and (2) clonal proliferation of AR-negative and/or independent tumour cells, which may be triggered by ADT.[25]

The eventual development of resistance of Prostate Cancers to various different types of hormonal therapy is now better understood. A key discovery was that ARv7+ve tumours typically show limited response to advanced hormonal therapies and therefore exhibit resistance. This can be identified as primary or adaptive. Primary resistant tumours already exhibit resistance at the time when they present but in secondary resistance unresponsiveness to androgens develop over time as the ARv7+ve tumour cells become more dominant when the clones of ARv7-ve tumour cells are eliminated by hormone therapy to which they are sensitive.

These features make prostate cancer a very complex, heterogeneous disease to manage. Survival data from clinical trials in mCRPC suggest that many patients now die of treatment resistant prostate cancer. As a result there is a growing awareness of the need for new treatments and better use of existing treatments either in terms of timing, sequencing or combination therapy or in terms of new mechanisms of action to overcome treatment resistance to existing medicines.

3.2. Effect of mCRPC on patients, carers and society.

Prostate cancer is usually a slowly progressing disease, which is asymptomatic in the early stages. In more advanced disease, a variety of symptoms occur, including frequent and difficult urination and in some cases haematuria, pain when ejaculating, testicle pain and erectile dysfunction. Metastatic disease is associated with a more extensive and severe pattern of symptoms. These are dependent on the location of metastases, and can include bone pain, lymphoedema, pain in the lower back, pelvis or upper thighs, and weight loss.[26]

Bone metastasis is a common form of metastatic disease in prostate cancer, with studies reporting percentages as high as 80%.[27-29] Bone metastases often lead to skeletal-related events (SREs), including pathological fractures, spinal cord compression, hypercalcaemia and severe pain requiring bone surgery, radiation therapy or opioid analgesics. Bone metastases and the pain associated with these, contribute substantially to the disease burden of patients with metastatic prostate cancer,[27] although emerging treatments can help to alleviate or delay symptoms.

In addition to the physical symptoms associated with prostate cancer there is an emotional impact of living with prostate cancer on patients, family members and carers. Prostate cancer is known to have an impact on quality of life (HRQL) for patients which deteriorates

with progression to metastatic disease.[30] Depression, anxiety, stress and psychosocial factors all affect the patient with prostate cancer.[31, 32] A higher rate of depression and anxiety in patients with a prostate cancer diagnosis has been described[33] and the prevalence of psychological distress among cancer patients is higher and associated with advances in disease progress and poor prognosis.[34, 35]

3.3. Clinical pathway of care contextualising the established use of cabazitaxel.

Treatment for prostate cancer is guided by cancer stage and grade (along with patient performance status and suitability for treatment). Once the disease has become refractory and there is biochemical evidence of hormone-relapsed disease, treatment options should be discussed by the urological cancer MultiDisciplinary Team (MDT) with a view to seeking an oncologist and/or specialist palliative care opinion, as appropriate.

Currently NICE[36] recommends first line chemotherapy with docetaxel as a treatment option for patients with hormone-refractory metastatic prostate cancer only if their Karnofsky performance-status score is 60% or more. Repeat cycles of treatment with docetaxel are not recommended if the disease recurs after completion of the planned course of chemotherapy. As shown in Figure 3 there are two treatment pathways relevant to NHS practice (described below) which are defined by the use of abiraterone or enzalutamide in either the pre- or post-docetaxel setting where both are licensed. The position of cabazitaxel in the context of current treatment pathways is also shown in Figure 3.

NHS standard practice

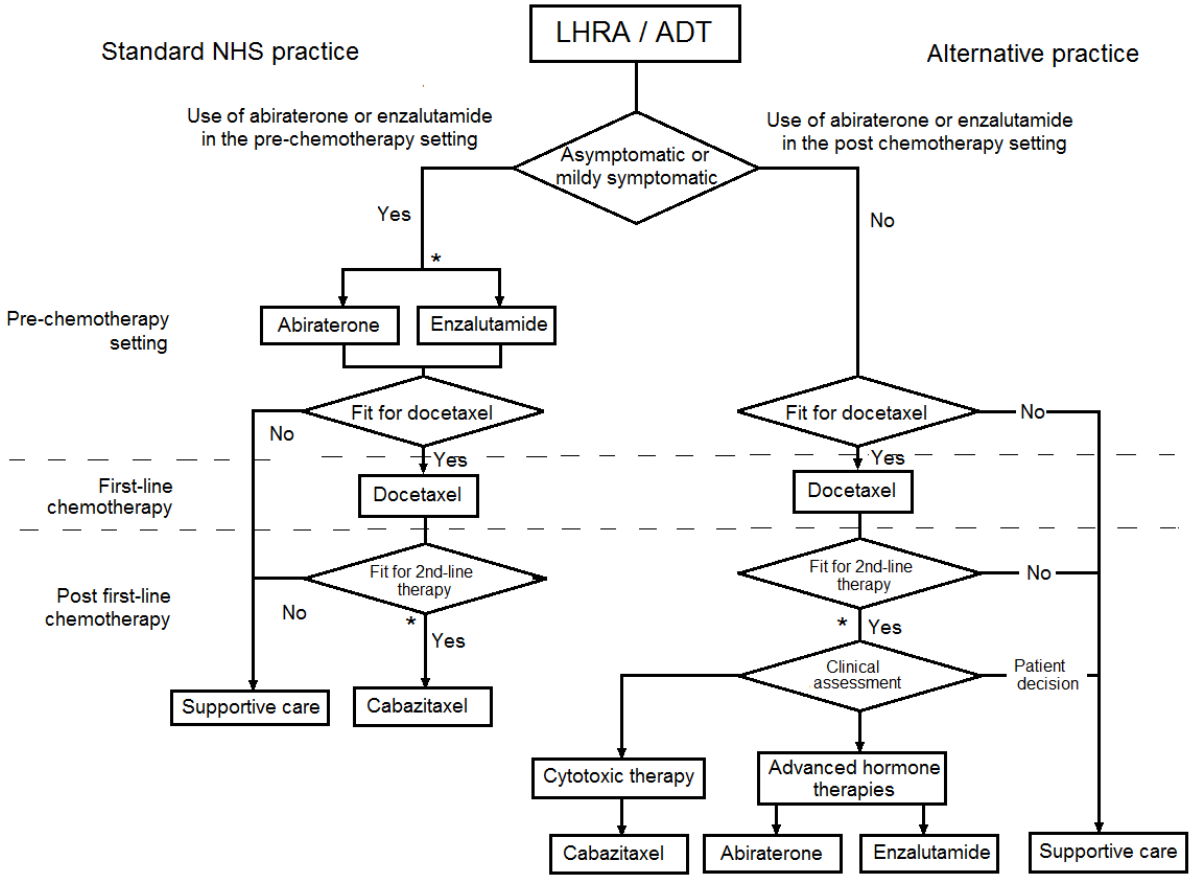
In standard NHS practice, comprising more than two thirds of patients in England (68%)[5] abiraterone and enzalutamide are currently established care and are funded by the CDF in the pre-docetaxel setting. Abiraterone and enzalutamide in the pre-chemotherapy setting are both currently under NICE review in this setting.The sequential use of these agents is outside NICE guidance[6, 7] and is explicitly excluded from Cancer Drugs Fund (CDF) funding arrangements. Those patients who subsequently progress following docetaxel are therefore not eligible for further treatment with abiraterone or enzalutamide. In this case cabazitaxel or best supportive care are currently the only options.

Alternative practice

In the alternative practice pathway, in which abiraterone or enzalutamide have not been used before docetaxel, patients have more options from which a suitable agent might be selected to meet their individual characteristics and requirements. For those patients whose disease has progressed following docetaxel-containing chemotherapy, either the androgen receptor signalling inhibitor, enzalutamide or the androgen biosynthesis inhibitor abiraterone in combination with prednisone or prednisolone (TA316 and TA259 respectively)[6, 7] are recommended by NICE within their marketing authorisations as options for treating mCRPC in adults. However, given the greater understanding of the mechanisms of resistance to hormonal therapy there are patients for whom cabazitaxel may be the most appropriate

treatment option, particulary those who progress during or rapidly (less than 3 months) after docetaxel exposure.

Figure 3. mCRPC: current disease management and existing place in therapy for cabazitaxel.



* Radium-223 is licenced for patients with two or more bone metastases but no visceral metastases

3.4. Life expectancy of people with mCRPC in England including the number of people with mCRPC for which cabazitaxel is being appraised.

Life expectancy

Despite newer agents becoming available, the life expectancy of patients with prostate cancer remains limited with 5 year survival rates of 30% in mCRPC[19] A recent literature review examined, life expectancy with castrate resistant prostate cancer (CRPC)[13]. In the 11 treatment groups identified that were treated with first-line docetaxel, median OS was 19 months (IQR: 17–20). In the post docetaxel setting survival is shorter. For example in the four main RCTs with results in the post-docetaxel setting the observed median OS for patients in the control arms were: TROPIC, 12.7 months, COU-AA-301 (abiraterone): 11.2 months, AFFIRM (enzalutamide): 13.6 months and ALSYMPCA (Radium-223): 11.3 months. These results suggest that typical life expectancy of patients suitable for cabazitaxel is considerably less than 24 months regardless of previous therapeutic interventions.

Eligible patient population

Table 10 provides overall estimates for the number of patients eligible to receive second-line chemotherapy.

Table 10. Calculation of second line chemotherapy eligible patients in England

Patients eligible for second line chemotherapy	%	N
Patients diagnosed with prostate cancer - England 2015 (inflated from 2011 assuming 0.75% per year)		40,980
Of these, castration-resistant metastatic prostate cancer patients	15%	6,147
Of these, patients receiving first-line treatment with docetaxel	50%*	3,073
Of these, patients eligible to receive second-line chemotherapy	55%*	1,690
*sanofi-aventis. Data on file: Market research: Usual 2nd line chemo options after docetaxel are Mitoxantrone, Stilbestrol or BSC – with minor variations from wave 1, 2011		

There were 40,372 diagnosed cases of prostate cancer in England in 2013 according to the latest figures available from the Office for National statistic, this accounted for 26.9% of total male cancer registrations.[23]

Figures from Cancer Research UK suggest that prostate cancer incidence rates have remained relatively static over the period 2003 to 2011[24] and so applying a conservative assumption that the rate rises by the observed annual rate of increase of 0.75% which is the average annual population increase over the last decade the number of patients diagnosed with Prostate cancer in England for 2015 is estimated to be 40,980.

There are very few estimates for the prevalence of mCRPC in patients with prostate cancer. The costing template for TA259: abiraterone estimates 19.5%. However in the systematic literature review by Kirby five studies were identified which examined the prevalence of mCRPC in patients with prostate cancer.[37] Together, the data indicate that 10–20% of prostate cancer patients develop mCRPC within approximately 5 years of follow-up. Taking the mid-point of this range as 15% the number of mCRPC patients may be estimated as 6,147.

In support of this, data from the ONS states that there were 10,153 prostate cancer deaths in England and Wales in 2014.[23] Given that the majority but not all deaths from prostate cancer are likely to occur in the mCRPC setting, the figure of 6,147 mCRPC appears valid.

Market research shows that 50% of patients treated by oncologists are eligible to receive docetaxel first line.[38] Of these patients, 55% are fit (PS 01) to receive further chemotherapy following docetaxel.[38] Thus, there are estimated to be around 1,690 mCRPC patients eligible for second-line chemotherapy in England.

With reference to the pathways discussed in Section 3.3 above 68%[5] of patients receive abiraterone or enzalutamide prior to docetaxel in the UK and are therefore not eligible for treatment with further advanced hormonal therapies. Cabazitaxel is the only active alternative for these patients. This corresponds to 1150 patients in standard NHS practice. Of course, in discussion with their clinicians a proportion of patients may elect not to receive further treatment.[14]

3.5 Details of NICE guidance, pathways and commissioning guides related to mCRPC for which cabazitaxel is being used.

There are several published NICE guidance documents relating to the treatment of hormone-refractory prostate cancer (HRPC) and mCRPC. Recommendations from these appraisals are provided overleaf. (Table 11).

The 2014 NICE Guideline CG175 entitled ‘Prostate cancer diagnosis and treatment’ updates the 2008 guideline CG58.[36] The recommendations for the treatment of hormone-relapsed metastatic prostate cancer are contained in section 1.5.10 to 1.5.16 of CG175 and are taken entirely from the 2008 guideline. In addition bone targeted therapies such as spinal MRI, bisphosphonates and strontium-89 for pain relief may be considered.

The advanced hormone agents received positive advice (TA259 and TA316) in the post-docetaxel setting after the publication of the guidelines. Marketing authorisations in the pre-docetaxel setting have also been granted since publication and technology appraisals are ongoing for this indication.

Table 11. Related NICE Health Technology Assessments

Ref.	Indication	Recommendation	Subgroups addressed
ID683	Enzalutamide for metastatic hormone-relapsed prostate cancer when chemotherapy is not yet clinically indicated	Advice in development (as of submission date for this appraisal). Advice expected: TBC. ACD published June 2015: not recommended). Draft: Enzalutamide is not recommended for treating metastatic hormone-relapsed prostate cancer in people who have no or mild symptoms after androgen deprivation therapy has failed, and when chemotherapy is not yet clinically indicated. The Committee concluded that with its preferred assumptions the resulting incremental cost-effectiveness ratio (ICER) for enzalutamide compared with best supportive care was above £40,000 per quality-adjusted life years (QALY) gained.	No subgroups were considered relevant
ID576	Radium-223 dichloride for treating metastatic hormone relapsed prostate cancer with bone metastases	Advice in development (as of submission date for this appraisal. Advice expected: TBC. ACD published May 2015: recommended). Draft: Radium-223 dichloride is recommended 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 Patient Access Scheme.	No subgroups were considered relevant
ID503	Abiraterone for treating metastatic hormone-relapsed prostate cancer not previously treated with chemotherapy	Advice in development (as of submission date for this appraisal. Advice expected: TBC. FAD published August 2014: Not recommended. The Committee concluded that current mean life expectancy in the population considered is unlikely to be less than 24 months,	Predefined subgroups based on baseline ECOG (0 or 1), BPI (0–1 or 2–3), bone metastasis only at study entry, age and baseline

Ref.	Indication	Recommendation	Subgroups addressed
		and abiraterone at this stage in the treatment pathway did not meet the end-of-life criterion for short life expectancy. Therefore the ICER was not in the range normally considered to be cost-effective.	prostate-specific antigen.
TA332	Sipuleucel-T for treating asymptomatic or minimally symptomatic metastatic hormone relapsed prostate cancer	Not recommended, February 2015: This appraisal has been withdrawn. This is because the marketing authorisation for sipuleucel-T was withdrawn on 19 May 2015	
TA316[7]	Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen'	Recommended July 2012: Enzalutamide is recommended within its marketing authorisation as an option for treating hormone-relapsed metastatic prostate cancer in adults whose disease has progressed during or after docetaxel-containing chemotherapy, only if the manufacturer provides enzalutamide with the discount agreed in the Patient Access Scheme.	Patients who had received 1 course of cytotoxic chemotherapy and in a separate analysis, patients who had received 2 or more courses of cytotoxic chemotherapy
TA259[6]	Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen'	Recommended June 2012: Abiraterone in combination with prednisone or prednisolone is recommended as an option for the treatment of castration-resistant metastatic prostate cancer in adults, only if: • their disease has progressed on or after one docetaxel-containing chemotherapy regimen, and • the manufacturer provides abiraterone with the discount agreed in the Patient Access Scheme.	A subgroup of the COU-AA-301 trial who had received one prior chemotherapy
TA255[4]	Cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen	Not recommended 2012. The Committee agreed that cabazitaxel was an effective, life-extending treatment but the Committee concluded that the additional weight that would need to be assigned to the QALY benefits would be too great to justify it as an appropriate use of limited NHS resources	Patients in TROPIC who received at least 225 mg/m^2 of docetaxel and had an ECOG performance score of 0 or 1.
TA101	Docetaxel for the treatment of hormone-refractory metastatic prostate cancer'	Recommended with the agreed confidential discount, June 2006 • Docetaxel is recommended, within its licensed indications, as a treatment option for men with hormone-refractory metastatic	None

Ref.	Indication	Recommendation	Subgroups addressed
		prostate cancer only if their Karnofsky performance-status score is 60% or more. • It is recommended that treatment with docetaxel should be stopped: - at the completion of planned treatment of up to 10 cycles, or - if severe adverse events occur, or - in the presence of progression of disease as evidenced by clinical or l laboratory criteria, or by imaging studies. • Repeat cycles of treatment with docetaxel are not recommended if the disease recurs after completion of the planned course of chemotherapy.	

3.6 Other clinical guidelines and national policies.

In the absence of current NICE guidance in the pre-docetaxel setting, hormonal therapies are funded through the CDF. However, there is recognition that cross-resistance between the advanced hormone therapies is likely and funding should be limited to a single course of which ever agent is deemed appropriate for the patient. Cabazitaxel is positioned for use according to its licence in the post-docetaxel setting. Table 12.

Table 12. National CDF listing

Ref.	Product	Indication	CDF criteria for NHS use
CABA1_V3.0	Cabazitaxel	Castrate-resistant Metastatic Prostate Cancer	1. Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy 2. Castrate-resistant Metastatic Prostate Cancer 3. Previous treatment with docetaxel based regimens
ENZ_V1.1	Enzalutamide	Chemotherapy naïve castrate-resistant Metastatic Prostate Cancer	1. Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy 2. a. Histologically/ cytologically confirmed adenocarcimoma of the prostate OR b. Clinical suspicion of prostate cancer is high due to high PSA value (>100ng/ml) and evidence of bone metastases (identified by a positive isotope bone scan or sclerotic metastases on plain radiographs) 3. Documented metastatic disease 4. Progressive disease despite the continued use of LHRH analogues or a previous bilateral orchidectomy 5. No previous chemotherapy for metastatic disease 6. Performance status 0 or 1 7. Asymptomatic (0 or 1) or mildly symptomatic (2-3) as scored on the Brief Pain Inventory Short Form question 3 8. No previous treatment with abiraterone unless abiraterone has had to be stopped within 3 months of its start solely as a consequence of dose-limiting toxicity and in the clear absence of disease progression
ABI1_V2.1	Abiraterone	Metastatic castration resistant prostate cancer	1. Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy 2. a. Histologically/ cytologically confirmed adenocarcimoma of the prostate OR b. Clinical suspicion of prostate cancer is high due to high PSA value (>100ng/ml) and evidence of bone metastases (identified by a positive isotope bone scan or sclerotic metastases on plain radiographs) 3. Documented metastatic disease 4. Either PSA progression according to Prostate Cancer Clinical Trials Working Party Group 2 criteria or radiographic progression

Ref.	Product	Indication	CDF criteria for NHS use
			5. Continuing androgen deprivation 6. Performance status 0 or 1 7. Asymptomatic (0 or 1) or mildly symptomatic (2-3) as scored on the Brief Pain Inventory Short Form question 3 8. No visceral disease 9. No previous chemotherapy 10. No previous treatment with enzalutamide unless enzalutamide has had to be stopped within 3 months of its start solely as a consequence of dose-limiting toxicity and in the clear absence of disease progression

NHS commissioning documents, SSC1438 and SSC1439 for abiraterone and enzalutamide respectively, recognise that abiraterone post enzalutamide (or vice versa) is not to be funded in England unless the alternative was stopped solely because of dose-limiting toxicities within 3 months and there is clear absence of disease progression. In line with this the Cancer Drugs Fund has stated that the sequential use of these agents will not be funded in the pre-chemotherapy setting with the same caveat as above.

Despite the relatively recent granting of the marketing authorisations for the advanced hormonal agents before docetaxel there is a body of growing evidence for effectiveness in this indication beyond the pivotal clinical trials (COU-AA-302[39] and PREVAIL[40]). This is reflected in the guidelines under development including NICE appraisals. This is the predominant positioning for these agents in UK clinical practice with 68% of patients[5] receiving these agents through the CDF ahead of docetaxel.

Key European guidelines are summarised in Table 13 overleaf.

Table 13. Key European guidelines for the treatment of mCRPC

Date	Title	Recommendation
American Society of Clinical Oncology[41]		
2014	Systemic Therapy in Men with Metastatic Castration-Resistant Prostate Cancer (CRPC): American Society of Clinical Oncology and Cancer Care Ontario Clinical Practice Guideline	• Continue androgen deprivation (pharmaceutical or surgical) indefinitely. Abiraterone acetate/prednisone, enzalutamide, or radium-223 should be offered; docetaxel/prednisone should also be offered accompanied by discussion of toxicity risk. Sipuleucel-T may be offered to asymptomatic/minimally symptomatic men. • For men who have progressed on docetaxel, cabazitaxel may be offered, accompanied by discussion of toxicity risk. Mitoxantrone may be offered, accompanied by discussion of limited clinical benefit and toxicity risk There is insufficient evidence evaluating optimal sequences or combinations of therapies. Palliative care should be offered to all patients
European Society of Medical Oncology[42]		
2015	Prostate cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up	**Recommendations (Level of evidence, grade of recommendation)** **Chemotherapy naive** • Abiraterone or enzalutamide are recommended for asymptomatic/mildly symptomatic men with chemotherapy-naïvemetastatic CRPC [I, A]. • Radium-223 is recommended for men with bone-predominant, symptomatic metastatic CRPC without visceral metastases [I, A]. • Docetaxel is recommended for men with metastatic CRPC [I, A]. • Sipuleucel-T is an option in asymptomatic/mildly symptomatic patients with chemotherapy-naïve metastatic CRPC [II, B]. The optimal sequence or combination of these agents (abiraterone,enzalutamide, radium-223, docetaxel and Sipuleucel-T) is unknown. In practice, sequencing decisions will be made in the light of the distribution, extent and pace of disease, co-morbidities, patient preferences and drug availability. **Post docetaxel** • In patients with metastatic CRPC in the post-docetaxel setting, abiraterone, enzalutamide, cabazitaxel and radium-223 (in those without visceral disease) are recommended options (1, A).
National Comprehensive Cancer Network		
2015	NCCN clinical practice guidelines in oncology on prostate	Docetaxel in combination with prednisone is recommended as first-line chemotherapy for patients with mCRPC

	cancer, v 1.2015	No consensus exists for the best additional therapy for mCRPC patients after docetaxel failure. Options include abiraterone, enzalutamide, radium-223 for bone-predominant disease without visceral metastases, cabazitaxel with prednisolone, spiuleucel-T if asymptomatic or minimally symptomatic and without visceral or liver metastases, clinical trial, docetaxel challenge, alternative chemotherapy (mitoxantrone) and secondary ADT. All patients should receive best supportive care.
European Association of Urology[21]		
2015	EAU guidelines on prostate cancer	**Recommendations (Level of evidence, grade of recommendation)** • Patients with mCRPC should be counselled, managed and treated by a multidisciplinary team. (3, A) • In non-metastatic CRPC, cytotoxic therapy should only be used in a clinical trial setting. (3, B) • Prior to treatment, the potential benefits of second-line therapy and expected side effects should be discussed with the patient. (N/A, C) • In patients with metastatic CRPC who are candidates for salvage cytotoxic therapy, docetaxel at 75 mg/m^2 every 3 weeks has shown a significant survival benefit. (1a, A) • Docetaxel chemotherapy improves HRQL and provides pain relief for men with symptomatic bone metastases due to mCRPC. (1a, A) • In patients with relapse following salvage docetaxel chemotherapy, cabazitaxel, abiraterone and enzalutamide are regarded as first-choice options for second-line treatment in mCRPC. (1a, A) • In men with mCRPC with symptomatic bone metastases, who are ineligible for or progressing after docetaxel, treatment with Ra 223 (alpharadin) has shown a survival benefit. (1b, A)
Scottish Intercollegiate Guidelines Network (SIGN)		
None identified		

The guidelines and associated literature consistently state that patients require options after progression on docetaxel and that there can be no single approach to treatment.

The primary literature is beginning to address the question of patient sub-groups who may benefit the most from the different available therapeutic options and biomarkers to predict response, but this information remains dispersed and yet to be synthesised into guidelines. For example a recent review by Fernandez[19] on identifying potential cabazitaxel patients addresses patient factors and Crawford reviews on predictors of response / relevant biomarkers.[43] These may include ECOG-PS, extent of metastases, duration of previous hormonal therapy, pain, rising PSA levels and time since last docetaxel dose. The

sequencing of advanced hormonal agents has been summarised in Section 3.3 and is discussed in more detail in Section 4.11.11.

3.7 Describe any issues relating to current clinical practice, including any variations or uncertainty about established practice.

There are a number of issues relating to current clinical practice and the availability of new medicines which, taken together with new discoveries about the cellular mechanisms and natural history of prostate cancer which signals change in thinking about the management of prostate cancer in general and metastatic castrate resistant prostate cancer (mCRCP) in particular.

Epidemiology and change in life expectancy.

Historically prostate cancer has been thought of as a hormone sensitive disease which patients die with rather than die of. However, when this concept was first suggested in 1997[44] life expectancy of men in the UK was 74 years whereas the average age at death for patients with prostate cancer was 77 years. Now according to the UK's OPCS the average age at death for men in the UK is 85 years. But the age at diagnosis of prostate cancer has probably not changed since the last century or has got earlier due to the success of screening and disease awareness programmes. Survival data from clinical trials in mCRCP suggest that many men now die of treatment resistant prostate cancer. As a result there is a growing awareness of the need for new treatments and better use of existing treatments either in terms of timing, sequencing or combination therapy or in terms of new mechanisms of action to overcome treatment resistance to existing medicines.

Drug, tumour and patient specific issues.

Prostate cancer is a heterogeneous disease. Some patients have more indolent disease and some have highly aggressive disease, the latter group being overrepresented in the mortality data. These patients also show variation in sensitivity to hormone therapy and also the speed at which hormone resistant disease becomes the predominant phenotype within the cancer. Hence as the disease progresses in a given patient the pattern of drug sensitivity and drug resistance changes [45] Such variations require different treatments and clinical approaches.

To demonstrate this oncologists in the UK are prescribing 13 drugs for prostate cancer but while they have 11 options which manipulate the androgen environment of prostate cancers they have only 2 licensed therapies which have cytotoxic modes of action (docetaxel and cabazitaxel) of which only one of (docetaxel) is currently approved by NICE and available for use in NHS England. Mitoxantrone has been used off-label in this setting but has been largely replaced.

3.8 Equity and equality

The risk for certain groups of people in the UK is higher than others. Prostate cancer is most prevalent in black men. A recent study estimating the lifetime risk over the period 2008 - 2010 for a man being diagnosed with prostate cancer in the UK by major ethnic group

suggests that approximately 1 in 4 (29.3%; 23.5–37.2%) black men will get prostate cancer at some point in their lives compared with approximately1 in 8 white men (13.3 %; 13.2–15.0%) [46, 47] The lifetime risk for Asian men was lower at approximately 1 in 13 (7.9%; 6.3 – 10.5%). Lifetime risk of dying from prostate cancer was estimated at 1 in 12; (8.7%; 7.6 - 10.6%) for black men, 1 in 24 (4.2%; 4.2 - 4.7%) for white men and 1 in 44 (2.3%; 1.9 - 3.0%,) for Asian men. This suggests that once diagnosed the risk of dying is about one third for all ethnicities but that proportionally more black men will die of the disease.

In the last few years attempts have been made by several charities and patient interest groups to raise the awareness of prostate cancer in the general and ethnic minority populations. The aim of these disease awareness programmes is to encourage men to present for screening tests so that early diagnosis can occur with the hope of improving treatment outcomes.

4. Clinical effectiveness

- The clinical effectiveness of cabazitaxel was established in the pivotal TROPIC study
  - Mean OS: 18.6 months for cabazitaxel and 14.5 months for mitoxantrone.
- Estimated mean incremental OS is consistently greater than 3.5 months irrespective of the parameterisation used for extrapolation (3.6 to 8.1 months).
- The Early Access Programme in the UK demonstrated that Health Related Quality of Life was maintained and even slightly improved whilst taking cabazitaxel.
- The safety profile of cabazitaxel has been shown to be more favourable in clinical practice than in the trial setting and this may be due to improvements in the early identification and management of adverse events.
- Network meta-analysis to compare outcomes for cabazitaxel with abiraterone and enzalutamide is challenging due to differences in patient characteristics, the PFS endpoint in the studies and consequent stopping rules along with the necessary assumption of equivalent efficacy for the control arms.
- Despite these issues overall survival is shown to be similar for cabazitaxel, abiraterone and enzalutamide
- Data from the real world shows that efficacy is maintained in whatever sequence cabazitaxel in used with the advanced hormonal agents.

4.1 Identification and selection of relevant studies

The following section describes the searches carried out for the original submission TA255. This is followed by a description of the updated search in Section 4.1.1 – 5.

Three searches were developed for the submission which informed TA255 for cabazitaxel in 2011.[4]

- The objective of the first search was to identify all studies of cabazitaxel versus any comparator, to identify the complete evidence base for cabazitaxel.
- The objective of the second search was to identify all randomised controlled trials (RCTs) in second-line metastatic hormone-resistant prostate cancer (mCRPC) (patients progressed after first-line docetaxel). This was done to identify any additional RCT evidence for comparators within the NICE scope that were not picked up by the first search (which would only pick up head-to-head evidence versus cabazitaxel).

- The objective of the third search was to identify all non-randomised studies in second-line mCRPC (post-docetaxel). This was done to identify any non-randomised evidence for cabazitaxel or comparators within the NICE scope that could potentially be relevant to the decision problem.

These searches were carried out in MEDLINE, MEDLINE In-Process, EMBASE and the Cochrane Library for the period January 1st 2000 to December 31st 2010. A full description of the strategy and results are provided in Appendix 3 (searches 1 and 2) and Appendix 4 (Search 3).

In summary the three literature reviews identified the following number of studies:

- The systematic review of studies of cabazitaxel identified one RCT sponsored by Sanofi-Aventis which met the criteria for inclusion. This was the TROPIC trial described in four publications.[48-51]
- The broader systematic review of all RCTs in second-line mCRPC identified seven trials published in 18 publications and as expected one of which was the TROPIC study. These studies are summarised in Table 14 overleaf.
- The review of non-randomised studies identified 40 studies published in 61 publications. These studies are described in Appendix 4.

Table 14. RCTs identified in the original literature review carried out for TA255 in second-line mCRPC (post-docetaxel).

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref	Study conclusion
EFC6193 (TROPIC) (NCT00417079)	Cabazitaxel plus prednisone or prednisolone	Mitoxantrone plus prednisone or prednisolone	Patients with mCRPC and disease progression during or after treatment with a regimen containing docetaxel	de Bono 2010[8]	Cabazitaxel provided significantly improved overall survival versus mitoxantrone (median improvement15.1 vs. 12.7 (HR 0.72: 95% CI 0.61 - 0.84)
COU-AA-301	Abiraterone acetate plus prednisone	Prednisone	Patients with mCRPC progressed after docetaxel	de Bono 2011[52]	Abiraterone produced a significant improvement in OS and PFS in comparison with prednisone alone
The SPARC trial	Satraplatin + prednisone	Prednisone	Patients with mCRPC progressed after docetaxel	Sternberg 2009[53], Witjes 2009,[54] Sartor 2008,[55]	Satraplatin did not improve OS, but did improve PFS, in comparison with prednisone
Saad 2009	Docetaxel + prednisone + custirsen	Mitoxantrone + prednisone + custirsen	Patients with mCRPC progressed after docetaxel	Saad 2008,[56] Saad 2011[57]	No statistical comparisons were reported; the authors reported both regimens were well tolerated and associated with better-than-expected survival
De Bono 2010	CNTO 328 + mitoxantrone	Mitoxantrone	Patients with mCRPC progressed after docetaxel	De Bono 2010[58]	CNTO 328 plus mitoxantrone did not improve OS, and enrolment was terminated after an interim analysis
Fleming 2010	Cetuximab + mitoxantrone + prednisone	Mitoxantrone + prednisone	Patients with mCRPC progressed after docetaxel	Fleming 2010[59]	Cetuximab plus mitoxantrone did not improve survival compared with mitoxantone alone and is not recommended for further study
Rosenberg 2007	Ixabepilone	Mitoxantrone + prednisone	Patients with mCRPC progressed after docetaxel	Rosenberg 2007[60]	Ixabepilone and mitoxantrone plus prednisone showed similar modest activity in docetaxel-refractory mCRPC

TROPIC[8] and COU-AA-301[11] are pertinent to the decision problem and as outlined below these studies were also identified in the updated literature search. Mitoxantrone was identified in the last four entries in Table 14, but as direct head-to-head evidence exists from TROPIC it is not necessary to include these small studies in a network for comparative purposes. The other chemotherapies for which RCT data were available in 2010 include satraplatin, which failed to demonstrate an OS benefit, docetaxel in combination with curtirsen and ixabepilone. Hence the final five studies presented in Table 14 are not discussed further because they do not provide data relevant to the decision problem.

A new search was carried out to identify efficacy and safety data from relevant randomized, controlled clinical trials of cabazitaxel and its comparators in patients with metastatic hormone-refractory prostate cancer (mCRPC) or metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel. In particular, this aimed to identify any evidence that may exist for comparators that have not been directly compared with cabazitaxel. This search is described in the following sections (4.1.2 to 4.2.2).

The update to the search to identify non-randomised evidence is presented in Section 4.11. Sanofi internal projects were also examined for relevant information.

4.1.1. Search strategy developed to identify relevant studies for cabazitaxel.

The following sections describe the search carried out to update the original systematic literature review described above.

In order to identify additional studies beyond those presented in Table 14 reporting data on the clinical effectiveness and safety of current interventions for patients with mCRPC or mCRPC previously treated with docetaxel, a systematic literature review covering the period from January 2010 to February 2015 was performed. The review was an adapted update of the systematic review conducted in 2010 and used similar search terms and sources. A full list of the search terms is provided in Appendix 4.

4.1.2 Description of the search strategies used to retrieve relevant clinical data.

A range of databases indexing published research were searched for studies about the clinical effectiveness and safety of cabazitaxel for people with mCRPC (defined as this or as metastatic castration-resistant prostate cancer [mCRPC]) who have progressed following treatment with docetaxel. The databases searched were Embase, MEDLINE (including MEDLINE In-Process) and the Cochrane Library in line with NICE methodological guidelines. Although the electronic databases contain information from a number of relevant conferences, these searches were supplemented by an electronic review of abstracts from several congresses, including:

- American Society of Clinical Oncology (ASCO)
- ASCO-Genitourinary (ASCO-GU)
- European Society for Medical Oncology (ESMO)

- American Urological Association (AUA)
- American Association for Cancer Research (AACR)
- European Association of Urology (EAU)
- Société Internationale d'Urologie (SIU)

English and non-English language studies were included and full details of the search strategies, databases and resources searched are provided in Appendix 4.

In order to be included in the systematic review, studies had to meet the inclusion criteria detailed in Section 4.1.3; Table 15. Similarly the exclusion criteria checklist is provided in

Table 16. This process was fully compliant with the 2009 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines for the reporting of systematic reviews and meta-analyses.[61]

4.1.3 Inclusion and exclusion selection criteria, language restrictions and the study selection process.

The inclusion and exclusion criteria along with justifications are presented in Table 15 and Table 16 respectively.

Table 15. Inclusion criteria (PICOS framework) used in search strategies

PICOS	Description	Rationale
Population	• mCRPC/mCRPC patients • Age: Adults (≥18 years) • Race: Any • Line of therapy: Second-line or later • Prior therapy: Previously treated with docetaxel-based regimen	• The patient population has been restricted to match the stated decision problem for the treatment of mCRPC/mCRPC in patients who have been treated with docetaxel in any previous regimen • Because prostate cancer is a disease affecting older adult men, studies including children or adolescents were excluded
Interventions	The following treatments for mCRPC/mCRPC used in the second line or later: • Jevtana (cabazitaxel) • Zytiga (abiraterone) • Xtandi (enzalutamide) • Novantrone (mitoxantrone) • Yervoy (ipilimumab) • Xofigo (radium-223) • Provenge (sipuleucel-T) • Emcyt (estramustine)	• Investigational agents used for the treatment of mCRPC/mCRPC following a previous docetaxel regimen are of interest for the review • 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

PICOS	Description	Rationale
Comparator	No limitation on comparator	• Any agent used for the treatment of mCRPC/mCRPC after a previous docetaxel regimen is of interest for the review as a comparator, thus the list was not limited • Comparators may include placebo, any chemotherapy, surgery, radiotherapy, and BSC
Outcomes	• OS • 1-year survival • PFS • TTP • Complete response • Partial response • Overall response • SREs • PSA response • TTPSA • Time to opiate use • TTPP • Safety/AEs • HRQL • Resource utilization	• These outcomes were chosen because they are well-established outcomes to assess efficacy and safety in oncology research and are frequently measured and reported in trials of mCRPC/mCRPC
Study design	RCTs with any blinding status in phases beyond Phase I	• The design of RCTs allow for selection bias to be minimized and allow for an assessment the relative efficacy of interventions through meta-analysis and/or indirect treatment comparison • To enhance the level of evidence, studies with double-blind, single-blind, and open-label design were included
Publication timeframe	• Publication timeframe: o From 2010 to present o Conference abstracts 2011–2015	• Publications from 2010 were included to identify studies not captured in a previous systematic review • Many congresses that took place in 2010 were searched as part of the previous review and it was assumed that data from any 2010 conferences that were not previously identified would likely be superseded by a full publication by 2015
Publication status	Published, unpublished and grey literature (for example, conference	To capture all published literature

PICOS	Description	Rationale
	abstracts) were eligible for inclusion	
Language restrictions	There was no language limitation	To capture all published literature
AEs, adverse events; BSC, best supportive care; HRQL, health-related quality of life; mCRPC, metastatic castration-resistant prostate cancer; mCRPC, metastatic hormone-refractory prostate cancer; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen; RCT, randomized controlled trial; SREs, skeletal-related events; TTP, time to disease progression; TTPP, time to pain progression; TTPSA, time to PSA progression.		

Table 16. Exclusion criteria checklist

Exclusion criteria	Rationale

• Non-mCRPC/non-mCRPC populations
  o No mCRPC/mCRPC subgroup analysis
  o Metastatic disease unclear
• Patients not pretreated with a docetaxel-based regimen
  o No docetaxel-pretreated subgroup analysis
  o Docetaxel pretreatment unclear
  o Line of therapy unclear
• Study population aged <18 years
• Study does not examine an intervention of interest
• Study does not include any outcomes of interest
• Phase I RCTs
• Study design is not an RCT (eg, nonrandomized controlled clinical trials, single-arm studies/uncontrolled trials, observational studies, letters, case reports)
• Published before 2010
	• Studies with no subgroup data for the disease (mCRPC/mCRPC), disease stage (metastatic), and prior treatment (docetaxel-treated) were not included to avoid introducing heterogeneity
	• Non-randomized evidence including case studies/series/reports were excluded as they are poor-quality evidence

mCRPC, metastatic castration-resistant prostate cancer; mCRPC, metastatic hormone-refractory prostate cancer; RCT, randomized controlled trial.	

Two reviewers screened articles for inclusion; any disputes were resolved through discussion between reviewers or consultation with a third reviewer. All publications that met the inclusion criteria, based on titles and abstracts, were obtained as full documents and reassessed against the inclusion criteria by the same reviewers.

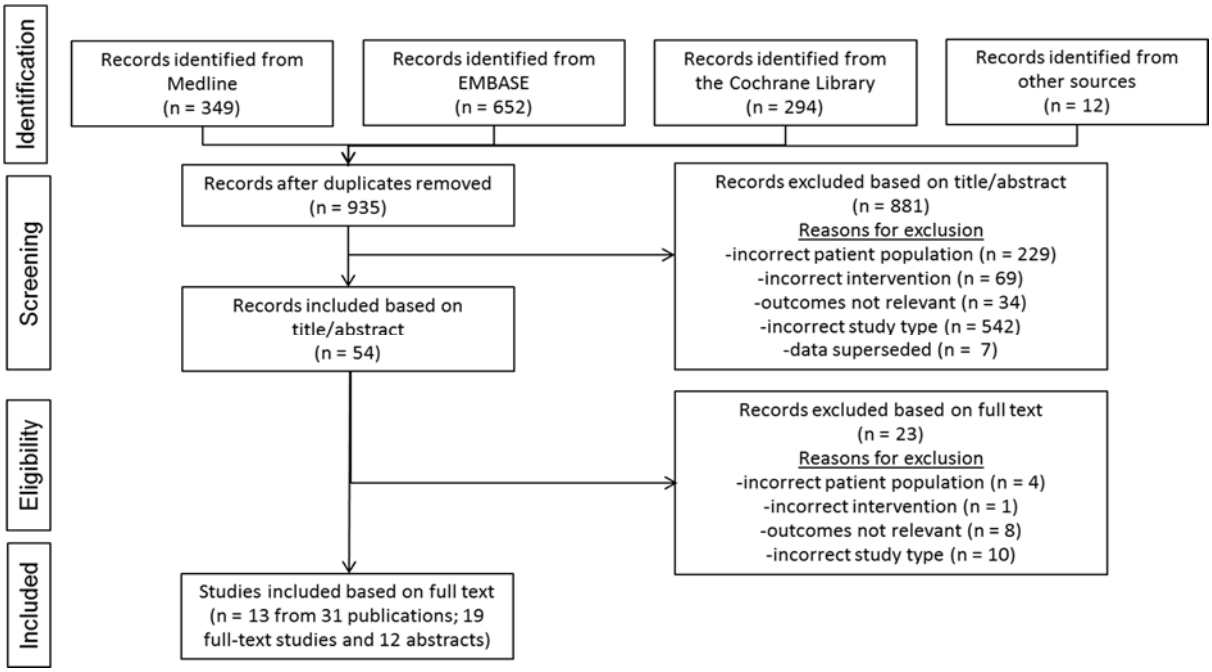
Data from relevant articles were subsequently extracted in parallel by two independent reviewers based on the extraction grid detailed in Appendix 4. Both sets of extracted data were compared and combined into a final data extraction table, which was subsequently verified for the accuracy of all content by an independent third reviewer.

Where multiple publications were identified for the same trial, the novel data reported in each publication were extracted separately.

4.1.4. Flow diagram of the numbers of studies included and excluded at each stage.

Studies were included or excluded according to the criteria described in Table 15 and Table 16. A flow diagram of the studies included and excluded at each stage is provided in Figure 4.

Figure 4. PRISMA flow diagram for the systematic literature review.



The database searches were run on 26 February 2015 and the supplementary abstract search was run on 8 March 2015.

In total, 935 unique records were identified for screening, which included 923 database search results and 12 congress abstracts. After screening 54 records were retained for full text review and of these 24 were excluded leaving a total of 30 articles. From this a total of 13 studies were identified for inclusion in the systematic review. The list of all articles obtained for full text review is provided in Table 17.

Table 17. List of articles retained for full text review with reason for exclusion if applicable

No.	Publication	Excluded?	Reason for exclusion
Included full papers			

No.	Publication	Excluded?	Reason for exclusion
1	Bahl, A., 2013[9]	INCLUDE	
2	Cella, D., 2015[62]	INCLUDE	
3	De Bono, J. S., 2011[52]	INCLUDE	
4	De Bono, J. S., 2010[8]	INCLUDE	
5	Fizazi, K., 2014[63]	INCLUDE	
6	Fizazi, K., 2012[11]	INCLUDE	
7	Fizazi, K., 2012[64]	INCLUDE	
8	Fleming, M. T., 2012[65]	INCLUDE	
9	Halabi, S., 2013[66]	INCLUDE	
10	Harland, S., 2013[67]	INCLUDE	
11	Hoskin, P., 2014[68]	INCLUDE	
12	Joly, F., 2015[69]	INCLUDE	
13	Kwon, E. D., 2014[70]	INCLUDE	
14	Logothetis, C. , 2012[71]	INCLUDE	
15	Ryan, C. J., 2013[72]	INCLUDE	
16	Saad, F., 2011[57]	INCLUDE	
17	Sartor, O., 2014[73]	INCLUDE	
18	Scher, H. I., 2012[10]	INCLUDE	
19	Sternberg, C. N., 2013[74]	INCLUDE	
Included abstracts			
20	Oudard, S., 2011[51]	INCLUDE	
21	Tombal, B., 2011[75]	INCLUDE	
22	Hao, Y., 2013[76]	INCLUDE	
23	Miller, K., 2013[77]	INCLUDE	
24	Scher, H., 2013[78]	INCLUDE	
25	Cislo, P., 2015[79]	INCLUDE	
26	Logue, J., 2014[80]	INCLUDE	
27	Nilsson, S., 2014[81]	INCLUDE	
28	Fizazi, K., 2014[82]	INCLUDE	
29	Hussain, M., 2012[83]	INCLUDE	
30	Basch, E.M., 2015[84]	INCLUDE	
31	Dawson, N.A., 2011[85]	INCLUDE	
Excluded articles			
32	No author listed. Cancer Discov. 2011 ec;1(7):OF1. doi: 10.1158/2159-8290.CD-NB111711OL-09. Epub 2011 Nov 17	EXCLUDE	Incorrect study type
33	Abraham, J., 2013[86]	EXCLUDE	Incorrect study type
34	Aggarwal, R., 2013[87]	EXCLUDE	Incorrect intervention
35	Amato, R., 2013[88]	EXCLUDE	Incorrect study type
36	Beer, T. M., 2011[89]	EXCLUDE	Incorrect patient population
37	Beer, T. M., 2013[90]	EXCLUDE	Incorrect patient population
38	Blumenstein, B., 2013[91]	EXCLUDE	Incorrect study type
39	Bono, J. S., 2014[92]	EXCLUDE	Outcomes not relevant
40	Buonerba, C., 2014[93]	EXCLUDE	Incorrect study type
41	Danila, D. C., 2011[94]	EXCLUDE	Incorrect study type
42	Di Lorenzo, G., 2011[95]	EXCLUDE	Incorrect study type

No.	Publication	Excluded?	Reason for exclusion
43	Goodman, O. B., 2014[96]	EXCLUDE	Outcomes not relevant
44	Jana, B. R. P., 2010[97]	EXCLUDE	Incorrect study type
45	Kantoff, P. W., 2010[98]	EXCLUDE	Incorrect patient population
46	Merseburger, A. S., 2015[99]	EXCLUDE	Outcomes not relevant
47	Mulders, P. F. , 2014[100]	EXCLUDE	Outcomes not relevant
48	Nilsson, S., 2013[81]	EXCLUDE	Incorrect patient population
49	Reid, A. H. M., 2010[101]	EXCLUDE	Incorrect study type
50	Ryan, C. J., 2013[102]	EXCLUDE	Outcomes not relevant
51	Ryan, C. J., 2014[103]	EXCLUDE	Outcomes not relevant
52	Saad, F., 2015[104]	EXCLUDE	Outcomes not relevant
53	Sternberg, C. N., 2014[105]	EXCLUDE	Outcomes not relevant
54	Thomsen, F. B., 2014[106]	EXCLUDE	Incorrect study type

4.1.5. Data sources for the trials considered in the analysis.

TROPIC (cabazitaxel vs. mitoxantrone)

In the systematic review of studies one Phase III RCT sponsored by Sanofi-Aventis evaluating the efficacy and safety of cabazitaxel + prednisolone vs. mitoxantrone + prednisolone, the TROPIC trial, was identified. The data presented in this submission have been drawn from the following sources:

- De Bono, J.S., et al., Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: A randomised open-label trial.[8]
- Bahl, A., et al., Impact of cabazitaxel on 2-year survival and palliation of tumour-related pain in men with metastatic castration-resistant prostate cancer treated in the tropic trial.[9]

The 2013 paper by Bahl et al. presents the updated analysis for TROPIC which includes patient follow-up until March 10th 2010.[9] The original publication from 2010 presented data until the cut-off at September 25th, 2009.[8] The primary study reference is the article by Bahl, 2013 from which data have been extracted for this appraisal; additional data were extracted from the clinical study report and de Bono, 2010 where necessary.

In addition to the TROPIC study COU-AA-301 and AFFIRM are included for the purposes of the scenario Indirect Treatment Comparison (ITC) outlined in detail in Appendices B. The studies identified in the literature search are listed below.

COU-AA-301 (abiraterone acetate vs. placebo)

In the systematic review of studies one Phase III RCT sponsored by Jansen evaluating the efficacy and safety of abiraterone acetate + prednisone vs. placebo + prednisone, the COU-AA-301 trial, was identified. The data presented in this submission have been drawn from the following sources:

- De Bono, J.S., et al., Abiraterone and increased survival in metastatic prostate cancer.[52]
- Fizazi, K., et al., Abiraterone acetate for treatment of metastatic castration-resistant[11]

AFFIRM (enzalutamide vs. placebo)

In the systematic review of studies one Phase III RCT sponsored by Astellas evaluating the efficacy and safety of enzalutamide vs. placebo, the AFFIRM trial, was identified. The data presented in this submission have been drawn from the following source

- Scher, H.I., et al., Increased survival with enzalutamide in prostate cancer after chemotherapy.[10]

4.1.6. Reference list for excluded studies.

Excluded studies have been tabulated in Section 4.1.4; Table 17 above.

4.2 List of relevant randomised controlled trials

TROPIC, which compared cabazitaxel to mitoxatrone was the only identified published RCT of and is described in detail below. In the context of the decision problem the comparison with mitoxantrone is valid as this is considered to be equivalent to best supportive care.

4.2.1. List of relevant RCTs comparing cabazitaxel with other therapies (including placebo) in the mCRPC patients.

The comparator, population and study reference for TROPIC are provided in Table 18. In addition the ongoing Phase III trial PROSELICA is listed as the results from this study may become available within the timeframe for this submission and if possible will form the basis for an addendum presented after the full dossier. PROSELICA aims to demonstrate the non-inferiority in OS of cabazitaxel 20 mg/m² vs. 25 mg/m² in in patients with mCRPC previously treated with a docetaxel-containing regimen.

Table 18. List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study reference
EFC6193 NCT00417079 (TROPIC)	Cabazitaxel 25 mg/m^2 plus prednisone or prednisolone	Mitoxantrone plus prednisone or prednisolone	n = 755 Patients with mCRPC and disease progression during or after treatment with a regimen containing docetaxel	de Bono 2010[8] Bahl, 2013[9]
NCT01308580 PROSELICA	Cabazitaxel 25 mg/m^2 plus prednisone or	Cabazitaxel 20 mg/m^2 plus prednisone or	n = ~1200 Patients with mCRPC and disease progression	TBC

	prednisolone	prednisolone	during or after treatment with a regimen containing docetaxel	

The comparators outlined in the decision problem include best supportive care, abiraterone, enzalutamide and mitoxantrone (Section 1.1).

Use of mitoxantrone has declined but may increase again if provision for cabazitaxel were not there. This was recognised in the response to the scope by the British Uro-oncology Group (BUG). Mitoxantrone was used as an active comparator in the TROPIC study. Mitoxantrone has been shown to contribute to palliation but not overall survival.[2] It is therefore considered to be a proxy for Best Supportive Care in this submission. This was recognised in TA259 for abiraterone where the committee accepted the assumption that overall survival and progression-free survival were the same for patients taking mitoxantrone and patients taking prednisolone and so outcomes with mitoxatrone could be considered equivalent to supportive care. In this submission we compare against mitoxantrone in the base-case and consider this as at least equivalent to best supportive care.

The impact of the newer hormonal therapies on pathways of care has been explored in Section 3.3 and, as highlighted for standard NHS practice (where abiraterone or enzalutamide are used in the pre-docetaxel setting), best supportive care is the only option available to patients.

4.2.2 Justification for the exclusion of other RCT data.

Radium-223 is licensed in a sub-population of mCRPC patients with two or more bone metastases and no visceral metastases and was evaluated in the ALSYMPCA study in comparison to placebo.[107] Radium-223 does not currently have a NICE recommendation and cannot be considered to reflect established practice or the standard of care.

Radium-223 is contraindicated in patients with liver metastases. Eleven percent of patients in TROPIC had liver metastases and this limits the applicability of the TROPIC dataset for indirect comparison with the radium-223 study ALSYMPCA.

For these reasons we do not consider that radium-223 is a primary comparator for cabazitaxel and the ALSYMPCA study has been excluded. It is worth noting that within the NICE ongoing appraisal of radium-223 the key comparators included abiraterone which is considered by physicians to be a choice for patients where cytotoxic therapy post-docetaxel is not considered appropriate.

The RCTs D9902B (IMPACT and supporting trials D9901A and D9901B) examining Sipuleucel-T have been excluded from the analysis as Sipuleucel-T has been withdrawn.

Similarly in line with the previous submission TA255, The SPARC trial (Satraplatin + prednisone vs. placebo + prednisolone), satraplatin + prednisone, CNTO 328, cetuximab and ixabepilone are considered out with the scope for comparison with cabazitaxel.

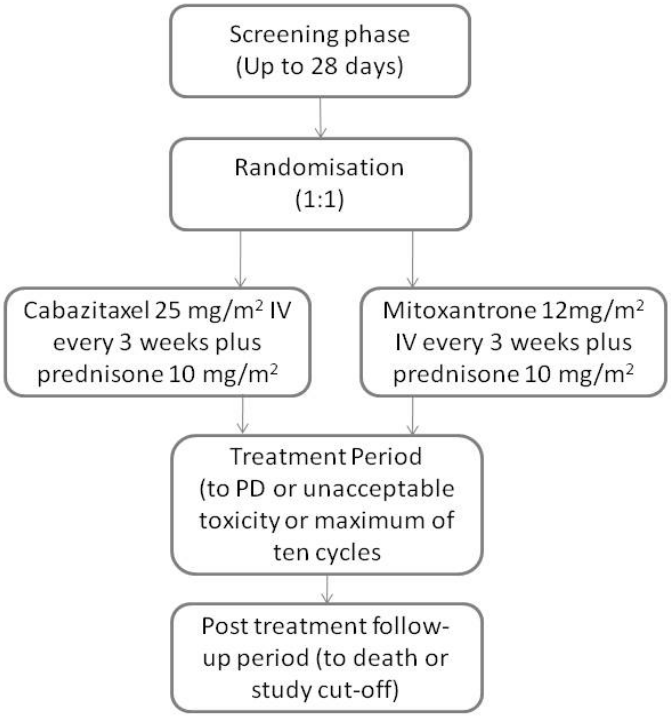
4.3 Summary of methodology of the relevant randomised controlled trials

Brief description of the TROPIC trial design

The TROPIC trial was a Phase III, randomised, open label, multicentre, multinational, comparative study in patients with mCRPC previously treated with a docetaxel-containing regimen.[8]

The primary objective was to determine whether cabazitaxel in combination with prednisone improves overall survival (OS) when compared to mitoxantrone in combination with prednisone.

Figure 5. TROPIC trial: study design



Inclusion criteria

To enter the study, patients had to have:

- Diagnosis of histologically or cytologically proven prostate adenocarcinoma, that was refractory to hormone therapy and previously treated with a docetaxel-containing regimen. Patients had documented progression of disease during or within six months after prior hormone therapy and disease progression during or after docetaxel-containing therapy
- Either measurable or non-measurable disease

- Patients with measurable disease had to have documented progression of disease by RECIST criteria demonstrating at least one visceral or soft tissue metastatic lesion (including new lesions). Lesions had to measure ≥10 mm in the longest diameter (or twice the slice thickness) on spiral CT scan or MRI (chest, abdomen, pelvis) or 20 mm on conventional CT or chest X-ray for biopsy proven, clearly defined lung lesion surrounded by aerated lung.
- Patients with non-measurable disease had to have documented rising PSA levels or appearance of at least one new demonstrable radiographic lesion. Rising PSA was defined as at least two consecutive rises in PSA to be documented over a reference value measured at least a week apart.

- Received prior castration by orchidectomy and/or luteinising hormone-releasing hormone (LHRH) agonist; anti-androgen withdrawal followed by progression had to have taken place at least four weeks (six weeks for bicalutamide) before enrolment.
- Adequate haematological, hepatic, renal and cardiac function; and a left ventricular ejection fraction (LVEF) of more than 50% assessed by multi-gated radionuclide angiography or echocardiogram.
- Life expectancy >2 months.
- ECOG performance status 0 to 2 (that is, patient was to be ambulatory, capable of all self-care, and up and about more than 50% of waking hours).
- Age ≥18 years.
- Inclusion criteria amendment. The criterion to exclude patients who had received a cumulative dose of docetaxel <225 mg/m^2 (the equivalent of three cycles of docetaxel = approximately 12 weeks' treatment) was added after the trial had begun, at a point when 59 patients had been recruited. This amendment was made on the basis of emerging guidelines for patients with mCRPC from the Prostate Cancer Clinical Trials Working Group (PCCTWG), which recommended a protocol-specified minimum exposure of 12 weeks for trials in the pre-chemotherapy or first-line chemotherapy setting, recognising that declines in serum PSA, if they occur, may not do so for several weeks and that a robust PSA-based surrogate for clinical benefit has yet to be identified

Exclusion criteria

- Previous treatment with mitoxantrone.
- Previous treatment with <225 mg/m^2 cumulative dose of docetaxel (in response to emerging guidelines the study protocol was amended for this criterion after study initiation – in total, 59 patients who had received <225 mg/m^2 were enrolled)
- Prior radiotherapy to ≥40% of bone marrow
- Prior surgery, radiation, chemotherapy, or other anti-cancer therapy within four weeks prior to enrolment in the study.
- Active Grade ≥2 peripheral neuropathy, stomatitis or other serious illness, including secondary cancer.
- History of congestive heart failure, myocardial infarction within last six months, uncontrolled cardiac arrhythmias, angina pectoris, and/or hypertension.
- History of severe hypersensitivity reaction (≥Grade 3) to polysorbate 80-containing drugs or prednisone.

- Participation in another clinical trial with any investigational drug within 30 days prior to study enrolment.
- For patients enrolled in the UK, the following exclusion criterion was applicable: Patient with reproductive potential not implementing accepted and effective method of contraception, described in Protocol Amendment 3.

Settings and locations where the data were collected.

This was a multicentre (146 centers) study carried out in 26 countries worldwide (Argentina, Belgium, Brazil, Canada, Chile, Czech Republic, Denmark, Finland, France, Germany, Hungary, India, Italy, Korea, Mexico, Netherlands, Russia, Singapore, Slovakia, South Africa, Spain, Sweden, Taiwan, Turkey, UK, and the USA) 402 (53%) patients were included from European countries. 37 patients (5%, from six centres) were included from the UK

Treatment was carried out in the secondary care setting in units specialising in the administration of cytotoxics.

Duration of the Study

755 patients from 146 centres in 26 countries were randomised between 2 January 2007 and 23 October 2008.[8] At the time of data cut-off (10 March 2010) for the updated analysis with time to death used as the duration of follow-up in patients who died before this date, and survival times censored for surviving patients, the median follow-up was 13.7 months. Alternatively, if deaths were censored and survival times were considered events, the median follow-up for both treatment groups combined was 25.5 months (interquartile range: 20.7–30.0 months). Sixty (15.9%) of 378 patients in the cabazitaxel group and 31 (8.2%) of 377 patients in the mitoxantrone group survived ≥2 years (odds ratio 2.11; 95% CI 1.33–3.33).[9]

Randomisation

Patients were randomised to one of two treatment groups by the interactive voice response system (IVRS) ClinPhone in a 1:1 ratio with stratification by the following factors:

- Measurability of disease per Response Evaluation Criteria in Solid Tumours (RECIST) (measurable versus non-measurable disease)
- ECOG performance status (0 or 1 versus 2).

A dynamic allocation method – method of minimisation – was used to avoid extreme imbalance of treatment assignment within a centre.

Method of blinding

As this was an 'active'-controlled trial and there were differences in administration between treatments, this study was an open label study, so patients and treating physicians were not masked to treatment allocation. The study was conducted under close monitoring from an Independent Data Monitoring Committee (IDMC) with the objective to review trial enrollment, compliance to protocol, safety of the administered treatments, quality of the data and to

conduct analyses on the data. The IDMC included two physicians and a statistician independent from the sponsor.

The study team was blinded to treatment assignments, except for those patients with SAEs reported to pharmacovigilance. To maintain the blinding of the study team, an external contract statistician independent from the sponsor provided unblinded results to the IDMC with the appropriate analyses for assessment.

The interim analyses were conducted and reviewed by the IDMC and the results not disclosed to the sponsor.

Trial drugs and concomitant medications

Cabazitaxel 25 mg/m^2 intravenously (Day 1) over one hour every three weeks, and prednisone 10 mg orally given daily (prednisolone was allowed in countries where prednisone was not commercially available – including the UK). Mitoxantrone 12 mg/m^2 intravenously (Day 1) over 15 to 30 minutes every three weeks, and prednisone 10 mg orally given daily (prednisolone was allowed in countries where prednisone was not commercially available).

Cycle length for both cabazitaxel and mitoxantrone was three weeks. Treatment was continued for a maximum of ten cycles. The ten-cycle maximum was imposed due to the fact that mitoxantrone is associated with cardiotoxicity and that this is increased with cumulative exposure.[2]

Following progression, mitoxantrone patients were not eligible to cross over to cabazitaxel. However, cabazitaxel patients could receive mitoxantrone. As mitoxantrone has not been associated with an effect on survival, it is assumed that this crossover would not affect the survival curves.

Overview of concomitant medications permitted and disallowed during TROPIC.[8]

Premedication, consisting of single intravenous doses of an antihistamine, corticosteroid (dexamethasone 8 mg or equivalent), and histamine H_2 antagonist (except cimetidine), was administered 30 minutes or more before cabazitaxel. Anti-emetic prophylaxis and other supportive care were given at the physician's discretion.

Prophylactic G-CSF was not permitted during the first cycle, but thereafter was permitted at physician's discretion and was mandated for prophylaxis after first occurrence of either neutropenia lasting seven days or more or neutropenia complicated by fever (>38.5°C or >38.1°C x 3 observations during a 24-hour period), or infection.

Concomitant therapy with agents known to have anticancer activity was not permitted during the treatment phase of the study. Treatment with radiotherapy, hormones or chemotherapeutic agents was also not permitted, with the exception of the following: LHRH agonists that were ongoing prior to study entry (without orchidectomy), steroids given for new adrenal failure and hormones administered for non-disease-related conditions (for

example, insulin for diabetes). The use of bisphosphonates was allowed; however, the dose had to be stable for 12 weeks prior to enrolment and during the study treatment period.

Patients were not allowed to take part in any other investigational trials while participating in the treatment phase of the trial.

Timings and assessments

Physical examinations and blood tests were repeated before each infusion of study drug and at the end of treatment. Complete blood counts were performed on Days 1, 8 and 15 of each three-week cycle and repeated as clinically indicated. Patients who progressed or started another anticancer therapy were followed up every three months. Patients who withdrew before disease progression were followed up every six weeks for the first six months and every three months thereafter. Serious adverse events (SAEs) were reported from the signature of informed consent up to 30-days after the last dose of study drug, after which ongoing events were followed until resolution or stabilisation. All AEs considered related to the study treatment were followed until resolution at the end of the study.

Duration of follow-up

Patients were followed until death to the cut-off date for analysis, 25 September 2009 and in the extension period to March 2010.

Patients who progressed or started another anticancer therapy were followed up every three months for a maximum of two years. The patients who discontinued the study treatment prior to documented disease progression and who had not started another anticancer therapy were followed up every six weeks for the first six months of the follow-up period, or until disease progression or start of another anticancer therapy. For the rest of the follow-up period patients were evaluated every three months.

The predefined primary and secondary outcomes in the TROPIC trial are summarised below.

Primary outcomes

The primary efficacy endpoint was Overall Survival (OS). This was defined as the time interval from the date of randomisation to the date of death due to any cause. In the absence of confirmation of death, the survival time was censored at the last date the patient was known to be alive or at the data cut-off date, whichever came first.

Secondary outcomes[8]

- **Progression-free survival** (PFS) was evaluated from the date of randomisation to the date of tumour progression, PSA progression, pain progression (pain progression supported by clinical evidence and/or radiological evidence of disease progression), or death due to any cause, whichever occurred first.

- **Tumour response rate** (TRR) (in patients with measurable disease): objective responses (complete response (CR) and partial response (PR)) for measurable disease as assessed by investigator according to RECIST criteria:
  - CR = disappearance of all target lesions;
  - PR = 30% decrease in the sum of the longest diameter of target lesions;
  - PD = 20% increase in the sum of the longest diameter of target lesions;
  - Stable Disease = small changes that do not meet other criteria).
  - Objective response had to be confirmed by repeat tumour imaging
- **Time to tumour progression (TTP):** Defined as the number of months from the date of randomisation to evidence of progressive disease (PD) based on tumour measurements (RECIST criteria). Patients without PD were censored at their last tumour assessment.
- **PSA progression (assessed in all patients):**
  - In PSA non-responders, progression was defined as a ≥25% increase over nadir (provided that the increase in the absolute value PSA level was at least 5 ng/ml).
  - In PSA responders and in patients not evaluable for PSA response at baseline, progression was defined as a ≥50% increase over the nadir (provided that the increase in the absolute value PSA level was at least 5ng/ml).
- **PSA response (assessed only in patients with baseline PSA ≥20 ng/ml):** Response required a PSA decrease of ≥50% confirmed by a second PSA value at least three weeks later. The duration of PSA response was measured from baseline to the last assessment at which the above criteria were satisfied.
- **Pain progression (assessed in all patients):** Pain was assessed using the Present Pain Intensity (PPI) scale on the McGill-Melzack pain questionnaire. Pain progression (cancer related) was defined as an increase of ≥1 point in the median PPI from its nadir noted on two consecutive three-week-apart visits, or ≥25% increase in the mean analgesic score (AS) compared with the baseline score and noted on two consecutive three-week-apart visits, or requirement for local palliative radiotherapy.
- **Pain response (assessed only in patients with median PPI ≥2 on McGill-Melzack scale and/or mean AS ≥10 points at baseline):** Pain response was defined as a two-point or greater reduction from baseline median PPI with no concomitant increase in AS, or a reduction of at least 50% in analgesic use from baseline mean AS with no concomitant increase in pain. Either criterion had to be maintained for two consecutive evaluations at least three weeks apart.
- **AEs in patients who had received at least one dose of study drug:** AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0,[108] and summarised using Medical Dictionary for Regulatory Activities (MedDRA) version 12.0 terminology. For each AE per patient and per cycle the worst NCI grade was used.
  - In addition adverse event rates were recorded in terms of laboratory test results and also from the perspective of clinical presentation. The rates for AEs with testing positive in the laboratory, particular for the haematological events, were much higher than those recorded by clinicians. The former are reported in the original de Bono publication.

4.3.2. Comparative summary of the methodology of the RCTs.

There is only one pivotal Phase III RCT for cabazitaxel which makes comparison with another treatment (mitoxantrone). This is the TROPIC trial described in Section 4.3.1 and below in Sections 4.4 to 4.8. In addition to this the Phase III RCT, PROSELICA may be pertinent to the decision problem.The PROSELICA methodology is described in detail Section 4.14. If available within the timeframe of this submission the results will form the basis for an addendum presented after the full dossier.

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

4.4.1 Trial populations[8]

There were two analysis populations, ITT and per protocol, defined for the efficacy analysis. The ITT population included all randomised patients (755 patients [n=378 cabazitaxel; n=377 mitoxantrone]); the per protocol population included all patients who received at least one dose of the study treatment (n=371 in each treatment group). The primary analysis of the primary efficacy endpoint was performed using the ITT population. The safety population was the same as the per protocol population and was used to summarise treatment compliance/administration and all clinical safety data.

In general, there was no imputation of missing data. For time to event analyses, missing data were handled based on censoring rules. For categorical data, missing data were reported as missing.

4.4.2 Statistical analysis

Time to event analyses (OS, PFS, TTP, time to PSA progression, and time to pain progression), were compared between the two treatment groups using the log-rank test procedure in the ITT population according to the stratification factors specified at the time of randomisation.

The estimates of the hazard ratio (HR) and corresponding 95% confidence intervals (CIs) were provided using a Cox proportional hazard model stratified by the same stratification factors specified at randomisation. Kaplan–Meier survival curves were generated. The chi square or Fischer's exact test methods were used to compare proportions.[8]

Analyses of AEs, vital signs, ECGs, LVEF and laboratory data were descriptive. For each of the safety parameters, a baseline value was defined as the last value or measurement taken up to the first dose in the study.

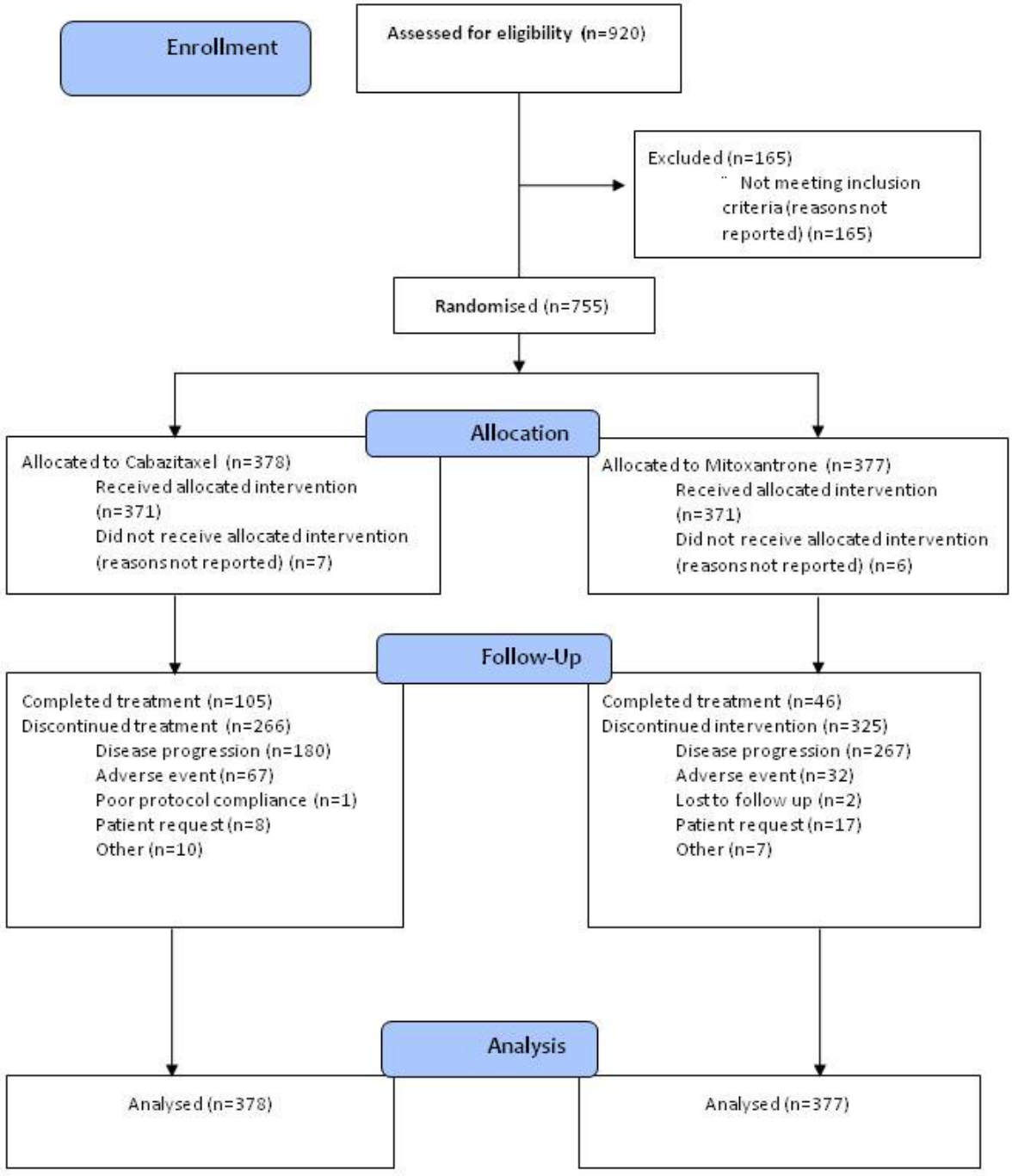
In previously untreated patients with metastatic prostate cancer, OS on mitoxantrone is 12 to 14 months.[109] At the time this study was initiated, no data on OS were available for mitoxantrone-treated patients who progressed following docetaxel treatment in the first-line setting; therefore, a median survival of eight months was assumed for the purpose of sample size calculation in this study.[8]

Assuming the median OS time in the comparator group was eight months, a total of at least 511 deaths in two treatment groups were needed to detect a 25% reduction in hazard rate in the cabazitaxel group relative to the comparator with a power of 90% at a two-sided 5% alpha level. To achieve the targeted number of events, approximately 720 (360 per group) patients needed to be randomised within 24 months for the study and 511 deaths had to be reached after 30 months from the first patient enrolment.[8]

4.5 Participant flow in the relevant randomised controlled trials

4.5.1. Patient numbers in TROPIC

Figure 6. CONSORT participant flow diagram



4.5.2. Baseline patient demographics.

Table 19. Characteristics of participants in the studies across treatment groups in the TROPIC trial.

TROPIC trial Baseline characteristic	Mitoxantrone + prednisone	Cabazitaxel + prednisone
(n=755)	**(n=377)**	**(n=378)**
Age, in years		
Median	67.0	68.0
75 and above	70 (18.6%)	69 (18.3%)
Race		
Caucasian/White	314 (83.3%)	317 (83.9%)
Black	20 (5.3%)	20 (5.3%)
Asian/Oriental	32 (8.5%)	26 (6.9%)
Other	11 (2.9%)	15 (4.0%)
ECOG performance status*		
0 or 1	344 (91.2%)	350 (92.6%)
2	33 (8.8%)	28 (7.4%)
Extent of disease		
Metastatic	356 (94.4%)	364 (96.3%)
Bone metastases	328 (87%)	303 (80%)
Visceral metastases	94(25%)	94 (25%)
Loco regional recurrence	20 (5.3%)	14 (3.7%)
Unknown	1 (0.3%)	0
PSA (in ng/ml)		
Number of patients	370	371
Median (IQR) serum PSA µg/l	127.5 (44.0–419.0)	143.9 (51.1–416.0)
Serum PSA ≥20 µg/l	325 (86%)	329 (87%)
Measurable disease		
Measurable disease	204 (54.1%)	201 (53.2%)
Not measurable disease	173 (45.9%)	177 (46.8%)
Pain at baseline†	168 (45%)	174 (46%)
Previous treatment		
Hormone‡	375 (99%)	375 (99%)
1 chemotherapy regimen	268 (71%)	260 (69%)
2 chemotherapy regimens	79 (21%)	94 (25%)
>2 chemotherapy regimens	30 (8%)	24 (6%)
Radiation	222 (59%)	232 (61%)
Surgery	205 (54%)	198 (52%)
Biological agent	36 (10%)	26 (7%)
Previous docetaxel regimens		
1	327 (87%)	316 (84%)
2	43 (11%)	53 (14%)
>2	7 (2%)	9 (2%)
Median (IQR) total previous docetaxel dose mg/m^2	529.2 (380.9, 787.2)	576.6 (408.4, 761.2)
Median (IQR) months from last dose of docetaxel to disease progression	0.8 (0.0, 3.1)	0.7 (0.0, 2.9)
Disease progression relative to docetaxel		

TROPIC trial Baseline characteristic	Mitoxantrone + prednisone	Cabazitaxel + prednisone
(n=755)	(n=377)	(n=378)
treatment During <3 months from last dose ≥3 months from last dose Unknown	104 (28% 181 (48%) 90 (24%) 2 (1%)	115 (30%) 158 (42%) 102 (27%) 3 (1%)
Key: ECG = echocardiogram; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; PSA = prostate-specific antigen * According to the protocol patients were stratified according to ECOG performance status 0 1, versus 2 † Pain was assessed using the McGill-Melzack PPI scale; analgesic score was derived from analgesic consumption (morphine equivalents) ‡ Two patients in the cabazitaxel group did not receive prior castration by orchidectomy or hormone therapy		

There were no significant differences in baseline patient characteristics between the two arms in the TROPIC trial.

4.6 Quality assessment of the relevant randomised controlled trials

Critical appraisal of the TROPIC RCT was carried out for TA 255. An updated summary of that appraisal is presented below.

4.6.1. Critical appraisal of TROPIC

The appraisal was conducted by one reviewer and checked independently by a second reviewer.

The trialists employed appropriate methods to generate the random allocation sequence and to ensure allocation concealment to minimise selection bias. A dynamic allocation method was also used to avoid extreme imbalance of treatment allocation within each study centre.

The care providers, participants and outcome assessors were not blind to treatment allocation. The lack of blinding could have introduced the potential for ascertainment bias in the subjective assessment of pain, symptom deterioration (both of which were included in the definition of PFS) and clinical (although not laboratory) assessment of AEs. In the ERG report accompanying TA255 the lack of justification for the unblinded nature of the trial was criticized. However the ERGs clinical advisors indicated that a double dummy procedure would have been difficult to implement due to the nature of the treatments and the requirement for premedication of patients receiving cabazitaxel. Outcome assessors were not blinded to treatment allocation and although this is unlikely to have introduced bias into the assessment of the primary outcome, overall survival, or objective assessments of tumour response or biochemical measurements such as PSA this could be a source of bias.

The patients in each treatment group were well balanced with regard to demographic and disease parameters, and previous treatment history. A protocol amendment was made after the start of the trial to exclude patients who had received a cumulative dose of docetaxel <225 mg/m2. Eight per cent of cabazitaxel patients and 7.7% of mitoxantrone patients

received cumulative docetaxel doses below that threshold, indicating that no imbalance between arms was introduced by this amendment.

Other than the required cabazitaxel premedication, there were no systematic differences in concomitant therapies allowed in both the comparator groups. G-CSF prophylaxis was permitted after Cycle 1 and usage was higher in the cabazitaxel arm due to the higher rate of neutropenia. Anti-emetic prophylaxis was also given at the physicians' discretion in both treatment groups.

The level of dropouts was low in both treatment groups and there were no unexpected imbalances between the groups (see CONSORT participant flow diagram, Figure 6. Only two patients, both in the mitoxantrone group, were lost to follow-up. A similar number of patients in each group (n=10 cabazitaxel, n=7 mitoxantrone) discontinued treatment due to events 'other' than disease progression or AEs.

Scrutiny of the published journal articles and the unpublished clinical trial report found no evidence to suggest bias in the reporting of study outcomes. The primary analysis of the primary outcome, OS, and all other time-to-event outcomes (PFS, tumour progression, PSA progression, and pain progression) was by intention-to-treat (ITT). Missing data were handled appropriately according to censoring rules (see Section 4.4.2). Where available case analyses were conducted, the number of patients analysed in each group was clearly stated.

4.6.2. Methods used for assessing risk of bias and generalizability.

A quality assessment of the TROPIC study is provided in Table 20 below.

Table 20. Quality assessment of the TROPIC study.[8]

Appraisal question	How addressed in the study	Adequate or not
Internal validity		
Was randomisation carried out appropriately?	Computer-generated random number sequence; stratified by prespecified 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 OS, PFS, or objective assessments of tumour response; potential for ascertainment bias in the subjective assessment of PPI and clinical (not laboratory) assessment	No, but unlikely to impact on the main outcomes. Outcome assessors should probably have been blinded to avoid the possibility of bias.

	of AEs.	
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 patients in each group (n=10 cabazitaxel, n=7 mitroxantrone) 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.	Yes
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 ITT. 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; 4.9% (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 EAP is available (described in Section 4.11) and this shows cabazitaxel use in a very similar patient population to the TROPIC study 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 IV infusion every three weeks (as in the summary of product characteristics) Mitoxantrone 12 mg/m^2 one-hour IV infusion every three weeks; recommended dosage for HRPC 12–14 mg/m² IV every three weeks. Mitoxantrone is not licensed for this indication in the UK but is licensed in the USA.	Yes

4.6.3 If there is more than 1 RCT, tabulate a summary of the responses applied to each of the quality assessment criteria.

There is only one completed pivotal Phase III RCT for cabazitaxel. This is the TROPIC trial[8] described above and below in Sections 4.7 and 4.8. A quality assessment of the PROSELICA study will be provided if the data becomes available for consideration by the committee.

4.7 Clinical effectiveness results of the relevant randomised controlled trials

Data from the ITT population are discussed in the following section. The subgroup of patients with ECOG PS 0 -1 and who have received at least 225 mg/m^2 docetaxel (See section 4.8 for results) are used in the base-case analysis presented in Section 5.

The treatment received by the participants in the TROPIC trial is summarised in Table 21.

Table 21. Treatment received in the TROPIC trial[8]

Treatment	Mitoxantrone	Cabazitaxel
Number of patients who received treatment	371 (98%)	371 (98%)
Number of treatment cycles (median)	4 (IQR 2, 7)	6 (IQR 3, 10)
Relative dose intensity (median)	97.3% (IQR 92.0, 99.3)	96.1% (IQR 90.1, 98.9)
Treatment delays (number of patients)*	56 (15%)	104 (28%)
Treatment delays (number of cycles) † ≥4 days ≤9 days >9 days	 (7.9%) 110 (6.3%) 28 (1.6%)	 (9.3%) 157 (7.0%) 51 (2.2%)
Dose reductions (number of patients)‡	15 (4%)	45 (12%)
Dose reductions (number of cycles)	88 (5.1%)	221 (9.8%)

* Delays of ≤2 weeks were allowed
† Percentages are of total number of treatment cycles (2,251 for the cabazitaxel group and 1,736 in the mitoxantrone group
‡ One dose reduction was allowed per patient, 20 mg/m^2 for cabazitaxel or 10 mg/m^2 mitoxantrone

Primary outcome: overall survival

The updated analysis indicates a median study follow-up of 25.5 months. Overall 277 deaths occurred in the cabazitaxel group and 308 in the mitoxantrone group.

ITT analysis of the primary outcome showed an OS benefit in favour of cabazitaxel (see Table 22 and Figure 7). Median survival was 15.1 months in the cabazitaxel group and 12.7 months in the mitoxantrone group. The treatment difference for OS was statistically significant in favour of the cabazitaxel group (p = 0.0002), which is less than the target statistical significance level of p= 0.0452. The hazard ratio (HR) was 0.72 (0.61 - 0.84) in favour of cabazitaxel corresponding to a 28% reduction in risk of death. At 12 months, 64% of patients were alive in the cabazitaxel group compared with 53% in the mitoxantrone

group. The probability of surviving ≥2 years was 27% (95% CI 23% to 32%) with cabazitaxel versus 16% (95% CI 12% to 20%) with mitoxantrone.

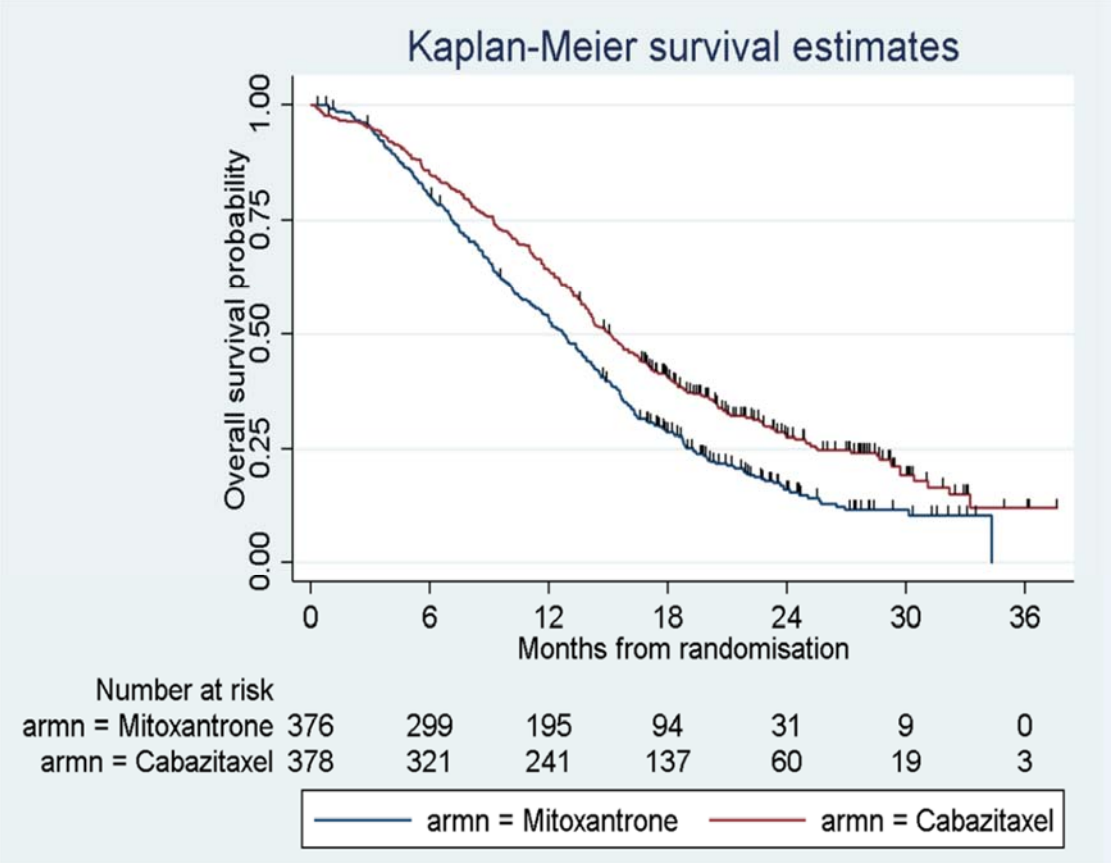
Table 22. Overall survival – ITT population

	Mitoxantrone + prednisone (n=377)	**Cabazitaxel + prednisone (n=378)**
Number of patients with deaths (%)	308 (81.7%)	277 (73.3%)
Number of patients censored (%)	69 (18.3%)	101 (26.7%)
Median survival in months (95%CI)	12.78 (11.53-13.73)	15.08 (13.96-16.49)
Hazard ratio (95% CI)*	0.72 (0.61 - 0.84)	
P value†	0.000	

Key: CI = confidence interval
* P value from stratified log rank test, stratifying for ECOG performance status and measurable disease at baseline
† Hazard ratio is estimated using a Cox proportional hazards regression model, HR <1 indicates a lower risk with cabazitaxel plus prednisone with respect to mitoxantrone plus prednisone

The Kaplan–Meier plots of OS are shown in Figure 7. The disparity in excess early TEAE deaths on cabazitaxel (18 deaths on cabazitaxel versus 7 on mitoxantrone) within 30 days explains the early inflection in the Kaplan-Maier curve for overall survival. The IDMC, in an ad hoc IDMC meeting, reviewed these deaths and was of the opinion that in the cabazitaxel group, seven deaths were due to neutropenic complications, most of them during Cycle 1 of study treatment, and two were due to renal failure secondary to dehydration. Based on IDMC recommendations the investigators were advised to follow the protocol strictly regarding dose delay and modifications and to treat neutropenia per ASCO guidelines. These recommendations were instituted and no new neutropenic deaths were reported.

Figure 7. Overall survival and number of patients at risk by study month (ITT population)



In addition to the median OS data presented above (Table 22), mean OS was estimated using patient level data from the TROPIC trial. A number of parametric functions were fitted to the Kaplan–Meier data from TROPIC and the goodness-of-fit tested. This identified a Weibull function as the best fit to the OS data for both arms. Details of the curve-fitting method are provided in Section 5.6.1. For the ITT population, based on the Weibull extrapolations, mean OS was estimated as 14.53 months the mitoxantrone arm versus 18.55 months in the cabazitaxel arm, a difference of 4.02 months in favour of cabazitaxel. The range of incremental OS extrapolations depending on the parameterisation used is between 3.6 months (Gompertz) to 8.1 months (Lognormal).

Secondary outcome: progression-free survival

The first secondary outcome in TROPIC was PFS defined as a composite endpoint, as the time between randomisation and the first date of progression as measured by PSA progression, tumour progression, pain progression or death. Median PFS (ITT population) was 2.8 months in the cabazitaxel group and 1.4 months in the mitoxantrone group (see Table 23). The difference in overall PFS was statistically significant in favour of the cabazitaxel group (p = 0.0002). The HR was 0.75 (95%CI, 0.65 - 0.87) in favour of cabazitaxel, corresponding to a 25% reduction in risk of progression (see Table 23). The Kaplan–Meier plots for PFS are presented in

Figure 8.The definition of PFS in TROPIC was conservative, including biochemical (PSA progression), which frequently precedes symptomatic or radiologic progression. As can be seen in Table 24, 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 the first sign of progression, including confirmed PSA progression. Hence the relatively short PFS duration shown in Table 23 (in comparison with other cancer types and other trials in this setting) reflects this definition of PFS.

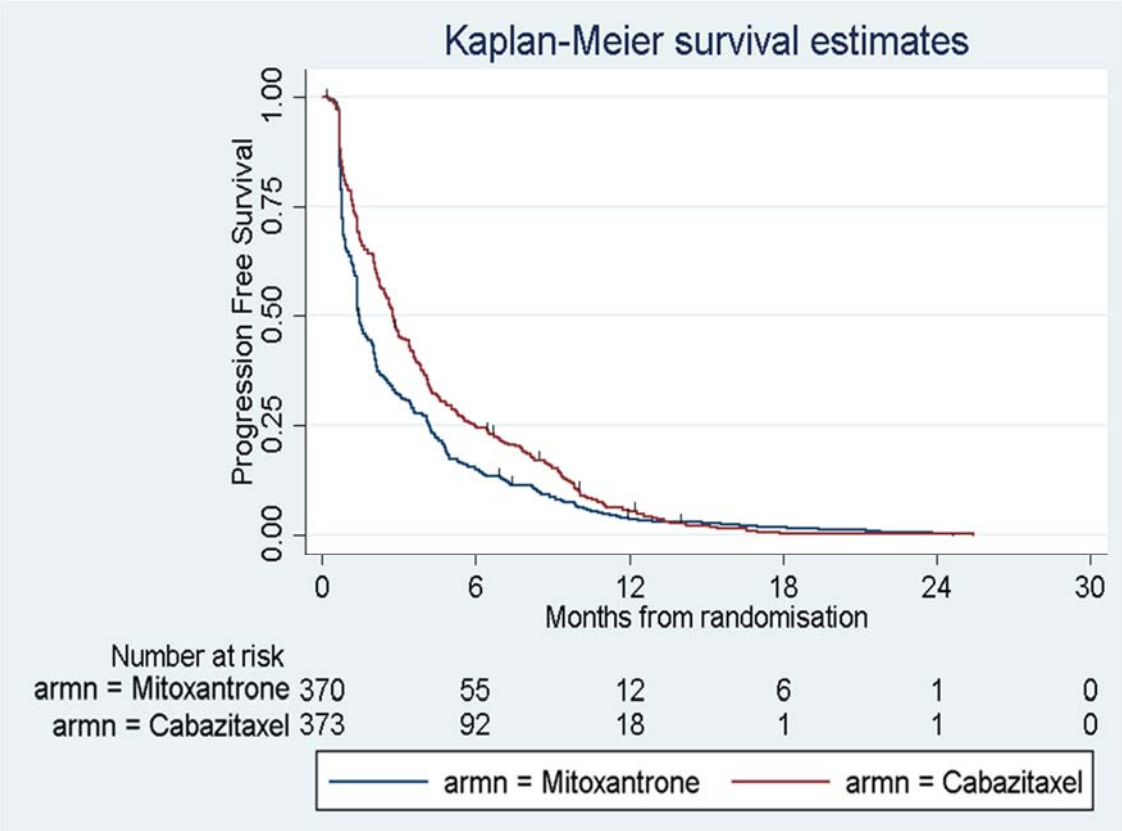
Table 23. Progression-free survival – ITT population

	Mitoxantrone + prednisone (n=377)	**Cabazitaxel + prednisone (n=378)**
Number of patients with PFS events (%)	370 (98.1)	367 (97.1)
Median PFS in months (95%CI)	1.41 (1.35-1.77)	2.76 (2.43-3.12)
Hazard ratio (95% CI)	0.75 (95%CI, 0.65 - 0.87)	
p value	0.0002	
Key: CI = confidence interval; PFS = progression-free survival PFS 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		

Table 24. Descriptive analysis of progression-free events – ITT population

	Mitoxantrone + prednisone (n=377)	**Cabazitaxel + prednisone (n=378)**
Number of patients with PFS events (%)	370 (98.1)	367 (97.1)
Death	33 (8.8)	41 (10.8)
Tumour progression	68 (18.0)	67 (17.7)
PSA progression	186 (49.3)	163 (43.1)
Pain progression	69 (18.3)	86 (22.8)
Symptom deterioration	14 (3.7)	10 (2.6)
Key: PSA = prostate-specific antigen; PFS = progression-free survival		

Figure 8. Kaplan–Meier curves of PFS and number of patients at risk by study month (ITT population)



4.8 Subgroup analysis

4.8.1 Details for the subgroup of patients with ECOG PS 0 -1 and having received at least 225 mg/m^2 docetaxel

A post-hoc subgroup analysis, previously considered by NICE as reflective of the population likely to be treated with cabazitaxel, was conducted following the outline for the ITT population. This subgroup represented patients with mCRPC previously treated with a docetaxel-containing regimen, with ECOG PS 0 -1 and who have received at least 225 mg/m^2 docetaxel.

Cabazitaxel is licensed for use in the post-docetaxel setting and in line with NICE guidance it is expected that all UK patients would receive sufficient exposure to docetaxel before consideration for cabazitaxel. The exclusion of patients receiving <225 mg/m^2 docetaxel (approximately 3 cycles) is consistent with an amendment introduced to the TROPIC protocol after the recruitment of 59 patients.

In TROPIC 61 (8.1%) patients had ECOG PS of 2. Clinical opinion, which was endorsed by the clinical advisors to the ERG in TA255, is that it is extremely unlikely those patients with an ECOG PS value of 2 would be treated with cabazitaxel in UK practice.

The subgroup analysis was conducted on the updated TROPIC dataset and represents 632 (83.7%) patients out of the ITT population of 755.

4.8.2 Characteristics of the participants in the subgroup.

The baseline patient characteristics for the patients with mCRPC previously treated with a docetaxel-containing regimen, with ECOG PS 0 -1 and who have received at least 225 mg/m^2 docetaxel are presented in Table 25 below.

The validity of this subgroup was accepted by the ERG in TA255 and the appropriateness to the UK setting is discussed above (Section 4.8.1).

Table 25. Characteristics of participants in the subgroup with ECOG PS 0 -1 and who have received at least 225 mg/m^2 docetaxel across treatment groups in the TROPIC trial.

TROPIC trial Baseline characteristic – subgroup cohort	**Mitoxantrone + prednisone**	**Cabazitaxel + prednisone**
(n=362)	**(n=313)**	**(n=319)**
Age, in years		
Median	66.0	68.0
75 and above	77 (24.6%)	77 (24.1%)
Race		
Caucasian/White	261 (83.4%)	270 (84.6%)
Black	19 (6.1%)	15 (4.7%)
Asian/Oriental	23 (7.3%)	22 (6.9%)
Other	10 (3.2%)	12 (3.8%)
ECOG performance status*		
0 or 1	313 (100%)	319 (100%)
2	0 (0%)	0 (0%)
Measurable disease		
Measurable disease	166 (53.1%)	168 (52.7%)
Not measurable disease	147 (47.0%)	151 (47.3%)
ECOG = Eastern Cooperative Oncology Group;* According to the protocol patients were stratified according to ECOG performance status 0 1, versus 2		

4.8.3 Details of the statistical tests used in the primary analysis of the subgroups, including any tests for interaction.

No statistical test has been applied to evaluate a difference for the treatment effect in the group excluded from the subgroup population and the subgroup with ECOG PS 0 -1 who have received at least 225 mg/m^2 docetaxel. This subgroup of interest represents 84% of the patients in the study and according to clinical opinion, is expected to be most representative of patients likely to be treated with cabazitaxel in clinical practice. This was also a view expressed by the clinical advisors to the ERG in TA255 who stated that it would be extremely unlikely for patients with an ECOG PS of 2 or more to be treated with cabazitaxel. The clinical advisors felt that '*it is plausible that the efficacy of cabazitaxel would be lower in*

patients who had received insufficient docetaxel' and the ERG report notes that '*the a priori belief for this subgroup is also supported by the amendment in the TROPIC protocol (after the recruitment of 59 patients) to exclude patients who had not received sufficient docetaxel.'* This subgroup was accepted as an appropriate cohort for analysis in TA255.

4.8.4 Summary of the results for the subgroup: patients with ECOG PS 0 -1 who have received at least 225 mg/m^2 docetaxel

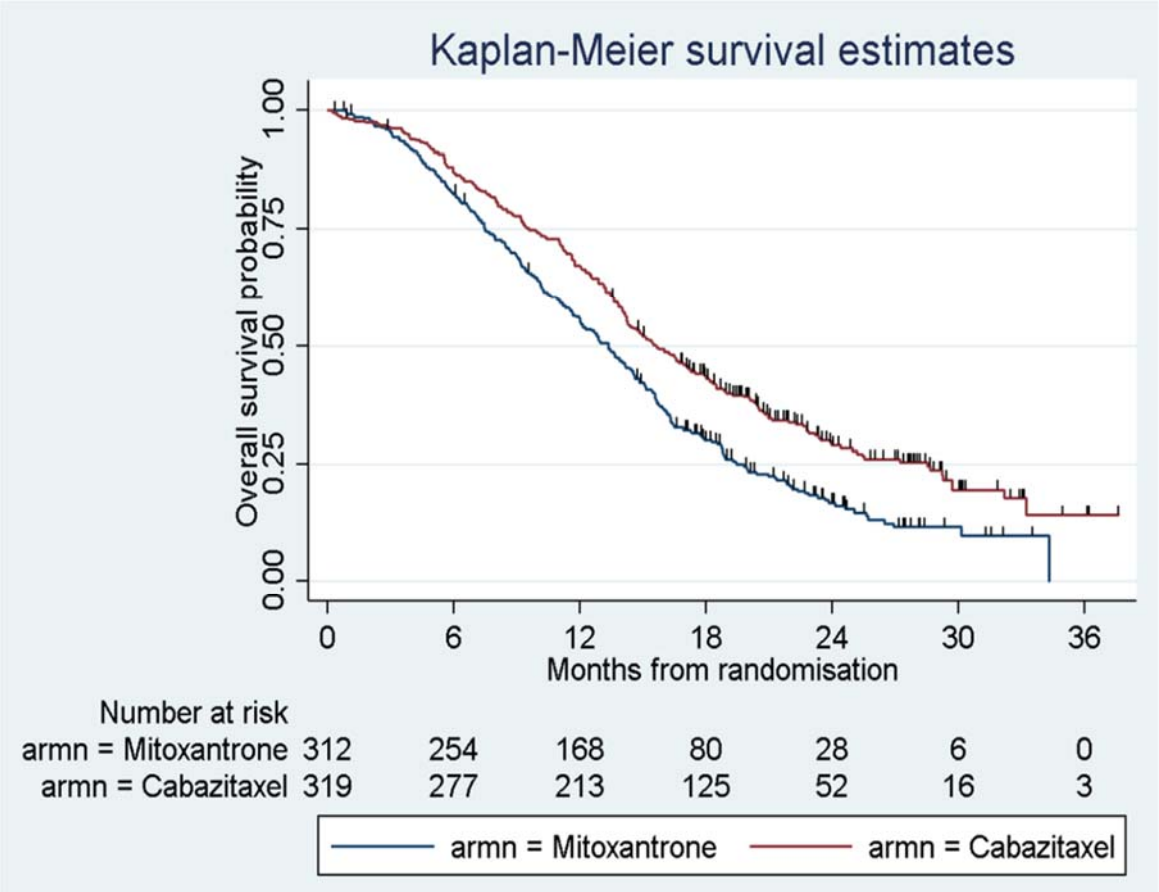
For the subgroup with ECOG PS 0 -1 who have received at least 225 mg/m^2 docetaxel Median survival was 15.61 (13.96 - 17.28) months in the cabazitaxel group and13.37 (11.99 - 14.52) months in the mitoxantrone group. The treatment difference for OS was statistically significant in favour of the cabazitaxel group (p = 0.000) and the hazard ratio (HR) was 0.69 (0.57 - 0.82) in favour of cabazitaxel. The Kaplan–Meier plots for PFS are presented in

Figure 9.

Table 26. Overall survival in the subgroup of patients with ECOG PS 0 -1 who have received at least 225 mg/m^2 docetaxel.

	Mitoxantrone + prednisone (n=313)	**Cabazitaxel + prednisone (n=319)**
Number of patients censored (%)	253 (80.83)	228 (71.47)
Median survival in months (95%CI)	13.37 (11.99-14.52)	15.61 (13.96-17.28)
Hazard ratio (95% CI)*	0.69 (0.57-0.82)	
P value†	<0.001	

Figure 9. Kaplan–Meier curves of overall survival in the subgroup with ECOG PS 0 -1 who have received at least 225 mg/m^2 docetaxel.

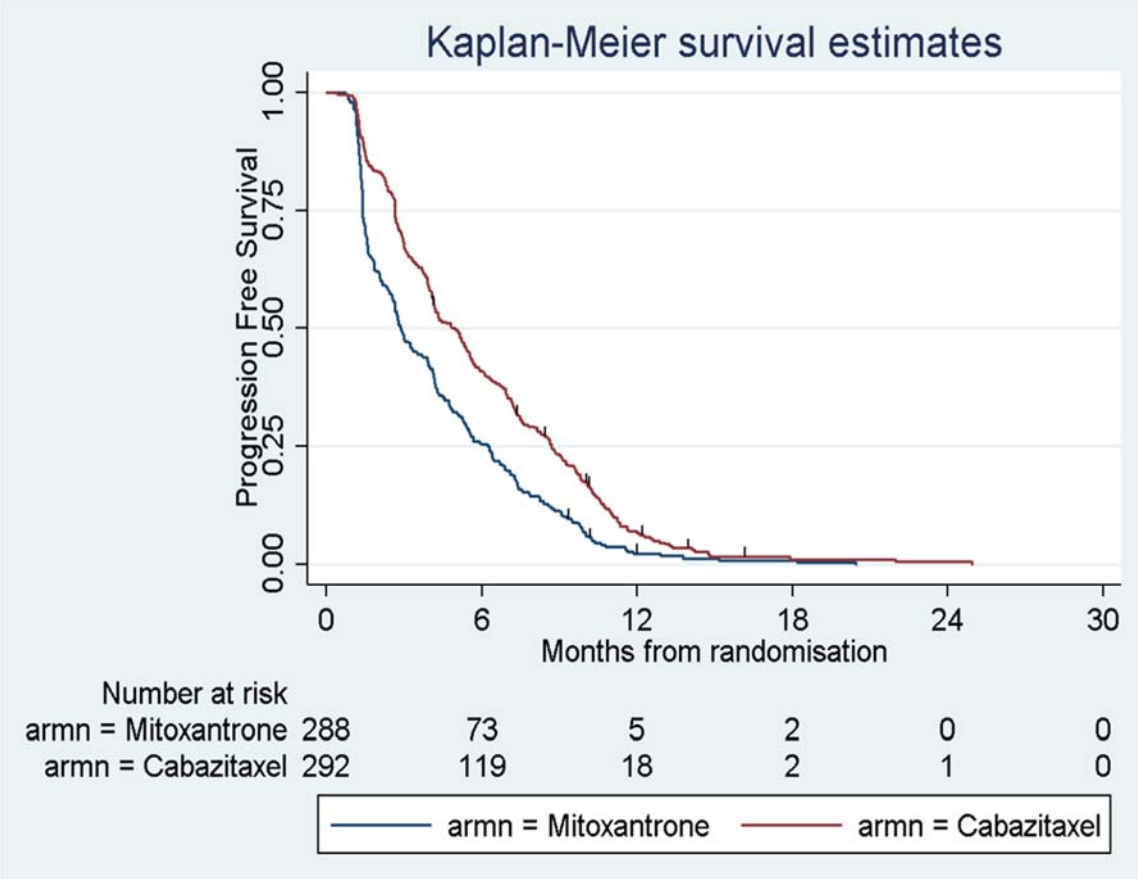


Median PFS in the subgroup was 2.76 (2.43-3.12) months in the cabazitaxel group and 1.41 (1.35-1.84) months in the mitoxantrone group (Table 27). The difference in overall PFS was statistically significant in favour of the cabazitaxel group (p = 0.001). The HR was 0.76 (0.65-0.89) in favour of cabazitaxel (Table 27). The Kaplan–Meier plots for PFS are presented in Figure 10.

Table 27. Progression-free survival in the subgroup with ECOG PS 0 -1 who have received at least 225 mg/m^2 docetaxel.

	Mitoxantrone + prednisone (n=377)	**Cabazitaxel + prednisone (n=378)**
Number of patients with PFS events (%)	304 (97.12)	305 (95.61)
Median PFS in months (95%CI)	1.41 (1.35-1.84)	2.76 (2.43-3.12)
Hazard ratio (95% CI)	0.76 (0.65-0.89)	
p value	0.001	
Key: CI = confidence interval; PFS = progression-free survival PFS 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 Source		

Figure 10. Kaplan–Meier curves of PFS survival in the subgroup with ECOG PS 0 -1 who have received at least 225 mg/m^2 docetaxel.



4.9 Meta-analysis

Meta-Analyses were not conducted as only one study per relevant treatment was found in the systematic review described in Section 4.1.

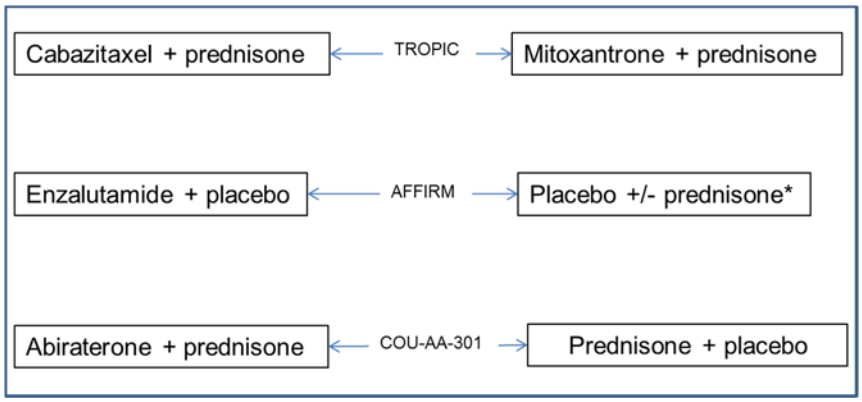
4.10 Indirect and mixed treatment comparisons

The base-case analysis presented in this dossier is for cabazitaxel versus mitoxantrone (which may be considered equivalent to Best Supportive Care (BSC)). We have established this to be the most relevant comparator for the treatment of mCRPC in the post docetaxel setting with cabazitaxel. This is on the basis that the NHS Standard Practice pathway precludes other comparators and the disease characteristics of a subset of the patients who follow the Alternative Practice Pathway mean cytotoxic therapy is the only active option.

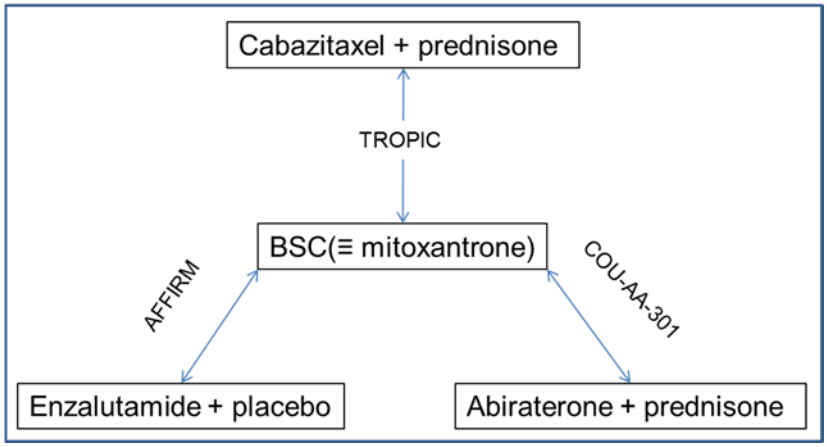
Nonetheless as required by the scope, we have carried out a scenario analysis to compare the clinical evidence from TROPIC with the outcomes in the COU-AA-301(abiraterone)[11] and AFFIRM (enzalutamide)[10] studies via their control arms using a Bayesian Indirect Treatment Comparison (ITC). These studies were identified in the systematic review and the latest data from each study was used to inform the ITC. This ITC analysis was then used in the

scenario comparative economic evaluations. The network diagrams are provided in Figure 11. Full details can be found in Appendices B.

Figure 11. Network diagrams for the included trials



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



Such comparisons rely on the strong assumptions that the study designs and trial populations are sufficiently alike, and that the respective control-arms of the trials deliver equivalent levels of efficacy with a similar safety profile. It is questionable whether these assumptions hold true and the results from the ITC and economic analysis should be treated with caution.

Whilst in terms of overall survival, the three control arms from these trials have previously been considered equivalent for the purposes of indirect comparison (TA255, TA259 and TA316), the definition of Progression Free Survival (PFS) is markedly different between trials and represents a problem for the present indirect comparison, and by extension the use of indirect PFS data in the economic model.

The main PFS definitions from the three trials are described elsewhere (Appendices B), but it is important to note that the principal definition of PFS in the TROPIC trial (main secondary endpoint), and which directly affected patients discontinuation of treatment, was more conservative than similar endpoints reported in the other trials. Consideration was therefore given to using measures of PFS with differing definitions for the indirect comparisons.

In order to facilitate a more coherent comparison for progression free time, radiographic PFS (rPFS) was derived from the patient level data from TROPIC. The aim of this was to reflect the end point was reported in both the COU-AA-301 and AFFIRM trial papers. Examination of the median time to rPFS in the three trials however, indicates the values of rPFS for the control arms are substantially different, indicating that for the purposes of the ITC they should not be considered equivalent.

Whilst cabazitaxel and enzalutamide reported similar median rPFS values of *academic in confidence information removed* months and 8.2 months respectively, patients receiving mitoxantrone had a median rPFS of *academic in confidence information removed* months, substantially larger than the control arm in AFFIRM trial; rPFS 2.9 months. The control arm of the COU-AA-301 trial was similar to that in AFFIRM with a median rPFS of 3.6 months.

The relatively poor performance of the control arms the AFFIRM and COU-AA-301 trial, compared to the almost double median rPFS for mitoxantrone in the TROPIC trial raises questions about the comparability of the control arms and comparability of measurements 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. As will be seen in Appendicies B, the application of these indirect comparisons for rPFS produce spurious results in the economic model

As well as possible differences in the effect of the control treatments on rPFS, examination of the trial participants themselves may also be a reason for the difference in performance observed. The patients entering the studies had different disease characteristics. For example in the COU-AA-301 trial[11] only 30% of patients were refractory to docetaxel whilst 70% in TROPIC had progressed whilst on docetaxel or within 3 months of receiving it. In the AFFIRM study the mean time to start of enzalutamide therapy from last docetaxel exposure was 9 months.These data are indicative of more aggressive disease in the TROPIC population but despite this similar OS was observed between the studies. These issues are discussed fully in Appendices B.

The methodology and complete set of results can be found in Appendices B. Key results from the scenario ITC are summarized in Table 28.

Table 28. Key results from the mixed treatment comparisons – ITT population

	Overall survival			Radiographic progression free survival		
	HR	Credible intervals		HR	Credible intervals	
Cabazitaxel vs mitoxantrone (≡BSC to facilitate NMA)	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
Abbreviations. HR: Hazard Ratio; BSC: Best Supportive Care.						

4.11 Non-randomised and non-controlled evidence

An update to the systematic literature search described in Section 4.1 and Appendix 5, was carried out to identify non-randomised evidence pertinent to the decision problem for the period January 2010 to February 2015. A brief description of the original search carried out for TA255 is provided in Appendix 6.

The following databases were searched according to the search strategies provided in Appendix 6.

- Embase
- MEDLINE (via the Embase interface)
- MEDLINE In-Process (via PubMed)

In addition to the published literature search, key conference proceedings were screened. The following conference proceedings were hand searched over the past 4 years:

- American Society of Clinical Oncology (ASCO)
- ASCO-Genitourinary (ASCO-GU)
- European Society for Medical Oncology (ESMO)
- American Urological Association (AUA)
- American Association for Cancer Research (AACR)
- European Association of Urology (EAU)
- Société Internationale d'Urologie (SIU)

English and non-English language studies were included.

Studies were selected on the basis of the following inclusion and exclusion criteria Table 29 and Table 30 respectively.

Table 29. Inclusion criteria (PICOS framework) used in the search strategies

PICOS	Description	Rationale
Population	• mHRPC/mCRPC patients • Age: Adults (≥18 years) • Race: Any • Line of therapy: Second-line or later • Prior therapy: Previously treated with docetaxel-based regimen	• The patient population has been restricted to match the stated decision problem for the treatment of mHRPC/mCRPC in patients who have been treated with docetaxel in any previous regimen • Because prostate cancer is a disease affecting older adult men, studies including children or adolescents were excluded
Interventions	The following treatments for mHRPC and mCRPC administered in the	• Investigational agents used for the treatment of mHRPC/mCRPC

PICOS	Description	Rationale
	second line or later: • Jevtana (cabazitaxel) • Zytiga (abiraterone) • Xtandi (enzalutamide) • Novantrone (mitoxantrone) • Yervoy (ipilimumab) • Xofigo (radium-223) • Provenge (sipuleucel-T) • Emcyt (estramustine)	following a previous docetaxel regimen are of interest for the review • 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
Comparator	No limitation on comparator	• Any agent used for the treatment of mHRPC/mCRPC after a previous docetaxel regimen is of interest for the review as a comparator, thus the list was not limited • Comparators may include placebo, any chemotherapy, surgery, radiotherapy, BSC, or no comparator
Outcomes	• OS • 1-year survival • PFS • TTP • Complete response • Partial response • Overall response • SREs • PSA response • TTPSA • Time to opiate use • TTPP • Safety/AEs (eg, anaemia and neutropenia) • HRQoL • Resource utilization	• These outcomes were chosen because they are well-established outcomes to assess efficacy and safety in oncology research and are frequently measured and reported in trials of mHRPC/mCRPC
Study design	• Nonrandomized controlled clinical trials • 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	• A previous review in this area suggested a limited evidence base available from RCTs; therefore, other study designs including observational studies were included in this review

PICOS	Description	Rationale
Limits	• Publication timeframe: o From 2010 to present o Conference abstracts from 2011−2015	• Publications from 2010 were included to identify studies not captured in a previous systematic review • Many congresses that took place in 2010 were searched as part of the previous review and it was assumed that data from any 2010 conferences that were not previously identified would likely be superseded by a full publication by 2015

AEs, adverse events; BSC, best supportive care; HRQoL, health-related quality of life; mCRPC, metastatic castration-resistant prostate cancer; mHRPC, metastatic hormone-refractory prostate cancer; OS, overall survival; PFS, progression-free survival; PICOS, population, intervention, comparators, outcomes, and study design; PSA, prostate-specific antigen; SREs, skeletal-related events; RCT, randomized controlled trial; TTP, time to disease progression; TTPP, time to pain progression; TTPSA, time to PSA progression.

Table 30. Exclusion criteria checklist

Exclusion criteria	Rationale
• Non-mHRPC and non-mCRPC populations o No mHRPC or mCRPC subgroup analysis o Metastatic disease unclear • Patients not pretreated with a docetaxel-based regime o No docetaxel-pretreated subgroup analysis o Docetaxel pretreatment unclear o Line of therapy unclear • Study population aged <18 years • Study does not examine an intervention of interest • Study does not include any outcomes of interest • Study design is an RCT • Study design is a case study, case series, or case report • Published before 2010	• Studies with no subgroup data for the disease (mHRPC/mCRPC), disease stage (metastatic), and prior treatment (docetaxel-treated) were excluded • A previous review including RCTs was available, therefore RCTs were excluded from this review • Nonrandomized evidence including case studies/series/reports were excluded as they are poor-quality evidence • Studies in which the patient population of interest was not clearly identified were excluded from this review

mCRPC, metastatic castration-resistant prostate cancer; mCRPC, metastatic hormone-refractory prostate cancer; RCT, randomized controlled trial.

Two reviewers screened articles for inclusion; any disputes were resolved through discussion between reviewers or consultation with a third reviewer. All publications that met the inclusion criteria, based on titles and abstracts, were obtained as full documents and reassessed against the inclusion criteria by the same reviewers.

Data from relevant articles were subsequently extracted in parallel by two independent reviewers based on the extraction grid detailed in Appendix 6. Both sets of extracted data

were compared and combined into a final data extraction table, which was subsequently verified for the accuracy of all content by an independent third reviewer.

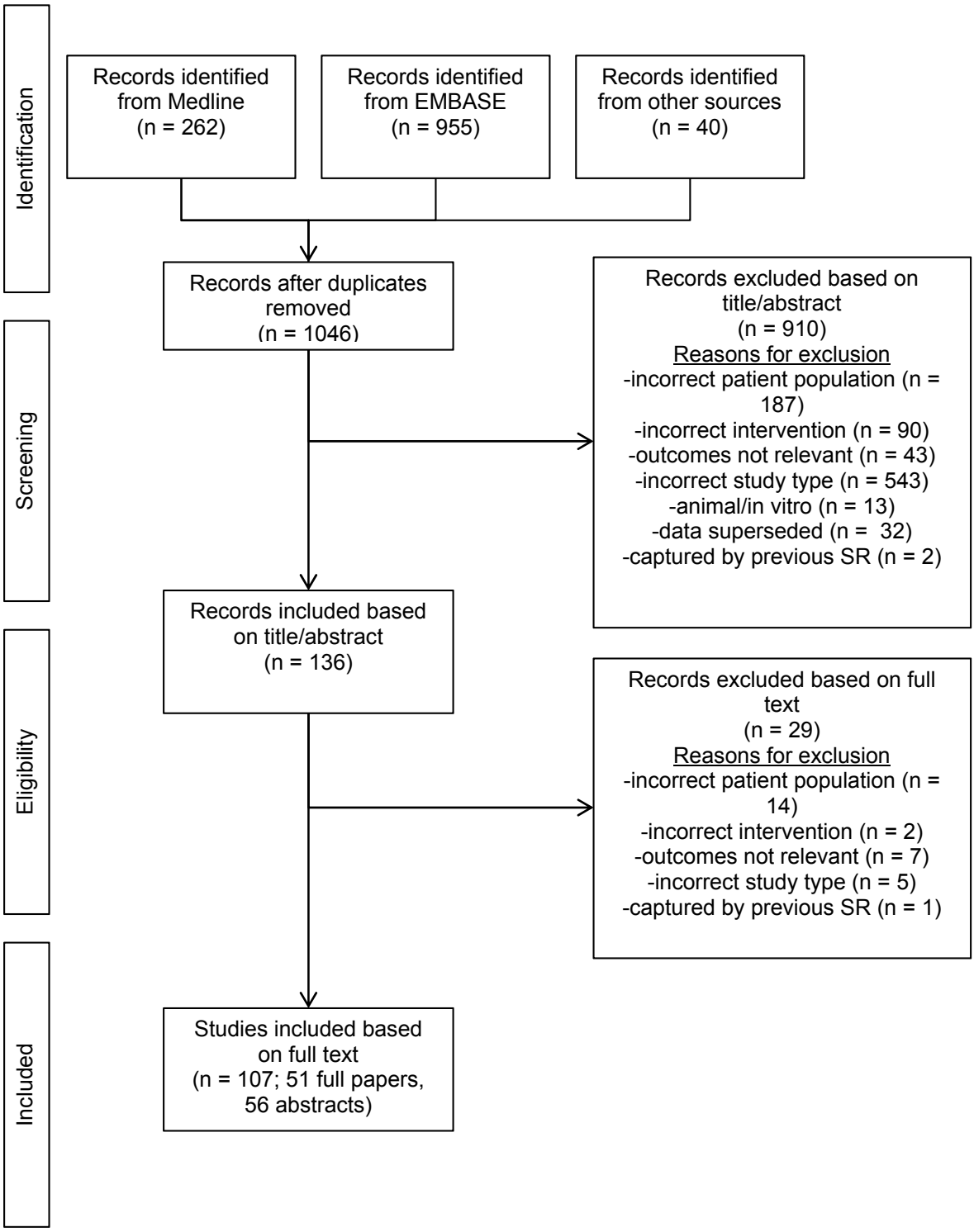
Where multiple publications were identified for the same trial, the novel data reported in each publication were extracted separately.

The database searches were run on 26 February 2015 and the supplementary abstract search was run on 8 March 2015. The additional searches for non-English studies were run on 3 May 2015; however, these searches were restricted to a cut-off date of 26 February 2015 to match the original search period and were integrated with the original search results.

In total, 1046 unique records were identified for screening, which included 1006 database search results and 39 congress abstracts. A total of 103 studies from 107 references (51 full publications and 56 congress abstracts) were identified for inclusion in the systematic review.

A flow diagram of the studies included and excluded at each stage is provided in Figure 12 overleaf. The outcomes included in the analysis, along with a description of their reliability, validity, and/or clinical relevance based on recent guidelines from the European Medicines Agency (EMA).[110]

Figure 12. PRISMA flow diagram for the literature review of non-randomised evidence



4.11.1 Results from the non-randomised and non-controlled evidence literature survey.

A full list of the 107 included non-randomised, non-controlled articles is provided in Appendix 6. A list of the excluded articles along with the reason is also provided in Appendix 6. The

discussion below will focus on those articles directly relevant to the decision problem which fall into the two categories:

- Safety of cabazitaxel in clinical practice
- Efficacy of cabazitaxel used in sequence with abiraterone or enzalutamide.

Safety reported in the Compassionate Use and Early Access Programs.

Key evidence pertinent to the decision problem which provides data to support the safety of cabazitaxel in clinical practice comes from the Compassionate Use Programs (CUP) and Early Access Programs (EAP) for cabazitaxel. These studies identified in the non-randomised and non-controlled evidence search are presented below.

Results from the TROPIC trial stimulated the CUP/EAPs which allowed access to cabazitaxel ahead of commercial availability. These were initiated in 33 countries worldwide (Australia; Austria; Belgium; Bosnia And Herzegovina; Bulgaria; Canada; Croatia; Czech Republic; Denmark; Finland; France; Hungary; India; Ireland; Israel; Italy; Kazakhstan; Luxembourg; Malaysia; Mexico; Philippines; Poland; Portugal; Romania; Serbia; Singapore; Slovakia; Spain; Sweden; Taiwan, Thailand; Province Of China; United Kingdom). In all cases a safety awareness program for health care professionals was implemented in each center to encourage the proactive management of adverse events. The objective of the CUP/EAP was to focus on aspects of safety during treatment with cabazitaxel and so efficacy outcomes were not collected centrally. Nonetheless in some cases these are reported on a country by country basis.

Pan-European and individual country results and have been published for several of these programs. In all reported cases the population considered was patients with mCRPC who had progressed on or after docetaxel and who had a ECOG performance status of 0 – 2 with 90% or more patients at ECOG 0-1 (with the exception of the Korean EAP where 19% of patients were ECOG 2). (See Table 33 for a summary of baseline patient characteristics). In general the populations in the CUP/EAP match the TROPIC population although in some cases patients are slightly older than in TROPIC.[111] A list of the interim and complete evidence presented in full publications is tabulated below Table 31. A poster detailing the UK experience of the EAP was identified in the evidence review (Table 34) but since this was carried out a full paper has been published.[12] This is included in Table 33 alongside the full publications from the review.

Table 31. Published evidence from the CUP/EAP

Country	Patients included	Objectives as stated in the publication	Primary study reference
Europe	746	This paper describes preliminary results synthesized from 20 from European CUPs/EAPs and focuses on the safety results in adults aged 70 years and over. In agreement with national regulations, no efficacy data were collected.	Heidenreich 2014[111]

Country	Patients included	Objectives as stated in the publication	Primary study reference
Korea	26	The primary objective was to assess safety, and the secondary objective was to document PSA response, time to PSA progression, time to treatment failure, time to composite progression, and OS.	Lee, 2014[112]
Germany	111	The primary objective was to document the safety according to the US National Cancer Institute's Common Terminology Criteria for Adverse Events v.4.0. The secondary objective was to document prostate-specific antigen (PSA) response rates, PFS and OS.	Heidenreich 2014[113]
Italy	218	Safety results are reported for the Italian program which represents the largest cohort within the CUP/EAP.	Bracarda 2014[114]
Netherlands	49	Safety and efficacy (OS and PFS) data are reported.	Wissing 2014[115]
Spain	153	The primary objective was to document the overall safety of cabazitaxel in mCRPC patients who had progressed during or after treatment with a docetaxel-containing regimen in Spain. Additionally, the efficacy (prostate-specific antigen [PSA] response and biochemical progression free survival) was analyzed however these patients were selected from the sites with higher recruitment rate and no formal selection was used.	Castellano, 2014[116]
UK	112	The objective was to compile the safety profile and quality of life (HRQL) data for patients with mCRPC treated with cabazitaxel in the UK	Bahl, 2015[12]

In addition to the full publications listed in Table 31 several posters have been presented at conferences more recently. These are described in Table 32 below.

Table 32. Additional CUP/EAP studies presented at conferences.

Country	Patients included	Objectives as stated in the abstract or poster	Primary study reference
Multiple (37)	1301	To assess real-world safety of cabazitaxel	Malik 2013 (ASCO)[117]
Multiple (12 countries)	451	To assess real-world safety of cabazitaxel	Heidenreich 2014 (ESMO)[118]

Canada	61	To collect safety, HRQL and efficacy data in patients from the global Expanded Access Program for cabazitaxel	Sridhar 2013 (ASCO)[119]
France	184	To assess real-world safety of cabazitaxel	Houede 2012 (ASCO)[120]
Thailand	40	To document overall safety of cabazitaxel in the real world.	Pripatnanont 2014 (SIU)[121]
UK	108	Safety profile and quality of life (HRQL) data for patients with mCRPC treated with cabazitaxel in the UK	Bahl, 2013 (ASCO-GU)[122]

4.11.2 Provide a comparative summary of the methodology of the studies in a table.

The primary objective of the CUP/EAP studies was to allow early access for patients in clinical practice and similar to those evaluated in the TROPIC trial (for which the licence was to be granted), access to cabazitaxel for the management of metastatic Hormone Refractory Prostate Cancer (mHRPC) The secondary objective was to document the overall safety of cabazitaxel in these patients.

The methodology of the studies was common across the programs.The CUP/EAPs were prospective, single arm, open label, observational studies. Each patient was treated with cabazitaxel 25 mg/m² intravenously every 3 weeks, in combination with oral prednisone or prednisolone 10 mg daily until disease progression, death, unacceptable toxicity, investigator's decision or up to 10 cycles. This is in accordance with the SmPC.[15] Patients were followed-up during treatment with cabazitaxel and for 30 days after last administration.

The main inclusion criteria were:

- Age ≥18 years
- Metastatic Hormone Refractory Prostate Cancer previously treated with a docetaxel-containing regimen
- Disease Progression during or after docetaxel containing regimen for mCRPC
- Surgical or medical castration
- Eastern Cooperative Oncology Group (ECOG) Performance Status (PS): 0-2
- Life-expectancy ≥3 months
- Adequate bone marrow, liver, and renal function: Neutrophils> 1500 /mm_3; Hemoglobin > 10 g/dL; Platelets > 100 x10_9/L; Bilirubin < ULN; SGOT (AST) < 1.5xULN; SGPT (ALT) < 1.5xULN; Creatinine < 1.5xULN
- Signed written informed consent obtained prior to Enrolment

The main exclusion criteria were:

- Prior radiotherapy to ≥ 40% of bone marrow
- Prior radionuclide therapy (samarium-153, strontium-89, P-32…)
- Prior surgery, radiation, chemotherapy, or otheranti-cancer therapy within 4 weeks prior to enrollment
- Active grade ≥2 peripheral neuropathy

- Active grade ≥2 stomatitis
- Active infection requiring systemic antibiotic or antifungal medication
- Active cancer (other than mCRPC) including prior malignancy from which the patient has been disease-free for ≤5 years (except superficial nonmelanoma skin cancer)
- Known brain or leptomeningeal involvement
- History of severe hypersensitivity reaction (≥grade 3) to docetaxel
- History of severe hypersensitivity reaction (≥grade 3) to polysorbate 80 containing drugs
- History of severe hypersensitivity reaction (≥grade 3) or intolerance to prednisone or prendnisolone
- Uncontrolled severe illness or medical condition (including uncontrolled diabetes mellitus)
- Concurrent or planned treatment with potent inhibitors or inducers of cytochrome P450 3A4/5 (a one week wash-out period is necessary for patients who are already on these treatments)
- Participation in a clinical trial with any investigational drug
- Patient with reproductive potential not implementing accepted and effective method of contraception

The outcomes measured in the CUP/EAP were based around safety, not efficacy. These were described by the incidence of clinically significant adverse events (AEs) including serious adverse events (SAEs). AEs were collected from the time the first dose of study treatment (cabazitaxel and prednisone or prednisolone) until 30 days after the administration of the last administration of cabazitaxel. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v 4.0) and summarized using MedDRA terminology. The number of cycles, cumulative dose received, and reason for End of Treatment (EOT) were also evaluated. In some cases efficacy data was collected, although this was on a country by country basis. (Table 31)

In the UK a specific amendment was agreed allowing for the collection of HRQL.[12]

The study started in the third quarter of 2010 in Europe and at the time of submission of cabazitaxel to local Regulatory Bodies in other participating countries.

Statistical analysis of the non-randomised and non-controlled evidence

4.11.3 Potential biases in the non-randomised evidence.

The CUP/EAPs were observational studies and no formal sample size calculation was performed. The safety population comprised all enrolled patients who received at least part of one dose of cabazitaxel in order to document safety. Only descriptive summaries were provided in most cases as per protocol although analysis of the influence of selected variables was reported in the results for the European CUP/EAP. A Generalised Estimating Equations (GEE) model which adjusts for the clustering of treatment cycles within a patient was used in order to reassess the risk of grade ≥3 neutropenia and/or neutropenic complications before each chemotherapy cycle.[123]

There is inherent selection bias in the CUP/EAP due to the non-randomised, observational nature of the study and enrolment of patients into self-selecting participating centres. In addition there may be imperfect data collected by retrospective review which is necessary to capture the previous history of the patients. Similarly efficacy data, where collected, was not systematic. For example in the Spanish CUP efficacy data was only collected from patients at sites with higher recruitment rates and no formal selection was used.

The UK EAP is unique in that it provides the first formal HRQL data specific to cabazitaxel in mCRPC. It was conducted as a trial but in a setting as close to real-world UK practice as possible. It provides for the first time evidence to suggest that cabazitaxel therapy is not associated with a worsening of HRQL, and, indeed, appears to be stable with a trend towards improved HRQL with increasing cycle number.[12] See Section 5.4.1 for more details.

Participant flow in the CUP/EAP studies

4.11.4 Description of the characteristics of the participants at baseline for each of the studies by country.

Table 33. Selected baseline patient characteristics for the CUP/EAP studies reported in full publications.

Country **Baseline characteristic**	**TROPIC: (cabazitaxel arm)**	**European EAP**	**Korea**	**Germany**	**Italy**	**Netherlands**	**Spain**	**UK**
Number of patients	378	746	26	111	218	49	153	112
Median age, in years Range	68 (62 – 73)	67.7 (SD: 7.5)	66.5 (53 -82)	67.9 (49 – 81)	70 (49 – 87)	64.6 (58.6 – 70.0)	70.0 (65-75)	67 (63.0–72.5)
ECOG performance status (%) 0 1 2	0 – 1: 93%	 38.7 50.9 10.5	 12 69 19	 45 49.5 5.5	 67.4 31.2 1.4	 6.1 71.4 24.5	 30.7 58.2 11.1	 42.0 51.8 6.3
Sites of metastases (%) Bone Lung Liver Regional lymph Distant lymph Visceral	 80 NR NR NR NR 25	 91.7 NR NR 31.6 30.1 25.3	 42 19 19 NR NR 31	 91 10.8 10.8 42.3 31.5 NR	 88.0 22.6 13.8 33.6 44.7 NR	 95.9 12.2 14.3 34.7 49.0 NR	 94.1 9.2 13.1 26.1 22.9 26.8	 92.0 14.3 8.0 41.1 27.7 NR
Baseline PSA, 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 mths post doc.)

Table 34. Selected baseline patient characteristics for the CUP/EAP studies reported in conferences abstracts.

Country Baseline characteristic	Multiple (37 countries)	Multiple (12 countries)	Canada	France	Thailand
Number of patients	1301	451	61	184	40
Median age, in years Range	68	68 (43–84)	65	67.2 (46–92)	72 (50–83)
ECOG performance status (%) 0 1 2		0 – 1: 90	0 – 1: 92	0 – 1: 85	0 – 1: 95
Sites of metastases (%) Bone Lung Liver Regional lymph Distant lymph Visceral	 91 NR NR 30 27 NR	NR	 82 NR NR NR NR 21	 88 NR NR NR NR 21	 92 NR NR NR NR NR

In general the populations reported in the CUP/EAP publications are similar with the exception of the Korean study which has a higher proportion of patients with ECOG performance score 2 and lower proportion of patients with bone metastases. In addition more patients had received exposure to cytotoxic agents other than docetaxel (62 vs. 33% in TROPIC) and the average baseline PSA measure was much lower than the other studies (where reported), but closer to the TROPIC population. Taxane metabolism is affected by ethnicity and grade 3–4 neutropenia is much higher in Asian patients[124] However here is little evidence in this group for the safety and efficacy of cabazitaxel beyond two Phase I studies which have examined pharmacokinetics and dose escalation.[125, 126] In TROPIC 7% of subjects were Asian so this is an important study for this population.The higher rate of grade ≥3 neutropenia may also translate in a higher survival benefit as suggested by a recent Phase II study with docetaxel[127] and a post-hoc analysis of TROPIC study[128] A relationship between overall survival and the occurrence of grade ≥3 neutropenia has also been reported in many other solud tumor types, both in adjuvant and metastatic settings.[129]

4.11.5 The quality assessment for the EAP

The UK Early Access Programme (EAP) which was part of the wider international studyis of particular relevance to the decision problem. This is because as well as being a UK population, it incorporated an amendment allowing for an evaluation of Health related QOL.[12] One hundred and twelve patients participated in the UK EAP at 12 UK Cancer Centres. All had mCRPC with disease progression during or after docetaxel and were similar in baseline patient characteristics to the population in TROPIC. In the study (as in TROPIC) patients received cabazitaxel 25mg/m^2 every 3 weeks with prednisolone 10mg daily for up to 10 cycles. As documented in TROPIC, UK EAP patients received a median of 6 cycles of

cabazitaxel. Safety assessments were performed prior to each cycle and HRQL recorded at alternate cycles using the EQ-5D-3L questionnaire and visual analogue scale (VAS). These results are presented in detail in Section 5.4.

The other published studies discussed above report the safety (and to a certain extent efficacy) of cabazitaxel in clinical practice but the results are not synthesized for use in the modelling. A discussion of the issues around comparison with the TROPIC data is included in Section 4.12.1. The study by Bahl describing the UK EAP is used to inform utilities of health states in the economic model presented in Section 5 The assessment of quality presented below in Section 4.11.7 is for Bahl study only.[12]

4.11.6 Assessment of the risk of bias in the UK EAP.

The Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies available from the National Institutes of Health (NIH)[130] was used to assess the quality of the study by Bahl.[12]This is reproduced along with answers in Table 35 below.

Table 35. Quality assessment of the UK EAP study entitled: Final quality of life and safety data for patients with metastatic castration-resistant prostate cancer treated with cabazitaxel in the UK Early Access Programme (EAP) (NCT01254279).[12]

Criteria	YES/ NO	Comment
1. Was the research question or objective in this paper clearly stated?	Yes	To compile the safety profile and quality of life (HRQL) data for patients with metastatic castration-resistant prostate cancer (mCRPC) treated with cabazitaxel in the UK Early Access Programme (UK EAP).
2. Was the study population clearly specified and defined?	Yes	Patients were included if they had confirmed mCRPC previously treated with a docetaxel-containing regimen and had experienced disease progression during or after docetaxel. Other inclusion criteria were defined. Exclusion criteria were not specified but a reference is given to the TROPIC study where these are defined.
3. Was the participation rate of eligible persons at least 50%?	Unclear, but likely	The study recruited patients in 12 centres but it is not specified what proportion of patients presenting were recruited. However the rate of recruitment was higher than expected. Approximately 20% more patients were recruited than planned. Given the existence of alternative therapies such as the advanced hormonal drugs, the authors suggest this indicates clinician and patient enthusiasm for

Criteria	YES/ NO	Comment
		the use of second-line chemotherapy.
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes	See question 2 above
5. Was a sample size justification, power description, or variance and effect estimates provided?	No	The study was not powered to deliver on an end point; rather this was an observational study seeking to provide descriptive statistics.
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Yes	The number of cycles of cabazitaxel treatment received was recorded.
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Yes	The study observed adverse events due to cabazitaxel treatment and measured quality of life. Both of these outcomes are contemporaneous with study drug administration.
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	No	As this was an observational study within the bounds of clinical practice, intervention to examine different levels of exposure to the study drug was not implemented. As might be expected for a chemotherapy, exposure may have varied as a result of treatment discontinuation, dose reductions or treatment delays due to adverse events or disease progression.
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Exposure of participants to cabazitaxel is reported in detail. The study was conducted across 12 separate centres but there is no reason to consider that exposure was different across the centres.
10. Was the exposure(s) assessed more than once over time?	Yes	Safety assessments were made before each cycle and peripheral blood tests were performed before each treatment and within 3 weeks of treatment, weekly blood counts were

Criteria	YES/ NO	Comment
		performed after cycle 1 to detect early signs of neutropenia. HRQL assessment was performed at baseline and before alternate cycles.
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Safety and HRQL outcomes were predetermined. There is no indication that implementation varied across study centers
12. Were the outcome assessors blinded to the exposure status of participants?	No	This is a single arm observational study.
13. Was loss to follow-up after baseline 20% or less?	Not stated	Loss to follow-up is not stated.
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	No	The study did not control for different baseline patient characteristics or adjust for other variables which might impact the results. However within-patient analysis was employed to explore whether the results observed for the stable (and rising) mean HRQL scores across all patients was, in fact, due to selection bias. No bias is reported.

4.11.7 If there is more than 1 non-randomised or non-controlled study, tabulate a summary of the responses applied to each of the quality assessment criteria.

Only the UK EAP[12] has been assessed since HRQL results from this study are directly included in the economic model. The assessment is provided above in Section 4.11.6.

4.11.8 Quality assessment for each study should be included.

The assessment for Bahl, 2015[12] is provided above in Section 4.11.6.

Clinical effectiveness results of the relevant non-randomised and non-controlled evidence

4.11.9 Data from trial analyses should be presented whenever possible and a definition of the included participants provided.

Evidence from the CUP/EAP studies is presented in Section 4.11.11 below. In addition a discussion of the literature on the efficacy of cabazitaxel in the post abiraterone or enzalutamide setting is included.

4.11.10 The information may be presented graphically to supplement text and tabulated data.

Evidence from the CUP/EAP studies is presented in Section 4.11.11 below.

4.11.11 Evidence from the CUP/EAP and other studies

The safety and, where available, efficacy results from the CUP/EAPs which have reported interim and complete results in full publications to date are presented in Table 36. Abstracts with details of further country specific and aggregate CUP/EAPs are presented in Table 37.

Table 36. Summary of the safety and efficacy results from the full publications for the CUP/EAPs for cabazitaxel

Primary Reference	Country	Cabazitaxel cycles	OS Months, (95% CI)	PFS* 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: de Bono 2010[8]	Mulitiple	6	Median:15.1 (14.0 – 16.5)	Median: 2.8 (2.4-3.0)	277 (61)	95.7	94 (82)†	8 (8)	97 (11)	47 (6)	34 (2)	37 (5)
Heidenreich 2014[111]	Europe (20 countries)	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)
Lee 2014[112]	Korea	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)
Heidenreich 2013[113]	Germany	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
Bracarda 2014[114]	Italy	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)
Wissing 2014[115]	Nether-lands	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)
Castellano 2014[116]	Spain	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)

Bahl 2015[12]	UK	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)

* 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). †In the EAP neutropenia was based on AE declaration, whereas in TROPIC data for haematogical adverse events were based on laboratory assessments. Routine FBC was performed prior to every cycle; for cycle 1 further FBCs were performed in weeks 2 and 3. NR: Not reported.NR: Not reported.

No survival data was presented in the conference abstracts identified in the literature search (Table 37).

Table 37. Summary of the safety results from the conference abstracts for the CUP/EAPs for cabazitaxel

Primary Reference	Country	Cabazitaxel cycles	Deaths n, (%)	Percentage of patients with adverse events All grades ≥3						
				Any	Neutropenia	Febrile neutropenia	Anaemia	Diarrhoea	Vomiting	Fatigue
Malik 2013 (ASCO)[117]	Multiple (37)	6 (1–22)	39 (3.0)	43%	18%	7%	NR	4%	NR	NR
Heidenreich 2014 (ESMO)[118]	Multiple (12 countries)	5 (1–34)	30 (6.7)	41.2%	16.9%	8.9%	6.0%			4.0%
Sridhar 2013 (ASCO)[119]	Canada	6	1* (1.6)	NR	NR	6.6%	9.8%	8.2%	NR	8.2%
Houede 2012 (ASCO)[120]	France	3 (1–6)	0*	NR	4%	3%	NR	2.7%	0.5%	0.5%
Pripatnanont 2014 (SIU)[121]	Thailand	7 (1–13)	5* (12.5)	87.5% (all grades)	45%	12.5%	15%	10%	5%	7.5%

*Cabazitaxel treatment related deaths

In addition the review of the non-randomised, non-controlled evidence found several conference abstracts have been published which consider the safety of weekly and bi-weekly cabazitaxel regimens. The list and results from these are collected in Table 42 in Section 4.12.1 below.

4.11.12 Efficacy of cabazitaxel in the post abiraterone or enzalutamide setting.

Resistance to advanced hormonal therapies

The mechanisms of resistance to advanced hormonal therapy are now becoming better characterised, in particular ARv7+ve tumours typically show limited response to abiraterone or enzalutamide. Patients progressing rapidly to castration with ADT are also unlikely to respond to abiraterone or enzalutamide. Resistance can be characterised as primary or adaptive and it has long been established that as tumours progress and become more aggressive hormone therapy becomes ineffective.[131]

Because they target the same signalling pathway, clinical cross-resistance between abiraterone and enzalutamide is possible. Retrospective studies of abiraterone in patients previously treated with both docetaxel and enzalutamide have been reported [132, 133] These show a decrease in the activity of abiraterone compared to that expected.[52] (Table 38).

Table 38. Studies examining the cross resistance in the sequence abiraterone : enzalutamide.

Author	n	Median abiraterone duration	Pts with ≥50% PSA decline	Median PFS
No prior enzalutamide				
De Bono 2011[52]	797	8 months	29%	5.6 months
Prior enzalutamide				
Loriot 2013[132]	38	3 months	8%	2.7 months
Noonan 2013[133]	30	3 months	3%	3.6 months

Similarly, enzalutamide treatment as third line therapy after docetaxel and after abiraterone has been evaluated and indication of cross resistance is emerging. (Table 39).

Table 39. Studies examining the cross resistance in the sequence enzalutamide: abiraterone.

Author	n	Median abiraterone duration	Pts with ≥50% PSA decline	Median PFS
No prior abiraterone				
Scher 2012[10]	800	8.3 months	54%	8.3 months
Prior abiraterone				
Schrader 2013[134]	35	4.9 months	29%	2.8 months
Thomsen 2013[106]	24	4.0 months	17%	2.8 months
Badrising 2014[135]	61	3.0 months	21%	2.8 months
Bianchini 2014[136]	39	2.9 months	23%	3.1 months
Schmid 2014[137]	35	2.8 months	10%	4.6 months
Azad 2015[138]	68	4.1 months	22%	-
Brasso 2014[139]	137	3.2 months	18%	-

Author	n	Median abiraterone duration	Pts with ≥50% PSA decline	Median PFS
Joshua 2015[140]	507	2.6 months	-	-

Reviews of the literature suggest that there is no clear evidence of a clinical benefit of sequential therapy with these agents[141, 142] Indeed a very recent systematic review of published studies suggested that patients treated with 2 advanced hormonal therapies in sequence post-docetaxel may have shorter OS than those sequences containing cabazitaxel[143]

In the literature review carried out for this submission three full papers and 11 conference abstracts were identified with evidence for abiraterone or enzalutamide in the post-docetaxel setting. Since the review was carried out four further papers have been published which contain similar evidence. These studies are summarized in Table 40. All of these studies were retrospective cohort studies with the exception of the study by Onstek which considered biomarkers assayed before the start of the first and the third cycle of cabazitaxel during the randomized, Phase 2, open-label, multicenter study in mCRPC on the pharmacodynamic effects of budesonide on cabazitaxel (Jevtana) (CABARESC). A further poster presentation by Oudard on the updated results from the FLAC database of mCRPC patients has become available after presentation at ECC 2015 (European Cancer Congress).[144]

In addition to the articles above, 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.[143]

These articles provide evidence to support the continuing efficacy of cabazitaxel after treatment with advanced hormonal therapy (post-docetaxel setting) and are listed in Table 40 overleaf and are discussed further in appendix 20.

Taken as a whole the available evidence suggests that cabazitaxel remains potent in patients previously treated with the advanced hormonal agents abiraterone and enzalutamide. This could be due, at least in part, to the differing modes of action for the chemotherapeutic and the androgen-axis targeted agents and these have been discussed earlier in Section 3.3.

These articles provide evidence to support the continuing efficacy of cabazitaxel after treatment with advanced hormonal therapy (post-docetaxel setting) and are listed in Table 40 overleaf and discussed below

Table 40. Studies with evidence on the effect of pre-treatment with abiraterone or enzalutamide on cabazitaxel efficacy.

Reference	Country	Outcome	Objective
Full papers			
Caffo, 2015[145]	Italy	OS (primary), PFS, PSA response (biochemical RR), ORR	To provide an estimate on the clinical outcomes relating to a large cohort of patients with mCRPC who received a third-line new agent after the failure of docetaxel and another new agent.
Pezaro, 2014[146]	UK	PSA response, PFS, OS, symptomatic benefit (reported here as pain)	To describe the antitumour activity of cabazitaxel after docetaxel and next generation endocrine agents
Sella, 2014[147]	Israel	PSA response, radiographic response, OS	To review the experience with cabazitaxel given to mCRPC patients whose disease had progressed after docetaxel-based chemotherapy and abiraterone.
Nakouzi, 2015[148]	Not reported	PFS (radiographic or PSA), OS	To evaluate the antitumour activity of cabazitaxel in mCRPC pretreated with abiraterone or enzalutamide.
Onsteck, 2015[149]	Netherlands	Primary end point was the association between the AR-V7 status and the circulating tumour cells Secondary end points: PSA response rate, OS	To investigate the association between AR-V7 expression in circulating tumour cells and resistance to cabazitaxel.
Van Soest, 2015[150]	Netherlands	OS (primary), PFS, PSA response	The primary objective was to explore the influence of prior abiraterone or enzalutamide use on the efficacy of cabazitaxel in patients with mCRPC
Sponvade, 2105[151]	US	OS and Time to Treatment Failure (TTF)	Objective 1: To characterize patients receiving different sequences of cabazitaxel and abiraterone after docetaxel. Objective 2: To estimate and compare clinical outcomes in patients receiving these different sequences of therapy.

Reference	Country	Outcome	Objective
Maines, 2015[143]	Multicountry	OS	To explore the clinical outcomes of mCRPC patients who were treated with third-line cabazitaxel, abiraterone or enzalutamide after having previously received docetaxel in order to determine if treatment sequence is important in terms of overall survival.
Conference abstracts			
Wissing, 2013[152]	Netherlands	OS (primary), PFS, biochemical PFS, best clinical and PSA response, safety	To report the clinical outcome of Dutch mCRPC patients treated with both cabazitaxel and abiraterone after receiving docetaxel as first-line therapy, evaluating antitumor activity and safety of both agents.
Bracarda 2013 (ASCO)[153]	Italy	PFS	To analyse patients treated with both abiraterone and cabazitaxel in terms of best sequencing evaluation and potential predictive and prognostic factors for different treatment sequences in a real world scenario.
Caffo 2015 (ASCO-GU)[154]	Italy	PFS, OS, ORR, PSA response	To assess the activity of new agents in patients who previously experienced a primary resistance to another new agent administered after docetaxel
Clement-Zhao 2015 (ASCO-GU)[155]	France	Safety, PSA response, TTP (biochemical), rPFS, OS	To evaluate safety and efficacy of a 2-weekly cabazitaxel schedule
Houts 2013 (ASCO's Quality Care Symposium)[156]	US	OS, PFS	To examine whether mCRPC patients progressing on docetaxel received cabazitaxel and/or abiraterone, in which sequence, and how they compared with patients not receiving cabazitaxel or abiraterone
Kellokumpu-Lehtinen 2015 (ASCO-GU)[157]	Finland	Safety (primary)	To evaluate the safety of 2-weekly cabazitaxel as post-docetaxel treatment for mCRPC
Oudard 2014	France,	PSA response, OS, PFS	To evaluate the impact of prognostic factors and sequencing on OS

Reference	Country	Outcome	Objective
(ESMO)[158]	Spain, Turkey		calculated from the first therapy post-docetaxel.
Pezaro 2013 (ASCO-GU)[159]	UK and France	Radiological response, PSA response, symptomatic benefit	To evaluate the antitumor activity of cabazitaxel after abiraterone
Pfister 2012 (ASCO-GU)[160]	Germany	PSA response rate, PSA stabilization, safety	To compare the PSA response and complication rate of these three different second-line treatment options: cabazitaxel, abiraterone and docetaxel re-challenge.
Saad 2014 (ASCO)[161]	Canada	PSA response, HRQL	To better understand the impact of prior abiraterone treatment on cabazitaxel efficacy and HRQL.
Sonpavde 2013 (ESMO)[162]	US	OS, TTF	To evaluate treatment patterns, OS, and TTF among post-docetaxel mCRPC patients receiving both abiraterone and cabazitaxel

4.12 Adverse reactions

4.12.1 Evidence from sources other than TROPIC.

The adverse event profile from the TROPIC study is presented Section 4.12.2 below.

The systematic review of the literature for non-RCT evidence described in section 4.11 above identified a number of studies which included safety of cabazitaxel as the primary end point. In particular the Compassionate Use Program / Early Access programmes (CUP/EAP) provide key data to supplement the results from TROPIC with data collected in clinical practice. The published interim results from these observational studies have been presented in Section 4.11.9 above (Table 36) for key adverse events and are discussed below in Section 4.12.3

In addition to these published data several registries are being conducted by Sanofi around the world and one in particular, the prospective product registry in Belgium (CABAZL06515: HRQLANA), has provided results not yet published. (09/02/2015) The aim of this study was to describe the use of cabazitaxel in combination with oral prednisone (or prednisolone) for the treatment of patients with mCRPC. This is also discussed below in Section 4.12.3.

In the UK the ECLIPSE study, described in Appendix 20, which aimed to describe the anti-cancer treatment pathways, clinical outcomes and patient characteristics for patients who have received cabazitaxel following prior docetaxel treatment has reported OS results. Analysis of adverse events is ongoing and may be available within the timeframe of this submission. Furthermore the period risk benefit evaluation report is presented in brief in Section 4.12.3.

4.12.2. Summary of adverse reactions.

Adverse events in TROPIC were collected from the time the first dose of the study drug until 30 days after the administration of the last cycle of study treatment. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0 (NCI CTCAE v. 3.0) and summarized using Medical Dictionary for Regulatory Activities (MedDRA) terminology Version 12.0.

Serious adverse events were reported from the signature of informed consent up to 30 days after the last dose of study medication. After the 30 day follow-up visit, ongoing SAEs were followed until resolution or stabilization. At the end of study treatment, all AEs and SAEs considered related to study treatment were followed until resolution.

Patients in the cabazitaxel group received a median of 6 cycles of treatment and patients in the mitoxantrone group received a median of 4 cycles of treatment (range: 1 to 10 cycles in both arms). The cumulative doses were consistent with the number of cycles received.

The median relative dose intensity (RDI) was 96.12% with a range of 49.0% to 108.2% for the cabazitaxel group and 97.25% with a range of 42.5% to 106.0% for the mitoxantrone group. This indicates that the intended dose of cabazitaxel and mitoxantrone could be

delivered. In the cabazitaxel group, 9.8% of cycles were administered with a dose reduction of ≥20% and 9.3% of cycles were delayed by ≥4 days compared with 5.1% of cycles dose reduced and 7.9% cycles delayed, respectively, in the mitoxantrone group.

Treatment emergent adverse events of Grade ≥3 occurred in 57.4% of patients in the cabazitaxel group and 39.4% of patients in the mitoxantrone group. Serious TEAEs were reported in 39.1% of patients in the cabazitaxel group and 20.8% of patients in the mitoxantrone group. The proportion of patients withdrawing from study treatment due to any TEAE (including disease progression reported as a TEAE) was 18.3% in the cabazitaxel group compared with 8.4% in the mitoxantrone group. The incidence of TEAEs (not coded as disease progression) leading to death was 4.9% in the cabazitaxel group and 1.9% in the mitoxantrone group.

The most common AEs (Grade ≥3 events occurring in ≥5% of patients in either treatment group) are summarised in Table 42. The most common events were neutropenia and its complications (febrile neutropenia and infections), asthenic conditions (asthenia and fatigue), and gastrointestinal toxicity (diarrhoea, nausea and vomiting).[8]

The most important AE associated with cabazitaxel is neutropenia, due to the potential for serious clinical complications. Neutropenia is to be expected when treating with taxane-based chemotherapy and is not necessarily difficult to manage for experienced centres [163] However, complications of neutropenia such as neutropenic sepsis and febrile neutropenia are serious clinical events. As can be seen in Table 42, patients treated with cabazitaxel had higher rates of neutropenia, (7.3% vs. 21.0% of patients based on adverse event declaration) and higher rates of infections and febrile neutropenia (1.6% vs. 7.3% of patients based on adverse event declaration).

The clinical consequences of neutropenia were the most frequent cause of adverse event related death in the cabazitaxel group, with seven neutropenia-related deaths in comparison with one in the mitoxantrone group. The occurrence of these deaths prompted advice to the TROPIC investigators to manage neutropenia by strictly following the protocol regarding dose modification and delay and treating neutropenia as per ASCO guidelines.[41] Following this, no new neutropaenic deaths were reported. This shows that it is critically important that, as with other similar chemotherapies, neutropenia is appropriately managed, particularly when patients are newly started on cabazitaxel treatment.

With the exception of the haematological adverse events the side effects (grades 3 and over) in both treatment arms were generally well balanced. The exceptions were grade ≥3 diarrhoea and fatigue which were more common for patients taking cabazitaxel (6.2% and 4.9%) compared with mitoxantrone (0.3% and 3.0%) Table 42.

The number of deaths in TROPIC are summarised in Table 41. Eighteen (5%) patients treated with cabazitaxel and nine (2%) treated with mitoxantrone died within 30 days of the last infusion. All of these deaths in the cabazitaxel group were considered related to TEAEs, whereas six in the mitoxantrone group were related to disease progression.[8]

Table 41. Deaths reported in the TROPIC trial – ITT population.

Outcome	Mitoxantrone + prednisone (n=377)	Cabazitaxel + prednisone (n=378)
Total deaths during the study (%)	308 (81.7)	277 (73.3)
Number of patients censored (%)	69 (18.3)	101 (26.7)

A total of 68 patients (18.3%) in the cabazitaxel group and 31 patients (8.4%) in the mitoxantrone group withdrew from the study due to AEs. The most common TEAEs leading to treatment discontinuation in the cabazitaxel group were neutropenia (2.4%), hematuria (1.3%), diarrhoea, fatigue, renal failure acute (1.1% each), and abdominal pain, febrile neutropenia, sepsis, and renal failure (0.8% each). In the mitoxantrone group the most common TEAEs leading to treatment discontinuation were asthenia, back pain, pulmonary embolism, cardiotoxicity, and ejection fraction decreased (0.5% each).

Table 42. Adverse events grade 3 or above reported in patients in TROPIC who received at least one dose of study treatment*. Subgroup ECOG-PS 0-1 with 225mg/m^2 prior docetaxel exposure and ITT populations.

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

*AEs reported by the investigator. (These do not include abnormal laboratory values).

4.12.3 Details of the additional studies that report additional adverse reactions.

A summary of the safety and efficacy results from the full publications for the CUP/EAPs for cabazitaxel which includes safety as a primary end point or reports adverse events as secondary outcomes has been presented in Section 4.11.11. The methodology used to identify these published articles and conference abstracts has been described in Section 4.11 and Appendix 6. In the following section adverse events in the CUP/EAP are described.

Further conference abstracts for ongoing studies are presented in brief and the results from the prospective cabazitaxel product registry in Belgium are discussed. In addition a brief summary of the Cabazitaxel Periodic Benefit Risk Evaluation Report is presented.

Adverse events in the CUP/EAP

The results of the EAP extend the knowledge of the safety profile reported in TROPIC to settings more reflective of everyday clinical practice. The first entry in Table 36 above contains the equivalent data from the TROPIC study. Note that the safety results reported in the original paper are associated with lab values for the hematological events.[8] Any comparison must be treated with some caution[113] for the following reasons:

- It is possible that the patients included in the TROPIC trial and CUP/EAP had a different disease burden.
- TROPIC was conducted in 26 countries in Europe, North America, Latin America, India, Asia and South Africa, and it appears that some centres were not sufficiently experienced in monitoring and managing the toxicities of chemotherapy.
- Haematology was monitored on a weekly basis in TROPIC while it was collected before each injection in the European CUP/EAP in order to reflect real-life practice.
- Prophylactic G-CSF at the first cabazitaxel cycle was not allowed in TROPIC (it was allowed at physicians' discretion after first occurrence of either neutropenia lasting 7 days or more or neutropenia complicated by fever or infection) while in the European CUP/EAP, prophylactic G-CSF was allowed from the first cycle, as per ASCO and EORTC guidelines.

With these caveats in mind the results from these interim analyses of the EAP shown in Table 36 above, suggest cabazitaxel to be a well-tolerated agent in clinical practice. This is despite concerns raised over the high incidence of neutropenia and neutropenic sepsis in the TROPIC trial.[3] Indeed there were comparatively low rates of neutropenia (7 to 34% vs. 82%[8] in TROPIC) and febrile neutropenia in the EAP cohorts (2 to 6 % vs. 8% in TROPIC: note the results from Lee (31%) are discussed below).[112] The lower incidence data may be partially due to a more rigorous application of the ASCO guidelines for prophylaxis with G-CSF and the general management of febrile neutropenia, as well as improved preventative (proactive) patient education regarding possible treatment-related adverse events. Note that prophylactic G-CSF was not permitted during the first cycle in TROPIC, but thereafter was permitted at physician's discretion and was mandated for prophylaxis after first occurrence of neutropenia.

Whilst other adverse events were of similar or lower incidence, febrile neutropenia was higher in the Korean population (n = 26) studied in the EAP than in TROPIC (31% vs. 7.3%).[112] In a previous Japanese Phase I study, grade 3–4 neutropenia developed in Whilst both of these studies were carried out in small numbers of patients and only 60% of patients in the Korean EAP received G-CSF prophylaxis these results could suggest that cabazitaxel maypossibly have a lower clearance than in caucasians resulting in higher circulating concentrations.. This is reminiscent of pharmacoethnicity effects on toxicities associated with docetaxel.[124] However, higher circulating concentrations may also results in a higher efficacy as suggested by a recent Phase II study comparing docetaxel (75mg/m2) plus prednisone

versus mitoxantrone plus prednisone in Chinese mCRPC patients. Docetaxel was associated with a higher rate of grade ≥3 neutropenia than in TAX327 (57.7% versus 32%) but the survival benefit was much higher (21.9 versus 13.7 months, HR 0.63) than in TAX327 (18.9 versus 16.5, HR 0.76).[127] Similar findings have been observed in a post-hoc analysis of TROPIC study suggesting that patients experiencing grade ≥3 have an improved OS, PFS and PSA response.[128] It is noteworthy that with the exception of one patient in the Korean EAP, no patients who received prophylactic G-CSF developed febrile neutropenia throughout the entire chemotherapy course. Nonetheless Lee et al. suggest that based on patient characteristics and efficacy results cabazitaxel demonstrates at least a comparable efficacy in Korean mCRPC patients and Western patients.[112]

In addition to the EAP there are a number of other studies seeking to evaluate the efficacy and safety of cabazitaxel as a weekly or bi-weekly infusion (the current label indicates dosing at 3 weekly intervals). Several conference abstracts have been published that include some results from these programs. (Table 43).

Table 43. Conference abstracts with safety information

Reference	Country	Dose	Regimen	n	Age	ECOG/WHO performance status, n (%)		Deaths	AEs grades ≥3 %					
						0	1 - 2		Any grade 3/4	Neutro-penia	Febrile neutro-penia	Anaemia	Diarrhoea	Nausea
Calvo 2015 (ASCO-GU)[164]	Spain	10 mg/m2	IV weekly	70	73 (54–84)	33%	67%	NR	NR	12.1	7.6	71.2	27.3	18.2
Clement-Zhao 2015 (ASCO-GU)[155]	France	16 mg/m2	IV every 2 weeks	26	66.5	69%	31%	NR	NR	23.8	NR	33.3	0.0	NR
Kellokumpu-Lehtinen 2015 (ASCO-GU)[157]	Finland	16 mg/m2	IV every 2 weeks	40	NR	33%	67%	NR	18 (45)	15.0	NR	5.0	NR	NR
Gonzalez 2014 (ASCO)[165]	Spain	NR	NR	99	70	77%	23%	NR	17 (17.2)	5.0	0.0	2.0	2.0	NR
Nicacio 2012 (ESMO)[166]	US	NR	NR	373	(45–88)	NR	NR	57	NR	7.2	NR	2.4	5.6	3.8

Safety results from the prospective product registry in Belgium

This study has reported internally.

This was a national, multicenter, observational (non-interventional on the therapeutic strategy) prospective product registry to assess the use of cabazitaxel in combination with oral prednisone (or prednisolone) in real-life for the treatment of mCRPC patients (HRQLana). Registry number: CABAZL06515. Data collection lasted until death or until registry cut-off, whichever came first. There was no protocol defined visit schedule and visits took place according to the clinical practice. The study population consisted of all patients eligible for a treatment with cabazitaxel for their prostate cancer, according to the Belgian reimbursement criteria and who presenting none of the contraindications listed in the SmPC and for whom the decision to start a cabazitaxel treatment had already been taken. Demographic data is provided in Table 44 below.

Table 44. Baseline patient characteristics for the patients enrolled in HRQLANA

Number of patients	*Academic in confidence information removed*
Mean age, years (SD) Median age, years (range)	
Median time since diagnosis	
median time since castration-resistant disease diagnosis	
Gleason score	
Baseline PSA	
ECOG performance score	

The most frequent first line therapies were chemotherapy alone for *Academic in confidence information removed* of the patients and together with other targeted therapies for *Academic in confidence information removed*, and hormono-targeted therapy alone (*Academic in confidence information removed*). About *Academic in confidence information removed* had a second line therapy, among which hormono-targeted therapy only was the most frequent (*Academic in confidence information removed* of the patients treated in second line), followed by chemotherapy only *Academic in confidence information removed* were treated in third line, *Academic in confidence information removed* of whom received chemotherapy and *Academic in confidence information removed* hormono-targeted therapy. *Academic in confidence information removed* were treated in fourth line, among which *Academic in confidence information removed* received chemotherapy and *Academic in confidence information removed* hormono-targeted therapy.

All *Academic in confidence information removed* patients only treated in first line received chemotherapy. Among the *Academic in confidence information removed* patients having received two lines of treatment most *Academic in confidence information removed* were treated with chemotherapy (docetaxel) followed by hormono-targeted therapy (abiraterone). Among the *Academic in confidence information removed* having received three lines of treatment *Academic in confidence information removed* were first treated with chemotherapy, followed by hormono-targeted therapy, and chemotherapy again.

Treatment-emergent adverse events (TEAEs) were reported for *Academic in confidence information removed*, SAEs for *Academic in confidence information removed*), AEs considered related to the study medication for *Academic in confidence information removed ,* AEs with NCI CTCAE grade of at least *Academic in confidence information removed .* AEs causing premature drug discontinuation for *Academic in confidence information removed* and AEs with fatal outcome for *Academic in confidence information removed*

The System Organ Class for which the occurrence of related AEs with NCI CTCAE grade at least 3 was the most frequent was blood and lymphatic system disorders (*Academic in confidence information removed)* followed by general disorders and administration site conditions (*Academic in confidence information removed)* and infections and infestations (*Academic in confidence information removed).* The most frequent Preferred Terms for related AEs with NCI CTCAE grade at least 3 were febrile neutropenia (*Academic in confidence information removed),* neutropenia (*Academic in confidence information removed),* anaemia (*Academic in confidence information removed)* and fatigue (*Academic in confidence information removed).*

The HRQLANA study population is more heterogeneous in terms of baseline patient, disease characteristics, and tumour heterogeneity than the TROPIC cohort and the changing treatment landscape in mCRPC with the emergence of new therapies since TROPIC mean that therapeutic pathways are now different. This means that direct comparisons are not possible.

However despite this heterogeneity the results suggest that cabazitaxel in the real-life setting has a similar safety profile to that seen in the CUP/EAP results discussed earlier. At the time of this interim analysis, *Academic in confidence information removed* patients discontinued treatment, from which *Academic in confidence information removed* presented disease progression. The median PFS at this stage is of *Academic in confidence information removed* days (*Academic in confidence information removed* months) for the entire study group. (In the TROPIC study, the median PFS for patients treated with cabazitaxel was *Academic in confidence information removed* months). For the OS results, the data at interim analysis are still immature with only *Academic in confidence information removed* deaths reported. Longer follow-up is needed to provide OS data.

Cabazitaxel Periodic Benefit Risk Evaluation Report

Cabazitaxel received marketing authorisation in all 27 countries of the European Union (EU) in March 2011 and so has been in use in clinical practice for approximately four years. An annual periodic safety update report is compiled by Sanofi which summarizes the information received from worldwide sources by the Sanofi Global Pharmacovigilance and Epidemiology department. The latest issue of this report covers the period from 17th June 2013 to 17th June 2014.

To date approximately 36 550 patients have been exposed to cabazitaxel around the world including 11 800 patients during the reference period covered by the latest report (17th June 2013 to 17th June 2014). Approximately 4502 cumulative subjects/patients were exposed to cabazitaxel in clinical trials up-to the data lock point of the report (17th June 2014).

The safety information presented in the Periodic Benefit Risk Evaluation Report is consistent with the known safety profile of cabazitaxel. The observed adverse reactions or any other safety data does not suggest a change in the benefit-risk profile of cabazitaxel. In conclusion, the extensive clinical and post-marketing experience with cabazitaxel is considered to have demonstrated the therapeutic value of the compound. The safety profile of cabazitaxel is comparable to that of other products in this therapeutic class. Overall, based on the review of safety and efficacy data, Sanofi considers that the benefit-risk balance of cabazitaxel in the treatment of mCRPC in patients previously treated with a docetaxel-containing regimen is favourable and in line with the findings in the EPAR, that routine pharmacovigilance is sufficient to monitor the safety profile of cabazitaxel.

Although subject to the limitations of the post-marketing voluntary adverse event reporting systems, the emerging safety profile of cabazitaxel is consistent with and indeed may be better than that observed in the TROPIC clinical trial setting.

Other studies

Published Phase III safety evidence for cabazitaxel is limited to the TROPIC study as discussed in Section 4.2 and the Early Access Program (EAP) (Section 4.11.9). No additional Phase III RCT evidence is currently available for cabazitaxel beyond the updated TROPIC analysis for which the safety and adverse event data has been described earlier in Section 4.12.2. At the time of writing (21/09/2015) there are 12 Phase III studies listed on ClinicalTrials.gov, completed or ongoing, examining the efficacy and/or safety of cabazitaxel, some of which are sponsored by Sanofi. (Table 45).

TROPIC and the EAP have been discussed earlier but amongst the other studies PROSELICA (NCT01308580), may provide additional information about the safety of cabazitaxel in mCRPC which could supplement the original TROPIC data within the timeframe of this submission. PROSELICA is discussed in more detail below in Section 4.14.

Table 45. Phase III cabazitaxel RCTs listed on clinicaltrials.gov (23/07/2015).

NCT Number	Acronym	Title	n	Completion Date	Sponsor/Collaborators
NCT00417079	TROPIC	XRP6258 Plus Prednisone Compared to Mitoxantrone Plus Prednisone in Hormone Refractory Metastatic Prostate Cancer	755	01/09/2009	Sanofi
NCT01083615		A Study Evaluating the Pain Palliation Benefit of Adding Custirsen to Docetaxel Retreatment or Cabazitaxel as Second Line Therapy in Men With Metastatic Castrate Resistant Prostate Cancer (mCRPC)	14	01/03/2013	OncoGenex Technologies|Teva Pharmaceuticals USA
NCT01254279	EAP	Early Access to Cabazitaxel in Patients With Metastatic Hormone Refractory Prostate Cancer Previously Treated With a Docetaxel-containing Regimen	984	01/12/2014	Sanofi
NCT01308580	PROSELICA	Cabazitaxel at 20 mg/mÂ² Compared to 25 mg/mÂ² With Prednisone for the Treatment of Metastatic Castration Resistant Prostate Cancer	1200	01/07/2015	Sanofi
NCT01308567	FIRSTANA	Cabazitaxel Versus Docetaxel Both With Prednisone in Patients With Metastatic Castration Resistant Prostate Cancer	1170	01/08/2015	Sanofi
NCT01578655	AFFINITY	Comparison of Cabazitaxel/Prednisone Alone or in Combination With Custirsen for 2nd Line Chemotherapy in Prostate Cancer	630	01/12/2015	OncoGenex Technologies|Teva
NCT02044354	CABA-DOC	Patient Preference Between Cabazitaxel and Docetaxel in Metastatic Castrate-resistant Prostate Cancer	174	01/02/2016	Gustave Roussy, Cancer Campus, Sanofi
NCT02074137		Evaluation of Safety of Cabazitaxel (Jevtana) in Patients With Metastatic Hormone Refractory Prostate Cancer	10	01/02/2016	Sanofi
NCT01649635	PROSPECT A	Study of Cabazitaxel Combined With Prednisone and Prophylaxis of Neutropenia Complications in the Treatment of Patients With Metastatic Castration-resistant Prostate Cancer	45	01/03/2016	Sanofi
NCT02441894	PEGAZUS	Combination of Cabazitaxel With Prednisolone With Primary Prophylaxis With PEG-G-CSF in Treatment of Patients With Prostate Cancer	25	01/12/2016	Sanofi
NCT01978873	SensiCab	Efficacy Study Evaluating Chemotherapy in Prostate Cancer	400	01/11/2019	Ã–rebro University, Sweden
NCT01952223	PEACE2	A Phase III of Cabazitaxel and Pelvic Radiotherapy in Localized Prostate Cancer and High-risk Features of Relapse	1048	01/09/2026	UNICANCER

PROSELICA is a Randomized, Open Label Multi-Centre Study designed to demonstrate non-inferiority in terms of overall survival (OS) for patients with mCRPC previously treated with a docetaxel-containing regimen taking cabazitaxel 20 mg/m² versus cabazitaxel 25 mg/m² in combination with prednisone. Secondary objectives include a comparative assessment of the tolerability and safety of the 20 mg/m² dose versus 25 mg/m².

PROSELICA is expected to achieve database lock in August/September 2015 and so adverse event data from PROSELICA is not presented here. However should this become available within the timeframe of this submission an addendum may be presented at the earliest appropriate opportunity. A description of the study is provided in

Table 47 along with further discussion about the relevance of the data to the decision problem.

The FIRSTANA (NCT01308567) study may also provide preliminary outputs within the timeframe of this appraisal; however this study is in patients who are chemotherapy naïve and so falls outside the indication discussed in this submission.

Other studies listed in Table 45 are not due to report until 2016 or later, or are not sponsored by Sanofi. Further description of ongoing studies is provided in Section 4.14.

4.12.4 Overview of the safety of the technology in relation to the decision problem.

The most common AEs observed in the cabazitaxel arm in TROPIC were neutropenia and its complications (febrile neutropenia and infections), asthenic conditions (asthenia and fatigue), and gastrointestinal toxicity (diarrhoea, nausea and vomiting) (Table 42). These are common to cytotoxic agents and the taxanes as a class.[18]

The emerging evidence from the EAP (Table 31 and Table 32) and other sources discussed above suggests that these AEs are managed well in clinical practice. Treatment with granulocyte colony-stimulating factor (G-CSF) may mitigate haematologic adverse events, whereas supportive treatment with antiemetic and antidiarrhoeal agents may ameliorate gastrointestinal symptoms as per ASCO guidelines.[41] A Phase III study is ongoing to investigate the prophylaxis of neutropenia complications in the treatment of mCRPC (POSTECTA, NCT01649635) Table 45, but this will not report within the timeframe of this submission. In addition patient education and close monitoring for development of neutropenia all contribute to this improved AE event profile in clinical practice.

European regulatory opinion, as reported in the EPAR, was that cabazitaxel had a positive risk-benefit profile, with no requirement for a specific risk management plan.[3] This reflects the fact that the side-effects of cabazitaxel are predictable and manageable. Further, the higher risk of AEs is outweighed by the efficacy of cabazitaxel, which results overall in increased survival. In the economic evaluation, the costs and disutilities associated with AEs (≥ Grade 3) are fully considered.

The safety information presented in the Periodic Benefit Risk Evaluation Report (Section 4.12.1) suggests that the safety profile of cabazitaxel in clinical practice is comparable to that

of other products in this therapeutic class and that routine pharmacovigilance is sufficient to monitor the safety profile of cabazitaxel.

4.13 Interpretation of clinical effectiveness and safety evidence

4.13.1 A statement of principal findings from the clinical evidence highlighting the clinical benefits and harms of the technology.

The TROPIC trial in mCRPC patients who have progressed after docetaxel, directly compared cabazitaxel with mitoxantrone. The primary outcome was Overall Survival (OS), which is clinically relevant and not susceptible to bias or limitations in assessment. The results of this study show a statistically and clinically meaningful prolongation in OS for the ITT population as measured by both median (difference of 2.3 months) and mean OS (difference of 4.02 months). Mean OS difference represents an increase in survival of approximately 30% for this patient group.

The most common adverse effects due to cabazitaxel observed in the TROPIC study were haematological, in particular neutropenia, leukopenia, and anaemia.[8] The most common nonhaematological grade 3 or higher adverse event was diarrhoea. (Table 42). Neutropenia in particular occurred at a high rate in the TROPIC trial population but it was shown to be less prevalent in the CUP/EAP where cabazitaxel was used in clinical practice (Overall results for the EU EAP, n= 746: 17% EAP vs. 21% in TROPIC[111]) (82% is reported in the original publication and in Heidenreich, 2014,[111] but this result is higher as it captures all positive laboratory results for neutropenia and not only those identified in clinical practice) (See also Section 4.12.1). Accumulating evidence from the CUP/EAPs around the world indicates that real-world toxicity of cabazitaxel is less than that experienced in the TROPIC trial and is manageable with appropriate prophylactic and supportive care measures.[111] The UK EAP has shown that cabazitaxel in combination with prednisolone is generally well tolerated after prior docetaxel chemotherapy. Patients treated with cabazitaxel also showed stable HRQL scores with a trend towards improvement and reduction in the incidence and severity of pain.[12] This suggests that cabazitaxel is not associated with a significant negative effect on utility, and may improve utility through stabilising disease and controlling symptoms. The EQ-5D results for the UK EAP are presented in Section 5.4.1.

It is important to consider how cabazitaxel and other therapies should be used at each point in disease and to reflect when the drug's mode of action is most appropriate for tackling the properties the prostate cancer is expressing and the particular patients' needs. Recently the underlying cellular and molecular mechanisms responsible for the heterogeneity observed within and between individual prostate cancers has become more clearly understood.

4.13.2 Discussion of the strengths, limitations, validity and relevance of the clinical evidence base for the technology.

TROPIC was a large (755 patients) multicentre trial. The study was well conducted and adequately powered and this was recognised in the ERG report to TA255.[4] Analysis of time-

to-event efficacy outcomes, including the primary outcome, was conducted on the ITT population providing internal validity. The interim analyses were conducted by an external contract statistician and reviewed by an IDMC and the results were not disclosed to the trial sponsor. The number of patients lost to follow-up was low.

Over 80% of the patients included in the TROPIC study had an ECOG PS of 0–1 and prior use of docetaxel of at least 225 mg/m^2 which is reflective of the population in whom cabazitaxel is used in clinical practice in the UK.

The dosing schedule used in the TROPIC trial was consistent with the dosing schedule detailed in the summary of product characteristics,[15] consisting of 25 mg/m^2 (Day 1) intravenous infusion over 60 minutes every three weeks, and prednisone 10 mg orally given daily. In clinical practice the median number of cycles of treatment observed is 6[117] and this was also the number observed in TROPIC. Not all patients who have progressed after docetaxel receive cabazitaxel rather; cabazitaxel is best used in a subset of patients with good performance status who are able and willing to tolerate further chemotherapy.[19] The patients included in TROPIC are representative of this group.

A criticism cited by the ERG in the report to TA255 was that the age of the population in TROPIC may have been *'younger than is typical of patients with docetaxel-resistant mHRPC who are generally seen in the UK'.* However the baseline patient characteristics from the UK EAP[12] and also the ECLIPSE study (see Appendix 20) indicate that patients treated in clinical practice with cabazitaxel in the UK are of a similar age to the TROPIC population (Mean age in years: UK EAP: 67.0 (IQR: 63 – 72.5); ECLIPSE: 69.4 (SD: 6.69); TROPIC: 68 (IQR: 62 – 73)). Similarly it was speculated that there may be fewer co-morbidities amongst the TROPIC population than would be expected in clinical practice. ECLIPSE provides an estimate of the co-morbid status of UK cabazitaxel patients in clinical practice. In this study 47% of patients had no co-morbidity, 40% had 1 and 9.6% had two or more co-morbidities with 0.4% of patients unknown.

The TROPIC trial directly compares cabazitaxel and mitoxantrone (both with prednisolone), in this population. Mitoxantrone is the most valid comparator for cabazitaxel in the pathways described (Figure 3) due to the established place of cabazitaxel in current practice and the likelihood that if cabazitaxel were to be removed, mitoxantrone, although a retrograde step, is likely to be its replacement. The nature of mCRPC and the requirement for different options (Section 3.1) and the changing needs of patients means that cabazitaxel, abiraterone, and enzalutamide must all be available for use at the physicians discretion as the patient's circumstances demand.

Indirect comparisons to abiraterone and enzalutamide, whilst technically possible, are of limited validity for several reasons. The data has significant limitations for comparison, including differences in the patient populations, variations in the endpoints reported, and indeed variations in the conduct of the trials particularly in relation to treatment continuations. Therefore whilst the results of the network meta-analysis highlight the similarity in the results, their respective roles are complimentary, rather than alternatives. (Appendices B).

The lack of a standard definition for PFS in mCRPC trials has proved problematic notably in the comparison with the COU-AA-301 and AFFIRM studies summarised in scenario analysis in Section 4.10 and Appendices B. TROPIC study was designed before the development of a standardised definition of PFS for prostate cancer trials. Disease progression was defined as the time between randomisation and the first date of progression as measured by PSA progression, tumour progression using RECIST criteria, pain progression or death. Although time to PSA progression is associated with PFS,[167] time to PSA progression usually precedes symptomatic or radiologic progression. Patients were withdrawn from study treatment on the first sign of progression, including confirmed PSA progression. The relatively short PFS duration (in comparison with other cancer types) reflects the definition of PFS used in TROPIC. This means that patients may have been withdrawn from the study drug earlier than might be expected from later studies and the main measure of PFS could therefore be somewhat truncated.

QoL data were not collected in the TROPIC trial. However, EQ-5D data have been collected from UK patients included in the cabazitaxel EAP and an interim analysis was presented in the original submission (TA255). The final analysis is now available and has been utilised for the purposes of this submission. (See Table 55 for the utility values used in the analysis).

Summary

In conclusion, cabazitaxel has robust evidence to demonstrate OS and PFS benefits versus a relevant comparator. Within the evolving treatment paradigm of mCRPC, cabazitaxel provides an important treatment option for patients who have acquired or innate resistance to the hormonal based therapies abiraterone or enzalutamide.

End of Life criteria

Life expectancy in people with mCRPC varies according to the nature of their disease. In a recent review of the literature West et al. estimated worst-case, typical and best-case scenarios for survival in patients starting systemic therapies for castration resistant prostate cancer (CRPC).[13] 23 trials (13,909 patients) were reviewed with 48 treatment groups including 28 of chemotherapy, and three of novel hormonal agents. In the 11 treatment groups treated with first-line docetaxel, median OS was 19 months (IQR: 17–20). Observed median OS for patients in the control arms of: TROPIC, 12.7 months, COU-AA-301 (abiraterone): 11.2 months, AFFIRM (enzalutamide): 13.6 months and ALSYMPCA (Radium-223): 11.3 months.

On the basis of the information above, the importance of optionality in the provision of therapies for patients with mCRPC and consideration of the pathways which have been discussed in Section 4 delimiting the use of abiraterone and enzalutamide, we believe that cabazitaxel meets the criteria for consideration as 'life-extending treatment at the end of life'. These data are summarised in Table 46 below.

Table 46 End-of-life criteria.

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Recent estimates suggest median OS of around 19 months for patients starting docetaxel based regimens.[13] Median OS in the control arms of TROPIC, COU-AA-301 AFFIRM and ALSYMPCA varied between 11.2 and 13.6 months.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	See Section 4.7. Mean survival for the ITT population in TROPIC for the mitoxantrone arm was 14.53 months and 18.55 months in the cabazitaxel arm. The difference in mean survival was 4.02 months. The difference in median survival was 2.4 months.
The treatment is licensed or otherwise indicated for small patient populations	See section 3.4, Table 10. It is estimated that there are 6,147 patients with mCRPC in England in 2015. Of these around 1690 will be eligible to receive second line chemotherapy.

4.14 Ongoing studies

Since the granting of marketing authorisation for cabazitaxel in March 2011 there have been a number of studies which have completed or are ongoing in a number of different indications.

Studies that are likely to complete or report in the next 12 months are tabulated in Appendix 7.

The key studies which may provide evidence within the timeframe of this submission are PROSELICA, ECLIPSE and FIRSTANA. These are discussed below and in appendix 20.

The PROSELICA study is likely to provide key additional information pertinent to the decision problem about the efficacy and safety of cabazitaxel which will supplement the original TROPIC data. It was a large Randomized, Open Label Multi-Center Study comparing cabazitaxel at 20 mg/m² and at 25 mg/m² every 3 weeks in combination with prednisone for the treatment of metastatic castration resistant prostate cancer previously treated with a docetaxel-containing regimen. A description of the study is provided in Table 47.

Table 47. PROSELICA study description.

	Study description
Title	Randomized, Open Label Multi-Center Study comparing cabazitaxel at 20 mg/m² and at 25 mg/m² every 3 weeks in combination with prednisone for the treatment of metastatic castration resistant prostate cancer previously treated with a docetaxel-containing regimen.
Study numbers	Sanofi internal: XRP6258-EFC11785 Clincinaltrials.gov: NCT01308580
Primary objective	To demonstrate the non-inferiority in terms of overall survival (OS) of cabazitaxel 20 mg/m² (Arm A) versus cabazitaxel 25 mg/m² (Arm B) in combination with prednisone in patients with metastatic castration resistant prostate cancer (MCRPC) previously treated with a docetaxel-containing regimen.
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: − Progression Free Survival (PFS) defined as the first occurrence of any of the following events: tumor progression per Response Evaluation Criteria In Solid Tumors (RECIST), PSA progression, pain progression or death due to any cause − Prostate-Specific Antigen (PSA)-Progression − Pain progression − Tumor response in patients with measurable disease (RECIST 1.1). − PSA response − Pain response in patients with stable pain at baseline. • To compare Health-related Quality of Life (HRQL) using the FACT-P tool • To assess the pharmacokinetics and pharmacogenomics of cabazitaxel
Study design	Phase III, randomized, open-label, multi-center, multinational study comparing cabazitaxel 20 mg/m² plus prednisone (Arm A) and cabazitaxel 25 mg/m² plus prednisone (Arm B) in patient with metastatic castration resistant prostate cancer (MCRPC) previously treated with a docetaxel-containing regimen.
Study location	Multinational, multicentre. Planned recruitment is from approximately 200 sites within 60 months.
Study population	Expected 1200 mCRPC patients with similar baseline characteristics to the TROPIC population. See Appendix 8 for main selection criteria.
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.

A graphical representation of the study is provided in Figure 13 overleaf.

We expect the data from PROSELICA to become available in late September and it is our intention to provide this as supplementary material as soon as we are able.

Figure 13. Graphical representation of the PROSELICA study design.

Academic in confidence information removed

5. Cost effectiveness

- In order to evaluate the incremental cost-effectiveness of cabazitaxel a markov model with 3 health states (stable disease, progressive disease and dead) was developed.
- The evaluation had a 10 year time horizon and was conducted from an NHS perspective.
- For the base-case the population considered is the subgroup of patients with ECOG PS 0-1 who have received at least 225mmg/m^2 docetaxel.
- The base case compares cabazitaxel to mitoxantrone (considered equivalent to BSC in terms of overall survival and is reflective of standard NHS practice)
- Scenario analyses comparing cabazitaxel to the hormonal agents abiraterone and enzalutamide were also performed, however these are limited by the significant weakness in the indirect treatment comparisons.
- The model was populated with updated clinical data from the TROPIC Phase III clinical trial and HRQL data from the EAP for cabazitaxel.
- The ICER for cabazitaxel versus mitoxantrone in the base case analysis is £49,327 per QALY.
- Deterministic sensitivity analyses demonstrate that the base case results are robust with ICERs varying from £44,290 to £56,656 per QALY
- The probability of cabazitaxel being cost-effective versus mitoxantrone was 46% at a WTP threshold of £50,000 per QALY

5.1 Published cost-effectiveness studies

5.1.1. Description of the strategies used to retrieve cost-effectiveness studies relevant to decision-making in England.

A systematic literature review was conducted for the original submission for cabazitaxel TA255.[4] No relevant studies were identified. The search strategy is provided in detail Appendix 9.

Since this search was carried out there have been a number of publications in this area and so we have updated this search to identify all relevant cost-effectiveness studies from the published literature. The PICOS framework is included below in Table 48.

Table 48. PICOS Framework

PICOS	Description
Population	• mHRPC and mCRPC patients • Age: Adults (≥18 years) • Race: Any • Line of therapy: Second-line or later • Prior therapy: Previously treated with docetaxel-based regimen
Interventions	The following treatments for mHRPC and mCRPC administered in the second line or later: • Jevtana (cabazitaxel) • Zytiga (abiraterone) • Xtandi (enzalutamide) • Novantrone (mitoxantrone) • Yervoy (ipilimumab) • Xofigo (radium-223) • Provenge (sipuleucel-T) • Emcyt (estramustine)
Comparators	No limitation on comparator
Outcomes	• Model description • Patient age • Life years gained • QALYs • Costs • ICER
Study design	Economic evaluations (CEA, CUA, CBA)
Limits	• Publication from 2010 to present • Conference abstracts from 2012 to present

The following data sources were searched:

Databases

Embase
MEDLINE (via the Embase interface)
MEDLINE in Process (via PubMed)
Cochrane (Technology Assessments and Economic Evaluations databases)
NHS EED
EconLit
NICE

Conferences

New conferences to search/screen (2012 to present)
Health Technology Assessment international (HTAi)[1]
International Health Economics Association (iHEA)[2]
International Society For Pharmacoeconomics and Outcomes Research (ISPOR)
Previously screened – no additional searching required (2012 to present)

[1] Only searchable abstracts from HTAi 2012 and 2014 were identified
[2] Only searchable abstracts from iHEA 2015 were identified

American Association for Cancer Research (AACR)
American Society of Clinical Oncology (ASCO)
American Society of Clinical Oncology-Genitourinary (ASCO-GU)
American Urological Association (AUA)
European Association of Urology (EAU)
European Society for Medical Oncology (ESMO)
Société Internationale d'Urologie (SIU)

The search strategies are provided in Appendix 10.

The PRISMA figure is provided overleaf in Figure 14.

Figure 14. PRISMA figure for the cost effectiveness searches.

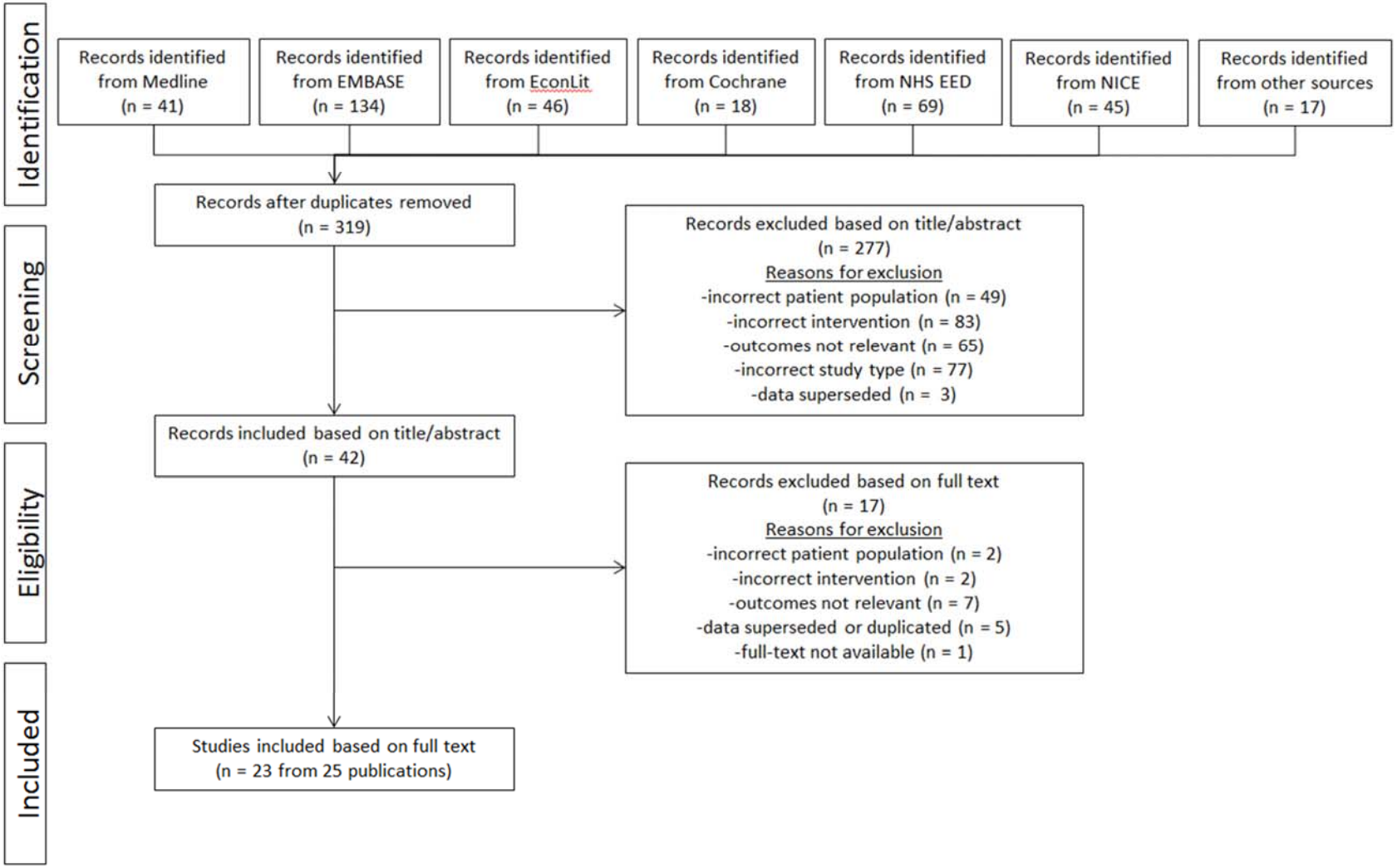


Table 49. List of published articles retained for full text review with reasons for exclusion

Publication	Excluded at full text review?	Reason for exclusion
HTA database Project record for cabazitaxel, 2011	Yes	Superseded by Kearns (see below)
HTA database Project record for enzalutamide, 2013	Yes	Superseded by TA316 (see below)
HTA database structured abstract for abiraterone, 2012	Yes	Superseded by TA259 (See below)
Adams, E., 2010[168]	Yes	Outcomes not relevant
Bergman, J., 2010[169]	Yes	Incorrect intervention
Breuer, J., 2013[170]	Yes	Outcomes not relevant
Connock, M., 2011[171]	No	
Dyer, M., 2012[172]	Yes	Duplicate
Grabner, M., 2011[173]	Yes	Incorrect intervention
Hayes, 2013[174]	Yes	Unavailable abstract (Radium-223)
Holko, P., 2014[175]	Yes	Incorrect patient population
Horizon Scanning Centre, 2014[176]	Yes	Outcomes not relevant
Kearns, B., 2013[177]	Yes	Duplicate
Nachtnebel, A., 2011[178]	Yes	Outcomes not relevant
Nachtnebel, A., 2011[179]	Yes	Outcomes not relevant
NHSC, 2011[180]	Yes	Outcomes not relevant
NICE TA259, 2012[6]	No	
NICE TA255, 2012[4]	No	
NICE TA316, 2014[7]	No	
NICE TA332, 2015[181]	Yes	Outcomes not relevant
Simpson, E. L., 2015[182]	Yes	Incorrect patient population
Zhong, L., 2013 [183]	No	

In addition to the articles cited above a further 20 congress abstracts were identified and included at full text review.

5.1.2. Overview of the included reports

The review identified 25 economic reports. These are detailed in Table 50 overleaf. These were supplemented by a hand search of the Scottish and Irish HTA agency databases. An additional 6 reports were identified and are listed in Table 51. The ongoing assessment by NICE of Radium-223 was not identified in the searches but is included in as the last entry in Table 50 overleaf for completeness.

Table 50. Cost-effectiveness evidence from economic analyses of post-docetaxel treatments for mHRPC and mCRPC (ICER per QALY gained)

Study	Summary of model	Patient age (avg.)	Interventions	Costs (currency, year)	QALYs	ICER (per QALY gained)
Chopra ASCO 2012[184]	A decision analytical model using clinical data from the COU-AA-301 pivotal Phase III trial designed to assess the cost-effectiveness of abiraterone in the treatment of advanced CRPC patients from a US payer perspective. Health utilities were derived from the available literature, while costs for drug acquisition, physician visits and laboratory tests were obtained from the Center for Medicare Services Drug Payment Table and Physician Fee Schedule and are represented in 2011 US dollars.	NR	Abiraterone + prednisone	NR (USD, 2011)	0.30[a,b]	$129,000[a]
He ISPOR 2013[185]	A survival-based Markov cohort model consisting of 3 health states (progression-free, progressed, and dead) to project cost-effectiveness from a US payer perspective over 10 year period. Progression between states was determined by OS and radiographic PFS. An indirect treatment comparison was conducted to determine the relative efficacy of abiraterone acetate and enzalutamide. Utilities were mapped from FACT-P to EQ-5D based on a review of the literature. Drug acquisition costs in the US were used since enzalutamide was approved only in the US at the time of analysis. Costs of scheduled and unscheduled follow-up visits were obtained from the Centers for Medicare Services Drug Payment Table and Physician Fee Schedule and represented in 2013 US dollars.	NR	Abiraterone	$115,531 (USD, 2013)	1.033	Dominates
			Enzalutamide	$128,852 (USD, 2013)	1.008	Dominated
Joulain ISPOR 2013[186]	A Markov cohort based cost-effectiveness model from the Swedish healthcare perspective using a lifetime horizon (~15 years) and 3% discount rate. The population included a TROPIC trial subgroup consisting of patients who initially responded to docetaxel but experienced disease progression <3 months since last docetaxel dose. Health state transitions that represented mCRPC disease progression (stable, progression, death) were estimated based on progression of disease and survival rates from the TROPIC trial. Resource inputs were obtained from literature, hospital data and key opinion leaders.	18% under 65 years	Cabazitaxel	SEK 699,176 (SEK, NR)	1.121	vs mitoxantrone + prednisolone: SEK 943,270 vs prednisolone alone: SEK 990,903 vs prednisolone alone: SEK 999,299 (subgroup)
			Mitoxantrone + prednisolone	SEK 320,491 (SEK, NR)	0.719	Reference
			Prednisolone	SEK 302,726 (SEK, NR)	0.721	Reference
TA259[6]	A survival-based decision model with three health states (pre-progression, post progression and dead) from the perspective of the NHS and personal social services with a time horizon of 10 years. The number of people remaining in each health state after each cycle of the model (3 weeks) was calculated directly from the OS and PFS curves from the one prior chemotherapy subgroup of the COU-AA-301 trial. The model used a time horizon of 10 years and discounted costs and benefits at 3.5%.	NR	Abiraterone + prednisolone	NR (GBP, NR)	NR	Base-case: £52,851 Whole trial: £63,233
			Mitoxantrone + prednisolone	NR (GBP, NR)	NR	Base-case: Dominated Whole trial: Dominated
			Prednisolone	NR (GBP, NR)	NR	Reference
TA255[4]	A cohort Markov model including three health states (stable disease, progressive disease and death) and comparing two treatment regimens. All patients entered the model in the stable disease state, from which transitions	NR	Cabazitaxel + prednisolone	NR (GBP, NR)	Initial model: 0.298[b] Second	Initial model: £74,908 First revision: £74,938 Second revision: £78,016

Study	Summary of model	Patient age (avg.)	Interventions	Costs (currency, year)	QALYs	ICER (per QALY gained)
	to progressive disease and death were possible. Once patients entered the progressive disease state, they would remain there until death. The model's perspective was that of the UK NHS and personal social services, where all future costs and benefits were discounted at a rate of 3.56% and treatment was modelled over a lifetime (14.4 years) with a cycle length of 3 weeks.				revision: 0.290[b]	<u>Population groups (initial/revised)</u> 1) All patients in TROPIC with ECOG performance score of 0 or 1 who had received ≥ 225 mg/m2 prior docetaxel therapy: £87,684/£86,008 2) European patients regardless of ECOG performance status and previous docetaxel therapy: £84,540/£87,348 3) All patients in TROPIC: £82,538/£91,134
			Mitoxantrone + prednisolone	NR (GBP, NR)	Reference	Reference
TA316[7]	A state-transition Markov cohort model simulating 3 states (stable disease, progressive disease and death) from the perspective of the UK NHS and personal social services with a time horizon of 10 years. The cycle length of the model was 3 weeks, in line with previous models for this indication, and applied a half-cycle correction except for direct drug costs. Costs and health effects were discounted at an annual rate of 3.5%. All patients entered the model in the stable-disease state and received enzalutamide, abiraterone or best supportive care. They could then remain in this state, move to the progressive-disease state or die.	NR	Enzalutamide	NR (GBP, NR)	NR	vs abiraterone: £14,795 vs BSC: £43,587
			Abiraterone	NR (GBP, NR)	NR	vs enzaluatmide: Dominated vs BSC: £102,751
			BSC	NR (GBP, NR)	NR	Reference
Obando ISPOR 2014a[187]	A three-health state cohort simulation Markov model (progression-free, post-progression and death) with a time frame of 10 years and a discount rate of 5% was developed based on overall and progression free survival data from COU-AA-301 and TROPIC. The perspective was that of the Public System of Health of Costa Rica, where all costs were presented in Costa Rican currency (CRC).	NR	Cabazitaxel + prednisone	CRC 41,981,207 (CRC, 2012)	0.71	Dominated
			Abiraterone + prednisone	CRC 33,881,184 (CRC, 2012)	0.79	Dominates
Obando ISPOR 2014b[188]	A three-health state cohort simulation Markov model (progression-free, post-progression and death) with a time frame of 10 years and a discount rate of 5% was developed based on overall and progression free survival data from COU-AA-301 and TROPIC. The perspective was that of the Public System of Health of the Dominican Republic, where all costs were presented in Dominican Republic currency (DOP).	NR	Cabazitaxel + prednisone	RD$ 2,732,365 (DOP, 2012)	0.71	Dominated
			Abiraterone + prednisone	RD$ 2,204,289 (DOP, 2012)	0.79	Dominates
Obando ISPOR 2014c[189]	A three-health state cohort simulation Markov model (progression-free, post-progression and death) with a time frame of 10 years and a discount rate of 5% was developed based on overall and progression free survival data from COU-AA-301 and TROPIC. The perspective was that of the Public System of Health of Panama, where all costs were presented in USD.	NR	Cabazitaxel + prednisone	$86,286 (USD, 2012)	0.71	Dominated
			Abiraterone + prednisone	$76,179 (USD, 2012)	0.79	Dominates
Pereira ISPOR	A cost-effectiveness Markov model that simulates disease progression and patient mortality from the Brazilian Private Health System perspective.	NR	Abiraterone	BRL 79,974 (BRL, NR)	0.7977	Dominates

Study	Summary of model	Patient age (avg.)	Interventions	Costs (currency, year)	QALYs	ICER (per QALY gained)
2012[190]	Efficacy data is informed by Phase III trials and is combined/adjusted via a mixed treatment comparison network meta-analysis to determine the relative efficacy of each comparator. Only direct medical costs were considered, while costs and outcomes were discounted at 5% yearly.		Cabazitaxel	BRL 90,025 (BRL, NR)	0.7329	Dominated
Persson ISPOR 2012[191]	A survival-based decision analysis model was developed incorporating 3 health states (PFS, post-progression survival, and OS) and populated using data from two placebo-controlled randomized clinical trials. Resource utilization and costs reflected Swedish treatment conditions within a broad societal perspective.	NR	Abiraterone	$103,100/€74,400 (USD/EUR, NR)	0.94	Dominates
			Cabazitaxel	$104,600/€75,500 (USD/EUR, NR)	0.83	Dominated
Persson ISPOR 2013[192]	A survival-based decision analysis model was developed incorporating 3 health states (PFS, post-progression survival, and OS) and populated using data from one placebo-controlled randomized clinical trial and from the name-patient-program in Sweden. Resource utilization and costs reflected Swedish treatment conditions within a broad societal perspective. The model incorporated a lifetime time horizon (10 years) and a 3% discount rate.	69.2 years	Abiraterone	$85,270/€67,300 (USD/EUR, 2012)	1.24	$69,800/€55,000
			Prednisone	$52,700/€41,600 (USD/EUR, 2012)	0.77	Reference
Shibahara ISPOR 2013[193]	A cost-effectiveness Markov model based on data from the COU-AA-301 trial and literature review conducted from the Japanese public healthcare payer's perspective. The base-case was assumed to be a 69 year-old man with metastatic CRPC. The model used a time horizon of 10 years and drug cost was estimated based on prices in the UK and the US. Both cost and outcomes were discounted at a 2% annual rate based on Japanese guidelines for economic evaluation.	69 years	Abiraterone + prednisolone	NR (JPY/EUR, NR)	NR[c]	Exceeded JPY 10 million (€80,000)
			Placebo + prednisolone	NR (JPY/EUR, NR)	NR	Reference
Shibahara ISPOR 2014[194]	A cost-effectiveness Markov model based on data from the COU-AA-301 trial and literature review conducted from the Japanese public healthcare payer's perspective. The base-case was assumed to be a 72 year-old man with metastatic CRPC. The model used a time horizon of 10 years and drug cost was estimated based on prices in four other countries. Resource use was estimated using a Japanese claims data set with 2000 claim data of prostate cancer patients from January 2005 to March 2013. Both cost and outcomes were discounted at a 2% annual rate.	72 years	Abiraterone + prednisolone	NR (JPY/EUR, NR)	NR[c]	Exceeded JPY 17 million (€120,000)
			Placebo + prednisolone	NR (JPY/EUR, NR)	NR	Reference
Vicente ISPOR 2015[195]	A cost-effectiveness Markov model from the Canadian perspective was developed to capture time spent by patients in various health states (progression, progression free survival and death). Transition probabilities were derived from patient-level data from AFFIRM and an indirect treatment comparison from available published literature. Direct medical costs were selected from the perspective of the Canadian Ministry of Health, with the second analysis focusing on the societal perspective. A 5% discount rate was applied to both costs and patient outcomes over a 10-year period.	NR	Enzalutamide	NR (CAD, 2013)	NR	vs abiraterone: $42,325 vs cabazitaxel: $43,105
			Abiraterone	NR (CAD, 2013)	NR	Reference
			Cabazitaxel	NR (CAD, 2013)	NR	Reference
Yeung ISPOR 2012[196]	A Markov model from a limited societal perspective using a lifetime horizon with 3 health states (pre-progression, post-progression, and death) and 1 month transitions. Transition probabilities for all health states were derived from the pivotal Phase III clinical trials (AFFIRM and COU-AA-301). A 3%	NR	Enzalutamide	$84,465 (NR, NR)	1.24	$55,070
			Abiraterone	$74,119 (NR, NR)	1.05	Reference

Study	Summary of model	Patient age (avg.)	Interventions	Costs (currency, year)	QALYs	ICER (per QALY gained)
	discount was applied to all costs and outcomes, where costs included drug acquisition costs, laboratory tests associated with treatment, as well as costs for grade 3/4 side effects management.					
Zhong 2013[183]	A decision-tree model to compare the cost-effectiveness of two mCRPC treatments versus two placebos over 18 months from a US societal perspective. Chance nodes include baseline pain as a severity indicator, grade III/IV side-effects, and survival at 18 months. Probabilities, survival and health utilities were from published Phase III studies. Model cost inputs included drug treatment, side-effect management and prevention, radiation for pain, and death associated costs in 2010 US dollars.	NR	Placebo	$75,366 (USD, 2010)	0.43	Reference
			Mitoxantrone	$83,171 (USD, 2010)	0.51	$100,675
			Abiraterone	$101,050 (USD, 2010)	0.70	$91,188
			Cabazitaxel	$156,140 (USD, 2010)	0.76	$955,863
NICE:ID576[197]	A semi-Markov model with time-dependent transition probabilities was developed based on survival analysis: the number of patients remaining in each of the health states is calculated in a per model cycle basis based on survival curves from the clinical trial.	N/A	Radium 223	£24,240 (av. Course of treatment taken from ERG report)	Redacted	Basecase ICER: £47,697
			Placebo	Unclear	Redacted	

[a]Reference group = not specified
[b]Incremental QALY
[c]Described as "higher than prednisolone alone"
AE, adverse events; CAD, Canadian Dollar; CRC, Costa Rican Colón; DOP, Dominican Peso; EUR, Euro; GBP, British Pound; ICER, incremental cost-effectiveness ratio; JPY, Japanese Yen; LYG, life year gained; mCRPC, metastatic castration-resistant prostate cancer; mHRPC, metastatic hormone-resistant prostate cancer; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year, NR, not reported; SEK, Swedish Krona; USD, United States dollars

In a separate hand search the reports from the SMC (Scotland) and NCPE (Ireland) were reviewed and are summarised in Table 51 below.

Table 51. Additional summary of HTA reports in mCRPC in Scotland and Ireland.

Country (HTA body, HTA id no.)	Study (Intervention)	Year	Summary of model	Patient population	QALYs (intervention comparator)	Costs (Based on list price)	ICER (per QALY gained)	Status
Ireland (NCPE)	AFFIRM (Enzalutamide)	2014	Three-state Markov model with a 10 year time horizon.	Patients with mCRPC whose disease has progressed on or after docetaxel therapy	Not available	Not available	Enzalutamide vs. BSC: €98,949 Cabazitaxel: €75,311 Abiraterone: €60,738	Not recommended

Country (HTA body, HTA id no.)	Study (Intervention)	Year	Summary of model	Patient population	QALYs (intervention comparator)	Costs (Based on list price)	ICER (per QALY gained)	Status
Scotland (SMC, 911/13)	AFFIRM (Enzalutamide)	2013			Not available	Cost per course: Enzalutamide: £n/a Cabazitaxel: £36,980 Docetaxel: £10,240 Mitoxantrone: £1,539	Enzalutamide vs. BSC: N/A Cabazitaxel: N/A Abiraterone: £15,696 (with PAS)	Accepted for use
Ireland (NCPE)	COU-AA-301 (Abiraterone acetate)	2012	Three-state survival based decision analysis model	mCRPC in adult patients whose disease has progressed on or after docetaxel based chemotherapy	Not available	Cost per course: Abiraterone: £n/a (£2,054 per cycle) Cabazitaxel: £36,980 Docetaxel: £9.026 Mitoxantrone: £1,549	Abiraterone + prednisone vs. placebo + pred.: €135,454 Mitoxantrone + pred.: €160,388	Not recommended
Scotland (SMC, 764/12)		2012					Abiraterone + prednisone vs. Placebo + pred.: £46,421 Mitoxantrone + pred.: £41,222	Accepted for restricted use
Ireland (NCPE)	TROPIC (Cabazitaxel)	2012	Three-state Markov model	Patients with mCRPC previously treated with a docetaxel-containing regimen	Not available	Not available	Cabazitaxel vs. Mitoxantrone: €120,084	Following HTA, recommendation was not to reimburse. Subsequently full reimbursement was approved for hospitals with prescribing protocol implemented by the NCCP as per licence.

Country (HTA body, HTA id no.)	Study (Intervention)	Year	Summary of model	Patient population	QALYs (intervention comparator)	Costs (Based on list price)	ICER (per QALY gained)	Status
Scotland (SMC, 753/11)		2011			Not available	Cost per course: Cabazitaxel: £36,975 Docetaxel: £9,662 Mitoxantrone: £1,539	Cabazitaxel vs. Mitoxantrone: £76,670	Not recommended
HTA, Health Technology Assessment; NICE, National Institute for health and Care Excellence; NCPE, National Center for Pharmacoeconomics; SMC, Scottish Medicines Consortium; mCRPC metastatic Castrate Resistant Prostate Cancer; QALY, Quality Adjusted Life Year; ICER, Incremental Cost Effectiveness Ratio; NCCP, National Cancer Control Program.								

5.1.3. Provide a complete quality assessment for each relevant cost-effectiveness study identified.

The review identified abstracts, HTA reports and one full article containing data on cost-effectiveness studies for products in the post-docetaxel 2nd line setting. Cabazitaxel is directly compared with mitoxantrone using the TROPIC data in the report for TA255 and in an abstract from the Swedish perspective. In both cases cabazitaxel is associated with a higher QALY gain but also higher cost than the mitoxantrone arm. A quality assessment is not provided for these reports as this dossier provides an update of the analysis presented in TA255. Cabazitaxel also features in TA259 for abiraterone, however in this analysis, cabazitaxel is only implemented as part of the post-treatment 2nd line treatment mix and so the results are not relevant here.

Of the remaining reports, several abstracts report comparisons of abiraterone with cabazitaxel carried out for populations in South and Central America, Sweden and Canada.[187-191] Whilst these are structured abstracts there is no detailed discussion of the methodology used to arrive at the conclusions beyond headline figures for costs and outcomes. Nonetheless these abstracts report higher QALY gains for the abiraterone arms in the comparisons and lower costs with the conclusion that abiraterone is the dominant strategy in most cases. We have argued that the comparisons between cabazitaxel and the advanced hormonal agents are limited by the heterogeneous definitions of survival outcomes in the trials, the patient populations included, and by the differing trial protocols not least around discontinuation rules. In our indirect comparisons we found no statistically significant increased survival for any of the agents. (Section 4.10). From the published information it is not possible to provide detailed commentary on these evaluations.

The review of the literature identified one published article by Zhong in which cabazitaxel was compared against standard of care and also versus abiraterone from a US societal perspective.[183] In this article a decision tree approach was taken to evaluate the various different comparisons and cabazitaxel was found not to be a cost-effective option. The approach taken differs in many respects to the methodology used to make the comparison reported in this dossier and indeed to that used for other comparisons more generally in oncology submissions. More usually a Markov model is implemented using hazard ratios derived from survival analysis and utilities and costs assigned to the Markov states. However it is interesting to reflect that in the study by Zhong, unlike those discussed above, there is a QALY gain associated with cabazitaxel treatment versus abiraterone of 0.06. The much higher cost in the cabazitaxel arm is reflective of the very high treatment cost for neutropenia in the US. Given the very different methodologies and perspective used for this analysis to the one presented here a quality assessment has not been carried out.

5.2 De novo analysis

5.2.1 Patient groups are included in the economic evaluation.

The base-case population considered in the model is the subgroup of patients with ECOG PS 0 -1 who have received at least 225 mg/m^2 docetaxel. The clinical outcomes observed in these patients along with the rationale for the choice of this group as the base-case population has been provided in Section 4.8 above. Amongst the participants in TROPIC, this cohort represents those patients most likely to be treated with cabazitaxel in UK clinical practice and therefore is the most relevant group to inform the decision problem. The ITT population from TROPIC is considered in scenario analysis.

5.2.2 Model structure.

In order to evaluate the cost-effectiveness cabazitaxel, a health economic state-transition model (i.e. Markov model) was developed. The model comprises a set of different health states each associated with costs, health effects and the probability of moving to any other state (Figure 15). When simulating a scenario, a cohort of defined patients progress through the model during the time period of choice, and it is assumed that transitions between states only occurs at equidistant time-points (cycles). The cycle length in the model is 3 weeks, corresponding to the length of one chemotherapy administration cycle. Transition rates between different states representing mCRPC disease progression were estimated based on progression of disease and survival estimates from the TROPIC trial.

The health states in a Markov model are typically defined based on a patient's possible health states specific to the disease. The states are mutually exclusive and collectively exhaustive, i.e. patients can only be in one single state at any one time, and the set of states should cover all relevant possibilities. The most important assumption of a Markov model is that future events only depend on the current health state of the patient, and not on prior events.

The following health states were chosen for use in the model to mirror the likely disease history of the patient population:

• Patients who have not progressed on 2nd line mCRPC therapy (stable disease)

• Patients who have progressed while on 2nd line mCRPC therapy (progressive disease)

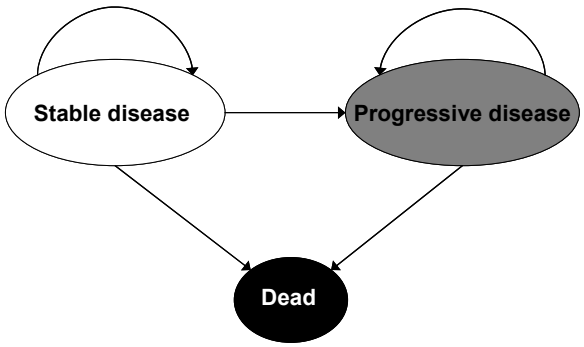
• Patients who have died (dead)

All patients begin in the "Stable disease" health state and are either treated with cabazitaxel or mitoxantrone. In each cycle, patients have a probability of remaining in their current state ("Stable disease" or "Progressive disease" states), moving to the other state ("Progressive disease" state) or dying (move to the absorbing "Dead" state) (see Figure 15) As this is a cohort model, patients are not followed individually. Costs and health utilities are assigned for each Markov health state.

Adverse events were not implemented as separate health states but were rather taken into consideration by assigning a cost and utility reduction in each cycle during the stable disease health state.

To account for the uncertainty of the underlying parameter estimates, second-order stochastic sensitivity analysis was performed. A detailed discussion is provided in Appendix 19.

Figure 15. Schematic model structure



5.2.3. Features of the de novo analysis.

A summary of the de-novo analysis is provided in Table 52 below.

Table 52. Features of the de novo analysis

Factor	Chosen values	Justification	Reference
Time horizon	10 years	To reflect all relevant costs and outcomes associated with treatment.	NICE MTA method guide
Cycle length	Three weeks	Because of the relatively short survival time of mCRPC patients, the cycle lengths in the model was set at 3 weeks, to get high precision in the model and to reflect the duration of treatment cycles	TROPIC
Half-cycle correction	Included	The method of half-cycle correction was used, by adding one extra cycle and assuming that the first and final cycles in the model are half as long as the cycles in between. This way, the over-estimation will be corrected. Half-cycle correction was not undertaken on the cost of therapy, since this would be incurred at the start of each cycle, regardless of the patient's movement thereafter.	NICE MTA method guide
Were health effects	Yes, health effects	As recommended in the	NICE MTA

Factor	Chosen values	Justification	Reference
measured in QALYs; if not, what was used?	measured in QALYs	Reference Case.	method guide
Discount of 3.5% for utilities and costs	Costs and benefits were discounted at 3.5%. Continuous discounting is applied within the model rather than the more traditional discounting year on year.	As recommended by the UK Treasury. Discount rates were varied in the sensitivity analysis. Continuous discounting avoids the 'stepped' changes in discount rate that occur due to the compounding effect of cycles discounted at discrete intervals. Continuous discounting provides a truer estimate of the value, since this offers a greater degree of granularity (i.e. infinite granularity, as opposed to the discrete three-weekly compounding).[198, 199]	NICE MTA method guide
Perspective (NHS/PSS)	The perspective of the analysis in that of the NHS in England.	As recommended in the Reference Case.	NICE MTA method guide
Key: mCRPC = metastatic hormone-refractory prostate cancer; NHS = National Health Service; PSS = Personal Social Services; QALYs = quality-adjusted life years			

5.2.4. Implementation of cabazitaxel and comparators in the model.

Cabazitaxel is compared to mitoxantrone in the model in line with the decision problem depicted in Table 5.

In line with the scope we, consider mitoxantrone to be a valid comparator and equivalent to best supportive care for comparisons within the ITC.

Cabazitaxel is implemented as per its marketing authorisation in the post docetaxel setting and the relative effect sizes for each therapy are taken from the survival analysis presented in Section 5.6.

The model arms for the comparison based on TROPIC are, therefore:

- Mitoxantrone, 12 mg/m^2 every three weeks in combination with 10 mg/day of prednisolone
- Cabazitaxel, 25 mg/m^2 every three weeks in combination with 10 mg/day of prednisolone.

For the base-case comparison with mitoxantrone, updated data from the TROPIC trial are modelled directly. For scenarios examining other comparisons, hazard ratios for OS and

rPFS derived from the ITC summarised in section 4.10 and Appendices B are applied to the TROPIC data.

Treatments are implemented in the model according to their marketing authorisations.

The model arms for the comparisons with TROPIC based on COU-AA-301 and AFFIRM therefore include the therapies at the cost and dose presented in the BNF as requested by NICE[18]

- Abiraterone, 1.0 g daily in combination with 10 mg/day of prednisolone. Pack price: £2930; 120 x 250 mg tablets.
- Enzalutamide, 120 mg daily. Pack price: £2734; 112 x 40 mg tablets.

5.2.5 Treatment continuation and discontinuation rules

In line with the SPC and the dosing regimen from the TROPIC trial, patients continue treatment from the start of the model until one or more of the following events occur:

- The patient progresses
- The patient dies
- The patient has received ten cycles of chemotherapy.

In TROPIC, 23% of patients in the cabazitaxel arm and 16% in the mitoxantrone arm discontinued for other reasons than progression. In order to reflect this, the rate of discontinuation was accounted for in the economic modelling. From the proportion of patients that discontinue treatment, a discontinuation rate (over 10 cycles) was derived and applied to patients on treatment: 2.6% in the cabazitaxel arm and 1.7% in the mitoxantrone arm. In sensitive analysis these discontinuation rates were excluded.

5.3 Clinical parameters and variables

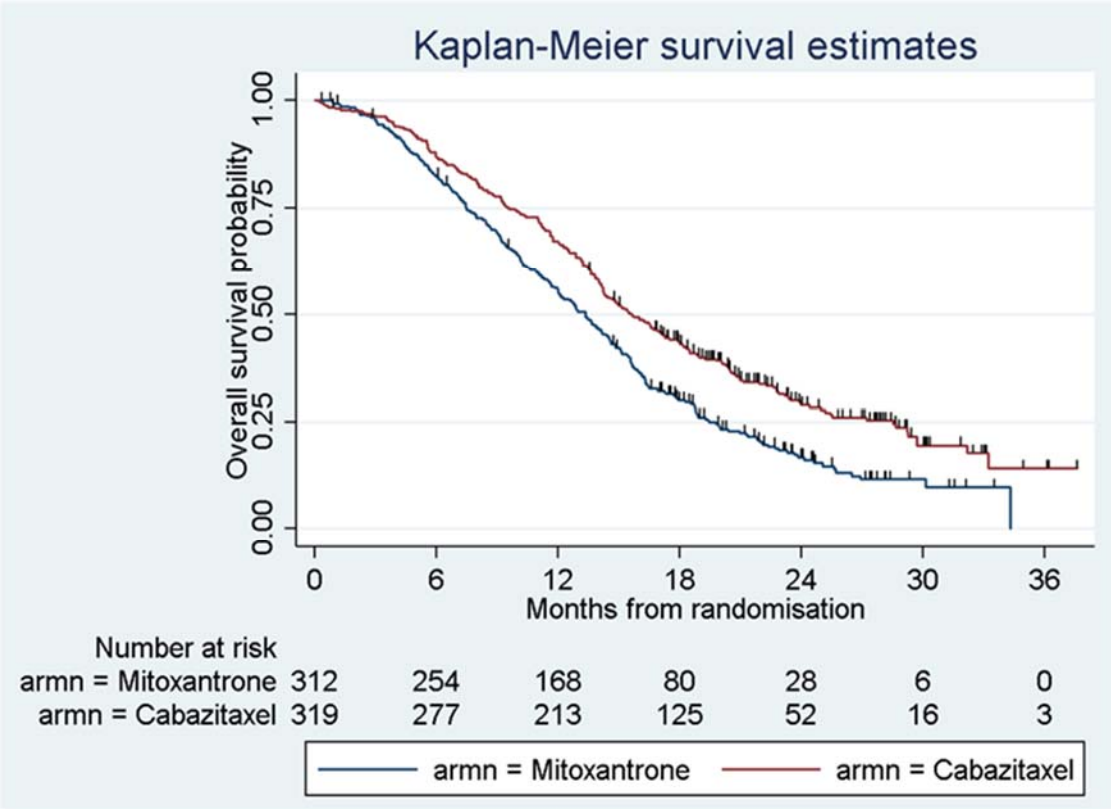
5.3.1. Description of how the clinical data were incorporated into the model.

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 adverse events associated with each treatment.

Overall survival

In the updated TROPIC trial, patients receiving cabazitaxel in the subgroup population demonstrated significantly longer overall survival (OS) compared to patients receiving mitoxantrone in the subgroup (HR: 0.69 [0.57 – 0.82], P-value <0.0001). The median survival for patients in the cabazitaxel group was 15.61 months in comparison to 13.37 months in the mitoxantrone group. The overall survival Kaplan-Meier (KM) curve from TROPIC for the sub-group population is shown below**.** KM curves for the ITT population are presented in Appendix 18**.**

Figure 16 Kaplan-Meier estimates of overall survival probability in TROPIC (subgroup population)



Extrapolation of OS and PFS data for the duration of the trial period and beyond was evaluated using five different parametric models: Weibull, exponential, Log-logistic, Gompertz and Log-Normal. The selection of the most appropriate model was based on Akaike's Information Criteria (AIC) and Bayesian Information Criterion (BIC) for each parametric distribution method. The AIC and BIC are criteria for selecting a model based on goodness of fit. Both can be described as a measure of fit, based on the likelihood function, with a complexity penalty. It is this complexity penalty that differs between the two, as well as some underlying assumptions. AIC's complexity penalty is an increasing function of the number of estimated parameters. BIC's complexity penalty is an increasing function of the number of estimated parameters and sample size. Which criterion to choose depends on the context, although both are often reported. When using these criteria for model section, one should choose the model with the lowest value.

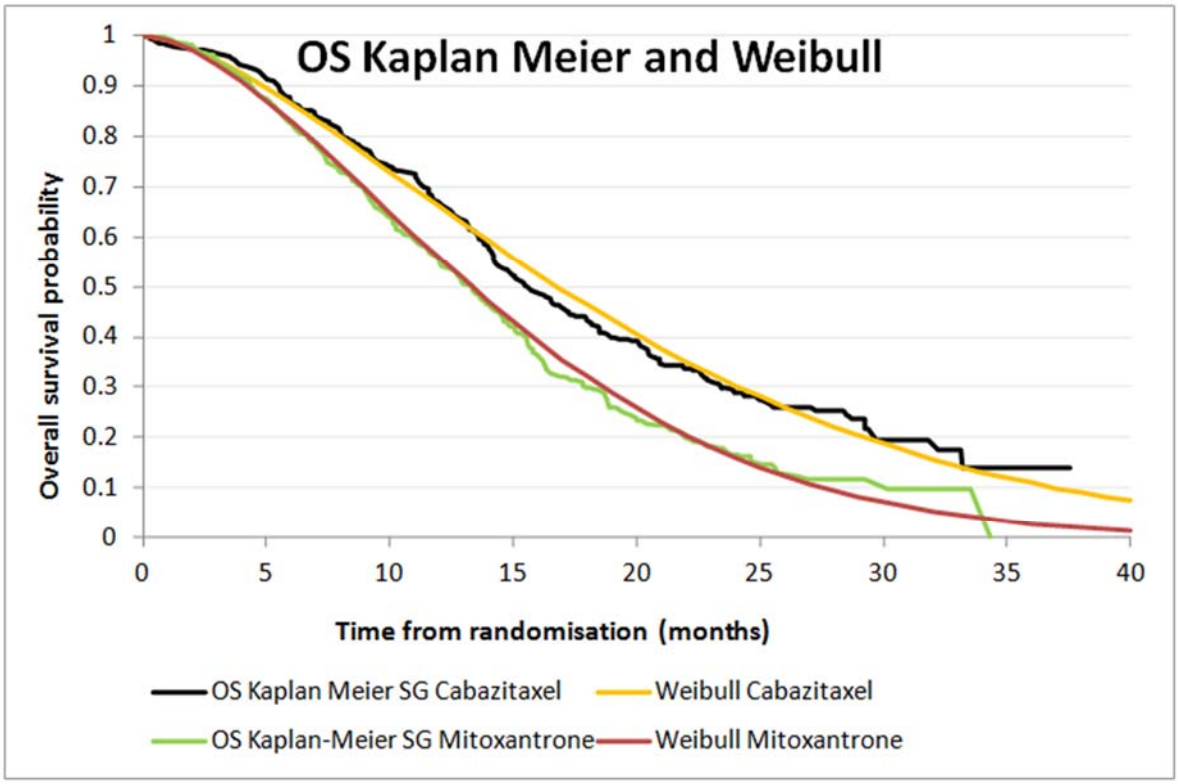
As seen in Table 53 the Weibull model provides the lowest AIC and BIC for Cabazitaxel OS, and the Log-logistic gives the minimum AIC and BIC for mitoxantrone OS. Ideally, the same parametric model type should be chosen for the two treatment arms unless there is a specific expectation that they should be different. To assess which parametric model to use when no specific justification exists for different functions to be applied, the AIC and BIC can be assessed for both arms; the sum of the AICs and BICs across the two treatment arms then informs the parametric model choice. The sum of the AICs and BICs, respectively,

supports the use of the Weibull extrapolation. For the base-case analysis, the Weibull extrapolation of the data was selected for the OS curves for both treatment arms.

Table 53. AICs and BICs for different parametric models for overall survival probability extrapolation

Parametric Model	Cabazitaxel		Mitoxantrone		Combination	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	801.62	805.38	771.59	775.33	1573.21	1580.71
Weibull	**757.69**	**765.22**	699.30	706.78	**1456.99**	**1472.00**
Gompertz	772.80	780.33	725.61	733.10	1498.41	1513.43
Log-logistic	758.91	766.44	**699.13**	**706.62**	1458.04	1473.06
Log-Normal	788.59	796.12	705.92	713.41	1494.51	1509.52

Figure 17. Weibull model for overall survival – subgroup population (compared to the TROPIC Kaplan-Meier data)



For OS, the following parameters were obtained for the Weibull distribution for the subgroup cohort:

- Mitoxantrone arm: λ and σ *Commercial in confidence information removed*
- Cabazitaxel arm: μ and *σ Commercial in confidence information removed*

The full survival analysis is available in Appendix 18.
In sensitivity analyses, the actual Kaplan Meier (KM) survival data from the TROPIC trial is also used in the model. The KM data for OS were used up 37.52 months. Thereafter, the parametric Weibull survival curves were used in order to extrapolate the KM data up to the lifetime of all patients.

Progression-free survival

PFS was also statistically significantly longer for patients receiving cabazitaxel compared to patients receiving mitoxantrone (HR: 0.76 [0.65– 0.89], P-value<0.0001). The progression-free survival KM curve from TROPIC for the sub-group population is shown in Figure 18. KM curves for the ITT population are presented in Appendix 18**.**

Figure 18. Kaplan-Meier estimates of progression-free survival in TROPIC (subgroup population)

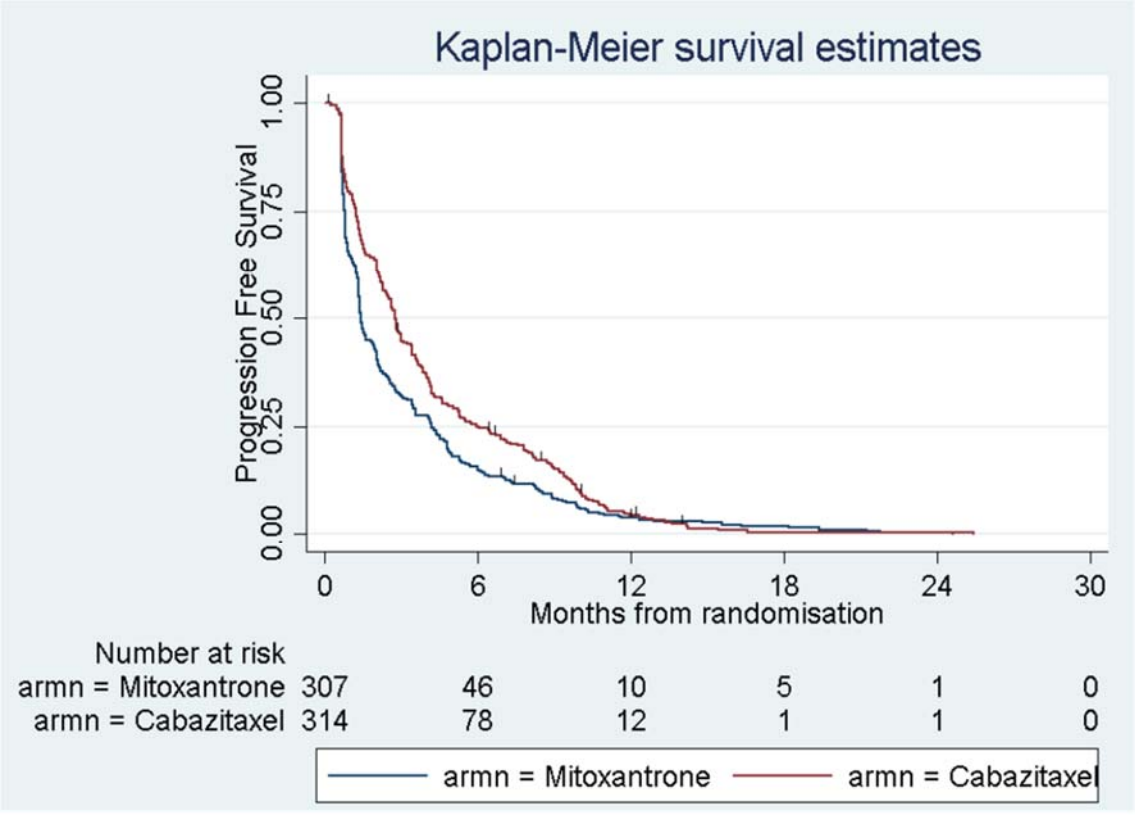


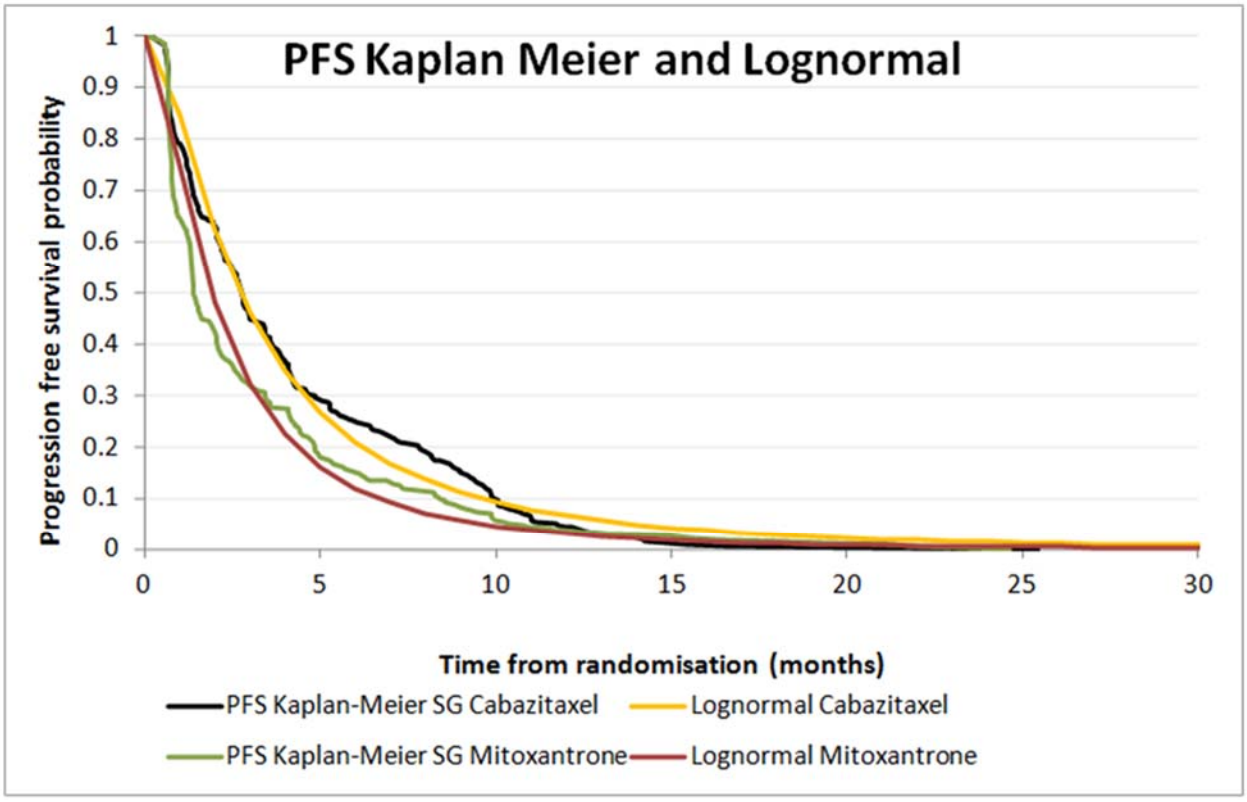
Table 54 presents the AICs and BICs for the extrapolations of the PFS data. The Log-Logistic model gives the minimum AIC and BIC for the Cabazitaxel PFS. The Log-Normal model gives the minimum AIC and BIC for the mitoxantrone arm. When assessing the most

appropriate fit for the PFS curve, the sum of the AICs and BICs for mitoxantrone and Cabazitaxel suggest the most appropriate fit is the Log-Normal model.

Table 54. AICs and BICs for different parametric models for progression-free probability extrapolation

Parametric Model	Cabazitaxel		Mitoxantrone		Combination	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	907.07	910.82	935.93	939.66	1843.01	1850.48
Weibull	903.14	910.63	937.72	945.17	1840.86	1855.81
Gompertz	908.11	915.61	926.82	934.28	1834.93	1849.89
Log-logistic	**900.25**	**907.74**	874.94	882.39	1775.18	1790.14
Log-Normal	900.88	908.67	**869.05**	**876.82**	**1769.93**	**1785.49**

Figure 19. Lognormal model for progression-free survival - subgroup population (compared to the TROPIC Kaplan-Meier data)



For PFS, the following parameters were obtained for the Lognormal distribution for the subgroup cohort:

- Mitoxantrone arm: μ and *σ Commercial in confidence information removed*
- Cabazitaxel arm: μ and *σ Commercial in confidence information removed*

In sensitivity analyses, the actual KM for progression-free survival data from the TROPIC trial is also used in the model. The KM data for PFS were used up 25.43 months. Thereafter, the parametric Log-Normal survival curves were used in order to extrapolate the KM data up to the lifetime of all patients

The model assumes only patients in the stable state receive second-line treatment with cabazitaxel or mitoxantrone, and that patients can receive up to a maximum of ten cycles of second-line treatment.

Following progression, for standard NHS practice the use of follow on chemotherapy is very limited. However, in the base-case, the post-second-line treatment mix is taken from the post-second-line treatments received by patients in the TROPIC trial. As a scenario analysis, the post-second-line treatment mix is based on those received by patients in an observation study of five major UK cancer centres (See Appendix 14). It is assumed that post-second-line treatment offers no differential effect between arms. Post-second-line treatment is only received for a relatively short duration (as shown by both TROPIC and the UK observational study) and the cost of these drugs is applied as a transition cost.

Typically, high costs are incurred at the end of life, when patients may require frequent hospitalisations and palliative care. Therefore, a specific cost for end-of-life care is calculated and applied as a transition cost on death. This is calculated based on the hospitalisations occurring in the last month as reported in the UK observational study and expert opinion on frequency of hospice care provision.

Adverse events

As mentioned in Section 5.5.7 Grade ≥3 AEs are incorporated into this model as costs and disutilities rather than separate events or states. Patients having an AE during the time they spend in a state also incur the associated cost and disutility. The AEs were only included in the stable disease state and not in the progressive disease health state because in the TROPIC trial there is only data for AEs occurring during treatment with cabazitaxel or mitoxantrone and up to 30 days after last cycle.

This approach of incorporating AEs is taken for several reasons. First, it is simpler and clearer to include the AEs in this manner. The alternative would be to have a greater number of health states, defined by a combination of disease stage and AE (for example, stable disease with deep vein thrombosis). This would make the model more complex and less transparent. Second, the available data on resource use, cost and utility associated with each AE are defined as the cost and disutility per event. This means that the data can be applied without unnecessary adjustment. The incidence of each AE per three-week cycle was included in the model along with the appropriate resource use, unit cost and disutility value.

AEs included in the model are listed in Table 70 in Section 5.5.7 together with AE rates in patients who experienced these events in each arm of the TROPIC trial. These AEs were chosen on the grounds that they were the most frequent treatment-emergent Grade ≥3 AEs. In addition, deep vein thrombosis and neuropathy according to clinical presentation were

added to the list of AEs, as they were classified as important based on clinical expert opinion.

5.3.2. Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix and describe the details of the transformation of clinical outcomes or any other relevant details here.

As is generally the case in oncology models the probability of transitioning between states is not based on a transition probability matrix. Instead, the percentage of time spent in each health state, is determined as the probability of survival, or progression at each time point. Effectively, average time spent in each health state is represented as the area-under-the-curve, or between the curves in the case of the progressive disease state.

5.3.3. If there is evidence that (transition) probabilities may change over time for the treatment effect, condition or disease, confirm whether this has been included in the evaluation.

The use of the Kaplan–Meier data and the fitted curves ensures that time dependent transitions between states are captured correctly.

5.3.4. Assessment of the applicability of the clinical parameters or approximations.

As part of initial model development, an advisory board was held with four oncologists on 30 November 2009. The criteria for selection were

- Specialism in prostate cancer
- UK-based (from different parts of the UK)
- Considered to be at least regional experts on the disease.

A number of follow-up conversations were held to seek further clinical opinion and validation of assumptions. Clinicians were asked to provide their opinion on the clinical validity of the key model assumptions, including UK-specific resource use data. (See Section 5.5 for further details).

This expert advice was used to estimate the UK-specific value for the BSA to be 1.9 m^2 and so the model base-case assumes a BSA of 1.9 m^2. The experts also reviewed the AEs in the model and deep vein thrombosis and neuropathy were added to the list of AEs based on their input. They also provided input on drug dosages related to AE treatment.

5.4 Measurement and valuation of health effects

5.4.1 Health-related quality-of-life (HRQL) data collected in the clinical trials

The Early Access Programme (EAP) for cabazitaxel (NCT01254279) evaluated utility in UK patients treated with cabazitaxel in the post docetaxel setting.[12]

Overall the mean (SD) EQ-5D-3L index score at baseline was 0.6821 (0.2571; n = 103) with a trend towards increased HRQL with increasing cycle number (utility at cycle 10 = 0.8185 (0.1870; n = 32). At Cycle 6 which was the median number of cycles received in both TROPIC and the UK EAP, the mean (SD) utility was 0.7518 (0.1925). As would be expected, as the number of cycles increased fewer patients remained on treatment (n = 103 at baseline vs. n = 32 at cycle 10). In order to explore selection bias 'within patient' analysis was conducted and this showed that for those patients completing 10 cycles of treatment the values and observed trends are consistent with those observed for the trial group as a whole.[12]. The overall utility value at 30 days post discontinuation was 0.6946 (SD: 0.2406). Full details are provided in Table 55.

As time passes in each health state average HRQL might be expected to worsen, however this was not observed. Indeed there was a non-significant trend towards increased HRQL with increasing cycle number (base line utility was 0.6821 (0.2571) and utility at cycle 10 was 0.8185 (0.1870)).[12] This is consistent with anecdotal evidence from clinicians treating patients with cabazitaxel (see Appendix 17 for representative opinion).

The cohort with utility values was also analysed according to evidence of disease progression by the end of the study. 39 patients were identified with progressive disease by the end of the study and 71 remained in the stable state. Of the patients with evidence of progression 25 had a recorded utility value 30 days after their last cycle of treatment.

The mean (SD) utility value recorded for progressive patients 30 days after their last treatment was 0.6266 (0.2978). As these were patients no longer on treatment and had documented evidence of progression this is assumed to accurately reflect utility for the progressed disease state. Progressive disease will lead to decreased utility due to the worsening symptoms. However, the definition of progression used in TROPIC included biochemical (PSA) progression as well as symptomatic or pain progression. It is unlikely that patients who only have PSA progression will experience a decline in utility until they also show symptomatic progression. Therefore, the constant utility assumption in the model may underestimate the health benefits of both treatments.

Table 55. Utility results from EAP

Baseline	N	103	**Cycle 6**	N	64
	Mean (SD)	0.6821 (0.2571)		Mean (SD)	0.7518 (0.1925)
	Min;Max	-0.594;1.000		Min;Max	0.208;1.000
Cycle 2	N	98	**Cycle 8**	N	39
	Mean (SD)	0.7284 (0.2038)		Mean (SD)	0.7892 (0.2142)
	Min;Max	0.159;1.000		Min;Max	0.055;1.000
Cycle 4	N	77	**Cycle 10**	N	32
	Mean (SD)	0.7495 (0.2262)		Mean (SD)	0.8185 (0.1870)
	Min;Max	-0.113;1.000		Min;Max	0.260;1.000

5.4.2. Mapping of HRQL data

Mapping was not undertaken as the utility data used in the modelling were collected directed.

5.4.3. Description of the systematic searches for HRQL data.

The search for studies reporting HRQL for mHRPC/mCRPC carried out for the original submission to NICE for cabazitaxel in 2011 (TA255) identified 59 reports of which 57 reports were rejected, either because no HRQL or EQ5D data were reported, the data related to early, or locally advanced disease.

Of the two studies retained, Sandblom[30] and Sullivan[200] provided estimates for utility decrements of 0.070 and 0.085 respectively which were applied to the estimated value for the stable disease state, itself derived from the interim analysis of the utility data from the UK EAP.

The updated clinical search for RCTs (discussed in Section 4.1.1 – 4.1.4) included search terms relevant to HRQL. This search identified five articles which included HRQL data for data extraction. These were associated with the included studies COU-AA-301 and AFFIRM. Both studies assessed HRQL using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire and also assessed patient-reported fatigue using the Brief Fatigue Inventory (BFI). A summary of the articles identified in the updated clinical literature review, including key results is provided in Section 5.4.4.

HRQL in mCRPC has been reviewed in several recent submissions to NICE, most recently by Bayer for radium-223. Only a handful of papers were identified by the updated review described above for the time period following the original cabazitaxel search and these included studies are summarised in Appendix 16.

Given the relatively short time period between the end of the HRQL search in the radium-223 submission (22nd February 2013) and the timeframe for the submission of this current dossier we have taken a pragmatic approach to updating the HRQL review. In order to capture the most recently published studies the PubMed database was searched on 26th August 2015. This was also a supplementary strategy adopted for the radium-223 submission where the authors note that PubMed captures e-publications ahead of journal publication and so is likely to provide the most up to date overview of the literature.

The search terms used for the PubMed search are reproduced in Table 56 below. These have been simplified and developed from the original search terms for TA255 reproduced in Appendix 13. The search term ("2013"[PDAT]: "3000"[PDAT]) is included to capture only those studies published since the beginning of 2013.

Table 56. PubMed search terms for HRQL in mCRPC

Search term	No. hits
Search ((((castration resistant prostate cancer OR hormone refractory prostate cancer OR mCRPC OR mHRPC) AND (health-related quality of life OR QoL or	74

HRQoL OR HRQL OR utility OR utilities OR EQ-5D OR EQ5D OR EuroQol OR sf thirtysix OR sf thirty six OR shortform thirtysix OR shortform thirty six OR short form thirtysix OR short form thirty six OR sf12 OR sf 12 OR short form 12 OR shortform 12 OR sf twelve OR short form twelve OR sf 6d OR sf6d OR short form 6d OR shortform 6d OR sf six OR shortform six OR short form six))) AND ("2013"[Date - Publication] : "3000"[Date - Publication]))	

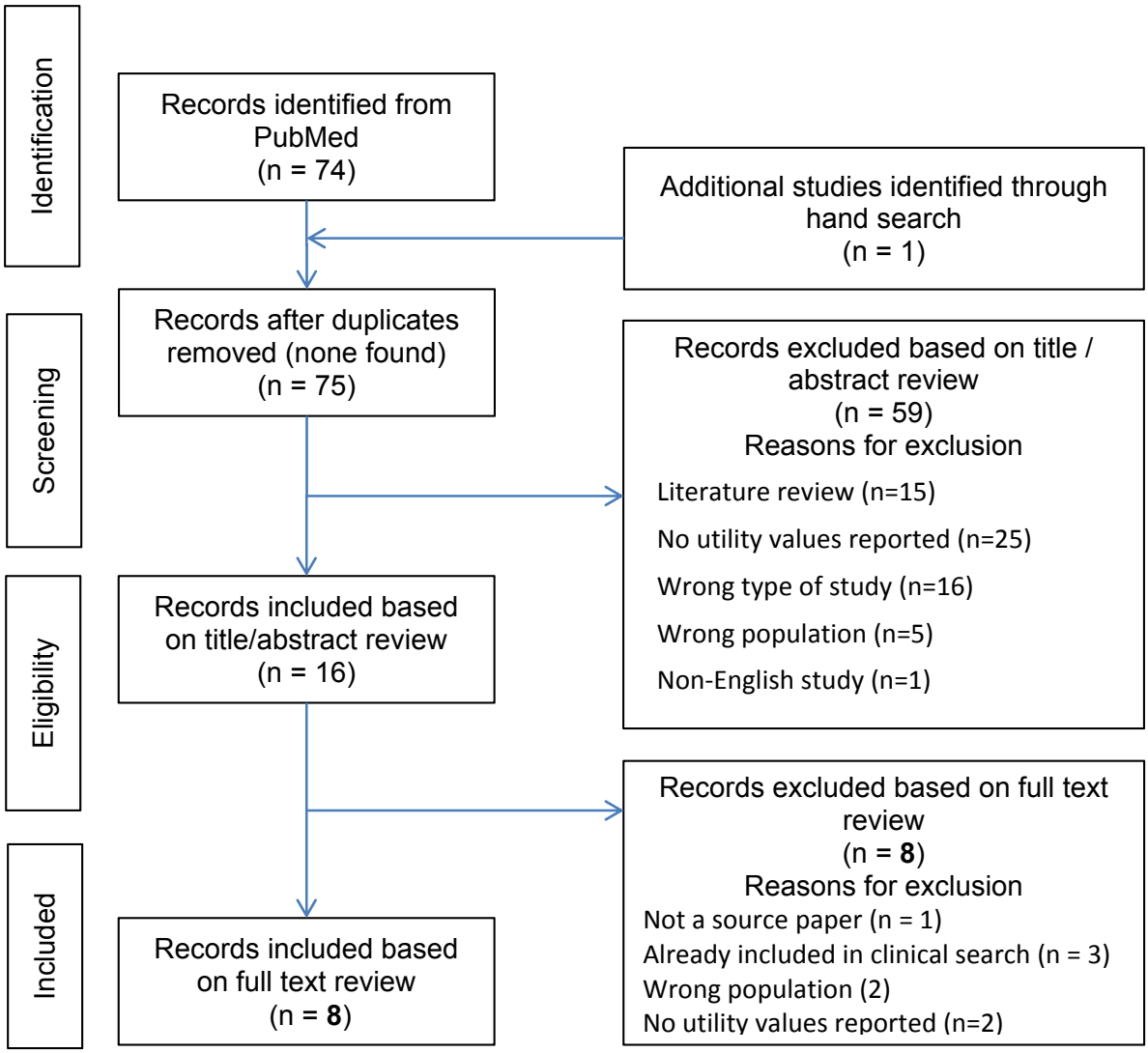
The inclusion and exclusion criteria applied to the results from the HRQL search conducted in PubMed are shown in Table 57 below.

Table 57. Inclusion and exclusion criteria applied to the search results from the HRQL PubMed search.

PICOS	Inclusion	Exclusion
Population	mCRPC/mCRPC patients Adults (≥18 years) Race: Any	Non-human populations Non-mCRPC / non-mCRPC populations No mCRPC / mCRPC subgroup analysis Metastatic disease unclear Study population aged <18 years
Interventions	All	None
Comparator	All	None
Outcomes	Health related quality of life (HRQL) Reported utility and disutility in mCRPC / mHRPC patients	Outcomes not relevant to HRQL
Study design	Reports of utility validation or elicitation exercises OR Reports of economic evaluations using utility measures gathered during the studies	None
Publication timeframe	From 1st January 2013 to 26th August 2015	Publications prior to 2013
Publication status	Published e-publication ahead of print	Editorials Notes Comments Letters Systematic reviews of EE
Language restrictions	English language	Non-English studies
EE, economic evaluations; HRQL, health-related quality of life; mCRPC, metastatic castration-resistant prostate cancer; mHRPC, metastatic hormone-refractory prostate cancer		

A flow diagram of the search is included in Figure 20 overleaf.

Figure 20. Flow diagram of the included studies from the PubMed search



A list of the articles retained for full text review with reasons for exclusion is provided in Table 58.

Table 58. List of articles retained for full text review from the PubMed search with reasons for exclusion

Publication	Excluded at full text review ?	Reason for exclusion
Cameron MG, 2015[201]	Yes	Wrong population
Loriot Y, 2015[132]	No	N/A
Bahl A, 2015[12]	No	N/A
Zhou T, 2015[127]	No	N/A
Cella D, 2015[202]	Yes	Included in the Clinical Searches
Diels J, 2015[203]	No	N/A
Fizazi K, 2014[63]	Yes	Included in the Clinical Searches

Publication	Excluded at full text review ?	Reason for exclusion
Clark MJ, 2014[204]	Yes	No utility values reported
Skaltsa K, 2014[205]	Yes	Not a source paper
Basch E, 2013[84]	No	N/A
von Moos R, 2013[206]	Yes	Wrong population
Harland S, 2013[67]	Yes	Included in the Clinical Searches
Li YF, 2013[207]	No	N/A
Fizazi K, 2013[208]	Yes	No utility values reported
Organ M, 2013[209]	No	N/A
Torvinen S, 2013[210]	No	N/A

5.4.4. Details of the included studies in which HRQL was measured.

Summaries of the studies identified in the clinical and PubMed searches are provided in Appendix 16.

5.4.5 Highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

The results from the FACT-P studies reported in the literature were mapped to EQ-5D for use in their respective submissions (for example TA259 and TA316). This data is generally redacted in the submissions and has not been used for the purposes of this submission due to the availability of directly measured utility data from the UK EAP.

EQ-5D utility values collected from the literature reviews (including the studies identified in Appendices 18 and 19 are tabulated below (Table 59). In most cases the assignment to the 'stable' and 'progressed' disease states is based on assumption and this is explored in the comments sections.

Utility values identified in the literature search relevant to the health states in the model are tabulated below. Table 59

Table 59. Utility values from the literature for the stable and progressive disease states

	Stable utility* (SD)	Progressed utility* (SD)	Comment
Bahl, 2015[12]	0.7281 (0.238) to 0.8185 (0.187)	0.6266 (0.298)	Data collected in the UK EAP for cabazitaxel. First utility reported here is for cycle 2. Interpolated utility at cycle 1 is used in the modelling. Discussed in Section 5.4.1, Table 55
Loriot, 2015[211]	0.85 (0.15)		Data collected in chemotherapy naïve patients in the Prevail study
Diels, 2015[203]	0.66 (0.02)	0.60 (0.03)	For the purposes of this table the 'stable' state is assumed to be for patients undergoing chemotherapy and the progressed utility is assumed for patients characterised as 'post chemotherapy'.

	Stable utility* (SD)	Progressed utility* (SD)	Comment
Torvinen, 2013[212]	0.74 (95% CI: 0.69 – 0.80)	0.59 (95% CI: 0.48 – 0.70)	For the purposes of this table the 'stable' state is assumed to be for metastatic patients on active treatment and the progressed utility is assumed for patients characterised as receiving palliative care.
Wolff, 2012[213]	Mean (SD) EQ-5D: 0.72 (0.30) No chemo: 0.81 (0.27) Post-chemo:0.66 (0.30) Ongoing chemo: 0.64 (0.31)		Published in conference proceedings in German patients.
Diels 2012[214]	0.67		Updated above in Diels 2015. Mean utility for all patients recorded.
James 2012[215]	-	0.63 (0.26)	Published in conference proceedings only. Utility is for mCRPC patients progressed after docetaxel.
Sullivan, 2007[200]	0.715	-0.07 decrement	Baseline utility recorded for the UK population studied with decrement for progression at -0.07
Sandblom, 2004[30]	-	0.538 (0.077)	Utility value recorded in the last year before death in patients who died of prostate cancer.
*Uncertainty is described as standard deviation unless otherwise noted.			

In the ERG report to TA 255 the interim utility values which were taken from the UK EAP (Bahl, 2015) were highlighted as an area of key uncertainty due to their premature nature (only the first 4 cycles in the UK EAP had been collected at the time by the early recruiting patients).

We have implemented the mature utility values from the UK EAP which we believe represent the most reliable source for estimates of utility in both the stable and progressive states and are treatment specific to cabazitaxel. The use of these values from the EAP for both states provides consistency in the analysis. The magnitude of these utility estimates is generally in line with the values reported in the literature and summarised in Table 59 above, which range from 0.66 to 0.85 for the stable state and from 0.54 to 0.66 for progressive disease.

Health-related quality-of-life data used in cost-effectiveness analysis

5.4.6. The effect of adverse reactions on HRQL

AEs will impact on HRQL and, as discussed in Section 4.12 earlier, cabazitaxel has a higher AE rate than mitoxantrone.

Disutility values for adverse events were not collected in the UK EAP or in TROPIC. In line with the approach taken in TA255 disutility values associated with experiencing each AE presented in the model were derived from literature data. When disutilities were found in two different sources, an average value was used in the model. The studies from which the disutility values were retrieved were not specific to prostate cancer patients. Instead, the studies described utility losses due to AEs for breast cancer patients and non-small cell lung cancer (NSCLC) patients. This is due to the lack of data specific to prostate cancer and because it was assumed that treatment-induced AEs would confer corresponding utility

losses irrespective of cancer type. For some of the AEs no disutility values were found. Disutility values used in the model are reported in Table 60.

The disutilities associated with neutropenia and diarrhoea were taken from a study eliciting health state utilities in patients with metastatic NSCLC, where members of the general public estimated the disutilities.[216] The disutilities for leukopenia and thrombocytopenia were assumed to be equal to the utility loss for neutropenia. The disutility of pulmonary embolism was estimated as an average from Gould *et al*[217] and Treasure *et al*[218] and the disutility of deep vein thrombosis was taken from Gould *et al*.[217] The disutility associated with febrile neutropenia, fatigue and nausea/vomiting were averages of disutilities retrieved from the studies by Nafees *et al*[216] and Lloyd *et al*. [219] The latter was a study eliciting health state utilities in patients with breast cancer, where members of the general public estimated the disutilities. From the same study, the utility loss determined for stomatitis was used for dehydration (based on clinical expert opinion that stomatitis cases are often filed under dehydration). The disutility for asthenia was assumed to be equal to the utility loss for fatigue.

For patients experiencing back and bone pain, the disutility value was based on the disutility associated with experiencing pain as estimated by Doyle *et al*.[220] The disutility values associated with anaemia were taken from a study of standard gamble interviews in members of the general public. The utility value for patients experiencing severe anaemia (patients with 7.0–8.0 g/dl which corresponds to Grade 3 and above) was estimated to 0.583, while the utility value for patients experiencing no anaemia was estimated at 0.708, whereby a disutility of -0.125 was included in the model.

Finally, the disutility for neuropathy was derived from another study on patients with metastatic NSCLC, where members of the general public estimated the disutilities (Lewis *et al*) and was estimated to -0.116.[221]

Table 60. Disutility due to treatment related adverse events used in the model*

State	Utility value	SE	Reference in submission	Justification
Neutropenia	-0.090	0.0157	Nafees *et al* (2008)[216]	Only available evidence
Febrile neutropenia	-0.120	0.0209	Lloyd *et al* (2006)[219] and Nafees *et al* (2008)[216]	Average of the two available studies.
Diarrhoea	-0.047	0.0082	Nafees *et al* (2008)[216]	Only available evidence
Fatigue	-0.094	0.0163	Lloyd *et al* (2006)[219] and Nafees *et al* (2008)[216]	Average of the two available studies
Asthenia (weakness)	-0.094	0.0163	Assumption	No data available – assumed to be equal to fatigue

State	Utility value	SE	Reference in submission	Justification
Leucopaenia	-0.090	0.0157	Assumption	No specific data available – assumed to be equal to neutropenia
Back pain	-0.069	0.0120	Doyle *et al* (2008)[220]	Only available evidence
Anaemia	-0.125	0.0217	Lloyd *et al* (2008)[222]	Only available evidence
Thrombocytopenia	-0.090	0.0157	Assumption	No specific data available – assumed to be equal to neutropenia
Pulmonary embolism	-0.145	0.0252	Gould *et al* (1999)[217] and Treasure *et al* (2009)[218]	Average of the two available studies
Dehydration	-0.151	0.0263	Lloyd *et al* (2006)[219]	Based on clinical expert opinion that stomatitis cases are often filed under dehydration
Nausea/vomiting	-0.076	0.0131	Lloyd *et al* (2006)[219] and Nafees *et al* (2008)[216]	Average of the two available studies
Bone pain	-0.069	0.0120	Doyle *et al* (2008)[220]	Only available evidence
Deep vein thrombosis	-0.160	0.0278	Gould *et al* (1999)[217]	Only available evidence
Neuropathy	-0.116	0.0202	Lewis *et al* (2010)[221]	Only available evidence

*Where more than one reference is available in the literature the average of the values has been used.

5.4.7 Patient experience of HRQL in the health states described by the model

The EAP provides EQ-5D based utility data for UK patients treated with cabazitaxel and prospectively followed up. These data are therefore considered to be consistent with the reference case. The UK EAP is described in detail in Sections 4.11.3 to 4.11.12 above.

EQ-5D responses were recorded in the UK EAP at every other cycle and so utility data is available for baseline and cycles 2,4,6,8 and 10. Utilities for cycles 1,3,5,7 and 9 have been interpolated. These values are implemented in the model at each cycle up to cycle 10 and then held constant thereafter for patients who do not progress. Patients progressing on an earlier line of therapy (baseline) experience increases to their initial health-related quality of life (albeit not statistically significant) and maintain this over time whilst on treatment in the stable disease. The list of values implemented in the model is provided in Table 61 below.

The utility value for the progressive disease state is captured from the UK EAP as the last recorded utility value 30 days after final cabazitaxel treatment in those patients with documented evidence of progression. As these were patients no longer on treatment and had documented evidence of progression this is assumed to accurately reflect utility for the progressed disease state. As might be expected this is lower than observed in the stable

disease state. In the absence of other evidence and in order to reflect later deteriorations and a terminal period a utility value of 0 is implemented in the last 3 months of life.

The EAP only considers patients treated with cabazitaxel however, the clinical advisors to the ERG for TA255 had no reason to believe that the utility for patients would be affected by the type of second-line chemotherapy used (i.e. cabazitaxel or mitoxantrone). Therefore these data are applied within the model regardless of the treatment administered, provided that they are in the same disease state.

We consider that the use of the updated, mature UK EAP data reduces uncertainty and provides the most appropriate figures to use for both the stable and progressed states

Treatment related adverse reactions

Whilst application of different values for stable and progressive disease state utilities allows for the differential effect on disease control to be captured, this approach does not account for effects of increased rates of AEs. To account for the potential for adverse events to affect utility, disutilities are applied as they are experienced in the model.

Fifteen AEs were included in the model. These are listed in above in Table 60 together with AE rates in patients who experienced these events in each arm of the TROPIC trial. These AEs were chosen on the grounds that they were the most frequent treatment-emergent Grade ≥3 AEs (occurring in more than 2% of the patients in any treatment arm of the TROPIC trial). In addition, deep vein thrombosis and neuropathy were added to the list of AEs, as they were classified as important based on clinical expert opinion.

Although early-stage disease may be asymptomatic, metastatic prostate cancer is associated with a range of symptoms that substantially affect HRQL (Section 3.2). Symptoms include lymphoedema, weight loss, pain, and Skeletal related Events (SREs) associated with bone metastases. Pain associated with bone metastases is considered one of the most important factors affecting HRQL in mCRPC. The patient's HRQL is also likely to be directly affected by various other factors, including fatigue and anxiety. Mitoxantrone was licensed in the first-line setting principally for its palliative benefits, including its impact on pain,[223] and its historic use in second line therapy illustrates the importance of effective symptom control in mCRPC.

In addition to the impact of the disease, AEs and general fatigue/ malaise associated with chemotherapy are also likely to affect HRQL. However, the use of active chemotherapy such as mitoxantrone even in the absence of a proven survival benefit suggests that clinicians perceive the benefits of chemotherapy in terms of symptom control to outweigh the negative impact of the therapy.

5.4.8 Clarify whether HRQL is assumed to be constant over time in the cost-effectiveness analysis. If not, provide details of how HRQL changes over the course of the disease or condition.

There is limited published data available to describe HRQL in mHRPC/mCRPC over time. Generally it is assumed that HRQL would remain reasonably constant while patients are in

the stable state and receiving regular chemotherapy, and that HRQL would decrease towards the last months of life, when patients have very advanced, progressing cancer. In fact the UK EAP has shown that HRQL in the stable state may increase with time on therapy and although not a statistically significant trend this is an observation supported by clinical opinion (see Appendix 17). Therefore in the stable disease state we have implemented the observed values from the UK EAP for cycles 1 to 10 and then made the assumption that after cycle 10 utility remains constant until progression (see Table 55 for the full utility data and Table 61 for a summary).

The usual approach taken to modelling progression in metastatic cancer is to assume lower HRQL in the progressed disease state compared with the stable disease state. This is the approach taken here informed by the last utility value measured 30 days after cabazitaxel cessation in patients with evidence of progression from the UK EAP. In reality this is unlikely to be a stepwise transition to a lower value as it is probable that a number of factors will affect HRQL, including presence of painful bone metastases, efficacy of pain control, receipt and type of further chemotherapy/BSC, and disease history as time in state continues.. There is no literature evidence for the evolution of utility over time in this state and so to account for the assumed decrease in utility the value is held constant until the last three months of life (four cycles in then model) whereupon it is set to 0.

5.4.9 Describe whether the baseline HRQL assumed in the cost-effectiveness analysis is different from the utility values used for each of the health states. State whether quality-of-life events were taken from this baseline.

There are three health states in the model: stable, progressive disease and dead. (Section 5.2.2). As discussed in Section 5.4.8 above, in the base-case for the cost-effectiveness analysis, baseline utility is taken from the UK EAP for the stable disease state (See section 5.4.1 above) and successive on treatment cycles are assumed to follow the values for each cycle observed in the UK EAP. Unlike the values used for the progressive state in the previous submission (TA255) where decrements were assumed from literature precedent to inform this state[30, 200] values from the UK EAP are now available. Hence a directly measured progressive disease utility value from a similar population to the TROPIC study is applied with no requirement for adjustment.

5.4.10 Adjustment of the health state utility values

The health state utilities derived from the UK EAP have not been adjusted.

5.4.11 Health effects found in the literature or clinical trials that were excluded from the cost effectiveness analysis

No additional health effects were found in the trials or literature.

5.4.12 Summary of the utility values for the disease states in the model.

A summary of the utility values implemented in the base-case for the three health states modelled is provided in Table 61

Table 61. Summary of utility values for cost-effectiveness analysis

State	Utility value	Reference in submission	Justification
Stable disease	Cycle / Stable Disease 1: 0.704 2: 0.728 3: 0.728 4: 0.750 5: 0.753 6: 0.752 7: 0.778 8: 0.789 9: 0.803 10 and therafter: 0.819	UK EAP (Section 5.4.1) [Bahl 2015][12]	The UK EAP provides utility data for the stable disease state in a UK specific population treated with cabazitaxel. It is not expected that patients treated with mitoxantrone would experience different utility in this state. Odd cycles are interpolated data as utility values were collected at baseline (0.682) and then even cycles thereafter.
Progressive disease	0.6266 until last 3 months of life which are set to 0	UK EAP (Section 5.4.1)	The UK EAP also provides a utility value for the progressive disease state. The measurement used is the value recorded 30 days (last record) after the last cycle of treatment received for patients with evidence of progression. This provides an estimate lower than that employed in TA255 There are no data in the literature (or from the UK EAP) which provide a time dependent estimate of utility post progression. In lieu of this, utility in the progressive disease state is maintained after progression until the last 4 cycles (3 months) whereupon it is set to 0 in the model. This estimate, albeit a step change, attempts to reflect the expected HRQL reduction across the health state
Dead	0.000	Assumption	Standard approach

In addition there is variation in HRQL for patients due to disutilities arising from AEs. To account for this, the disutility estimated from the literature for a specific AE is multiplied by the average duration of the AE as experienced in TROPIC and by the risk per cycle as experienced in TROPIC to give the per cycle disutility for that AE. The disutility for all AEs is then summed and incorporated within the calculation of QALYs for each cycle. Disutilities are only applied in the stable disease state, as AE rates are only available for this period. Disutility due to adverse events used in the model are summarised in Table 60 above.

5.5 Cost and healthcare resource use identification, measurement and valuation

5.5.1 All parameters used to estimate cost effectiveness should be presented clearly in a table with details of data sources.

Tables detailing costs and estimates for resource usage along with sources are presented in the following sections.

5.5.2 Describe how relevant cost and healthcare resource use data for England were identified.

On the basis that there were limited published data available on resource use in second-line mCRPC a full literature search was not carried out for the original submission TA255. Rather service evaluations were undertaken at five major UK centres to provide relevant and robust data for the model. The service evaluations included patients who received docetaxel for first-line treatment of mCRPC on or after 1 June 2007 and for whom records were available. Approximately 20–25 patients were included from each of the five centres. The study provided resource use estimates for patients on second-line cytotoxic chemotherapy, and on post-second-line chemotherapy and post-second-line BSC, which are applied as appropriate in the model. Full methods are reported in Appendix 14.

The literature review carried out for this submission described in Section 4.1 included terms for health resource utilisation. A list of the studies identified in the review along with abstracted cost and hospital resource utilisation information is provided in Appendix 15. No UK studies were found and little information relevant to this submission was available in these reports. Hospital resource utilization data for adverse events were available in the CAST study in 63 patients in Dutch hospitals[152] This study looked at sequences including cabazitaxel and abiraterone. Regardless of treatment or sequence, median length of stay (for the aggregate of all adverse events) was consistently 5 days in CAST. These results are comparable to those identified in the UK treatment audit. For example costly events such as febrile neutropenia resulted in 6 to 10 days in hospital on cabazitaxel treatment (depending on line of therapy) in the CAST study and 5.4 in the UK treatment audit. Neutropenia in CAST was observed at 1 to 2 days but in the UK treatment audit was longer at 4.5 days (see Table 70 for the average length of stay from the UK treatment audit). Other events reported in the CAST study are generally in line with observed UK rates.

Treatment cost data were provided in nine studies identified by the review (See Appendix 21) however no studies reported UK cost of treatment.

The large observational study described above provided an estimate for resource use at the time of the last submission for cabazitaxel (TA255). As there continues to be a dearth of UK evidence we believe these data remain the most robust source available for resource use information for second-line mCRPC in UK clinical practice and the findings have been applied in the modelling for this submission. Costings from standard sources (such as NHS reference costs, *BNF* drug costs) were updated from TA255 and applied to these resource use estimates in the model.

5.5.3 When describing how relevant unit costs were identified, comment on whether NHS reference costs or payment-by-results (PbR) tariffs are appropriate for costing the intervention being appraised.

Because the treatment is likely to have a number of consequences on the resource usage by patients, it is appropriate to consider NHS reference costs in this analysis.

5.5.4 Clinical expert assessment of the applicability of the cost and healthcare resource use values

For the purposes of the previous submission (TA255) an advisory board was held to obtain advice from four oncologists on UK-specific resource use data. The estimates of resource use which were elicited were used to supplement missing values from the UK-based retrospective observational study of five major cancer centres described above (Section 5.5.2). These included rates of use of liver function test, PSA test and ECG, and the rates of secondary G-CSF prophylaxis. In addition, clinicians made estimates around palliative care requirements in the last month of life. This was necessary as the observational study was based on hospital records and did not estimate directly palliative care received elsewhere (e.g. in a hospice). (Data on inpatient hospitalisations occurring in the last month of life were available from the study and were used.)

5.5.5. Summary of the cost and associated healthcare resource use of each treatment.

A summary of the unit costs used in the model is provided in Table 62.

Table 62. Unit costs associated with the technology in the economic model

Items	Cabazitaxel	Ref. in subm[n]	Mitoxantrone	Ref. in subm[n]	Abiraterone	Ref. in subm[n]	Enzalutamide	Ref. in subm[n]
Drug cost (unit)	*Commercial in confidence information removed*	Section 2.3.3	£100 per vial	Section 2.3.2	£2930.00 per 120 tablet pack	Section 2.3.1	£2734.67 per 112 capsule pack	Section 2.3.1
Administration cost / per cycle	*Commercial in confidence information removed*	Section 5.5.6	*Commercial in confidence information removed*	Section 5.5.6	n.a.	Section 5.5.6	n.a.	Section 5.5.6
Pre- & Concomitant medication / cycle	*Commercial in confidence information removed*	Section 5.5.6	*Commercial in confidence information removed*	Section 5.5.6	*Commercial in confidence information removed*	Section 5.5.6	*Commercial in confidence information removed*	Section 5.5.6
Adverse event management costs (total / risk adjusted for length of AE episodes)	£105.18 (total)	Section 5.5.7	£53.78 (total)	Section 5.5.7	£5.15	Section 5.5.7	£5.05	Section 5.5.7
Progressive disease : active treatment / per cycle	*Commercial in confidence information removed*	Section 5.5.6	*Commercial in confidence information removed*	Section 5.5.6	*Commercial in confidence information removed*	Section 5.5.6	*Commercial in confidence information removed*	Section 5.5.6
Progressive disease: BSC treatment cost / per cycle	*Commercial in confidence information removed*	Section 5.5.6	*Commercial in confidence information removed*	Section 5.5.6		Section 5.5.6		Section 5.5.6
End of life cost – one off cost applied when patients transition to the dead state	£1952.15	Section 5.5.6	£1952.15	Section 5.5.6	£1952.15	Section 5.5.6	£1952.15	Section 5.5.6

5.5.6 Summary of the costs included in each health state.

Costs in the stable disease state comprise acquisition costs for active treatment, acquisition costs for pre-medications and concomitant medications, costs of chemotherapy administration, cost of disease management including hospitalisations and testing, and adverse event costs. Resource use data are summarised in Table 63, and unit costs in Table 64. Adverse event costs are summarised separately below in section 5.5.7.

Drug acquisition costs were sourced from the BNF and the cost of cabazitaxel was modified by the PAS discount. (See Section 2.3.2).

Down titration of the cabazitaxel dose is recommended according to the SPC if there are adverse reactions or if patients have compromised liver function (Table 8). This is captured in the model according to the mean dose intensity received in TROPIC (0.9259 and 0.9398 for cabazitaxel and mitoxantrone respectively).

Assumptions around pre- and concomitant medications are summarised in Table 63 below. The most complex is granulocyte-colony stimulating factor (G-CSF) prophylaxis, which is discussed separately below.

In the stable disease state, costs for active treatment, pre-medications and chemotherapy administration are applied for ten cycles, corresponding to the maximum number of cycles allowed in TROPIC. Concomitant LHRH agonist therapy and disease management costs (hospitalisations and so forth) are applied for the entire duration of stable disease. In most cases estimates for the resource use are derived from the UK treatment audit which provided values for a 3 month period. These values are presented in the tables below where appropriate. (Table 63 and Table 67). The model calculates the per cycle usage.

Table 63. Resource use estimates for stable disease state

Resource use item	Resource use estimate per 3 weekly cycle	Source/ justification
Arm-specific resource use		
Active intervention: cabazitaxel	47.50 mg per 3 weekly cycle plus daily 10 mg prednisolone	Based on dose of 25 mg/m^2, BSA of 1.9 m^2 assuming no wastage.
Comparator: mitoxantrone	1 or 2 vials of 20 mg plus daily 10 mg prednisolone	Based on dose of 12 mg/m^2, BSA of 1.9 m^2 and assumption of no vial sharing
Comparator: abiraterone	1g once daily plus daily 10 mg prednisolone	BNF September 2015
Comparator: enzalutamide	160 mg once daily	BNF September 2015

Resource use item	Resource use estimate per 3 weekly cycle		Source/ justification
Premedications – cabazitaxel arm	100% patients receive premedication with antihistamine, H2-antagonist, anti-emetic, and corticosteroid once per 3-week cycle 25% patients receive primary prophylaxis with G-CSF per cycle		Mandated premedication regimen TROPIC data showed 100% patients received anti-emetics (based on proportion of patients who received the four most common anti-emetics ondansetron, ondansetron-HCl, granisetron and granisetron-HCl).
Premedications – mitoxantrone arm	Premedications as follows: antihistamine (9%), H_2 antagonist (25%), anti-emetics (100%), corticosteroids (56%), G-CSF as primary prophylaxis (10%) per cycle.		Data from TROPIC for treatments received TROPIC data showed 100% patients received anti-emetics (based on proportion of patients who received the four most common anti-emetics ondansetron, ondansetron-HCl, granisetron and granisetron-HCl)
Premedications – abiraterone arm	Assumption – same as mitoxantrone arm in TROPIC, not including G-CSF		As above
Premedications – enzalutamide arm	Assumption – same as mitoxantrone arm in TROPIC, not including G-CSF		As above
General resource use per 3 weeks			
Concomitant medications	100% patients receive concomitant LHRH agonist therapy		Based on data from TROPIC and confirmed by clinical opinion. In absence of further data assume 50-50 split between leuprorelin and goserelin
Chemotherapy administration	One visit per 3 weeks, plus cost of pharmacist time		In line with treatment regimen. Pharmacist time required to prepare drug for infusion
Oncology ward (ALoS, Inpatient care)	8.17	0.681	UK observational study
General ward (ALoS, Inpatient care)	8.17	0.681	

Resource use estimate per 3 months

Description	Value	SD*	Source/ justification
Visit to Clinical oncologist/ 3 weeks - caba	4.3	0.358	UK observational study
Visit to nurse/3 weeks	0	0.000	
Visit to Clinical oncologist/week	4.3	0.358	
Visit to nurse/week	0	0.000	
Urologist (Outpatient care)	0.07	0.006	

GP (Outpatient care)	0	0.000	
Nurse (Outpatient care)	0	0.000	
A & E (Outpatient care)	0	0.000	
Oncology ward (Inpatient care)	0.030	0.003	
General ward (Inpatient care)	0.04	0.003	
Hospice home	0	0.000	
CT scan	0.15	0.013	
MRI	0.04	0.003	
Bone scan	0.09	0.008	
Ultrasound	0.04	0.003	
Conventional X-ray	0.13	0.011	
Complete blood count	4.96	0.413	
Chemistry panel	6.06	0.505	
Liver function test	2	0.167	
PSA	2	0.167	
ECG	1	0.083	
Echocardiography	0	0.000	

*PERT approximation for standard deviation [Max-Min]/6 with Min/Max of distribution assumed : mean +-25% SD = [1,25*Mean - 0,75*Mean]/6 = Mean / 12

Table 64. Unit cost inputs for stable disease state

Cost	Cost (£) / unit	Unit	Comment
Active treatment			
Mitoxantrone	5.00	Mg	Cost per vial; £100 (2 mg/ml; 10 ml vial) – Online BNF June 2015
Cabazitaxel	*Commercial in confidence information removed*	Mg	*Commercial in confidence information removed* per 60 mg vial according to PAS discount
Abiraterone acetate	0.10	Mg	Based on 250 mg tablet, net price 120-tab pack = £2930.00
Enzalutamide	0.61	mg	Based on 40 mg capsule, net price 112-cap pack = £2734.67
Premedication			
Antihistamines	0.45	Mg	Based on cost for chlorphenamine - Online BNF June 2015
H2 inhibitors	0.01	Mg	Based on cost for ranitidine – Online BNF June 2015
Anti-emetics	0.58	Mg	Based on cost for ondansetron – Online BNF June 2015
Corticosteroids	0.52	Mg	Based on cost for dexamethasone – Online BNF June 2015
G-CSF	175.67	Mg	Based on cost for filgrastim - Online BNF June 2015
Concomitant medication			

Prednisolone	0.01	Mg	Online BNF June 2015
Goserelin	18.06	Mg	Online BNF June 2015 (based on price of Zolodex)
Leuprorelin	20.06	Mg	Online BNF June 2015 (based on price of Prostap)
Chemotherapy administration			
Clinical oncologist (chemotherapy admin.)	320	Per administration	Total HRG tab - Currency code SB15Z - NHS Ref Cost 2013-2014
Pharmacist cost per cabazitaxel administration	10.50	Per administration	Table 13.6 - (PSSRU 2014). No preparation prior to administration is required. Based on 15 minutes of pharmacist time required to order the appropriate dose of cabazitaxel.
Pharmacist cost per other chemotherapy administration	42	Per administration	Table 13.6 - (PSSRU 2014). Based on 1 hour of pharmacist time including chemotherapy preparation prior to administration.
Supportive care costs			
Clinical Oncologist (regular visit)	143	Per visit	Out-patients consultant led tab - Currency code WF01A - Service code 370 - (NHS Ref Cost 2013-2014)
Urologist	92	Per visit	Out-patients consultant led tab - Currency code WF01A - Service code 101 - (NHS Ref Cost 2013-2014)
Inpatient care: oncology ward	537	Per 24 h	Non elective inpatients short stay tab - average of currency codes LB06H, LB06J, LB06K, LB06L, LB06N, LB06P, LB06Q, LB06R, LB06S (NHS Ref Cost 2013-2014)
Inpatient care: general ward	537	Per 24 h	Non elective inpatients short stay tab - average of currency codes LB06H, LB06J, LB06K, LB06L, LB06N, LB06P, LB06Q, LB06R, LB06S (NHS Ref Cost 2013-2014)
Imaging: CT scan	124	Per scan	Diagnostic imaging tab - service code (DIAGIMOP) - service description (outpatient) - RA10Z (NHS Ref Cost 2013-2014)
Imaging: MRI	212	Per scan	Diagnostic imaging tab - service code (DIAGIMOP) - service description (outpatient) - RA03Z (NHS Ref Cost 2013-2014)
Imaging: bone scan	204	Per scan	Diagnostic imaging tab - service code (DIAGIMOP) - service description (outpatient) - RA36Z (NHS Ref Cost 2013-2014)

Imaging: ultrasound	57	Per scan	Diagnostic imaging tab - service code (DIAGIMOP) - service description (outpatient) - Average of RA23Z-RA24Z (NHS Ref Cost 2013-2014)
Imaging: X-ray	204	Per scan	Diagnostic imaging tab - service code (DIAGIMOP) - service description (outpatient) - RA36Z (NHS Ref Cost 2013-2014)
Lab tests: complete blood count	3	Per test	DAPS tab - DAPS05 (NHS Ref Cost 2013-2014)
Chemistry panel	1	Per test	DAPS tab - DAPS04 (NHS Ref Cost 2013-2014)
Liver function test	3	Per test	DAPS tab - DAPS08 (NHS Ref Cost 2013-2014)
PSA	1	Per test	DAPS tab - DAPS04 (NHS Ref Cost 2013-2014)
ECG	121	Per test	Total HRGs tab, code EA47Z, NHS Reference costs 2013-2014
Echocardiogram	72	Per test	IMAG tab - DIAGIMOP RA60A - Direct Access (NHS Ref Cost 2013-2014)

G-CSF prophylaxis

In the base-case scenario for the comparison of cabazitaxel and mitoxantrone, the proportion of patients receiving G-CSF as primary prophylaxis (before any clinical event of neutropenia Grade ≥ 3 or febrile neutropenia) was derived from TROPIC. G-CSF usage in the TROPIC trial was analysed to give an average rate per cycle of 25% for cabazitaxel and 10% for mitoxantrone. The average length of G-CSF treatment as primary prophylaxis per cycle (4.1 days) was also derived from the TROPIC trial and was based on the mean duration of G-CSF treatment for all treated patients.

In the model, there is a possibility to change the proportion of patients receiving G-CSF treatment as primary prophylaxis, to reflect country-specific treatment practice. In general UK clinicians follow EORTC guidelines and apply primary G-CSF prophylaxis. Around 20 – 25% of patients are managed in this way, however this is variable and may be lower; for example in a recent audit of patients treated in Preston and Lancashire, *Academic in confidence information removed* % of patients received prophylactic G-CSF. If the proportion of patients that receive G-CSF as primary prophylaxis is increased, the risk of having neutropenia or febrile neutropenia will consequently decrease. The rate per cycle of G-CSF prophylaxis is varied in sensitivity analysis (see Table 79 for the one-way sensitivity analyses). The risk of having neutropenia and febrile neutropenia after primary prophylaxis treatment with G-CSF is adjusted by applying the relative risk presented in a publication on breast cancer[224] When applying the relative risk derived from this paper, the predicted risks of having neutropenia or febrile neutropenia without any G-CSF prophylaxis coincides with the observed risks of having neutropenia or febrile

neutropenia without any G-CSF prophylaxis in the TROPIC trial, thus validating the use of the relative risk from Vogel *et al*.[224] The varying use of G-CSF as primary prophylaxis is added as a sensitivity analysis.

It is recommended that patients who experience febrile neutropenia should be treated with G-CSF as secondary prophylaxis in every remaining cycle after the event. However, as this is a cohort model, the prophylaxis use cannot be modelled for each patient individually. Rather, the proportion of patients in the cohort treated with G-CSF as secondary prophylaxis in each cycle was estimated by clinical expertise and is used in the model.

For the comparisons with abitraterone and enzalutamide no G-CSF prophylaxis is assumed in the abitraterone or enzalutamide arms.

Progressed disease state

Costs in the progressed disease state comprise acquisition costs for post-second-line active chemotherapy and BSC treatments, costs of chemotherapy administration, and cost of disease management including hospitalisations and testing. Resource use data are shown in Table 67 and unit costs for items not already covered within the stable disease state are shown in Table 68.

Post-progression treatment

It is assumed a proportion of patients will receive active post-second-line chemotherapy, while a proportion will receive BSC only. In the base-case, this proportion comes from TROPIC and is 44% for the base-case population. The mix of post-second-line chemotherapies received also is taken from TROPIC. The proportion of UK patients receiving BSC (80%) and a UK-specific treatment mix, both taken from the treatment audit, are applied as a sensitivity analysis.

The use of abiraterone or enzalutamide in this mix is not considered due to the pathway arguments put forward earlier. Where patients have received abiraterone or enzalutamide before docetaxel (standard NHS practice) they are prohibited under the current guidelines from receiving a second course of treatment. (For the case where they have not received these treatments ahead of cabazitaxel a scenario comparison is presented in Section 5.7 based on the Indirect Treatment Comparison).

Post-second-line chemotherapy is applied as a transition cost on transition from stable to progressive disease. No separate survival advantage is attributed to the post-second-line treatment whether with BSC or post-second-line chemotherapy: the post-second-line treatment will solely add to the total cost in each cycle. The TROPIC post-second-line treatment mix is based on the ten most commonly prescribed drugs after patients had progressed on their study treatment in the trial, and which more than 2% of patients in any of the treatment arms received. To define

the top ten post-second-line treatment mixes, the following post-second-line treatment / antineoplastic off label agents were grouped together:

- Cisplatin and cisplatin W
- Estramustine and estramustine phosphate sodium (latter not in top ten on its own)
- Gemcitabine and gemcitabine hydrochloride
- Mitoxantrone and mitoxantrone hydrochloride
- Vinorelbine and vinorelbine tartrate.

The frequencies presented in Table 65 represent the proportion of patients in each arm receiving the respective types of chemotherapeutic agents post-second-line.

Table 65. Frequency of post-second-line chemo for the base-case population

Treatment	Frequency	
	Cabazitaxel (n=142)	Mitoxantrone (n=142)
Carboplatin	0.04	0.08
Cyclophosphamide	0.07	0.09
Docetaxel	0.11	0.17
Estramustine	0.10	0.08
Etoposide	0.08	0.08
Mitoxantrone	0.35	0.11
Paclitaxel	0.06	0.07
Vinorelbine	0.04	0.09
Cisplatin	0.02	0.01
Gemcitabine	0.00	0.03

The assumption is made that the mitoxantrone treatment mix is received in the abiraterone and enzalutamide comparisons.

The UK-specific post-second-line treatment mix obtained from the clinical audit is presented in Table 66. It should be noted that carboplatin was used in a mixture of regimens, with no one regimen used in more than one patient.

Table 66. The treatments that constitute the UK-specific post-second-line treatment mix[42]

Treatment	Frequency (n): Mitoxantrone and cabazitaxel arm	Source
Docetaxel	0.54 (6)	UK observational study
Mitoxantrone	0.18 (2)	
Carboplatin-based regimens	0.27 (3)	

BSC treatment

BSC is comprised of analgesics, steroids, palliative radiotherapy and bisphosphonates. These were selected as being the most important types of treatment, although clearly, other treatments are likely to be used as supportive medications throughout mCRPC. BSC medications are assumed to be received throughout the progressive disease state on an ongoing per cycle basis.

Concomitant medications

LHRH agonists are applied on an ongoing basis until death.

Additional care costs

Additional care costs, such as lab tests and hospitalisations, are applied on an ongoing per cycle basis. Resource use estimates for these come from the UK observational study.(Appendix The per-cycle cost for patients receiving post-second-line chemotherapy was higher than that for BSC. As discussed above, post-second-line chemotherapy is only applied for a relatively short time, and therefore the cost for BSC is applied to all patients on an ongoing basis, with the incremental cost for post-second-line chemotherapy applied as a transition cost (as is done for the drug costs).

End-of-life care costs

Costs are higher towards the end of life, and based on advice from the clinical experts at the advisory board, a separate ‘end-of-life’ cost is incorporated in the model to account for this. This is applied as a transition cost on death.

It was not possible to break down all the resource use data from the audit to provide specific estimates for resource use in the last month of life. This was done, however, for hospitalisations. The audit showed a notably higher rate of hospitalisations in the last month of life. It would have been inaccurate to apply a hospitalisation rate including these hospitalisations on an ongoing per-cycle basis throughout the progressive disease state. Therefore, the hospitalisations occurring during the last month of life were applied as a separate end-of-life transition cost. Expert opinion was used to provide estimates for other resource use items during the last month of

life, including hospice care and palliative care at home; these were not available from the audit as this was based on hospital records.

Resource use estimates for the progressive disease state used in the model are provided in Table 67 below.

Table 67. Resource use estimates for progressive disease state

Resource use item	**Resource use estimate per 3 months (SD*)**				**Source/justification**
Post-second-line chemotherapy mix	As detailed in Table 65 and Table 66				TROPIC and UK observational study
BSC treatment: analgesics	Received by 43% (SD: 0.0358) patients – assumed 50-50 split between diclofenac and co-codamol				UK observational study
BSC treatment: palliative radiotherapy	Received by 43% (SD: 0.0358) patients – assumed 50-50 split between strontium-89 and external beam radiotherapy				
BSC treatment: corticosteroids	Received by 51% (SD: 0.0425) patients – assumed 50-50 split between prednisolone and dexamethasone				
BSC treatment: bisphosphonates	Received by 17% (SD: 0.0142) patients – assumed all patients receive zoledronate				
Chemotherapy administration	Once every 3 weeks for post-second-line chemotherapy for duration of chemotherapy				In line with treatment regimen. Pharmacist time required to prepare drug for infusion (mitoxantrone) or ordering (cabazitaxel)
Resource use (visits) by post second line mix					
	Receiving post-second-line chemotherapy mix		Receiving post-second-line BSC		
	Value	SD*	Value	SD*	
Urologist (outpatient)	0.000	0.000	0.050	0.004	UK observational study
GP(outpatient)	0.000	0.000	0.000	0.000	
Nurse (outpatient)	0.000	0.000	0.000	0.000	
A & E (outpatient)	0.000	0.000	0.000	0.000	
Oncology ward (Inpatient care)	0.200	0.017	0.130	0.011	Average LOS 6.5 days: UK treatment audit
General ward (Inpatient care)	0.060	0.005	0.090	0.008	
Urology ward (Inpatient care)	0.000	0.000	0.020	0.002	

Resource use item	Resource use estimate per 3 months (SD*)				Source/justification
Urologist (Inpatient care)	0.400	0.033	0.000	0.000	UK observational study
CT scan	0.090	0.008	0.470	0.039	
MRI	0.130	0.011	0.150	0.013	
Bone scan	0.000	0.000	0.140	0.012	
Ultrasound	0.050	0.004	0.000	0.000	
Conventional X-ray	0.050	0.004	0.840	0.070	
Complete blood count	3.470	0.289	4.120	0.343	
Chemistry panel	4.440	0.370	3.890	0.324	
Liver function test	2.000	0.167	2.000	0.167	
PSA	2.000	0.167	2.000	0.167	
ECG	1.000	0.083	0.000	0.000	
Echocardiography	0.000	0.000	0.020	0.002	
End-of-life resource use					
			Value	SD*	Expert estimate
Hospice home			2	0.167	
Palliative care at home			6	0.500	
Palliative hospital outpatients visits			0.8	0.067	
Palliative care - hospital inpatient			0.32	0.027	
Hospice home: ALoS per episode			5	0.417	
Palliative care - hospital inpatient ALoS per episode			8	0.667	

*PERT approximation for SDs: [Max-Min]/6 with Min/Max of distribution assumed : mean +- 25% SD = [1,25*Mean - 0,75*Mean]/6 = Mean / 12

Unit costs for the progressive disease state are provided in Table 68 below.

Table 68. Unit costs for progressive disease cost items

Cost	Cost/unit	Unit	Comment
BSC			
Analgesics – co-codamol	0.058	Tablet	Cost per tablet 30/500 – Online BNF June 2015
Analgesics – diclofenac	0.004414286	Tablet	Cost per tablet – Online BNF June 2015
Strontium-89	234	Dose	NHS Ref Cost (Currency SC29Z)
External beam radiation	103	Fraction	NHS Ref Cost (Currency SC22Z)
Bisphosphonate – zoledronic acid	50.676	mg	Online BNF June 2015

Post-second-line chemotherapy mix drugs			
Etoposide	0.12	mg	Online BNF June 2015
Estramustine	1.71	Tablet	Online BNF June 2015
Cyclophosphamide	0.02	mg	Online BNF June 2015
Paclitaxel	2.23	mg	Online BNF June 2015
Vinorelbine (tartrate)	2.90	mg	Online BNF June 2015
Carboplatin	0.40	mg	Online BNF June 2015
Cisplatin	0.59	mg	Online BNF June 2015
Gemcitabine	0.15	mg	Online BNF June 2015
Docetaxel	6.68	mg	Online BNF June 2015
Palliative care			
Palliative homecare (nurse)	66	Per home visit	Section 10.1 - Community nurse per hour of patient-related work with qualifications (PSSRU 2014)
Palliative homecare (GP)	114	Per home visit	Table 10.8b - PSSRU (2013) - inflated to 2014 cost
Palliative hospital outpatients visits	139	Per visit	Specialist Palliative Care Tab - (service description - outpatient) - SD04A (NHS Ref Cost 2013-2014)
Hospital inpatient	537	Per 24 h	Non elective inpatients short stay tab - average of currency codes LB06H, LB06J, LB06K, LB06L, LB06N, LB06P, LB06Q, LB06R, LB06S (NHS Ref Cost 2013-2014)

5.5.7 Summary of adverse reaction unit costs and resource use included in the de novo cost-effectiveness analysis.

Costs for drugs used to treat AEs were retrieved from the BNF (Table 69). Costs per inpatient bed-day (24 h) were based on NHS Trusts Non-Elective Inpatient (Short Stay) HRG Data from the National Schedule of Reference Costs and are shown in Table 70.

Table 69. Cost for drugs used to treat AEs*

AE treatment drug	Cost/unit	Unit	Comment
Gentamicin	£0.04	Mg	Based on injection
Teicoplanin	£0.02	Mg	
Imodium	£0.04	Mg	Based on tablet formulation (generic form - loperamide)
Blood transfusion	£147	Unit	The estimated cost of a unit of red blood cells including the laboratory services in our hospital is £132 (2008) - inflated to 2014 cost

AE treatment drug	Cost/unit	Unit	Comment
Platelet transfusion	£241	Pool	Approximately £200 per adult dose (2005) - inflated to 2014 cost
Intravenous drip	£63	Day	Calculated as £60 from 2010 source and inflated to 2014 cost
Warfarin	£0.04	Mg	Tablet form
Domperidone	£0.01	Mg	Tablet form
Metoclopramide	£0.004	Mg	Tablet form
Cyclizine	£0.002	Mg	Tablet form
Amitryptiline	£0.004	Mg	Tablet form

*Unless otherwise stated costs are taken from the BNF June 2015.

Table 70. Costs of adverse events

Reason for hospitalisation	Unit cost (per 24 h)	Average length of stay (days)	SD: average length of stay	HRG currency code
Neutropenia	£493	4.65	0.3875	Weighted average SA08G, SA08H, SA08J
Febrile neutropenia	£999	5.4	0.4500	Weighted average PM45A, PM45B, PM45C, PM45D
Diarrhoea	£477	4.32	0.3600	Weighted average: FZ91A, FZ91B, FZ91C, FZ91D, FZ91E, FZ91F, FZ91G, FZ91H, FZ91J, FZ91K, FZ91L, FZ91M
Fatigue	£413	1.61	0.1342	Weighted average: AA31C, AA31d, AA31E, DZ38Z
Asthenia (weakness)	£413	1.61	0.1342	Weighted average: AA31C, AA31d, AA31E, DZ38Z
Leucopenia	£493	4.65	0.3875	Weighted average: SA08G, SA08H, SA08J
Back pain	£425	9.55	0.7958	Weighted average: HD26D, HD26E, HD26F, HD26G
Anaemia	£517	6.46	0.5383	Weighted average: SA04G, SA04H, SA04J, SA04K, SA04L
Thrombocytopenia	£571	5.88	0.4900	Weighted average: SA12G, SA12H, SA12J, SA12K
Pulmonary embolism	£494	6.32	0.5267	Weighted average: DZ09D, DZ09E, DZ09F, DZ09G, DZ09H
Dehydration	£449	7.37	0.6142	Weighted average: KC05G, KC05H, KC05J, KC05K, KC05L, KC05M, KC05N

Reason for hospitalisation	Unit cost (per 24 h)	Average length of stay (days)	SD: average length of stay	HRG currency code
Nausea / vomiting	£477	4.32	0.3600	Weighted average: FZ91A, FZ91B, FZ91C, FZ91D, FZ91E, FZ91F, FZ91G, FZ91H, FZ91J, FZ91K, FZ91L, FZ91M
Bone pain	£425	9.55	0.7958	Weighted average: HD26D, HD26E, HD26F, HD26G
Deep vein thrombosis	£405	4.65	0.3875	Weighted average: YQ51A, YQ51B, YQ51C, YQ51D, YQ51E
Neuropathy	£590	2.77	0.2308	

*PERT approximation for SDs: [Max-Min]/6 with Min/Max of distribution assumed: mean +-25% SD = [1,25*Mean - 0,75*Mean]/6 = Mean / 12

The AE rate is equal to the cumulative risk of the AE over the follow-up time in TROPIC. This risk was transformed to a probability per three-week cycle, which was implemented in the model.

Since drugs filed in the TROPIC database cannot easily be correctly assigned to every AE, treatment of every specific AE was based on UK clinical expert opinion. It was assumed that treatment of all AEs requires no extra outpatient visits apart from the regular visits patients make for the purpose of therapy administration, an assumption that was supported by clinical expert opinion. The rate of hospitalisation for every SAE was available in the TROPIC trial and was collected in the case report form (CRF). As hospitalisation for SAE in TROPIC was defined as new hospitalisations or a prolongation of an ongoing hospitalisation, the rates of hospitalisation estimated in TROPIC may overestimate the rate of hospitalisations in clinical practice (since patients may already be hospitalised, and if the box is checked in the CRF, it could just be because the hospitalisation was prolonged). The TROPIC-derived SAE hospitalisation rates were, therefore, validated by UK clinical expertise to make sure that the rates applied in the model are appropriate estimates and reflect the clinical practice. The rates validated and adjusted by clinical expertise were then used to populate the model. The hospitalisation rate for every SAE used in the model was based on an average of all hospitalisations for this SAE, irrespective of treatment arm (Table 71). The average length of stay for each hospitalisation episode was based on HRG data, using appropriate currency codes.50

Table 71. Hospitalisation rates by severe adverse event (Grade ≥3)

Severe adverse event (Grade ≥3)	Rate of hospitalisation	SD*: rate of hospitalisation
Neutropenia	0.02	0.0051

Severe adverse event (Grade ≥3)	Rate of hospitalisation	SD*: rate of hospitalisation
Febrile neutropenia	0.75	0.0158
Diarrhoea	0.10	0.0109
Fatigue	0.01	0.0036
Asthenia (weakness)	0.01	0.0036
Leucopenia	0.02	0.0051
Back pain	0.15	0.0130
Anaemia	0.15	0.0130
Thrombocytopenia	0.05	0.0079
Pulmonary embolism	0.80	0.0146
Dehydration	0.25	0.0158
Nausea	0.00	0.0000
Bone pain	0.02	0.0051
Deep vein thrombosis	0.30	0.0167
Neuropathy	0.00	0.0000

*PERT approximation for SD: [Max-Min]/6 with Min/Max of distribution assumed: mean +-25% SE = [1,25*Mean - 0,75*Mean]/6 = Mean / 12

5.5.8 Additional costs and healthcare resource not been covered elsewhere.

There are no additional costs or healthcare resource use.

5.6 Summary of base-case de novo analysis inputs and assumptions

5.6.1 Summary of base-case de novo analysis inputs

Efficacy and safety inputs were derived from the patient level data of the TROPIC trial.

Parametric functions fitted to patient-level data were used to describe PFS and OS. The statistical analyses and selection of functions for the model were performed in accordance with best practice guidelines.

Extrapolation was made using different parametric distributions (exponential, Weibull, Lognormal, Log-logistic and Gompertz distributions).

The choice of the parametric distribution that best fit the data is done using the Akaike's Information criteria (AIC), the Bayesian Information Criteria (BIC) and graphical method to evaluate the goodness-of-fit of the distributions. The preferred model is the one with the lowest AIC and BIC value, i.e. the model that best explains the data with a minimum of parameters.

Patients receiving cabazitaxel demonstrated statistically significant longer overall survival (OS) compared to mitoxantrone (p<0.0001). The hazard ratio was 0.72 (95%CI, 0.61, 0.84) corresponding to a 28% reduction in risk of death. The median survival for patients in the cabazitaxel group was 15.1 months in comparison to 12.7 months in the mitoxantrone group.

Progression-free survival (PFS) defined as the earliest progression in tumour, PSA or pain or death was also statistically significantly longer in the cabazitaxel group compared to the mitoxantrone group (hazard ratio was 0.75 (95%CI, 0.65, 0.87); median progression-free survival was 2.8 months versus 1.4 months.

The economic model was populated with updated (cut-off date on 10th March, 2010) efficacy and safety inputs derived from the patient level data of the TROPIC trial.

Extensive survival analyses were conducted in order to determine the best fitting parametric functions to inform extrapolation. These statistical analyses and selection of functions for the model were performed in accordance with best practice guidelines.

Extrapolation was made using different parametric distributions (Exponential, Weibull, Log-Normal, Log-logistic and Gompertz distributions).

The choice of the parametric distributions that best fit the data was done using the Akaike's Information criteria (AIC) and the Bayesian Information Criteria (BIC) to evaluate the goodness-of-fit of the distributions; eyeballing of survival curves was also conducted. The preferred model is the one with the lowest AIC and BIC value, i.e. the model that best explains the data with a minimum of parameters. Tables reporting AIC and BIC for all parametric functions and respective survival curves are presented at the end of this section.

The parametric functions used in the economic model, based on the criteria above, are tabulated in Table 72 below and presented graphically in Appendix . For the comparisons with abiraterone and enzalutamide hazard ratios (HR) derived from a network meta-analysis were applied to the function that best fit the cabazitaxel parametric function. Note that the function that best fits cabazitaxel PFS is the Log-Normal. As the proportionality of the hazard does not hold for this function the HRs for PFS were applied to the Weibull distribution, which is the function that has the second best fit.

Table 72. Best fit Parametric Functions used in the CEA vs mitoxantrone

	Overall Survival		Progression Free Survival	
	ITT	SG	ITT	SG
Cabazitaxel vs Mitoxantrone - SG	Weibull	Weibull	Log-Normal	Log-Normal
Cabazitaxel vs Mitoxantrone - ITT	Weibull	Weibull	Log-Normal	Log-Normal

Table 73. Summary of key variables applied in the economic model

Variable	Value	CI (distribution)	Ref in submission
Model settings			
Cycle length (weeks)	3.00	NA	Section 5.2.3
Time horizon (years)	10.00	1 – 10	Section 5.2.3
Discount rate: costs	3.5%	0.0% – 6.5%	Section 5.2.3
Discount rate: Outcomes	3.5%	0.0% – 6.5%	Section 5.2.3
Effectiveness			
Median OS – cabazitaxel (months)	15.1	14.0 – 16.5	Section 4.7
Median OS – mitoxantrone	12.8	11.5 – 13.7	Section 4.7
Median PFS – cabazitaxel	2.8	2.4 – 3.1	Section 4.7
Median PFS – mitoxantrone	1.4	1.4 – 1.8	Section 4.7
Drug costs: cabazitaxel			
Cabazitaxel (£/mg)	*Commercial in confidence information removed*	NA	Section 2.3.1
Dose (mg / m^2)	25	NA	Section 2.3.1
Body surface area (m^2)	1.9		Section 2.3.1
Frequency	Per cycle	NA	Section 2.3.1
Cost of administration (£)	*Commercial in confidence information removed*	Calculated from multiple variables. Section 2.3.1	
Premedication and concomitant drugs (£)			
Drug costs: mitioxantrone			
Mitoxantrone (£/mg)	5.00	NA	Section 2.3.1
Dose (mg / m^2)	12.0	NA	Section 2.3.1
Body surface area (m^2)	1.9		Section 2.3.1
Frequency	Per cycle	NA	Section 2.3.1
Cost of administration per cycle (£)	*Commercial in confidence information removed*	Calculated from multiple variables. See Section 2.3.1	
Premedication and concomitant drugs per cycle (£)			
Other drug costs: progressive disease state			
Cost per cycle: chemotherapy drugs and administration, premedication and concomitant medication	70.93	Calculated from multiple variables. See Section 5.5.6	
Share of patients receiving BSC. The balance receive chemotherapy mix	0.44 (TROPIC)	0.8 (UK treatment audit)	Section 5.5.6
Cost per cycle - other non-chemotherapy or AE-related health care			
Stable disease state (£)	*Commercial in confidence information removed*	Calculated from multiple variables. See Section 5.5.6	
Progressive disease state (£)			
Dead (£)			
Adverse event costs (Stable disease state)			
Cabazitaxel (£)	*Commercial in confidence information removed*	Calculated from multiple variables. Section 5.5.7	
Mitoxantrone (£)			
Utility			

		Point estimate	SD	
Stable disease state	Cycle 1	0.704	0.033	Section 5.4.1
	Cycle 2	0.728	0.021	
	Cycle 3	0.728	0.033	
	Cycle 4	0.750	0.026	
	Cycle 5	0.753	0.035	
	Cycle 6	0.752	0.024	
	Cycle 7	0.778	0.042	
	Cycle 8	0.789	0.034	
	Cycle 9	0.803	0.048	
	Cycle 10	0.819	0.033	
Progressive disease state	Per cycle followed by last 4 cycles at 0	0.6266	0.0187	
Dead		0	NA	Usual practice
SD: standard deviation; CI: confidence interval				

Table 74. Assumptions used in the modelling.

Assumption	Justification
It was assumed that patients would receive 'second-line' treatment only while they were in the stable disease state. Once progressed, patients would discontinue treatment.	Reflects the protocol of the TROPIC trial.
Patients cannot return to the 'stable disease' state from the 'progressive disease' state.	Assumption made to minimise the complexity of the model and the available data.
After failing second-line treatment, patients receive a mix of third-line treatments (with some patients receiving BSC alone).	Reflects clinical management of mCRPC patients in TROPIC and in the UK
Patients receiving post-progression treatment incur the cost but do not derive benefits beyond those observed in the trial.	There are no data showing a survival benefit with any of the treatments used in this setting and it is expected OS data reported from TROPIC would capture all of these benefits.
Utility values change over time for the first 10 cycles on treatment in the stable state and then remain stable thereafter. Utility is constant in the progressive state until the last 3 months of life whereupon it is set to 0.	Reflects available utility data from the UK EAP up to the point of progression and just beyond. There is no data available to describe utility as a function of time in the progressed disease state so a constant value is applied until the last 3 months whereupon it is set to 0..

5.7 Base-case results

5.7.1 Base-case incremental cost effectiveness analysis results

The base-case results are presented in Table 75 below. Cabazitaxel is a more effective treatment option than mitoxantrone in the treatment of mHRPC. The expected incremental life expectancy (discounted) is 0.338 Life Years Gained or 4.02 months (4.37 months undiscounted, 95% CI: 2.12 to 5.95). This additional survival translates into an incremental QALY gain of 0.232 (or 2.78 months discounted (2.99 undiscounted)).

Cabazitaxel is also a more costly treatment option. The expected incremental cost of treating patients is £11,450. This increment is not only driven by the cost of treatment, including administration, pre- and concomitant medication and the management of AEs, but also by the costs associated with increased survival. This granularity is provided in Table 76 and Table 77 below.

The Incremental Cost-Effectiveness Ratio (ICER) is £49,327 per QALY, when compared to mitoxantrone.

Table 75. Base-case results: cabazitaxel vs. mitoxantrone - SG: ECOG PS 0-1, tottax ≥225.

Technologies	Cabazitaxel	Mitoxantrone
Total costs (£)	*Commercial in confidence information removed*	
Total LYG		
Total QALYs		
Incremental costs (£)	£11,450	-
Incremental LYG	0.338	-
Incremental QALYs	0.232	-
ICER (£) versus baseline (QALYs)	£49,327	-
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years		

5.7.2 Disaggregated results of the base-case incremental cost effectiveness analysis

Table 76. Summary of QALY gain by health state for the comparison versus mitoxantrone - SG: ECOG PS 0-1, tottax≥225.

Health state	QALY intervention (cabazitaxel)	QALY comparator (Mitoxantrone)	Increment	Absolute increment	% absolute increment
Stable	*Commercial in confidence information removed*				
Progressive					
Total	*Commercial in confidence information removed*			0.232	100%
QALY, quality-adjusted life year Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

5.7.3 Summary of costs by health state

Table 77. Summary of costs by health state for the comparison versus mitoxantrone - SG: ECOG PS 0-1, tottax≥225.

Health state	Cost intervention (Cabazitaxel)	Cost comparator (Mitoxantrone)	Increment	Absolute increment	% absolute increment
Stable	*Commercial in confidence information removed*				
Progressive					
End-of-life costs					
Total	*Commercial in confidence information removed*		£11,450	£11,450	100%
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Note that *Commercial in confidence information removed* % of the incremental costs are associated with the progressive disease state which is by definition post-treatment. By removing the costs in both treatment arms associated with additional survival (post-progression), the base-case ICER is reduced to £ *Commercial in confidence information removed* / QALY.

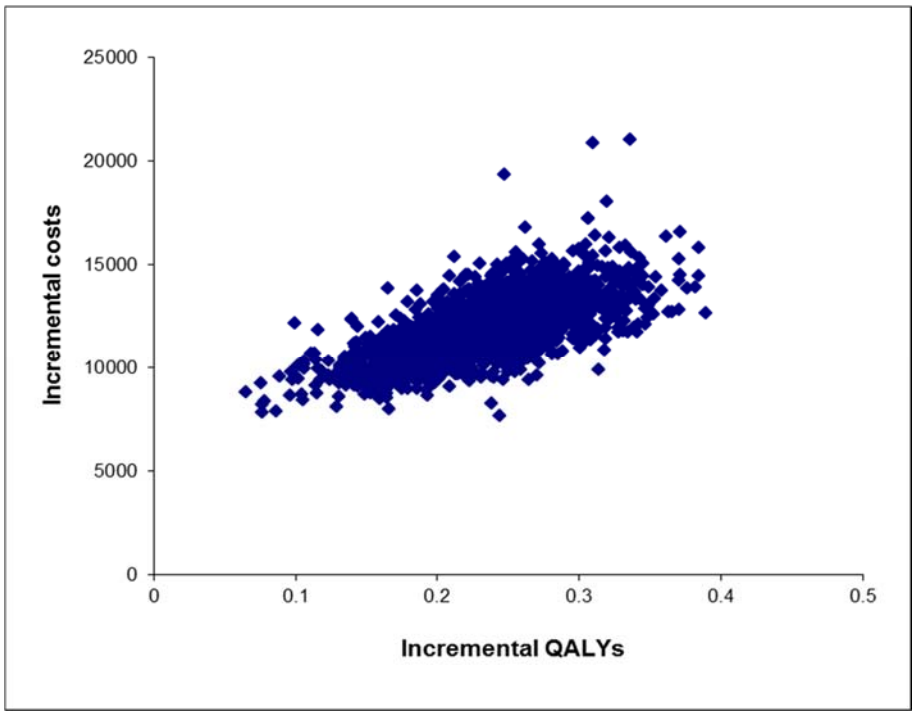
5.8 Sensitivity analyses

5.8.1 Probabilistic sensitivity analysis

Results for the probabilistic sensitivity analysis

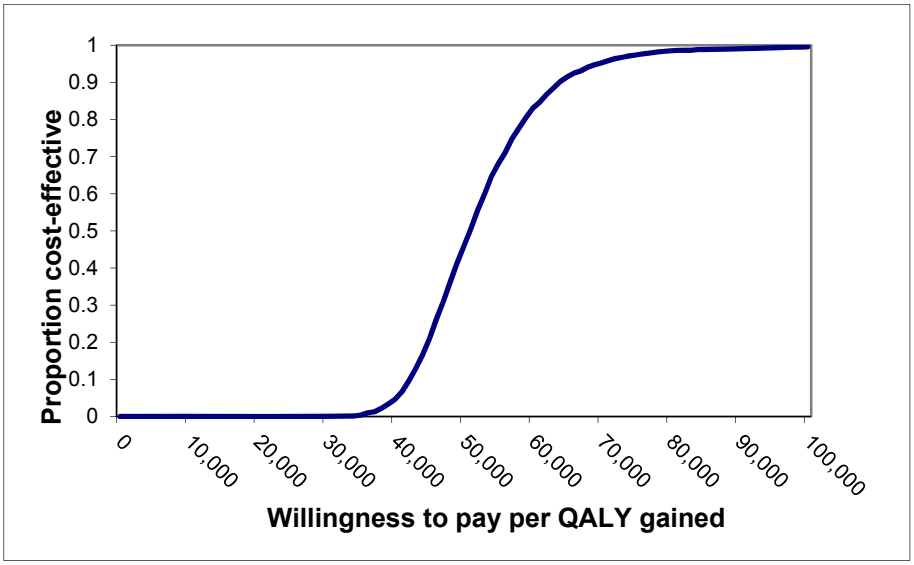
The results of the probabilistic sensitivity analysis (PSA) are presented in Figure 21 below. These are based on 2,000 simulations.

Figure 21. Cost-effectiveness plane based on 2000 probabilistic simulations



The cost effectiveness acceptability curve derived from the PSA is shown in Figure 22.

Figure 22. Cost-effectiveness Acceptability Curve (CEAC)



At a Willingness to Pay (WTP) threshold of £50,000/QALY the probability of cabazitaxel being a cost-effective treatment when compared to mitoxantrone is 46%.

5.8.2 Deterministic sensitivity analysis

All variables subjected to one-way sensitivity analysis are shown below. These analyses were conducted to demonstrate the relative impact of changes in each of these parameters on results.

Table 78. One-way sensitivity analyses implemented in the model

One-way sensitivity analysis variable	Variation	Rationale
State utility values	±20%	To investigate the relative impact of utility values (both SD and PD) on results
Time horizon	3 and 5 years	The time horizon is typically important in economic evaluations
Discount rates	0, 3.5 and 6% rates applied to costs and effects	Varied between 0% and 6%, in line with NICE guidelines
BSC as post-2nd line treatment for all arms	0, 20, 40, 60, 80 and 100% proportions applied	Variations may occur in clinical practice; important to investigate the impact of such variations
Key: BSC = best supportive care; G-CSF = granulyte colony-stimulating factor; NICE = National Institute for Health and Clinical Excellence		

The one way sensitivity analyses in the population of patients with ECOG PS 0 -1 and who have received at least 225 mg/m^2 docetaxel are presented in Table 79 and below.

Table 79. One-way sensitivity analyses for the comparison versus mitoxantrone - SG: ECOG PS 0-1, tottax≥225.

Sensitivity analysis	Incremental cost	Incremental QALYs	Incremental LYs	ICER per QALY	ICER per LY
Base-case	11,450	0.232	0.338	49,327	33,917
Utilities					
AE disutilities excluded	11,450	0.233	0.338	49,138	33,917
SD utility +20%	11,450	0.240	0.338	47,655	33,917
SD utility -20%	11,450	0.224	0.338	51,121	33,917
PD utility +20%	11,450	0.259	0.338	44,232	33,917
PD utility -20%	11,450	0.206	0.338	55,749	33,917
Time horizon					
3 years	10,600	0.192	0.274	55,291	38,672
5 years	11,396	0.229	0.334	49,666	34,163
Discount rates					
Costs: 0%, Effects: 0%	11,817	0.249	0.364	47,711	32,444
Costs: 3.5%, Effects: 0%	11,474	0.249	0.364	46,323	31,500
Costs: 0%, Effects: 3.5%	11,794	0.232	0.338	50,807	34,934
Costs: 6%, Effects: 6%	11,207	0.221	0.320	50,527	35,018
BSC as post-2nd line treatment for all arms					
Share of patients: 0%	11,683	0.232	0.338	50,327	34,604
Share of patients: 20%	11,577	0.232	0.338	49,873	34,291
Share of patients: 40%	11,472	0.232	0.338	49,418	33,979
Share of patients: 60%	11,366	0.232	0.338	48,964	33,666
Share of patients: 80%	11,261	0.232	0.338	48,509	33,354
Share of patients: 100%	11,155	0.232	0.338	48,055	33,041

The one-way sensitivity analyses indicates that the results are robust for the majority of the parameters tested. The impact of adverse events on the overall results is marginal. Also, in the unlikely scenario of a 5-year time horizon the ICER is still below £50,000/QALY.

The model is most sensitive to variations in the Progressive Disease utility values, which is consistent with the base-case results as the majority of the QALY gain (*Commercial in confidence information removed*) is obtained in this health state.

5.8.3 Scenario analysis – cabazitaxel versus mitoxantrone

The scenarios tested around the different OS and PFS distributions are presented here only for completeness as the most appropriate distributions were used in the base-case. Note that, as expected, the choice of the distribution used for OS extrapolation impacts the cost-effectiveness results. For example, using the Log-

logistic distribution, which is the second-best fit distribution (with very similar AIC and BIC estimates) produces an ICER of £41,920/QALY. The Log-logistic distribution is, however, characterised by having a long tail which may produce unrealistic survival results. Interestingly, truncating the model to a 5-year time-horizon the resulting ICER is £46,865/QALY. The same logic applies when the Log-Normal distribution is tested: truncating the model to a 5-year time-horizon the resulting ICER is £42,696/QALY.

We note that the use of KM data and extrapolation thereafter increases the ICER to above £50,000/QALY but this analysis has to be interpreted with caution as the point from which the extrapolation starts is arbitrary and difficult to justify.

Table 80. Additional Sensitivity analyses for the comparison versus mitoxantrone

Parameter/Assumption	Base-Case	Scenario tested	Incremental Costs	Incremental QALYs	ICER
Base-Case			£11,450	0.232	£49,327
Overall Survival	OS 2yrs IPD-Weibull	OS 2yrs IPD-Exponential	£12,631	0.295	£42,838
		OS 2yrs IPD-Gompertz	£11,155	0.215	£51,967
		OS 2yrs IPD-Log logistic	£12,724	0.304	£41,920
		OS 2yrs IPD-Lognormal	£13,969	0.373	£37,496
Progression Free Survival	PFS Cab 2yrs IPD-Lognormal	PFS 2yrs IPD-Exponential	£11,587	0.226	£51,229
		PFS 2yrs IPD-Weibull	£11,985	0.225	£53,283
		PFS 2yrs IPD-Gompertz	£11,950	0.222	£53,764
		PFS 2yrs IPD-Log logistic	£11,356	0.237	£47,921
Extrapolation	Entirely parametric	KM data and extrapolation (2yrs IPD-Weibull – OS and 2yrs IPD-Lognormal - PFS)	£12,016	0.235	£51,168
BSA	1.9	2	£11,852	0.232	£50.985
Pharmacist cost per cabazitaxel administration	15 minutes of pharmacist time required to order the appropriate dose of cabazitaxel	30 minutes of pharmacist time required to order the appropriate dose of cabazitaxel	£11,504	0.232	£49,556

Discontinuation	Inclusion of discontinuation for other reasons than progression (23% in cabazitaxel arm; 16% in mitoxantrone arm)	Exclusion of discontinuation for other reasons than progression (0% in cabazitaxel arm; 0% in mitoxantrone arm)	£11,693	0.232	£50,370
Population	SG (ECOG 0-1, tottax≥225)	ITT	£11,141	0.215	£51,833
Proportion with G-CSF as primary prophylaxis	Caba 25% & Mitox: 10%	Caba 25% & Mitox: 0%	£11,549	0.232	£49,749
Share of BSC as post second line treatment	44% BSC 66% chemo. mix	80% BSC, 20% chemo. mix	£11,261	0.232	£48,509

5.8.4 Scenario analysis – Comparison with abiraterone and enzalutamide

The aggregate comparisons vs. abiraterone and enzalutamide are presented as scenario analysis in Table 81 and Table 82 overleaf

At the request of NICE we have modelled the cost-effectiveness results for the comparisons versus abiraterone and enzalutamide using the PAS adjusted cost of cabazitaxel and the list prices for the comparators. However interpretation of these results is problematic on the basis of the unrealistic prices used for the comparators. Further results including sensitivity analysis can be found in Appendices B.

The ITT population is implemented in these analyses and the definition of PFS used is radiographic PFS. See Appendices B for a discussion of the differing definitions of PFS used in the TROPIC, COU-AA-301 and AFFIRM studies. In order to fulfil the requirement for proportional hazards the Weibull distribution was used to fit rPFS and OS for both abiraterone and enzalutamide.

Abiraterone

Table 81 Scenario results vs abiraterone

	Cabazitaxel	Abiraterone
Total costs (£)	*Commercial in confidence information removed*	
Total LYG		
Total QALYs		
Incremental costs (£)	-£17,430	-
Incremental LYG	0.029	-
Incremental QALYs	0.022	-
ICER (£) versus baseline (QALYS)	-£808,425	-

Under the limitations of the analysis described in previous sections and Appendices B, cabazitaxel is the dominant strategy as it is less costly and more effective although these results should be treated with caution.

Enzalutamide

Table 82 Scenario results vs enzalutamide

	Cabazitaxel	Enzalutamide
Total costs (£)	*Commercial in confidence information removed*	
Total LYG		
Total QALYs		
Incremental costs (£)	-£37,850	-
Incremental LYG	-0.132	-
Incremental QALYs	-0.179	-
ICER (£) versus baseline (QALYs)	£212,038	-

As for the comparison with abiraterone, these results need to be interpreted with caution. Cabazitaxel is less effective but at the same time less costly than enzalutamide and so the point estimate for the ICER is located in the south west quadrant of the cost-effectiveness plane. This presents a challenge in the interpretation of the results that is discussed in section 5.11 below.

5.9 Subgroup analysis

There are no further subgroups considered in the analysis.

5.10 Validation

Before conducting the final analyses, validation analyses were carried out to verify the technical validity of the model. 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.

5.11 Interpretation and conclusions of economic evidence

The analysis presented is based on a good quality head-to-head randomised controlled trial that directly compared cabazitaxel with mitoxantrone and in scenario analysis, on the indirect comparisons with abiraterone and enzalutamide. As previously discussed these comparisons should be treated with caution.

Base-case: Results for comparison with mitoxantrone

No indirect comparison was required to derive the relative treatment effects between cabazitaxel and mitoxantrone. This allows the analysis to be more sound and robust given that the number of assumptions made around treatment effects are minimised. The PFS and OS data from the TROPIC trial are relatively mature; almost all patients had reached the PFS endpoint and the majority had reached the OS endpoint within the trial follow-up period. Nevertheless, extrapolation was necessary to characterise OS but the extent of this extrapolation in the model was small. In order to validate this extrapolation, multiple alternative parametric functions were assessed according to best practice using statistical and visual tests to find the best fitting functions to the data. Structural uncertainty arising from alternative possible parametric survival functions has been fully explored in sensitivity analysis.

The cost-effectiveness analysis shows that cabazitaxel is associated with a QALY gain over mitoxantrone (ΔQALY of 0.232). This is driven by the increase in OS (ΔLY of 0.338) and PFS; this finding is consistent with the demonstrated statistically significant benefits observed in the TROPIC trial. On the other hand, cabazitaxel is a more costly strategy than mitoxantrone in the second line treatment of prostate cancer patients. This is caused not only by the costs associated with cabazitaxel (drug and administration) but also by the increased post-progression costs as a result of increasing patient survival. The ICER presented in the base-case analysis is £49.327 per QALY.

The sensitivity analyses conducted revealed that the base-case results are robust. The base-case ICER varied between £44,290 and £55,656 per QALY for the parameters tested in the deterministic sensitivity analyses.

The probability of cabazitaxel being cost-effective versus mitoxantrone was 46% at a WTP threshold of £50,000 per QALY..

Interpretation and conclusions

We have argued that the nature of mCRPC is such that a wide range of treatments is required by patients and clinicians and that a single therapeutic choice is not appropriate for everybody. Consideration of the pathways of care in which abiraterone or enzalutamide feature in the pre- or post-docetaxel setting preclude

their use in many patients. Indeed standard NHS practice renders cytotoxic therapy the only active option for most patients in the post-docetaxel setting. In the alternative practice pathway clinicians will identify the 'chemotherapy patient' using clinical judgement based on prognostic characteristics. This means that for these patients the choice of the advanced hormone therapies is not a relevant one. These considerations have led us to present the evaluation versus mitoxantrone in the base-case.

The results from the economic analysis show that cabazitaxel is an effective use of NHS resources in the second line treatment of mCPRC in England. In our analysis, the most plausible ICER estimate does exceed £30,000 per QALY gained. Nevertheless, the cost per QALY is only part of a wider judgment of the value of a new medicine and a number of factors that can be applied to medicines with a cost per QALY above £30,000 to allow their approval.

We consider that cabazitaxel falls within the End of Life (EoL) criteria, which allows greater flexibility in the appraisal of life-extending medicines used at the end of life. These criteria require an extension to life of at least an additional 3 months, compared to current NHS treatment. In the TROPIC trial the reported median OS was 2.4 months. However, the mean survival times are recognised by NICE as being more relevant than the median statistic for estimating cost-effectiveness as they takes into account the entire survival curve including continued divergence beyond the median. Cabazitaxel not only improved mean OS but also produced significant and clinically meaningful improvements in PFS and overall response rate in patients. Mean OS was increased by an estimated 4.02 months. The 95% confidence interval estimated from the PSA is 2.17 to 5.91 months.

As cabazitaxel has become, through its use via the CDF, the established 2nd line chemotherapy in mCRPC patients previously treated with docetaxel, it is logical to consider what would replace it were it no-longer available on the NHS. Mitoxantrone use is currently very limited due to the availability of newer treatment options. However if provision for cabazitaxel is withdrawn then it is likely that, through necessity, mitoxantrone use would increase. This is the expectation of the British Uro-oncology Group as highlighted in their response to the draft scope; '*the likelihood is that if provision for cabazitaxel is not there then mitoxantrone use would increase'*.

Consequently, the NHS would be in the position of funding a treatment which delivered less health to patients, but at the same time achieving some cost savings. In this situation, health economists might look at the net-monetary benefit of such a decision.

Mitoxantrone would on average, deliver 0.232 less QALYs, at a cost saving of approximately £11,500 per patient. In Net Monetary Benefit terms (NMB), assuming the NHS would accept to 'sell QALYs' at a higher rate than it 'buys' them (in our example doubling the typical upper threshold for purchase of QALYs from £30,000 to £60,000/QALY) then the NMB of a move from cabazitaxel back to mitoxantrone

would equate to a negative net monetary benefit of -£2,469 (-0.232*£60,000) [value of QALYs foregone] less £11,500 [cost savings realised]. In other words, moving back to mitoxantrone would sacrifice more QALYs than would be warranted by the savings released.

Scenario analysis: Results for comparisons with abiraterone and enzalutamide

There is limited value in the comparison between cabazitaxel and abiraterone or enzalutamide on the basis of current treatment pathways and also because the trial designs, outcomes and patients in TROPIC are not directly comparable to the COU-AA-301 and AFFIRM studies. Nonetheless in line with the stated requirements in the scope the indirect treatment comparison summarised in Section 4.10 and described in detail in Appendices B was used to examine these competing strategies.

Fully parametric Weibull fits were used in the analysis for all strategies for both OS and rPFS. The cost of cabazitaxel was set at the PAS adjusted cost and as directed by NICE the unit costs for abiraterone and enzalutamide were set at list price.

These analyses shows that cabazitaxel is associated with a QALY gain over abiraterone (∆QALY of *Commercial in confidence information removed*; OS: ∆LY of *Commercial in confidence information removed*) and a QALY loss versus enzalutamide (∆QALY of *Commercial in confidence information removed*; OS: ∆LY of *Commercial in confidence information removed*). In both cases the incremental costs were lower in the cabazitaxel arms (abiraterone arm: *Commercial in confidence information removed*; enzalutamide arm: *Commercial in confidence information removed*). These differences were principally driven by drug costs. The larger cost differential in the enzalutamide arm reflects increased rPFS for enzalutamide and as a consequence increased duration of therapy in the stable state. The ICER presented for the comparison versus abiraterone indicates that cabazitaxel dominates and for enzalutamide that cabazitaxel is in the South West Quadrant (SWQ) of the cost-effectiveness plain.

In line with advice received from the secretariat we have not presented multiple incremental scenarios examining different levels for the manufacturer discounts for the advanced hormone therapies. However we have modelled discounts of 50% to the list price for each therapy. Cabazitaxel continues to dominate abiraterone at this discount (incremental cost = *Commercial in confidence information removed*) and whilst the point estimate for the ICER is still in the south west quadrant versus enzalutamide, the ICER is *Commercial in confidence information removed*.

6. Assessment of factors relevant to the NHS and other parties

6.1 Estimation of patient numbers

The number of patients who may be eligible for cabazitaxel in 2015 has been described in Section 3.4. and is reproduced below for clarity.

Table 83. Estimation of mCPRC patients eligible for second-line chemotherapy in England

	Percentage	Number of patients
Estimated number of patients diagnosed with prostate cancer - England 2015		40,980
Of these, mCRPC patients[37]	15%	6,147
Of these, patients receiving first-line treatment with docetaxel.[38]	50%	3,073
Of these, patients eligible to receive second-line chemotherapy.[38]	55%	1,690

In discussion with their clinicians a proportion of patients may elect not to receive further treatment or may not receive it for other reasons and so this estimate of eligible patients is likely to be higher than the expected number of patients treated.

Cabazitaxel has been available under the CDF since April 2013. The total number of notifications (patients) received was 352 in 2013 and 531 in 2014. Note that the data available for 2013 covers the period from April do December.[14]

Should positive opinion be received from NICE, the estimated number of patients receiving cabazitaxel has been calculated on the basis of the CDF figures and a 10% year-to-year growth for the uptake of cabazitaxel (calculated from the 2014 figure) assumed for the first three years following this appraisal (2016 – 2018). Thereafter no growth is expected. Table 84.

Table 84. Estimated number of patients receiving cabazitaxel

	CDF figures		Estimated figures					
Year	2013	2014	2015	2016	2017	2018	2019	2020
Number of patients	352	531	584	643	707	777	777	777

6.2 Estimation of pharmacy cost

An average patient is expected to consume 1 vial of cabazitaxel during each course of therapy. This is calculated on the basis of a patient with body surface area of 1.9m^2 receiving 47.5mg of cabazitaxel taken from a 60 mg vial with no vial sharing. The list price of a vial is £3696.

On the assumption that each patient will receive 6 courses of cabazitaxel according to usage in TROPIC and the observational data from the real world setting described in Section 4, the estimated cost of cabazitaxel to the NHS per year could rise from £12.95M in 2015 to £17.24M.

Table 85. Estimated pharmacy cost of cabazitaxel.

Year	2015	2016	2017	2018	2019	2020
Cost of cabazitaxel	£12.95M	£14.25M	£15.67M	£17.24M	£17.24M	£17.24M

6.3 Net budget impact to the NHS

A Patient Access Scheme is proposed in this appraisal which will be a simple confidential reduction off the list price at the point of invoice. Therefore the pharmacy cost to the NHS of cabazitaxel is anticipated to be less than shown in Table 85.

Cabazitaxel is an established medicine in clinical practice and has received funding through the Cancer Drugs Fund. This arrangement is expected to continue should positive opinion be received and as such there is no expectation of a net budget impact.

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Single Technology Appraisal (STA)

Cabazitaxel for hormone-relapsed metastatic prostate cancer previously treated with a docetaxel-containing regimen (review of TA255) [ID 889]

Dear [redacted]

The Evidence Review Group, Sheffield School of Health and Related Research, and the technical team at NICE have now had an opportunity to take a look at the submission received from Sanofi on the 30th September. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5 pm on 6th November**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be uploaded to NICE Docs/Appraisals.

If you have any further queries on the technical issues raised in this letter then please contact Victoria Kelly, Technical Lead (victoria.kelly@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (Jeremy.powell@nice.org.uk in the first instance.

Yours sincerely

Melinda Goodall
Associate Director – Appraisals

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Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

A1.**Priority Question**: The final scope states that radium-223 is a comparator for one of the subgroups that should be considered. Additionally our clinical advisors and the expert submissions indicate that radium-223 is a viable treatment option in some people with symptomatic bone-only disease. As we expect that the Appraisal Committee would want an estimate of the relative effectiveness of cabazitaxel and radium-223 in the appropriate patient group, please re-run the network meta-analysis incorporating radium-223, highlighting the limitations of such an analysis.

A2.**Priority Question**: Please clarify what evidence is available to support the assertion on page 39 that use of abiraterone or enzalutamide in the pre-chemotherapy is 'standard NHS practice'. As part of this clarification please provide details on the validity and robustness of the Sanofi data (page 14, reference 5) and how these data were collated. It is noted that neither abiraterone nor enzalutamide have been recommended by NICE in the pre-chemotherapy setting and that data from the Cancer Drugs Fund (http://www.england.nhs.uk/ourwork/pe/cdf/ - report: April - March 2014/15) indicates that the most common setting for notifications of enzalutamide is in the post-chemotherapy setting (1164/1971 notifications).

A3.Please justify why the estimate (Table 10, page 41) of second line chemotherapy eligible patients in England (n=1690) is substantially different to the estimates reported in the Evidence Review Group evaluation report on enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen in table 2.1, page 24 (http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0004/82579/ERGReport-10-49-01.pdf) which suggest that approximately 3000 patients would be eligible for second line chemotherapy.

A4.Please clarify if the marketing authorisation for Cabazitaxel limits its use to 10 cycles. If it does not, please comment on the potential implications for UK clinical practice.

A5.Please clarify why abnormal laboratory values were excluded when calculating the proportion of adverse events in TROPIC (Table 42, page 113).

A6.Please report rates of hospitalisation in TROPIC by arm in Table 71 (page 177).

A7.Please explain what the relative risks refer to in Table 45 (Appendix A, page 117) and please could you provide the full bibliographic details of the two references that do not have superscript links to the references section (that is, Doyle et al. and Vogel et al.).

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Literature searching

A8.Please clarify the discrepancy in Figure 4 (page 59) which states that 30 studies met the inclusion criteria and 24 studies were excluded, whereas Table 17 (page 59) states that 31 studies were included and 23 studies were excluded.

A9.Please clarify and explain why the systematic review includes studies of interventions (Figure 4 and Table 17; pages 59-61) which are not discussed further in the submission (such as mitoxantrone containing regimens [Fizazi 2012, Fleming 2012, Joly 2015, Ryan 2013, Saad 2011, Hussain 2012, Basch 2015] and ipilimumab [Kwon 2014; Fizazi 2014]). Further, please provide an evidence network for all the included studies similar to Figure 1, page 48 of the ERG report for TA255 (http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0004/82579/ERGReport-10-49-01.pdf).

A10.In the original submission (TA255) a search was conducted to identify all studies relating to cabazitaxel in any context. Please clarify why the same search strategy was not used for the latest submission.

A11.Please provide details (including sources and details of any alterations made) for the validated filter that was used to identify RCTs (Appendices pages 25). Please also clarify whether validated filters were employed for the non-RCT and economic studies searches, providing details of sources if so and justifying if not.

Systematic review process

A12.Please confirm if study selection, data extraction and quality assessment were undertaken independently by a minimum of two reviewers for each systematic review in the clinical and cost section. If not, please justify.

A13.Please clarify/define what is meant by best supportive care in the systematic reviews of the clinical evidence (Table 15, pages 56-58; Section 4.10, page 85; table 29, pages 88-90)

Quality assessment, data synthesis and analysis

A14.Please confirm whether there is any overlap in data across studies reported within Table 31 and between studies in Table 31 and 32 (pages 93-4). For example, does the study by Heindrich 2014 (reference 87), which includes preliminary results from 20 European Compassionate Use and Early Access Programs, include data from the other European studies reported in Table 31?

A15.Please provide further details on the effect of cabazitaxel on cardiac and renal complications in the TROPIC trial including any additional supporting evidence from post-marketing surveillance data and other sources, if applicable.

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A16.Please provide details on dose modification (including relative dose intensity) in the Compassionate Use and Early Access Programs detailed in Tables 33 and 34 (pages 83-84). If dose modifications due to adverse events have been made in the Compassionate Use and Early Access Programs, what is the likely or expected impact (even if not recorded in the individual programs) on efficacy and health related quality of life. In addition, how many patients discontinued treatment in each of the programs (of these, how many presented disease progression)?

A17.Please provide further comments (page 97 company submission) on the strength, robustness and limitation of the data from the Compassionate Use and Early Access Programs from around the world including variation in practice.

A18.Please provide a summary table listing the proportion of patients that suffered adverse events across the four pivotal trials for cabazitaxel, abiraterone, enzalutamide and radium-223.

Indirect treatment comparison (ITC)

A19.**Priority Question**: Please clarify why the ITC and associated modelling are based on hazard ratios (which assume proportional hazards), and why this approach was selected over methods that allow the relative treatment effects to vary over time. For the abiraterone pivotal trial Fizazi (2012) noted that the proportional hazards assumption is not met. Please clarify the likely impact on the results.

A20.**Priority Question**: Please clarify why the random effects ITC used an uninformative prior despite the fact that there was insufficient data to update the prior distribution. Please undertake an analysis with a weakly informative prior that reflects reasonable prior beliefs, as recommended in Spiegelhalter, Abrams and Myles (2004) Bayesian approaches to clinical trials and health-care evaluation. Wiley, New York (doi: 10.1002/0470092602), in order to provide confidence intervals that better reflect the observed heterogeneity between trials.

Section B: Clarification on cost-effectiveness data

B1.**Priority Question**. Please clarify why the use of piecewise curves to represent overall survival and progression-free survival was not considered. It is noted within TA255 that the Committee considered the use of piecewise curves to be the most appropriate approach.

B2.**Priority Question**. Please provide an amended version of the economic model that allows for a fully incremental analysis (including cabazitaxel, best supportive care [mitoxantrone], abiraterone and enzalutamide) based on the results of the probabilistic sensitivity analyses.

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B3.**Priority Question**: Please clarify what supporting evidence is available for vial sharing of cabazitaxel in clinical practice, as the base-case analysis assumes that there is no wastage for cabazitaxel, but there is for mitoxantrone.

B4.**Priority Question**: Please provide an estimate of the ICER for cabazitaxel versus mitoxantrone based on the probabilistic sensitivity analysis.

B5.**Priority Question**. We believe that transition probabilities that add up to greater than one are used in the model when the estimated proportion of patients in the stable disease in the following cycle is fewer than the proportion alive. This will reduce the estimated number in the progressed state. Please comment on how amending the model to address this issue would affect the ICER.

B6.**Priority Question**: We believe that the following problems exist in relation to patients who discontinue:

a. Underestimated drug costs in the base-case. Assuming that the patients discontinue after the dosage of drug has been received, the drug costs should not be reduced in that cycle

b. Overestimation of the utility in the base-case. Patients who have discontinued are assumed to still be associated with the increased utility related to additional treatment cycles

c. Overestimation of drug costs. Currently only a non-cumulative proportion of drug costs are removed due to discontinuations rather than cumulative rates which should be adjusted for the proportion of patients who discontinue that subsequently progress.

If these problems exist, please comment on how amending the model to address these issues would affect the ICER. It is unlikely that the points could be completely resolved without explicitly defining patients who discontinue with stable disease as a separate health state.

B7.Please provide a sensitivity analysis using the electronic market information tool (eMIT) price for all generic drugs in the model, including mitoxantrone.

B8.Please clarify why the proportion of patients experiencing an adverse event (for cabazitaxel and mitoxantrone) and the odds ratios for the rates of adverse events (for abiraterone and enzalutamide) were not varied within the probabilistic sensitivity analyses.

B9.Please provide a sensitivity analysis that uses a single utility value (the mean of the observed utility values in the UK EAP) at all times for the stable disease state.

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B10.Within the economic model, hazard ratios are used to derive rates of adverse events for abiraterone / enzalutamide (tab 'Hazard Ratios') - please provide details regarding the derivation of these values.

B11.An assumption of zero utility for the last three months spent in the progressive disease (PD) health state is used in the model. This is implemented as a disutility. The current disutility appears to be calculated based on all patients who die (not the subgroup of patients who die from the PD health state). Please confirm that this is as intended. If not, please amend. In addition, the disutility incurred should be constrained by the time spent in the PD health state (for example, if it is two months, then at most only two months will be spent with a disutility of zero). Please comment on how amending the model to address these issues would affect the ICER.

B12.Please clarify why the proportions of patients receiving 10 cycles of cabazitaxel differ between the modelled estimate (17%) and those observed in the TROPIC ITT population and the Early Access Programme (approximately 30%). Please confirm the proportion of patients who received 10 cycles in the population of interest within the TROPIC trial.

B13.Please justify why data from the TROPIC trial (page 171, Table 65) were used in preference to those from the UK audit (page 171, Table 66) for post second line treatment in the economic model.

B14.On page 171 it states that ’The assumption is made that the mitoxantrone treatment mix is received in the abiraterone and enzalutamide comparisons.’ However, in the economic model, abiraterone values are taken from the UK audit, whilst the enzalutamide values are taken from the post-cabazitaxel arm. Please comment on this discrepancy.

B15.Please clarify if the proportion of patients receiving best supportive care as post second line treatment should be varied in the probabilistic sensitivity analysis. Currently, this is varied, but only for enzalutamide. Please amend as appropriate.

B16.Please clarify why the value of body surface area used in the model (1.9, based on clinical opinion) has changed from the value used in TA255 (2.01 from the TROPIC trial),.

B17.Please clarify why the quality of life data (section 5.4, page 150) from the EAP is different to that reported in reference 12 (http://www.ncbi.nlm.nih.gov/pubmed/25639506). Please confirm that the data used in the submission is the most up-to-date.

B18.Please clarify how secondary G-CSF use is implemented in the company’s model (table 63, page 166).

B19.When adverse event treatment is costed in the Model, (tab 'AE Care') some grade 3+ events receive neither inpatient care nor drugs (for example, for neutropenia 2% require

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inpatient care and 50% receive filgastrim, so at least 48% receive neither). Please confirm that this is as intended and justify why.

B20.Please provide further details about the evidence used for the rates of drug use for adverse events.

B21.The submission states (Table 61, page 161 - Utility in the stable disease state) that odd cycles are interpolated. Please provide details about how these interpolated values were derived, and justify this method over linear interpolation between cycles (for example, the cycle 3 value would be the mean of the values observed for cycles 2 and 4).

B22.Please provide information (with references) about the proportion of patients requiring each end-of-life resource component (Table 67 and 68, pages 172-175): Please also provide a cost (with reference) for a hospice home stay.

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Section A: Clarification on effectiveness data

A1.**Priority Question: The final scope states that radium-223 is a comparator for one of the subgroups that should be considered. Additionally our clinical advisors and the expert submissions indicate that radium-223 is a viable treatment option in some people with symptomatic bone-only disease. As we expect that the Appraisal Committee would want an estimate of the relative effectiveness of cabazitaxel and radium-223 in the appropriate patient group, please re-run the network meta-analysis incorporating radium-223, highlighting the limitations of such an analysis.**

The inclusion of radium-223 as a comparator for cabazitaxel was discussed at the decision-problem meeting held with NICE and representatives of the ERG in July. During this meeting we expressed our concerns about the applicability and feasibility of this comparison. We recognise that radium-223, in time, may become a relevant comparator for part of the population, but have not included radium-223 in the NMA and subsequent economic analysis for the reasons that we put forward in our response to the draft scope and at the decision-problem meeting.

We would like to take this opportunity to highlight again the reasons that we do not to consider the comparison to be valid and the limitations and difficulties of such an analysis were it to be performed.

Radium-223 is licensed in a sub-population of mCRPC patients with two or more bone metastases and no visceral metastases; the TROPIC trial did not have the same inclusion criteria. In addition radium-223 is contraindicated in patients with liver metastases and eleven percent of patients in TROPIC had liver metastases. This raises questions over the suitability of indirect comparison of the population within the ALSYMPCA study.

More importantly, technical difficulties also arise when considering inclusion of radium in the network of evidence. We have discussed the definitions of progression free survival (PFS) used in the NMA for the TROPIC, COU-AA-301 and AFFIRM studies at length in the dossier and commented on the issues around comparability between studies. In order to estimate a comparable value of rPFS for the TROPIC and the COU-AA-301 and AFFIRM populations it was necessary to synthesize a measure of radiographic PFS from the TROPIC data. A comparable measure of rPFS is not available from the ALSYMPCA study.

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.

Notwithstanding the comments above we appreciate that the committee might wish to be reminded of the efficacy of radium-223 when considering their views on cabazitaxel. The

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table below reports the summary statistics for overall survival in the cohort of patients with previous docetaxel use from ALSYMPCA and the TROPIC ITT population. We present these here side by side but with no further analysis.

	Active therapy (cabazitaxel, radium-223)	Placebo (mitoxantrone for cabazitaxel)	Difference	Hazard ratio
TROPIC (ITT)	15.1 (14.0 – 16.5)	12.8 (11.5 – 13.7)	2.3 months	0.72 (0.61 - 0.85)
ALSYMPCA(1) (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)

A2.**Priority Question: Please clarify what evidence is available to support the assertion on page 39 that use of abiraterone or enzalutamide in the pre-chemotherapy is 'standard NHS practice'. As part of this clarification please provide details on the validity and robustness of the Sanofi data (page 14, reference 5) and how these data were collated. It is noted that neither abiraterone nor enzalutamide have been recommended by NICE in the pre-chemotherapy setting and that data from the Cancer Drugs Fund (http://www.england.nhs.uk/ourwork/pe/cdf/ - report: April - March 2014/15) indicates that the most common setting for notifications of enzalutamide is in the post-chemotherapy setting (1164/1971 notifications).**

The information referred to on page 14 (reference 5) is a summary of market research undertaken on behalf of Sanofi by Kantar Health between 14th April 2015 and 26th May 2015. Data was collected via online surveys completed by 55 Oncologists managing 795 mCRPC patients that had recently been treated in clinic. Three-hundred and twenty-seven of these patients were on 1st line therapy. Forty-seven percent of patients had received Abiraterone 1st line, 21% had received Enzalutamide 1st line and 30% had received Docetaxel 1st line.

This market research was repeated between 26th June 2015 and 4th August 2015 with 56 oncologists looking at 896 patients. Three-hundred and forty patients were on 1st line therapy which comprised 44% Abiraterone, 31% Docetaxel and 22% Enzalutamide.

The sample overlap between these waves was 36 (65%).

Hence two thirds of patients in England were receiving abiraterone and enzalutamide in the chemotherapy naïve setting. We believe that these therapies, which are funded by the CDF in the pre-docetaxel setting pending NICE decisions, represent current established practice this setting.

Table 1 shows the CDF data referenced in the question.

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Table 1. CDF notifications for abiraterone and enzalutamide*

Year	2014									2015			Total Apr 14 : Mar 15
Month	**Apr**	**May**	**Jun**	**Jul**	**Aug**	**Sept**	**Oct**	**Nov**	**Dec**	**Jan**	**Feb**	**Mar**	
Abiraterone													
Pre-chemo setting	193	258	253	211	205	157	148	122	73	92	120	80	**1912**
Enzalutamide													
Post doc. setting	68	57	81	65	77	94	145	154	74	94	167	88	**1971**
Pre-chemo setting	0	0	0	0	0	82	72	90	141	128	138	156	

*https://www.england.nhs.uk/ourwork/pe/cdf/ *accessed 02/11/2015*.

Enzalutamide received positive guidance from NICE in July 2014 and so should have been available for baseline commissioning 90 days thereafter. Therefore it is surprising to see any notifications for enzalutamide on the CDF in the post-docetaxel setting in late 2014 and early 2015.

We have queried this with the CDF and they have informed us that the figures are published as reported to them. However they did look into this apparent anomaly as post docetaxel use came off the CDF in September 2014, three months after publication of the final TAG.

The CDF have confirmed that there were errors in reporting and that one region was incorrectly notifying that all their pre-docetaxel notifications were post-docetaxel. The other regions reported use switching in Sept/Oct 14.

Therefore the CDF have advised that the majority of notifications reported as post-docetaxel should be counted as pre-docetaxel from Sep/Oct 2014 onwards.

The CDF reiterated to us that the criteria are very clear that sequencing of these agents is not allowed.

A3.**Please justify why the estimate (Table 10, page 41) of second line chemotherapy eligible patients in England (n=1690) is substantially different to the estimates reported in the Evidence Review Group evaluation report on enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen in table 2.1, page 24 (http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0004/82579/ERGReport-10-49-01.pdf) which suggest that approximately 3000 patients would be eligible for second line chemotherapy.**

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The link provided in the question points to the original ScHARR report for TA255 cabazitaxel. We have located the ERG report on enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen by Kleijnen Systematic Reviews Ltd at http://www.nice.org.uk/guidance/TA316/documents/prostate-cancer-hormone-relapsed-metastatic-enzalutamide-after-docetaxel-evaluation-report4 and assume that this is the document referred to in the question.

Table 2.1 from the ERG report above is reproduced below along with details of the estimate from the current submitted cabazitaxel dossier and the radium-223 dossier for comparative purposes.

Table 2. Estimates of the eligible population.

	Enzalutamide submission	Abiraterone submission	Radium-223 submission	Current submission
Prevalence of mCRPC in England and Wales	12,029 (No valid reference in the MS estimate in 2013)	10,448 (NICE estimate in 2006)	6,142 (based on 40,948 pts diagnosed in 2010 assuming 0.75% inflation according to ONS of whom 15% are castrate resistant)	6,147 (based on 40,980 pts diagnosed diagnosed in 2011 assuming 0.75% inflation according to ONS of whom 15% are castrate resistant)
Eligible for docetaxel	33% eligible (3,969 patients)	40% eligible (4,400 patients)	N/A	50% eligible (3,073)
Eligible for second-line treatment of interest	75% of 3, 969 mCRPC patients eligible (2,977patients)	75% of 4,400 mCRPC patients eligible (3,300 patients)	N/A	55% eligible (1,690)

The estimate of between 10,488 and 12,029 mCRPC patients in the enzalutamide and abiraterone dossiers is higher than the one accepted by the committee during the radium-223 submission (6,142). We have updated our figure based on the latest available evidence for the number of diagnosed patients from the ONS and implemented an estimate of the percentage of these who are castrate resistant taken from a review of the literature by Kirby(2). These data indicate that 10–20% of prostate cancer patients develop mCRPC within approximately 5 years of follow-up. We have taken the mid-point of this range, 15% and applied it to the number of patients diagnosed. The number implemented in the abiraterone submission was 19.5%, in the radium submission 15% was used.

Our market research indicated that 50% of patients will be eligible for docetaxel and we have applied that figure in the calculations.

The manufacturers of abiraterone or enzalutamide estimate that 75% of patients who become refractory to docetaxel will be eligible for second line treatment. As these drugs are

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administered orally, and may be suited particularly for patients not fit enough or willing to embark on second line chemotherapy, it is not unreasonable to expect more patients might be expected to be eligible for enzalutamide. Our estimate of 55% eligibility for a second line chemotherapy has been obtained from market research.

The estimates for enzalutamide and abiraterone are for England and Wales. In line with NICE requirements we have presented the figures for England only. In Wales according to the latest figures available from the Welsh Cancer Intelligence and Surveillance Unit from 2013 there were 2,634 people diagnosed with prostate cancer.(3) Assuming 15% of these are castrate resistant patients there may be 401 mCRPC patients in Wales and applying the proportions above around 110 of these would be eligible for second line treatment.

In TA255 the ERG estimated that there would be 1,823 patients eligible in England and Wales. According to the estimates above the combined number presented here would therefore be 1800 (1,690 +110).

For these reasons we believe that the estimate presented above is robust.

A4.**Please clarify if the marketing authorisation for Cabazitaxel limits its use to 10 cycles. If it does not, please comment on the potential implications for UK clinical practice.**

The license has never limited cabazitaxel usage to a maximum of 10 cycles nor has this been mandated by the Cancer Drug Fund.

In TROPIC the maximum number of cycles given was 10 but this was a trial protocol decision to balance the arms of the study; mitoxantrone has dose limiting cardiotoxicity meaning it cannot be given for more than 10 cycles. During treatment in TROPIC the median number of cycles received by patients was 6.

In the UK EAP, a protocol amendment was implemented to enable clinicians to continue treating patients with cabazitaxel beyond 10 cycles if further clinical benefit was anticipated; bring the design in line with the license, rather than mirroring the pivotal trial. Similar to the TROPIC trial, the median number of cycles received was 6.

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.

A5.**Please clarify why abnormal laboratory values were excluded when calculating the proportion of adverse events in TROPIC (Table 42, page 113).**

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In examining the safety and tolerability of a new medicine, the regulatory authorities require 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 - where tests are not performed as per clinical trial protocol – or may not manifest as clinical symptoms requiring intervention.

Adverse events that manifested as clinically significant issues requiring medical intervention by the investigator, (such as dose reductions, dose modifications, use of supportive treatment, or treatment discontinuation) were captured as part of the trial case-report-forms, and were considered the most appropriate information to include in the economic model. Clinical manifestations requiring intervention will clearly incur a cost and a disutility, whereas laboratory anomalies alone are more likely to be asymptomatic in nature and less likely to be 'observed' or 'felt' by patients in real world clinical practice compared to a protocol driven trial with heightened measurement frequency.

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%.

A6.**Please report rates of hospitalisation in TROPIC by arm in Table 71 (page 177).**

The rates of hospitalisation observed in both arms in TROPIC for grade 3 and above AEs are presented in Table 3. The rates used in the model are also tabulated for comparative purposes.

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Table 3. Hospitalisation rates in TROPIC

Severe adverse event (Grade ≥3)	Rate of hospitalisation in TROPIC		Hospitalisation rate used in the model
	Cabazitaxel	Mitoxantrone	
Neutropenia	0.18	0.00	0.02
Febrile neutropenia	0.86	0.80	0.75
Diarrhoea	0.26	0.00	0.10
Fatigue	0.06	0.00	0.01
Asthenia (weakness)	0.12	0.00	0.01
Leucopenia	0.21	0.00	0.02
Back pain	0.14	0.40	0.15
Anaemia	0.08	0.40	0.15
Thrombocytopenia	0.11	0.00	0.05
Pulmonary embolism	0.57	0.40	0.80
Dehydration	0.50	0.00	0.25
Nausea	0.14	0.00	0.00
Bone pain	0.00	0.00	0.02
Deep vein thrombosis	0.29	0.30	0.30
Neuropathy	0.00	0.30	0.02

The rates used in the model differ from those observed in TROPIC. This is explained below.

As hospitalization for SAE in TROPIC was defined as new hospitalisations or a prolongation of an ongoing hospitalization, the rates of hospitalisation estimated in TROPIC may overestimate the rate of hospitalisations in clinical practice (since patients may already be hospitalised, and if the box is checked in the CRF, it could just be because the hospitalisation was prolonged).

The TROPIC-derived SAE hospitalisation rates were therefore validated by UK clinical experts to make sure that the rates applied in the model are appropriate estimates and reflect UK clinical practice. The rates were subsequently adjusted before use and are applied according to AE type in the model.

Therefore the modelled rates reported in table 71 of the dossier and reproduced in Table 3 above do not reflect arm specific treatments.

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These rates are used to calculate costs. Hence the general rate for adverse events described above is applied to the cost of an inpatient spell for that particular event type.

In order to calculate arm specific costs, the risk per cycle of experiencing the adverse event in each arm is then multiplied by this total cost to find the cost per patient per adverse event.

A7.**Please explain what the relative risks refer to in Table 45 (Appendix A, page 117) and please could you provide the full bibliographic details of the two references that do not have superscript links to the references section (that is, Doyle et al. and Vogel et al.).**

Relative risk refers to the calculation of relative risk of the proportion of patients requiring GCSF prophylaxis.

The relevant tables in the model can be found on the 'Risk AEs' worksheet encompassed by cells AD45:AT86.

We will amend this entry in the redacted version of the dossier to be supplied by 11th December 2015 as per the Procedure note.

We apologise for the minor technical issues we experienced in the automatic referencing of both the appendices and the main dossier prior to submission. We provided updated documents which contained full lists of references via NICE docs a few days after the submission deadline which addressed these issues. To confirm, the Doyle and Vogel references omitted from the first submission are again provided below.

Doyle, S. et al., Health State utility scores in advanced non-small cell lung cancer. Lung Cancer 2008, 63, 374-380.

Vogel, C.L. et al. First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: a multicenter, double-blind, placebo-controlled phase III study. J Clin Oncol 2005; 23: 1178-1184.

Literature searching

A8.**Please clarify the discrepancy in Figure 4 (page 59) which states that 30 studies met the inclusion criteria and 24 studies were excluded, whereas Table 17 (page 59) states that 31 studies were included and 23 studies were excluded.**

Thank you for pointing out this typological discrepancy. The error is in Figure 4.

We provide an updated PRISMA diagram (Figure 1 overleaf) which includes the correct number of records included and excluded. The number of studies and detail contained in Table 17 is correct. .

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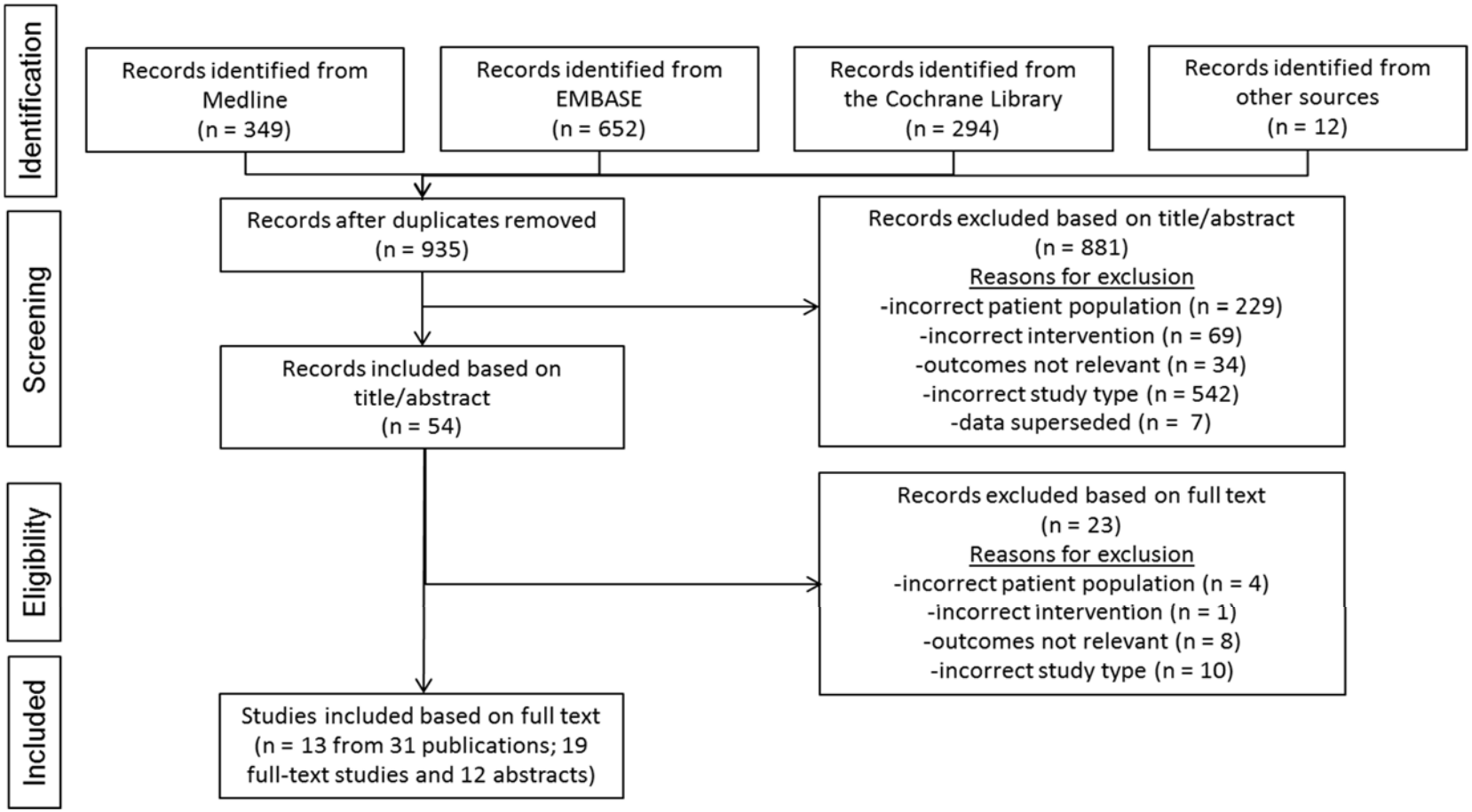
Figure 1. PRISMA flow diagram for the systematic literature review of RCT studies.



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A9.**Please clarify and explain why the systematic review includes studies of interventions (Figure 4 and Table 17; pages 59-61) which are not discussed further in the submission (such as mitoxantrone containing regimens [Fizazi 2012, Fleming 2012, Joly 2015, Ryan 2013, Saad 2011, Hussain 2012, Basch 2015] and ipilimumab [Kwon 2014; Fizazi 2014]). Further, please provide an evidence network for all the included studies similar to Figure 1, page 48 of the ERG report for TA255 (http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0004/82579/ERGReport-10-49-01.pdf).**

The systematic review of RCTs in mCRPC was carried out with a wide remit. This was because we are aware that since the original SLRs were conducted there have been a large number of interventions and major studies approved and published. We felt that it would be prudent to capture the entire evidence base within the inclusion criteria and to focus on those studies with direct relevance to the decision problem in the document. In fact it was noted during the decision problem meeting that focus would be needed due to the extensive literature base.

The final scope for this appraisal identified abiraterone, enzalutamide, mitoxantrone and best supportive care as the key comparators. In addition Radium-223 dichloride was included for people with bone metastasis only.

The advanced hormonal agents have been studied in the COU-AA-301(4) and AFIRM(5) studies and these were identified in the SLR. Mitoxantrone was the control arm in the pivotal cabazitaxel study TROPIC(6) which was also identified. Therefore we have based our analyses on these three studies and the relevant key papers have been critically reviewed within the submission document.

We have argued that Radium-223 is not a valid comparator both in the submission and also in question 1A above. Hence we have not discussed the ALSYMPCA study at length.

We recognise that we should have provided a rationale for not discussing further the remaining therapies that were identified.

These interventions and studies were not included in the review for a number of reasons. Siproleucel-T has been withdrawn. All but one of the other therapies do not have licences for the treatment of mCRPC and are either not used in UK clinical practice or are experimental technologies in this space. Beyond cabazitaxel, docetaxel is the only other licensed chemotherapy agent for the treatment mHRPC but the CUOG Trial P-06c study was not discussed further as this is, by definition in the wrong patient group. (The licence for cabazitaxel is in the post-docetaxel setting). None of the therapies identified would be considered to be best supportive care in clinical practice.

We note that mitoxantrone is not licensed in mCRPC but at the time of the TROPIC trial was considered to be standard of care and we have argued that it may be considered at least

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equivalent to best supportive care today. Many of the studies shown in the evidence network below included mitoxantrone in the control arm. However we judged that it would not be informative to discuss this evidence further as it is not clear how these studies could increase the robustness of the NMA.

The requested the evidence network from the SLR is provided in Figure 2 below and summary information including references for each publication related to the 13 studies and the study Phase is presented in Table 4.

Figure 2 Evidence network.

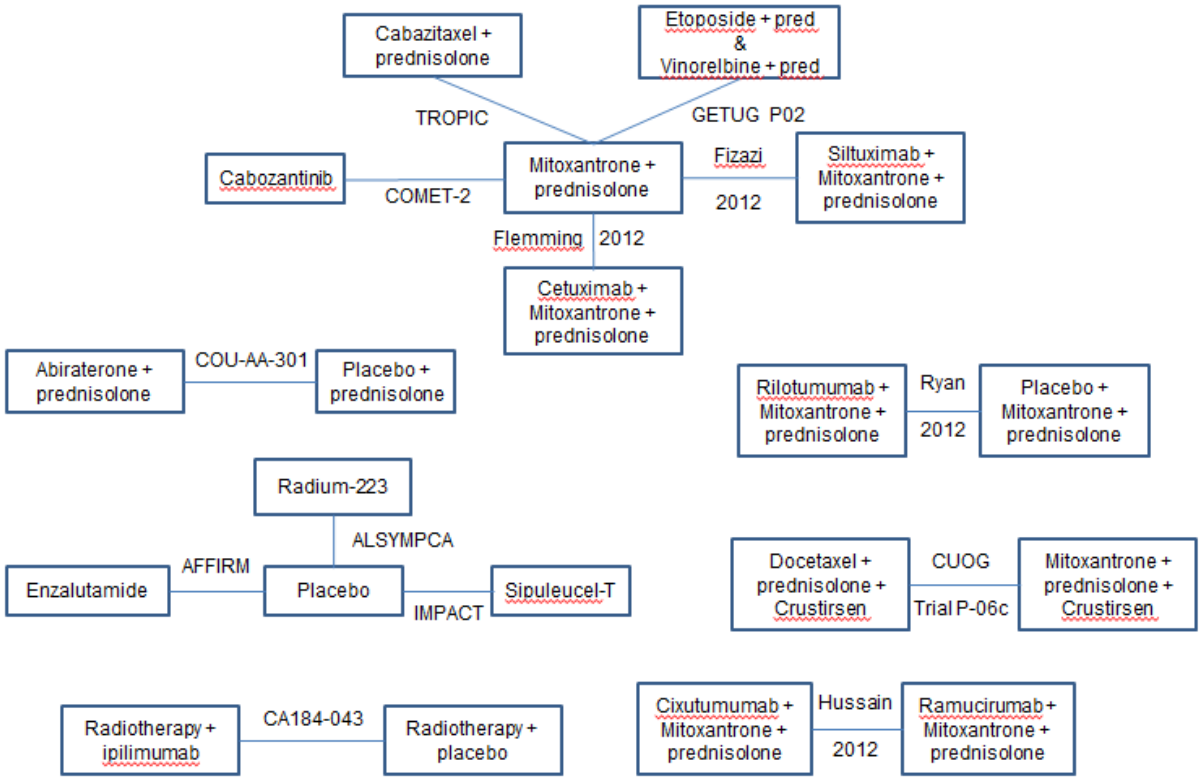

Table 4. Summary information of the included RCTs

Trial name (citations)	N	Intervention arm	Comparator arm	Phase
COU-AA-301 study 2013(4;7-10)	1195	Abiraterone acetate + prednisone	Placebo + prednisone	Phase III
TROPIC study 2013(6;11-14)	755	Cabazitaxel + prednisone	Mitoxantrone + prednisone	Phase III
Fizazi 2012(15)	97	Siltuximab + mitoxantrone +	Mitoxantrone +	Phase II

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		prednisone	prednisone	
Fleming 2012(16)	115	Cetuximab + mitoxantrone + prednisone	Mitoxantrone + prednisone	Phase II
ALSYMPCA study 2015(1;17-20)	526[a]	Radium-223 + BSC	Placebo + BSC	Phase III
GETUG P02 study 2015(21)	92	Etoposide + prednisone	Mitoxantrone + prednisone	Phase II
		Vinorelbine + prednisone		
CA184-043 study 2014(22;23)	799	Radiotherapy + ipilimumab	Radiotherapy + placebo	Phase III
Ryan 2013(24)	142	Rilotumumab + mitoxantrone + prednisone	Placebo + mitoxantrone + prednisone	Phase II
CUOG Trial P-06c study 2011(25)	45	Docetaxel + prednisone + custirsen	Mitoxantrone + prednisone + custirsen	Phase II
AFFIRM study 2015(5;26-29)	1199	Enzalutamide	Placebo	Phase III
Hussain 2012(30)	132	Cixutumumab + mitoxantrone + prednisone	Ramucirumab + mitoxantrone + prednisone	Phase II
COMET-2 study 2015(31)	119	Cabozantinib	Mitoxantrone + prednisone	Phase III
IMPACT study 2011(32)	512	Sipuleucel-T	Placebo	Phase III

A10.**In the original submission (TA255) a search was conducted to identify all studies relating to cabazitaxel in any context. Please clarify why the same search strategy was not used for the latest submission.**

At the time of TA255 there was far less published literature in the area of castrate resistant prostate cancer and few studies relating to cabazitaxel directly. The original search strategy was conducted in three distinct parts:

1. The objective of the first search was to identify all studies of cabazitaxel versus any comparator, to identify the complete evidence base for cabazitaxel.
2. The objective of the second search was to identify all randomised controlled trials (RCTs) in second-line metastatic hormone-resistant prostate cancer (mCRPC) (patients progressed after first-line docetaxel). This was done to identify any additional RCT evidence for comparators within the NICE scope that were not picked up by the first search (which would only pick up head-to-head evidence versus cabazitaxel).

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3. The objective of the third search was to identify all non-randomised studies in second-line mCRPC (post-docetaxel). This was done to identify any non-randomised evidence for cabazitaxel or comparators within the NICE scope that could potentially be relevant to the decision problem.

Given the changed landscape and the anticipated increase in the number of studies (that may not be relevant, for example cabazitaxel in head and neck cancer) a slightly different strategy was adopted for the current submission. Four literature reviews were carried out and these are presented in the latest submission.

Three were fully systematic literature reviews covering the RCT and non-RCT evidence in mHRPC/mCRPC, and one examining cost-effectiveness literature. The fourth review was a pragmatic review of the very recent literature for HRQL carried out as a PubMed search.

- The new searches for clinical data in mHRPC/mCRPC were not conducted exclusively to address the NICE decision-problem and as such had broader search terms to include interventions in use or under investigation across the European Union: Jevtana (cabazitaxel)
- Zytiga (abiraterone)
- Xtandi (enzalutamide)
- Novantrone (mitoxantrone)
- Yervoy (ipilimumab)
- Xofigo (radium-223)
- Provenge (sipuleucel-T)
- Emcyt (estramustine)

Hence this search amalgamated search terms from the reviews described as 1 and 2 from the original TA 255 above.

A11.**Please provide details (including sources and details of any alterations made) for the validated filter that was used to identify RCTs (Appendices pages 25). Please also clarify whether validated filters were employed for the non-RCT and economic studies searches, providing details of sources if so and justifying if not.**

We employed the EMBASE versions of the Scottish Intercollegiate Guidelines Network (SIGN) search filters within our RCTs, non-RCT, and economic study searches. Additional indexed and free-text synonyms were added to the SIGN filters within all of our searches to increase the sensitivity of our search results. The citation for the SIGN search filters is: Scottish Intercollegiate Guidelines Network. *Search Filters*. 2014 [cited 2015 March 25]; Available from: http://www.sign.ac.uk/methodology/filters.html.

We chose the SIGN filters as these have a good balance of sensitivity and specificity (see McKibbon 2009 for an example of balance(33)). This balance allows for an effective and

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efficient review. In addition, before using these terms we confirmed they were included in the the InterTASC Information Specialists' Sub-Group Search Filter Resource (cite: InterTASC Information Specialists' Sub-Group. *Search Filter Resource*. Accessible at: http://www.york.ac.uk/inst/crd/intertasc/), which is referenced in the York CRD systematic review guidelines as resource for identifying search filters.

Systematic review process

A12.**Please confirm if study selection, data extraction and quality assessment were undertaken independently by a minimum of two reviewers for each systematic review in the clinical and cost section. If not, please justify.**

For the RCT, non-RCT and Cost-effectiveness reviews two reviewers screened articles for inclusion first based on titles and abstracts, and subsequently by full text. Any disputes were resolved through discussion between reviewers or consultation with a third reviewer.

Data from relevant articles were subsequently extracted in parallel by two independent reviewers, and studies were critically appraised using both a qualitative appraisal and a study grade. Both sets of extracted data were compared and combined into a final data extraction table, which was subsequently verified for the accuracy of all content by an independent third reviewer.

Where multiple publications were identified for the same trial, the novel data reported in each publication were initially extracted separately and then grouped together to create the most complete data extraction while avoiding double counting of the patients.

For the pragmatic review of HRQL data carried out using Pubmed two reviewers screened articles for inclusion first based on titles and abstracts, and subsequently by full text. Data from relevant articles were subsequently extracted and tabulated by one reviewer, with verification by the second reviewer. A quality assessment of the study by Bahl which presented the results from the UK EAP was carried out as the HRQL data contained therein were used in the modelling.(34) No quality assessments of the other HRQL studies identified in the review described above were carried out. This was because the data from these studies were not used in the evaluation directly, rather they provided supportive information to validate the magnitude of the utility values from Bahl 2015.(34)

A13.**Please clarify/define what is meant by best supportive care in the systematic reviews of the clinical evidence (Table 15, pages 56-58; Section 4.10, page 85; table 29, pages 88-90)**

Best supportive care (BSC) is a blanket term used within clinical studies to describe the routine standard of care taking place at whatever centre is involved in the trial of interest. For mCRPC this can include analgesics, local external beam radiotherapy, glucocorticoids, antiandrogens, ketoconazole, bisphosphonates or oestrogens such as diethylstilbestrol or

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estramustine. The mix and sequencing of these treatments is likely to vary between patients and between centres according to individual patient disease characteristics and local preferences. BSC is expected to provide symptomatic relief but not to extend survival.

For the purposes of the literature review BSC has no definition beyond that stated above and is cited in the aggregate in the outputs of the literature review.

For the economic modelling, BSC in the base-case is defined as the treatment mix received by patients in the TROPIC study once they had progressed and were no longer taking active chemotherapy treatments.

Table 5. Best supportive care in TROPIC

Therapeutic class	Proportion of patients on therapy	Therapy
Analgesics	**0.43**	Co-codamol
		Diclofenac
Steroids	**0.51**	Dexamethasone
		Prednisone
Palliative Radiotherapy	**0.43**	Strontium-89
		External beam RT
Bisphosphonates	**0.17**	Zoledronic acid

Quality assessment, data synthesis and analysis

A14.**Please confirm whether there is any overlap in data across studies reported within Table 31 and between studies in Table 31 and 32 (pages 93-4). For example, does the study by Heindrich 2014 (reference 87), which includes preliminary results from 20 European Compassionate Use and Early Access Programs, include data from the other European studies reported in Table 31?**

Data from the EAP/CUP programmes has been reported at the country, regional (including EU) and worldwide levels.

Full papers are available for the following countries: Germany,(35) UK,(34) Korea,(36) Netherlands,(37) Spain(38) and Italy.(39) Conference abstracts have been published for Canada,(40) France(41) and Thailand.(42)

Patients from all European CUP/EAPs were included in the study reported in full by Heidenreich(43) cited above so there is overlap in terms of some of the European data, however this paper focuses on safety in senior (>70 years) patients.

Heidenreich also presented a poster at ESMO 2014 in which data on 451 patients from 12 countries from around the world (Bangladesh, Korea, Lebanon, Thailand, Turkey, Germany, Greece, Netherlands, Norway, Slovenia, Brazil and Peru) were pooled.(44)

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Malik has presented an interim analysis in poster form in which the data from all the 37 countries taking part in the programmes has been pooled.(45) As yet there is no full publication which discusses this analysis. As this abstract presents interim analysis and is not a full paper this was not the focus of the discussion in the dossier.

A15.**Please provide further details on the effect of cabazitaxel on cardiac and renal complications in the TROPIC trial including any additional supporting evidence from post-marketing surveillance data and other sources, if applicable.**

The committee reflected at there was uncertainty about the effects of cabazitaxel on renal and cardiovascular safety during the evaluation of cabazitaxel for TA255. In our response to the ACD we were able to take the opportunity to address these concerns. (Our response can be found in the committee papers here: http://www.nice.org.uk/guidance/TA255/documents/prostate-cancer-cabazitaxel-sanofi2) and is reproduced as part of the answer below.

We noted that these data have already been explored in detail with the regulatory bodies and agencies. Indeed, the UK regulatory agency, the MHRA, was the co-rapporteur of the EMA review of cabazitaxel. Both the FDA and EMA concluded that there was a positive benefit-risk profile for cabazitaxel, with no need for a further risk-management plan beyond that proposed.

Cardiac disorders in TROPIC

- There were five cardiac-related deaths in TROPIC in the cabazitaxel arm, and none in the mitoxantrone arm (noted by the EMA and De Bono 2010(6); the FDA deemed four deaths to be cardiac-related).(46) None of these were considered by the investigators to be related to the study drug – this fact was highlighted by one of the clinical experts at the Appraisal Committee meeting, referring to the letter published by De Bono et al in the Lancet.(47)

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

- In TROPIC, all Grade cardiac events were more common on cabazitaxel of which 6 patients (1.6%) had Grade ≥3 cardiac arrhythmias, compared with 1 patient (0.3%) on mitoxantrone. The incidence of tachycardia on cabazitaxel was 1.6%, none of which were Grade ≥3. The incidence of atrial fibrillation was 1.1% in the cabazitaxel group. Cardiac failure events were more common on cabazitaxel, the event term being reported for 2 patients (0.5%), versus none on mitoxantrone (EPAR 2011;

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TROPIC clinical study report). As expected, more events of LV dysfunction and EF decrease occurred on the mitoxantrone arm (all grades - 3 patients versus 1 patient) (TROPIC CSR). As stated in the EPAR, there is a lack of clear evidence to suggest that cabazitaxel contributed to these cardiac events. In light of the unknown aetiology of the increased incidence of cardiac deaths and arrhythmias, the potential risk for cardiac conduction disorders was included in the SmPC

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

Maison-Blanche also conducted an open-label study assessing the cardiovascular safety of cabazitaxel, based on thorough evaluation of QT and non-QT variables, and the relationship between pharmacokinetic and pharmacodynamic ECG profiles and the occurrence of Grade ≥3 cardiovascular adverse events.(48) The authors concluded that cabazitaxel had no clinically significant cardiovascular adverse effects in the 94 patients with advanced solid tumours.

Renal effects in TROPIC

- The EMA and the De Bono study reported 3 renal deaths, although the FDA attributed 4 deaths to renal failure, on the cabazitaxel arm, versus none in the mitoxantrone arm.

- After considering the available data, the CHMP commented: “Renal failure was often multi-factorial in origin and a direct causal relationship with cabazitaxel cannot be determined. Haematuria is very common in patients with prostate cancer. Although more frequent in the cabazitaxel group, a possible explanation for the observed haematuria was found in most cases. Haematuria should be closely monitored”.

- In response to the FDA review, an expert advisory board was convened to evaluate renal events occurring in the seven completed cabazitaxel studies (TROPIC, the Phase II breast cancer study, and the Phase I studies). This board concluded that, for the vast majority of the patients with an AE renal failure, at least one concomitant risk has been identified, such as an AE (e.g. diarrhoea, dehydration, severe infection plus or minus septic shock), local obstruction/progression, medications (eg, NSAID, zoledronic acid, vancomycin, aminosides), contrast given for repeated CT scans, or

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co-morbidity (e.g. diabetes) and stated: “It is difficult to assess retrospectively the exact level of implication of each of these risk factors of renal failure in the completed studies.”

- With regards to the pharmacokinetics of cabazitaxel, cabazitaxel is minimally excreted via the kidney (2.3% of the dose) (EPAR). No formal pharmacokinetic studies were conducted with cabazitaxel in patients with renal impairment. However, the population pharmacokinetic analysis carried out in 170 patients that included 14 patients with moderate renal impairment (creatinine clearance in the range of 30 to 50 ml/min) and 59 patients with mild renal impairment (creatinine clearance in the range of 50 to 80 ml/min) showed that mild to moderate renal impairment did not have meaningful effects on the pharmacokinetics of cabazitaxel. To further investigate the pharmacokinetics in patients with moderate and severe renal impairment, a study (POP12251) was undertaken. This is described below.

- POP12251: An open-label pharmacokinetic and safety study of cabazitaxel in patients with solid tumors with moderately and severely impaired and with normal renal function. This study has been completed and the clinical study report (CSR) preparation is in progress. The primary objective of this study was to study the effect of moderate and severe renal impairment on the pharmacokinetics (PK) of cabazitaxel (CBZ).

- [redacted]

[redacted]

Periodic safety update

The latest periodic safety update covering the period 17th June 2013 to 17th June 2014 states that approximately 36 550 patients were exposed cumulatively to cabazitaxel in marketing experience including 11 800 patients during the reference period, and approximately 4502 cumulative subjects/patients were exposed to cabazitaxel in clinical trials up-to the data lock point of this report.

Cardiovascular safety in the Periodic safety update

Cardiac arrhythmia, Torsade de pointes/QT prolongation, cardiac arrhythmia terms (incl. bradyarrhythmias and tachyarrhythmia’s are listed as important potential risk of JEVTANA in the EU-RMP and specified for review in each periodic safety update. A search was performed in AWARETM using MedDRA version 16.1 to detect all cases involving diagnoses

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of arrhythmia related investigations for cabazitaxel for the time period of 17 June 2013 to 17 June 2014. No new information that would indicate a new safety signal for cabazitaxel was identified.

Renal safety in the Periodic safety update

In the latest periodic safety update the results from the analysis of studies EFC11784* and EFC11785** are presented. This was analysis was carried out in response to the US FDA post marketing requirement to submit integrated analyses of renal toxicity from these two trials every 6 months for 3 years from the initiation of the clinical trial. The 6th and final integrated renal safety analysis from these 2 ongoing randomized Phase 3 studies has been completed for the cut-off date of 27 February 2014.

Analyses were performed on 2,321 treated patients with at least 1 cycle of study treatment completed at the cut-off date of 27 February 2014, including 1,934 patients treated with cabazitaxel and 387 patients treated with docetaxel. The covered period was from 04 May 2011 to 27 February 2014.

Based on the information presented in this 6th integrated renal report, no new findings have been identified in the 2 ongoing Phase 3 studies that would require a change in the study monitoring or in the current assessment of the potential impact of cabazitaxel on renal function. This was the sixth and last integrated renal safety report. On 3 July 2014, the US FDA confirmed that the corresponding Post-Marketing Requirement was duly fulfilled.
The advice remains in the SPC that for patients with renal impairment No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance (CLCR): 50 to 80 mL/min). Data in patients with moderate (CLCR: 30 to 50 mL/min) and severe renal impairment (CLCR<30 mL/min) or end-stage renal disease is limited; therefore these patients should be treated with caution and monitored carefully during treatment

*EFC11784: A Phase 3 randomized, open label, multicenter study comparing cabazitaxel at 25 mg/m2 and at 20 mg/m2 (CBZ25 and CBZ20, respectively) in combination with prednisone every 3 weeks to docetaxel in combination with prednisone in patients with metastatic castrati on resistant prostate cancer not pretreated with chemotherapy.

**EFC11785: A Phase 3 randomized, open label, multicenter study comparing cabazitaxel at 20 mg/m2 and at 25 mg/m2 (CBZ20 and CBZ25, respectively) every 3 weeks in combination with prednisone for the treatment of metastatic castration resistant prostate cancer previously treated with a docetaxel-containing regimen.

A16. **Please provide details on dose modification (including relative dose intensity) in the Compassionate Use and Early Access Programs detailed in Tables 33 and 34 (pages 83-84).**

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- If dose modifications due to adverse events have been made in the Compassionate Use and Early Access Programs, what is the likely or expected impact (even if not recorded in the individual programs) on efficacy and health related quality of life.
- In addition, how many patients discontinued treatment in each of the programs (of these, how many presented disease progression)?

The relative dose intensity, discontinuation and dose reductions are reported in the full papers which have been published for the EAP/CUP programmes. These data are provided in Table 6.

Table 6. Relative dose intensity, discontinuation and dose reductions reported for the EAP/CUP

Country	Median Relative dose intensity	Discontin'n for disease progression	Dose reduction due to any cause	Dose reduction due to AEs
Italy(39)	98.3%	44.9%	21%	17%
Spain(38)	99.7%	48.5%	18.2%	15.2%
Germany(35)	99.3%	14.5%	NR	10%
Korea(36)	99.6%	58%	43%	39%
UK(34)	97.8% (mean)	27.7%	30.4%	29.5%
Netherlands(37)	N/A	N/A	26.5%	NR
EU pooled results in elder populations(44)	98.9	38.4%	17.4%	NR

Discontinuation for any cause in the EAP/CUP programs was near to 100% in all cases since patients either die whilst on treatment (not a discontinuation event), reach the end of the number of cycles allotted or discontinue due to other reasons. In Germany discontinuation was also recorded at the point cabazitaxel became commercially available ((n = 71, 64.5% of patients).

The results in the Korean EAP stand out from the European studies with a greater proportion of patients discontinuing for reasons of disease progression and experiencing a higher rate of dose reductions. We have commented in the submission document that it is widely accepted that taxane metabolism is effected by ethnicity and that the results from this study suggest that caution should be exercised when treating Asian patients, especially those prone to cabazitaxel-induced complicated febrile neutropenia, such as patients >65 years, or with a poor performance status, extensive prior radiotherapy, or poor nutritional status.

We are unable to speculate on the effect on HRQL and efficacy due to dose reduction. However the PROSELICA study which is evaluating the safety and efficacy for the 25mg/m^2 and 20mg/m^2 doses of cabazitaxel may provide evidence to support this. We indicated in the

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dossier that if these results become available within the timeframe of the NICE process we would endeavour to provide these data in an addendum.

A17.**Please provide further comments (page 97 company submission) on the strength, robustness and limitation of the data from the Compassionate Use and Early Access Programs from around the world including variation in practice.**

We will follow up with a quality assessment of the EAP/CUP studies using the quality assessment tool that was used for the UK EAP in the submission.

A18.**Please provide a summary table listing the proportion of patients that suffered adverse events across the four pivotal trials for cabazitaxel, abiraterone, enzalutamide and radium-223.**

The table with the adverse events from TROPIC, COU-301-AA and AFFIRM used to inform the ITC is provided as part of the answer to Question B10 below.

The table of adverse events from the ALSYMPCA study for radium-223 taken from Hoskin 2014(1) is reproduced below:

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Table 7. Adverse events in the ALSYMPCA study(1)

	Previous docetaxel use								No previous docetaxel use							
	Radium-223 (n=347)				Placebo (n=171)				Radium-223 (n=253)				Placebo (n=130)			
	All grades	Grade 3	Grade 4	Grade 5	All grades	Grade 3	Grade 4	Grade 5	All grades	Grade 3	Grade 4	Grade 5	All grades	Grade 3	Grade 4	Grade 5
Patients with at least one adverse event	330 (95%)	126 (36%)	38 (11%)	49 (14%)	168 (98%)	79 (46%)	12 (7%)	37 (22%)	228 (90%)	82 (32%)	15 (6%)	48 (19%)	122 (94%)	43 (33%)	5 (4%)	29 (22%)
Haematological adverse events that occurred in at least 5% of patients in either treatment group																
Anaemia	120 (35%)	42 (12%)	8 (2%)	0	61 (36%)	23 (14%)	1 (1%)	1 (1%)	67 (27%)	24 (10%)	3 (1%)	0	31 (24%)	14 (11%)	1 (1%)	0
Leukopenia	21 (6%)	5 (1%)	0	0	1 (1%)	1 (1%)	0	0	4 (2%)	2 (1%)	1 (<1%)	0	0	0	0	0
Neutropenia	24 (7%)	8 (2%)	3 (1%)	0	2 (1%)	1 (1%)	0	0	6 (2%)	1 (<1%)	1 (<1%)	0	1 (1%)	1 (1%)	0	0
Thrombocytopenia	53 (15%)	15 (4%)	16 (5%)	0	13 (8%)	4 (2%)	1 (1%)	0	16 (6%)	5 (2%)	2 (1%)	1 (<1%)	4 (3%)	1 (1%)	0	0
Non-haematological adverse events that occurred in at least 10% of patients in either treatment group																
Constipation	62 (18%)	3 (1%)	0	0	35 (21%)	1 (1%)	0	0	46 (18%)	3 (1%)	0	0	29 (22%)	3 (2%)	0	0
Diarrhoea	85 (25%)	2 (1%)	0	0	30 (18%)	4 (2%)	0	0	66 (26%)	7 (3%)	0	0	15 (12%)	1 (1%)	0	0
Nausea	137 (40%)	8 (2%)	0	0	71 (42)	3 (2%)	0	0	76 (30%)	2 (1%)	0	0	33 (25%)	2 (2%)	0	0
Vomiting	83 (24%)	9 (3%)	0	0	24 (14%)	5 (3%)	0	0	28 (11%)	1 (<1%)	0	0	17 (13%)	2 (2%)	0	0
Fatigue	94 (27%)	14 (4%)	2 (1%)	0	45 (26%)	9 (5%)	1 (1%)	0	60 (24%)	7 (3%)	1 (<1%)	0	32 (25%)	7 (5%)	1 (1%)	0
Peripheral oedema	39 (11%)	6 (2%)	0	0	20 (12%)	1 (1%)	1 (1%)	0	37 (15%)	4 (2%)	0	0	10 (8%)	2 (2%)	0	0
Urinary tract infection	26 (8%)	3 (1%)	0	0	17 (10%)	3 (2%)	1 (1%)	0	21 (8%)	4 (2%)	0	0	11 (9%)	1 (1%)	0	1 (1%)
Weight decreased	48 (14%)	4 (1%)	0	0	33 (19%)	5 (3%)	0	0	21 (8%)	0	0	0	11 (9%)	0	0	0
Anorexia	58 (17%)	4 (1%)	0	0	34 (20%)	2 (1%)	0	0	44 (17%)	5 (2%)	0	0	21 (16%)	0	0	0
Bone pain	185 (53%)	73 (21%)	1 (<1%)	0	116 (68%)	51 (30%)	2 (1%)	0	115 (46%)	47 (19%)	4 (2%)	0	71 (55%)	23 (18%)	1 (1%)	0
Malignant neoplasm progression	41 (12%)	4 (1%)	1 (<1%)	30 (9%)	23 (14%)	3 (2%)	1 (1%)	18 (11%)	36 (14%)	5 (2%)	3 (1%)	25 (10%)	21 (16%)	1 (1%)	0	15 (12%)

Data are n (%). Patients might have experienced more than one adverse event, but were only counted once in the total. The total number of patients with at least one adverse event might be higher than the column total because adverse events might have occurred in other categories that did not meet the criteria for inclusion in the table (adverse events of any grade that occurred in at least 5% [haematological adverse events] or at least 10% [non-haematological adverse events] of patients in either treatment group).

Table 3: **Adverse events, by docetaxel subgroup (safety population)**

Indirect treatment comparison (ITC)

A19.**Priority Question: Please clarify why the ITC and associated modelling are based on hazard ratios (which assume proportional hazards), and why this approach was selected over methods that allow the relative treatment effects to vary over time. For the abiraterone pivotal trial Fizazi (2012) noted that the proportional hazards assumption is not met. Please clarify the likely impact on the results.**

Of the modelling approaches considered, adapting and updating the model presented to the Appraisal Committee in TA255 represented significant advantages of simplicity and continuity, not least because we believe the main comparator of interest is that of mitoxantrone. Application of Hazard ratios to the modelled treatment effects from cabazitaxel within this modelling framework is also easy to implement transparently and robustly, and lends itself to full examination in probabilistic sensitivity analyses.

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The issues arising from the examination of the trial design, populations and results of the NMA as discussed at the decision-problem meeting, in the dossier, and elsewhere, raised significant concerns about the reliability of the ITC results.

We 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.

The proportional hazards assumption was the approach taken for the primary endpoint analysis reported in Table 14, page 53 of the Janssen submission to NICE for TA259 and in the Fizzazi paper and no detailed characterisation of how the hazards change over time has been reported to our knowledge.

Modelling these results as proportional is however a conservative approach since we make the assumption that the beneficial treatment effect for abiraterone vs. placebo holds over time; thus favouring abiraterone in comparison with cabazitaxel.

This was seen as a reasonable approach given the limitations with the data and the comparisons in general.

A20.**Priority Question: Please clarify why the random effects ITC used an uninformative prior despite the fact that there was insufficient data to update the prior distribution. Please undertake an analysis with a weakly informative prior that reflects reasonable prior beliefs, as recommended in Spiegelhalter, Abrams and Myles (2004) Bayesian approaches to clinical trials and health-care evaluation. Wiley, New York (doi: 10.1002/0470092602), in order to provide confidence intervals that better reflect the observed heterogeneity between trials**.

In the DSU Technical Support Document 2 (A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials, 2011), NICE recommends that vague or flat priors, such as N (0, 1002) be used for Bayesian analyses. This specifies that informative priors for relative effect measures require special justification. For example if there are multiple clinical trials with large numbers of subjects, the standard deviation around the variance can be estimated for the meta-analysis using these posterior distributions.

When we were considering the evidence for the ITC we identified only three RCTs to inform the network. These were TROPIC (cabazitaxel), COU-AA-301 (abiraterone) and AFFIRM (enzalutamide). We based our approach to priors in the Bayesian analysis on the fact that no other RCT data was available and so there was no evidence upon which to base prior beliefs. Moreover we felt that using the identified studies to inform the priors would be inappropriate.

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Hence, we followed the NICE recommended approach and used vague priors. Details can be found in the WinBugs code provided in Appendices B.

In considering our answer to this question we have reflected upon the fact that there are a number of observational studies and treatment audits that have been published in which the sequencing of abiraterone or enzalutamide with docetaxel or cabazitaxel has been examined. Many of these studies were summarised in Appendices A. The general finding has been that the efficacy of cabazitaxel is undiminished before or after the use of the advanced hormonal agents. These results should be treated with caution as they are often in small uncontrolled studies and as none of these are controlled head-to-head studies there is no robust data upon which to determine the relative treatment effect of the agents at the same point in the treatment pathway. The null hypothesis, that there is no difference, therefore stands and the use of vague priors remains justified.

Rather than attempting to define arbitrary weakly informative priors we would welcome guidance from the ERG to help us specify these distributions so that sensitivity analysis may be run.

Section B: Clarification on cost-effectiveness data

B1.Priority Question. Please clarify why the use of piecewise curves to represent overall survival and progression-free survival was not considered. It is noted within TA255 that the Committee considered the use of piecewise curves to be the most appropriate approach.

As discussed at the Decision Problem meeting, Sanofi raised several concerns and considerations in the approach to data extrapolation methodologies, particularly in light of the strong request for Sanofi to undertake indirect comparisons with abiraterone and enzalutamide despite issues with data limitations and apparent key differences in the underlying nature of the data – e.g. lack of a common underlying proportionality in hazards.

It was noted that in 2011 the Appraisal Committee considered a piece-wise modelling of the TROPIC data represented the preferred modelling approach – of those options presented at the time – and we understand this was in part following advice from the ERG that the piece-wise approach might minimise the impact of early deaths from cabazitaxel-induced neutropenia. However whilst such an approach may well offer a better characterisation of the TROPIC data in and of itself, it creates challenges of interpretation when using hazard ratios derived from indirect comparison methods.

Arguably, the application of a single Hazard Ratios derived from indirect comparisons that rely on the published primary endpoints, to an underlying cabazitaxel survival curve that reflected varying hazards across its individual ‘pieces’ would create questionable derived curves for the comparator arms and by extension significantly increase the complexity of,

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and confound the interpretation of the result outputs. In particular, examining alternative assumptions about the interplay of these hazards would add additional complexity and create excessive computational challenges of implementation, particularly in regards to the execution of probabilistic sensitivity analyses.

In the ERG report to TA255 highlighted that fact that the ERG felt the use of parametric curves throughout is preferable compared with directly using the Kaplan-Meier curves followed by the transition proportions from the curves. This is primarily for two reasons: firstly the Kaplan-Meier curves are likely to overfit the data and be less generalisable; secondly the choice of time point at which the data from the Kaplan-Meier curves are considered unreliable has a marked effect on the ICER. These concerns expressed during TA255 on, for example, the point of transition between KM data and parametric extrapolation were 'heeded' and as a result the base-case model applies a parametric function derived from the underlying data throughout the entire period of follow-up. However, the approach adopted for curve fitting is ultimately parsimonious in nature, seeking instead to maintain an inherent continuity between the curve-fitting approach and the hazard ratios derived from the indirect comparisons.

Whilst we may, in hindsight have settled on an alternative approach to fitting survival curves had the comparison between limited to mitoxantrone alone, and could be based exclusively on data which could be accessed at the individual patient level, we considered it would be more appropriate to apply a consistent approach to all comparisons.

In recognition that the OS data to 2.1 months in the cabazitaxel arm of TROPIC presents a visual 'kink' in the KM plot we have refitted the Weibull distribution from a cut-off point of 2.1 months onwards as was discussed in section 3.32 in TA255. We present this as a scenario analysis below for the comparison with mitoxantrone only. The issue of proportional hazards discussed above prevents such an analysis being applied to the comparisons with abiraterone or enzalutamide.

In this analysis the KM data is used for OS in the cabazitaxel arm until 2.1 months and from there onwards the newly fitted Weibull extrapolation is implemented. The mitoxantrone arm utilises the previously fitted Weibull curve.

Table 8. Results (using KM followed by Weibull using 2.1 months cut-off point)

	Cabazitaxel	Mitoxantrone	Increment
2nd line chemotherapy (includes administration, pre- & concomitant medication)	[redacted]		
Costs associated with treating Adverse events during 2nd line chemotherapy			
Total health care cost during 2nd line chemotherapy (=SD)			
Total health care cost during progressive disease (=PD)			
End-of-life costs			

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Total life-time cost per patient	**£29,666**	**£18,098**	**£11,568**
QALYs	**0.884**	**0.647**	**0.238**
Life-years	1.550	1.203	0.347
Progression-free life years	0.361	0.969	0.127
Cost per QALY gained (ICER)	**£48,543**		
Cost per Life-year gained	£33,303		

B2.Priority Question. Please provide an amended version of the economic model that allows for a fully incremental analysis (including cabazitaxel, best supportive care [mitoxantrone], abiraterone and enzalutamide) based on the results of the probabilistic sensitivity analyses.

A fully incremental analysis is technically possible and as requested by the ERG would need to be accommodated through changes to the company model. For example the model does not currently provide an estimate of costs in each arm when the PSA is run; rather it presents the incremental costs.

However we are not comfortable with providing this analysis as we have concerns about the fundamental nature of such a set of comparisons. We have discussed in the submission that differences in the definitions of PFS between the studies led us to create a highbred definition of rPFS that was applied to the TROPIC data for use in the ITC. We also reflected that this definition provided counterintuitive results in the enzalutamide comparison.

The base-case versus mitoxantrone does not use this rPFS definition. So in order to undertake a fully incremental analysis it would be necessary to either, use two definitions (PFS from TROPIC (the base-case) for the cabazitaxel vs. mitoxantrone comparison and then the synthesised rPFS metric used in the ITC) or to use only the rPFS definition for all analyses. The use of the rPFS definition for the mitoxantrone comparison is nonsensical particularly as discontinuation in TROPIC was linked to PFS and so patients came off treatment earlier than they might have done in the COU-AA-301 and AFFIRM studies. This might be expected to have an effect on overall survival and also on costs. Such an analysis would be sub-optimal.

In addition to the issues around PFS the populations used for the base-case and the analyses versus abiraterone and enzalutamide were different (SG and ITT). Moreover the design of the trials and the baseline patient characteristics were also different and so for all these reasons we believe that to combine the outputs from the PSA for each comparison into a fully incremental analysis is not advisable.

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From the deterministic analyses we would expect the rank order to be mitoxantrone followed by cabazitaxel, abiraterone and then enzalutamide and that abiraterone would be extendedly dominated but we are uncomfortable about providing figures to support this assumption. We would prefer to maintain the more credible comparison of cabazitaxel versus mitoxantrone using the base-case settings.

We would welcome comment from the ERG if they are able to provide a solution or make recommendations to accomplish the incremental analysis without the compounding effect of these issues.

B3.Priority Question: Please clarify what supporting evidence is available for vial sharing of cabazitaxel in clinical practice, as the base-case analysis assumes that there is no wastage for cabazitaxel, but there is for mitoxantrone.

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. Such a supply mechanism, is a practice already in very common usage in NHS cancer centres across a range of products and diseases, and therefore supports the assumption of zero wastage. As Sanofi does not supply mitoxantrone, the zero wastage assumption cannot be addressed in this way.

B4.Priority Question: Please provide an estimate of the ICER for cabazitaxel versus mitoxantrone based on the probabilistic sensitivity analysis.

Using the base case settings in the model and 2000 simulations the probabilistic ICER is estimated to be £50,659. In the submitted model v12 the proportion of patients receiving best supportive care as post second line treatment were not varied in the probabilistic sensitivity analysis. The analysis presented here has been performed using an updated version of the model amended to correct errors highlighted by the ERG (See also question B15 to clarify model settings and update).

B5.Priority Question. We believe that transition probabilities that add up to greater than one are used in the model when the estimated proportion of patients in the stable disease in the following cycle is fewer than the proportion alive. This will reduce the estimated number in the progressed state. Please comment on how amending the model to address this issue would affect the ICER.

The proportions of patients in each health state are driven by the survival curves for PFS and OS. The proportion in the PD state is determined by the delta between those curves.

The calculation of the proportion in the PD state (see below, third bullet point) protects against these values becoming more than 1. However as a consequence of this it is possible at the very end of the tails in the model for the PD proportion to become negative. In order to

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prevent this happening there an IF statement is implemented in the SD calculations. (Second bullet point below).

- The proportion in the dead state (e.g. cycle 3; H7) is calculated by multiplying the transition probability of death at cycle 3 (E7) by the proportion of patients in the stable and progressed disease states in cycle 2 (F6+G6) and then adding this 'new deaths' figure to accumulated proportion of deaths up to and including cycle 2 (H6).
    - H7 = H6+E7*(F6+G6)
- The proportion in the stable disease state (cycle 3; F7) is then calculated by multiplying the proportion in the stable disease state in cycle 2 (F6), by the probability of remaining in the state (D7). However at this stage there is a check in place (IF statement) such that if this value is greater than the proportion alive (i.e. one minus the proportion in the dead state; H7) it is set equal to one minus the proportion in the dead state.
    - F7 = IF((F6*D7)>(1-H7),(1-H7),(F6*D7))
- The proportion in the progressed disease state at cycle 3 (G7) is then equal to one minus the proportion in the dead (H7) or stable disease states (F7).
    - G7 =1-F7-H7

Inspection of the calculations sheet indicates that this 'correction' (implementation of the alternative in the IF statement discussed above) occurs at cycle 126 (week 378) in the base-case for cabazitaxel and at cycle 89 (week 267) in the mitoxantrone arm where the proportion in the PD state falls to 0. If the IF statement is removed then the values in the PD state go negative from these points onwards. The ICER is unaffected by this change as patient numbers alive, albeit all now in the SD state are so small by this point.

The process described in the bullet points above ensures that the total proportion of patients across all states cannot exceed one. We concede that this may 'sacrifice' patients in the PD state in keeping the proportion to one but the numbers are so small that there is no substantive effect on the outcomes.

B6.Priority Question: We believe that the following problems exist in relation to patients who discontinue:

a. Underestimated drug costs in the base-case. Assuming that the patients discontinue after the dosage of drug has been received, the drug costs should not be reduced in that cycle

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Patients labelled as discontinuing in cycle n actually discontinue between the beginning of cycle n-1 and the beginning of cycle n. For example, the 1.59% of patients in SD who are labelled as discontinuing in cycle 1 incur the cost of treatment at the beginning of cycle 0 and discontinue between the beginning of cycle 0 and the beginning of cycle 1. Therefore, no drug cost is incurred for these patients in cycle 1 as they are never treated at the beginning of cycle 1.

Further to that we have applied the proportion of patients on treatment to incur drug costs in the stable disease state, leaving the proportion of patients off treatment in the stable disease state (discontinued) without a cost for drugs for that cycle.

For the following 2 questions we have made some amendments to the model according to the proportion of patients who are on and off treatment but still in the stable disease state. The amendments are described in these sections and the effect on the ICER is presented after question B6c.

b. Overestimation of the utility in the base-case. Patients who have discontinued are assumed to still be associated with the increased utility related to additional treatment cycles

We have considered this issue and agree that there are patients who discontinue but remain in the SD state thus continuing to accrue utility at the SD levels.

We have performed a quick and crude analysis (still to be verified) of the patient level data from TROPIC from which we have retrieved those patients who were on cabazitaxel treatment without progressing and those patients who were off cabazitaxel treatment (discontinued) without progressing for the first 10 cycles. These proportions are shown below along with the overall proportion of patients in the SD state for completeness.

Table 9. Proportion of patients on and off treatment in the stable disease state for the first 10 cycles- SG population.

Patients in SD state	Proportion in the SD in the model	Proportion off Tx in the SD state	Proportion on Tx in the SD state
cycle 0	1.000000	[redacted]	
cycle 1	0.917866		
cycle 2	0.753990		
cycle 3	0.608505		
cycle 4	0.493353		
cycle 5	0.403917		
cycle 6	0.334204		
cycle 7	0.279326		
cycle 8	0.235633		
cycle 9	0.200452		

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In order to calculate the associated QALYs for the SD state we have applied the varying utilities observed in the early access programme (EAP) for the first 10 cycles to the proportion of patients on treatment without progressing in the normal way. Those patients off treatment without progressing (discontinued) but who are still in the SD state have been assigned the progressive disease utility (0.627) as a conservative assumption.

c. Overestimation of drug costs. Currently only a non-cumulative proportion of drug costs are removed due to discontinuations rather than cumulative rates which should be adjusted for the proportion of patients who discontinue that subsequently progress.

Further to that we have applied the proportion of patients on treatment to incur drug costs in the stable disease state, leaving the proportion of patients off treatment in the stable disease state (discontinued) without a cost for active drug for that cycle.

If these problems exist, please comment on how amending the model to address these issues would affect the ICER. It is unlikely that the points could be completely resolved without explicitly defining patients who discontinue with stable disease as a separate health state.

The results based on the updated estimates described above for the proportion of patients on and off treatment in the model are presented below in Table 10. This has a minimal increasing effect on the ICER from £49,327 to £49,420.

Table 10. Results based on proportion of patients on and off treatment for the first 10 cycles

	Cabazitaxel	Mitoxantrone	Increment
Total life-time cost per patient	**£29,513**	**£18,098**	**£11,415**
QALYs	**0.876**	**0.645**	**0.231**
Life-years	1.541	1.203	0.338
Progression-free life years	0.361	0.969	0.127
Cost per QALY gained (ICER)	**£49,420**		

B7.Please provide a sensitivity analysis using the electronic market information tool (eMIT) price for all generic drugs in the model, including mitoxantrone.

All costs for generic drugs in the model have been replaced with the current eMIT prices taken from the https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit accessed 26/10/2015. A table showing the changes made to the model default values (BNF) and the eMIT costs replacing these is presented overleaf. (Table 11).

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Table 11. Model default costs for generic drugs and eMIT costs

BNF Prices in V12 model.			**Prices taken from eMIT (https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit *accessed 26/10/2015*)**		
Drug	**Pack price**	**Cost/mg**	**Drug description in eMIT**	**Pack price**	**Cost/ mg**
Mitoxantrone	£100	£5.00	Mitoxantrone 20mg/10ml solution for infusion vials / Packsize 1	£29.37	£1.47
Docetaxel	£1069.50	£6.68	Docetaxel 140mg/7ml solution for infusion vials / Packsize 1	£54.60	£0.39
etoposide	£12.15	£0.12	N/A		
estramustine	£171.28	£1.71	N/A		
cyclophosphamide	£9.20	£0.02	Cyclophosphamide 500mg powder for solution for injection vials / Packsize 1	£8.87	£0.02
paclitaxel	£66.85	£2.23	Paclitaxel 30mg/5ml solution for infusion vials / Packsize 1	£3.78	£0.13
vinorelbine (tartrate)	£29.00	£2.90	Vinorelbine 10mg/1ml solution for injection vials / Packsize 1	£4.51	£0.45
carboplatin	£20.00	£0.40	Carboplatin 50mg/5ml solution for infusion vials / Packsize 1	£3.43	£0.07
cisplatin	£5.85	£0.59	Cisplatin 10mg/10ml solution for infusion vials / Packsize 1	£3.71	£0.37
gemcitabine	£29.80	£0.15	Gemcitabine 2g/20ml (100mg/ml) concentrate for solution for infusion vials / Packsize 1	£29.03	£0.01
chlorphenamine	£4.47	£0.45	Chlorphenamine 10mg/1ml solution for injection ampoules / Packsize 5	£14.47	£0.29
ranitidine	£0.54	£0.01	Ranitidine 150mg tablets / Packsize 60	£0.50	£0.0001
ondansetron	£46.58	£0.58	Ondansetron 8mg orodispersible tablets / Packsize 10	£15.88	£0.20
dexamethasone	£1.99	£0.52	Dexamethasone 3.3mg/1ml solution for injection ampoules / Packsize 10	£3.70	£0.11
Filgrastim	£52.70	£175.67	N/A		
Goserelin	£65.00	£18.06	N/A		
Leuprorelin	£75.24	£20.06	N/A		
Co-codamol	£5.80	£0.06	Co-codamol 30mg/500mg capsules / Packsize 100	£3.01	£0.001
Diclofenac	£6.18	£0.00	Diclofenac sodium 50mg gastro-resistant tablets / Packsize 28	£0.56	£0.0004
Dexamethasone	£1.99	£0.52	Dexamethasone 3.3mg/1ml solution for injection ampoules / Packsize 10	£3.70	£0.11
Prednisone	£1.29	£0.01	Prednisolone 5mg tablets / Packsize 28	£0.37	£0.003
Zoledronic acid	£253.38	£50.68	Zoledronic acid 5mg/100ml solution for injection bottles / Packsize 1	£67.79	£13.56
Genatmicin	£1.40	£0.04	Gentamicin 80mg/2ml solution for injection ampoules / Packsize 5	£4.21	£0.01
Imodium	£2.15	£0.04	N/A		

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BNF Prices in V12 model.			**Prices taken from eMIT (https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit *accessed 26/10/2015*)**		
Drug	**Pack price**	**Cost/mg**	**Drug description in eMIT**	**Pack price**	**Cost/ mg**
Warfarin	£1.04	£0.04	Warfarin 5mg tablets / Packsize 28	£0.25	£0.002
Domperidone	£1.75	£0.01	Domperidone 10mg tablets / Packsize 30	£0.58	£0.002
Amitryptylline	£1.05	£0.004	Amitriptyline 10mg tablets / Packsize 28	£0.34	£0.001
Teicoplanin	£3.57	£0.02	N/A		
Metoclopramide	£0.97	£0.035	Metoclopramide 10mg tablets / Packsize 28	£0.22	£0.001
Cyclizine	£10.97	£0.002	Cyclizine 50mg tablets / Packsize 100	£6.17	£0.001
N/A: not available in eMIT					

The effect on the ICER due to sensitivity analysis around the eMIT prices is provided in Table 12. The base-case results are also included for comparative purposes along with the differences to the incremental costs.

Table 12. Costs, outcomes and Incremental differences for the sensitivity analysis using eMIT prices.

	Base-case (MIMS costs)			**Sensitivity analysis (eMIT costs)**			**Difference in incremental costs**
	Cabazitaxel	**Mitoxantrone**	**Increment**	**Cabazitaxel**	**Mitoxantrone**	**Increment**	
2nd line chemotherapy (includes administration, pre- & concomitant medication)							
Costs associated with treating Adverse events during 2nd line chemotherapy							
Total health care cost during 2nd line chemotherapy (=SD)							
Total health care cost during progressive disease (=PD)							
End-of-life costs							
Total life-time cost per patient	**£29,548**	**£18,098**	**£11,450**	**£28,902**	**£16,906**	**£11,995**	**£545**

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	Base-case (MIMS costs)			Sensitivity analysis (eMIT costs)			Difference in incremental costs
	Cabazitaxel	**Mitoxantrone**	**Increment**	**Cabazitaxel**	**Mitoxantrone**	**Increment**	
QALYs	**0.878**	**0.645**	**0.232**	**0.878**	**0.645**	**0.232**	
Life-years	1.541	1.203	0.338	1.541	1.203	0.338	
Progression-free life years	0.361	0.234	0.127	0.361	0.234	0.127	
Cost per QALY gained (ICER)	**£49,327**			**£51,675**			
Cost per Life-year gained	£33,917			£35,530			

As might be expected the lower drug costs have reduced the cost in both arms. The small overall difference in the costs of £545 results in an increase in the ICER from £49,327 to £51,675. The difference in the costs is evenly split between the stable and progressive disease states (£263 and £282 respectively). The additional incremental cost in the stable disease state comes from the reduction in the cost of mitoxantrone and in the progressive disease state from the survival benefit due to cabazitaxel. If the incremental cost due to survivorship is removed from the calculation and costs in the progressive disease state are not considered then the ICER is £41,446.

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B8.Please clarify why the proportion of patients experiencing an adverse event (for cabazitaxel and mitoxantrone) and the odds ratios for the rates of adverse events (for abiraterone and enzalutamide) were not varied within the probabilistic sensitivity analyses.

This was an oversight and these inputs have been varied in PSA in the analyses below.

To vary the proportion of patients experiencing adverse events in the PSA, a beta distribution has been applied. Based on the number of patients experiencing the event (r) and patients at risk (n), the alpha and beta parameters were calculated as follows:

$\alpha = r$

$\beta = n - r$

To vary the odds ratios derived in the ITC for abiraterone and enzalutamide in the PSA, a lognormal distribution has been applied. The odds ratios and associated credible intervals were transformed to the log scale and samples taken from a normal distribution with median equal to the median log odds ratio and SE calculated from the log of the upper and lower 95% credible intervals assuming a normal distribution. For those odds ratios where the lower credible interval was 0, the upper credible interval was used as it was assumed that the 95% credible intervals were symmetric about the mean on the log scale.

The impact of including the proportion of patients experiencing an adverse event in the PSA as well as the odds ratios of adverse events for abiraterone and enzalutamide were minimal.

Table 13 Probabilistic ICER for cabazitaxel versus mitoxantrone

Mean difference in costs:	£ 11,781
Mean difference in effects:	0.2323 QALYs
Incremental cost-effectiveness ratio	£50,708 per QALY gained

The probability of being cost-effective at a willingness to pay of £50,000 is £45.8%. At a WTP of £51,000 the probability of being cost-effective is 51%.

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Figure 3. Scatterplot for cabazitaxel vs. mitoxantrone (After inclusion of additional inputs in PSA)

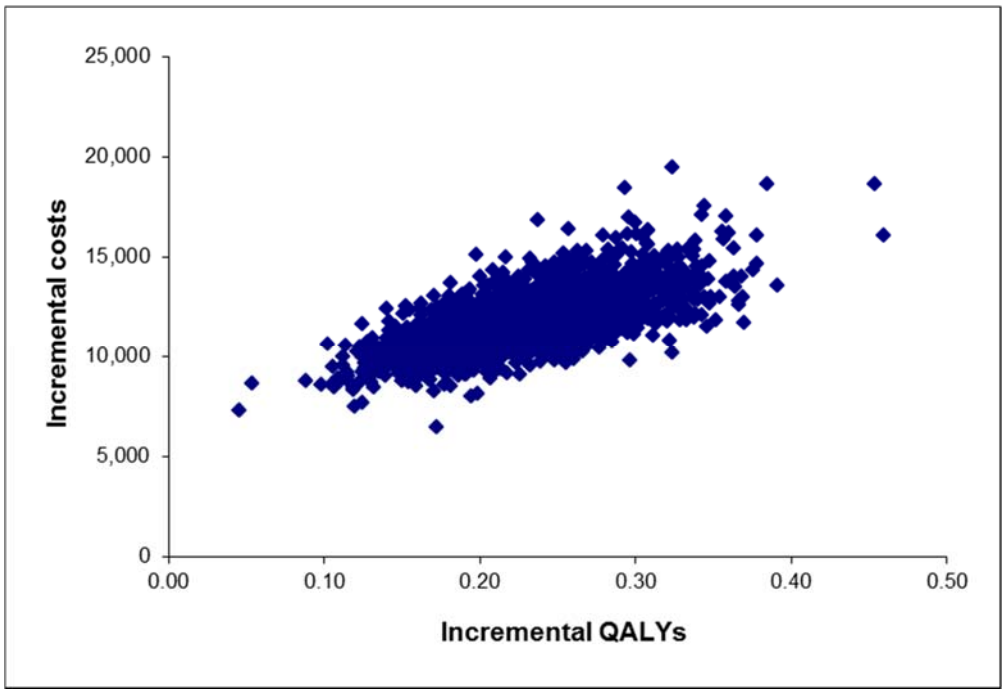
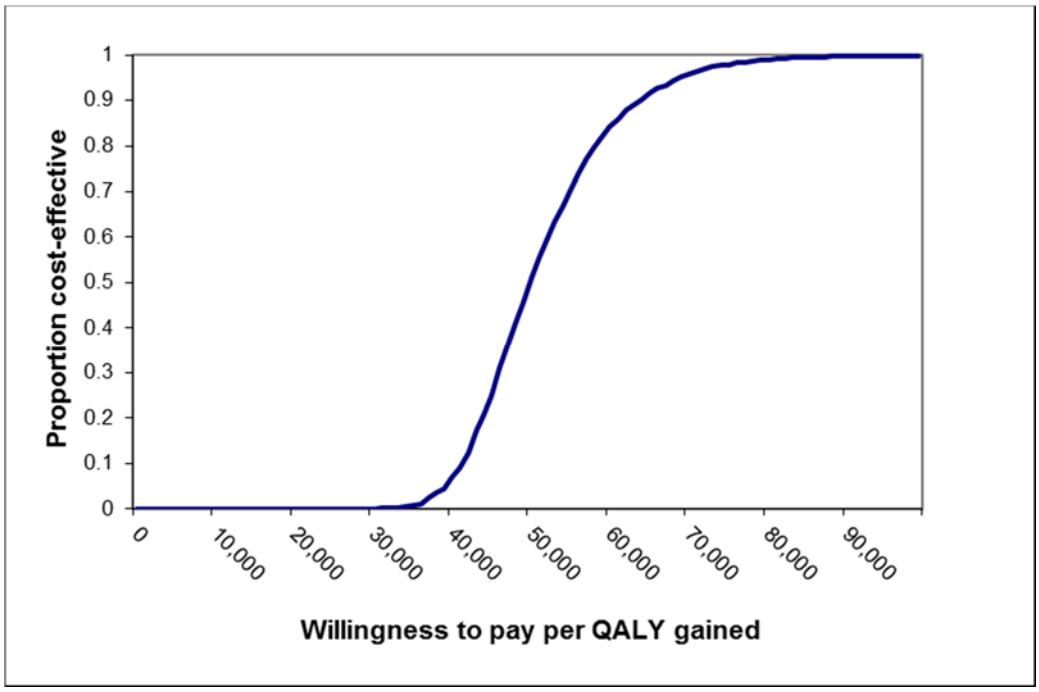


Figure 4. Cost-effectiveness acceptability curve (cabazitaxel vs. mitoxantrone) - After inclusion of additional inputs in PSA



The PSA results for abiraterone and enzalutamide are summarised in

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Table 14. Updated PSA results for abiraterone and enzalutamide

	Cab vs. Enzalutamide	Cab vs. Abiraterone
Mean difference in costs:	-£38.230	-£17,723
Mean difference in effects:	-0.1793	0.0228
Incremental cost-effectiveness ratio:	£213,256	-£776,567

B9.Please provide a sensitivity analysis that uses a single utility value (the mean of the observed utility values in the UK EAP) at all times for the stable disease state.

In the base-case we have implemented the observed utilities from the UK EAP at each cycle in order to reflect as accurately as possible what might be expected for UK patients remaining on treatment. This study suggested that for those patients who persist on treatment utility may increase. We have made an assumption that patients who reach 10 cycles and who do not show evidence of progression remain at the utility observed at the last cycle (cycle 10) in the UK EAP.

The mean of the observed utility values in the UK EAP for the stable disease state is 0.7533. Sensitivity analysis under the assumption that patients remain at this utility for the whole of the stable state is provided in Table 15 below.

Table 15. Sensitivity analysis using the mean of the utility values observed in the UK EAP.

	Base-case (MIMS costs)		
	Cabazitaxel	Mitoxantrone	Increment
2nd line chemotherapy (includes administration, pre- & concomitant medication)	[redacted]		
Costs associated with treating Adverse events during 2nd line chemotherapy			
Total health care cost during 2nd line chemotherapy (=SD)			
Total health care cost during progressive disease (=PD)			
End-of-life costs			
Total life-time cost per patient	**£29,548**	**£18,098**	**£11,450**
QALYs	**0.879**	**0.647**	**0.232**
Life-years	1.541	1.203	0.338
Progression-free life years	0.361	0.969	0.127
Cost per QALY gained (ICER)	**£49,423**		
Cost per Life-year gained	£33,917		

The median number of cycles received in TROPIC was 6. This was also the median number of cycles observed in the EAP programs conducted internationally. On this basis further sensitivity analysis is provided for the utility observed at the average number of cycles received (SD utility = 0.7518). (Table 16).

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Table 16 Sensitivity analysis using the mean of the utility values observed in the UK EAP.

	Base-case (MIMS costs)		
	Cabazitaxel	Mitoxantrone	Increment
2nd line chemotherapy (includes administration, pre- & concomitant medication)			
Costs associated with treating Adverse events during 2nd line chemotherapy			
Total health care cost during 2nd line chemotherapy (=SD)			
Total health care cost during progressive disease (=PD)			
End-of-life costs			
Total life-time cost per patient	**£29,548**	**£18,098**	**£11,450**
QALYs	**0.879**	**0.647**	**0.232**
Life-years	1.541	1.203	0.338
Progression-free life years	0.361	0.969	0.127
Cost per QALY gained (ICER)	**£49,447**		
Cost per Life-year gained	£33,917		

The base-case ICER is £49,327. Changes to the utility described above do materially not impact this. (£49,423 and £49,447 respectively).

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B10.Within the economic model, hazard ratios are used to derive rates of adverse events for abiraterone / enzalutamide (tab 'Hazard Ratios') - please provide details regarding the derivation of these values.

Adverse events were extracted from the primary papers for the COU-AA-301 and AFFIRM studies(4;5). These are presented below in Table 17.

Table 17. Adverse events in TROPIC, COU-AA-301 and AFFIRM studies.

Grade ≥3	Mitoxantrone	Cabazitaxel	%	Abiraterone	Placebo plus prednisone	%	Enzalutamide	Placebo	%
Haematological†									
Neutropenia	215	303	81.67%	1	1	0.13%	nr	nr	nr
Febrile neutropenia	5	28	7.55%	0	0	0.00%	nr	nr	nr
Leukopenia	157	253	68.19%	nr	nr	nr	nr	nr	nr
Anaemia	18	39	10.51%	62	32	7.84%	62	38	7.75%
Thrombocytopenia	6	15	4.04%	11	2	1.39%	8	3	1.00%
Non-haematological									
Diarrhoea	1	23	6.20%	9	5	1.14%	9	1	1.13%
Fatigue	11	18	4.85%	72	41	9.10%	50	29	6.25%
Asthenia	9	17	4.58%	26	8	3.29%	20	10	2.50%
Back pain	11	14	3.77%	56	40	7.08%	40	16	5.00%
Nausea	1	7	1.89%	17	11	2.15%	12	13	1.50%
Vomiting	0	7	1.89%	21	12	2.65%	9	10	1.13%
Haematuria	2	7	1.89%	12	9	1.52%	12	4	1.50%
Abdominal pain	0	7	1.89%	18	8	2.28%			0.00%
Pain in extremity	4	6	1.62%	24	20	3.03%	14	14	1.75%
Dyspnoea	3	5	1.35%	14	9	1.77%	5	6	0.63%

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Grade ≥3	Mitoxantrone	Cabazitaxel	%	Abiraterone	Placebo plus prednisone	%	Enzalutamide	Placebo	%
Constipation	2	4	1.08%	10	4	1.26%	6	5	0.75%
Pyrexia	1	4	1.08%	3	5	0.38%			0.00%
Arthralgia	4	4	1.08%	40	17	5.06%	20	7	2.50%
Urinary-tract infection	3	4	1.08%	12	3	1.52%	10	3	1.25%
Pain	7	4	1.08%	7	8	0.88%			0.00%
Bone pain	9	3	0.81%	51	31	6.45%	18	13	2.25%
OTHER									
Cardiac disorders	3	7	1.89%	41	9	5.18%	7	8	0.88%
Abnormalities in liver function tests	nr	nr	nr!	30	14	3.79%	3	3	0.38%
Hypertension	1	1	0.27%	10	1	1.26%	16	5	2.00%
Hypokalaemia	0	2	0.54%	35	3	4.42%			0.00%
Fluid retention or oedema	1	2	0.54%	20	4	2.53%	8	3	1.00%
Seizure	0	1	0.27%			0.00%	5	0	0.63%

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The hazard ratios for adverse events utilised in the model were calculated in the indirect treatment comparison.

For these safety analyses, given the low number of studies and events in most of the trial arms, only fixed effects models were used; using random effects models under these circumstances would produce unstable results associated with credible intervals which were excessively wide.

The odds ratios were calculated from the number of events in the studies tabulated above. For example the data for anaemia that was used in the WinBugs code was derived in the following way – see Table 18.

Table 18 Derivation of odds ratios for use in the ITC for anemia

r[,1]	n[,1]	r[,2]	n[,2]	STUDY ID	ODDS c	ODDS t	OR
18	371	39	371	TROPIC	0.05	0.12	2.30
32	394	62	791	COU-AA-301	0.09	0.09	0.96
38	399	62	800	AFFIRM	0.11	0.08	0.80

Where r = number of events in arm 1 or arm 2, n = number of subjects in arm 1 or arm 2

The odds ratios were implemented in the Winbugs code presented in Appendices B.

The results are tabulated below. (**Error! Not a valid bookmark self-reference.** to Table 27).

Table 19. Hazard ratios for neutropenia.

Neutropenia FE	OR	lCr.Int.	u.Cr.Int
BSC vs Cabazitaxel	0.31	0.22	0.43
BSC vs Abiraterone	2	0.05	77.5
Cabazitaxel vs BSC	3.24	2.33	4.53
Cabazitaxel vs Abiraterone	6.54	0.16	251
Abiraterone vs BSC	0.5	0.01	20
Abiraterone vs Cabazitaxel	0.15	0	6.29

Table 20. Hazard ratios for anaemia

Anaemia FE	OR	lCr.Int.	u.Cr.Int
BSC vs Cabazitaxel	0.43	0.23	0.76
BSC vs Abiraterone	1.03	0.66	1.61
BSC vs Enzalutamide	1.25	0.81	1.91
Cabazitaxel vs BSC	2.33	1.31	4.29
Cabazitaxel vs Abiraterone	2.42	1.16	5.09
Cabazitaxel vs Enzalutamide	2.91	1.42	6.14

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Anaemia FE	OR	lCr.Int.	u.Cr.Int
Abiraterone vs BSC	0.97	0.62	1.52
Abiraterone vs Cabazitaxel	0.41	0.2	0.86
Abiraterone vs Enzalutamide	1.21	0.65	2.24
Enzalutamide vs BSC	0.8	0.52	1.23
Enzalutamide vs Cabazitaxel	0.34	0.16	0.71
Enzalutamide vs Abiraterone	0.83	0.45	1.53

Table 21. Hazard ratios for anaemia

Thrombocytopenia FE	OR	lCr.Int.	u.Cr.Int
BSC vs Cabazitaxel	0.38	0.13	0.96
BSC vs Abiraterone	0.32	0.04	1.27
BSC vs Enzalutamide	0.69	0.14	2.49
Cabazitaxel vs BSC	2.66	1.04	7.74
Cabazitaxel vs Abiraterone	0.85	0.1	4.91
Cabazitaxel vs Enzalutamide	1.83	0.29	9.82
Abiraterone vs BSC	3.11	0.79	23.7
Abiraterone vs Cabazitaxel	1.18	0.2	10.4
Abiraterone vs Enzalutamide	2.16	0.26	22.6
Enzalutamide vs BSC	1.45	0.4	7.28
Enzalutamide vs Cabazitaxel	0.55	0.1	3.51
Enzalutamide vs Abiraterone	0.46	0.04	3.85

Table 22. Hazard ratios for diarrhoea

Diarrhoea FE	OR	lCr.Int.	u.Cr.Int
BSC vs Cabazitaxel	0.03	0	0.18
BSC vs Abiraterone	1.08	0.32	3.21
BSC vs Enzalutamide	0.16	0.01	1.05
Cabazitaxel vs BSC	33.4	5.66	1070
Cabazitaxel vs Abiraterone	36.7	4.16	1370
Cabazitaxel vs Enzalutamide	5.59	0.12	306
Abiraterone vs BSC	0.92	0.31	3.14
Abiraterone vs Cabazitaxel	0.03	0	0.24
Abiraterone vs Enzalutamide	0.15	0.01	1.42
Enzalutamide vs BSC	6.1	0.95	155
Enzalutamide vs Cabazitaxel	0.18	0	8.23

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Diarrhoea FE	OR	lCr.Int.	u.Cr.Int
Enzalutamide vs Abiraterone	6.73	0.7	189

Table 23. Hazard ratios for fatigue

Fatigue FE	OR	lCr.Int.	u.Cr.Int
BSC vs Cabazitaxel	0.59	0.26	1.27
BSC vs Abiraterone	1.16	0.77	1.74
BSC vs Enzalutamide	1.17	0.73	1.87
Cabazitaxel vs BSC	1.7	0.79	3.82
Cabazitaxel vs Abiraterone	1.96	0.83	4.86
Cabazitaxel vs Enzalutamide	1.98	0.8	5.08
Abiraterone vs BSC	0.87	0.58	1.3
Abiraterone vs Cabazitaxel	0.51	0.21	1.21
Abiraterone vs Enzalutamide	1.01	0.54	1.88
Enzalutamide vs BSC	0.85	0.54	1.38
Enzalutamide vs Cabazitaxel	0.5	0.2	1.24
Enzalutamide vs Abiraterone	0.99	0.53	1.84

Table 24. Hazard ratios for fatigue

Asthenia FE	OR	lCr.Int.	u.Cr.Int
BSC vs Cabazitaxel	0.51	0.21	1.14
BSC vs Abiraterone	1.16	0.76	1.73
BSC vs Enzalutamide	0.99	0.43	2.09
Cabazitaxel vs BSC	1.98	0.88	4.74
Cabazitaxel vs Abiraterone	2.28	0.93	5.99
Cabazitaxel vs Enzalutamide	1.94	0.61	6.15
Abiraterone vs BSC	0.87	0.58	1.31
Abiraterone vs Cabazitaxel	0.44	0.17	1.08
Abiraterone vs Enzalutamide	0.85	0.34	2.01
Enzalutamide vs BSC	1.01	0.48	2.33
Enzalutamide vs Cabazitaxel	0.52	0.16	1.63
Enzalutamide vs Abiraterone	1.18	0.5	2.93

Table 25. Hazard ratios for back pain

Back pain FE	OR	lCr.Int.	u.Cr.Int
BSC vs Cabazitaxel	0.77	0.33	1.74

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Back pain FE	OR	lCr.Int.	u.Cr.Int
BSC vs Abiraterone	1.48	0.97	2.27
BSC vs Enzalutamide	0.79	0.42	1.39
Cabazitaxel vs BSC	1.29	0.57	3.01
Cabazitaxel vs Abiraterone	1.92	0.77	4.89
Cabazitaxel vs Enzalutamide	1.01	0.36	2.81
Abiraterone vs BSC	0.68	0.44	1.03
Abiraterone vs Cabazitaxel	0.52	0.2	1.3
Abiraterone vs Enzalutamide	0.53	0.25	1.08
Enzalutamide vs BSC	1.27	0.72	2.39
Enzalutamide vs Cabazitaxel	0.99	0.36	2.76
Enzalutamide vs Abiraterone	1.9	0.92	4.01

Table 26. Hazard ratios for nausea

Nausea FE	OR	lCr.Int.	u.Cr.Int
BSC vs Cabazitaxel	0.1	0	0.68
BSC vs Abiraterone	1.29	0.57	2.79
BSC vs Enzalutamide	2.23	1.01	5.04
Cabazitaxel vs BSC	9.69	1.47	252
Cabazitaxel vs Abiraterone	12.6	1.6	355
Cabazitaxel vs Enzalutamide	22	2.74	618
Abiraterone vs BSC	0.78	0.36	1.76
Abiraterone vs Cabazitaxel	0.08	0	0.63
Abiraterone vs Enzalutamide	1.73	0.57	5.49
Enzalutamide vs BSC	0.45	0.2	0.99
Enzalutamide vs Cabazitaxel	0.05	0	0.37
Enzalutamide vs Abiraterone	0.58	0.18	1.74

Table 27. Hazard ratios for bone pain

Bone pain FE	OR	lCr.Int.	u.Cr.Int
BSC vs Cabazitaxel	3.31	0.93	15.8
BSC vs Abiraterone	1.24	0.77	1.97
BSC vs Enzalutamide	1.45	0.69	2.98
Cabazitaxel vs BSC	0.3	0.06	1.07
Cabazitaxel vs Abiraterone	0.37	0.07	1.43
Cabazitaxel vs Enzalutamide	0.43	0.08	1.89

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Bone pain FE	OR	lCr.Int.	u.Cr.Int
Abiraterone vs BSC	0.81	0.51	1.3
Abiraterone vs Cabazitaxel	2.68	0.7	13.7
Abiraterone vs Enzalutamide	1.17	0.49	2.78
Enzalutamide vs BSC	0.69	0.34	1.45
Enzalutamide vs Cabazitaxel	2.3	0.53	12.8
Enzalutamide vs Abiraterone	0.85	0.36	2.03

B11.**An assumption of zero utility for the last three months spent in the progressive disease (PD) health state is used in the model. This is implemented as a disutility. The current disutility appears to be calculated based on all patients who die (not the subgroup of patients who die from the PD health state). Please confirm that this is as intended. If not, please amend. In addition, the disutility incurred should be constrained by the time spent in the PD health state (for example, if it is two months, then at most only two months will be spent with a disutility of zero). Please comment on how amending the model to address these issues would affect the ICER**.

To apply the disutility to the deaths attributed to the PD state only is appealing, as the implementation of this penalty is indeed intended to address the concern often raised that the PD health states in oncology models carry a constant utility, despite an expectation that patient quality of life might deteriorate over time. However, the disutility is applied in the model to all patients who die, irrespective of the state they previously occupied. This is as intended and was chosen because it is computationally simple since deaths from the PD state are not separately tracked in the model on a cycle by cycle basis. Applying the penalty to all deaths, from where ever they originate has the effect of reducing the overall utility gains achieved within the model and is therefore considered to be more conservative.

Whilst the second part of the question relating to the duration in the PD is not relevant in the context of the implementation of the penalty to all deaths, it is noted that an amendment should be made to implement a reduced penalty in the first few cycles commensurate with the time experienced to date. That is to say, a patient who dies in cycle 2 can only incur a penalty of two cycles, not four. Amending the model to include 0, 1, 2 and 3 months' worth of disutility at the start of the model increases the ICER from £49,327 to £49,362. This is due to a marginal decrease in incremental utility from 0.23213 to 0.23197.

Table 28. Base-case results amended to incorporate the appropriate number of disutility cycles at the start of the model.

	Cabazitaxel	Mitoxantrone	Increment
2nd line chemotherapy (includes administration, pre- & concomitant medication)	[redacted]		
Costs associated with treating Adverse events during 2nd line			

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chemotherapy	[redacted]		
Total health care cost during 2nd line chemotherapy (=SD)			
Total health care cost during progressive disease (=PD)			
End-of-life costs			
Total life-time cost per patient	**£29,548**	**£18,098**	**£11,450**
QALYs	0.87934	0.64737	0.23197
Life-years	1.54064	1.20303	0.33761
Progression-free life years	0.36104	0.23408	0.12696
Cost per QALY gained (ICER)	£49,362.15		
Cost per Life-year gained	£33,916.50		

B12.Please clarify why the proportions of patients receiving 10 cycles of cabazitaxel differ between the modelled estimate (17%) and those observed in the TROPIC ITT population and the Early Access Programme (approximately 30%). Please confirm the proportion of patients who received 10 cycles in the population of interest within the TROPIC trial.

The proportion of patients in the subgroup population receiving 10 cycles is 20.04% (we have retrieved these figures from the model engine 'calculations' sheet from the row referring to the cycle 9 as patients receive cabazitaxel start treatment at cycle 0). The relevant figure for the ITT population is 20.17%. These are the figures that were derived by fitting the lognormal parametric distribution to the KM data.

The observed data from the TROPIC trial, when deriving the Kaplan Meier data indicates that the proportion of patients in the subgroup population receiving 10 cycles is 25% (please refer to cell EU106, "KM new" tab in the company's model) and 24.6% for the ITT population (please see cell AO115 in the same sheet).

The small discrepancy between the model and trial estimates of patients receiving 10 cycles noted above occur because the parametric distribution and the Kaplan Meier data from the trial after 10 treatment cycles are not identical. Please see below the lognormal and KM curves for the SG base case population plotted on the same graph. Please note that cycle 9 takes place at 6.21 months (or 27 weeks), where a divergence between the Kaplan Meier and lognormal parametric distribution curves can be observed.

In addition to these considerations the model does not capture other issues such as dose delay that may contribute to this discrepancy. Hence whilst we have chosen the most robust way to model the KM data we recognise that the calculations for PFS and OS to derive populations on treatment may not be absolutely reflective of trial reality.

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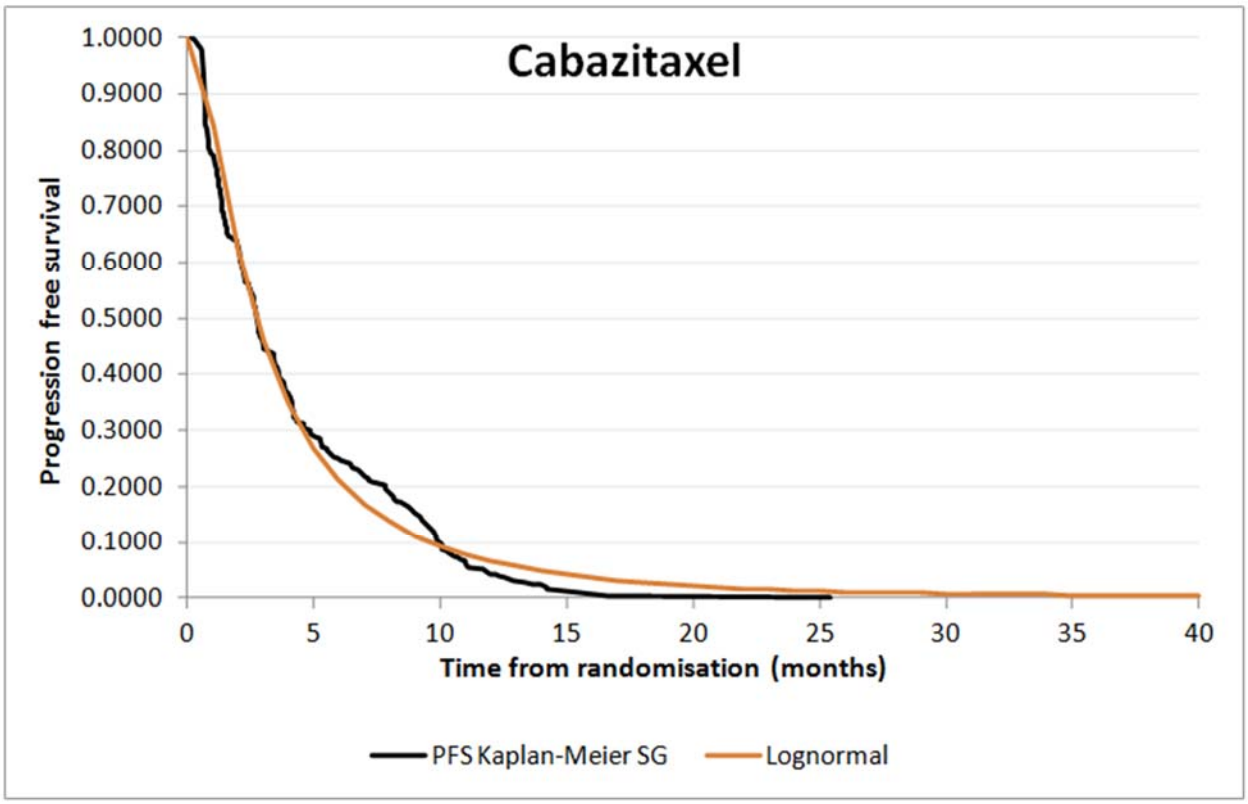
Figure 5. Comparison of lognormal distribution and KM data



B13.Please justify why data from the TROPIC trial (page 171, Table 65) were used in preference to those from the UK audit (page 171, Table 66) for post second line treatment in the economic model.

The data from the TROPIC study was used to maintain consistency with what was done in the trial and so when this treatment mix is costed it provides the most robust estimate for the post-second line setting.

The UK information was provided as part of a sensitivity analysis, but only recognising costs.

B14.On page 171 it states that 'The assumption is made that the mitoxantrone treatment mix is received in the abiraterone and enzalutamide comparisons.' However, in the economic model, abiraterone values are taken from the UK audit, whilst the enzalutamide values are taken from the post-cabazitaxel arm. Please comment on this discrepancy.

Thank you for pointing out this discrepancy in the abiraterone and enzalutamide Markov traces. This has now been fixed by including the variable 'transRewMitoxTropic' on both sheets in place of 'transRewGeneralCountry' and 'transRewCabaTropic' in column X.

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The updated results are provided in Table 30. For comparative purposes the original results are presented in Table 29.

Table 29. Results for the incremental analysis versus abiraterone and enzalutamide presented in the dossier

	Cabazitaxel	Abiraterone	Difference	Enzalutamide	Difference
2nd line chemotherapy (includes administration, pre- & concomitant medication)					
Costs associated with treating Adverse events during 2nd line chemotherapy					
Total health care cost during 2nd line chemotherapy (=SD)					
Total health care cost during progressive disease (=PD)					
End-of-life costs					
Total life-time cost per patient	**£31,734**	**£49,165**	**-£17,430**	**£69,585**	**-£37,850**
QALYs	0.922	0.901	0.022	1.101	-0.179
Life-years	1.485	1.456	0.029	1.617	-0.132
Progression-free life years	0.817	0.793	0.024	1.316	-0.499
Post-progression survival	0.668	0.663	0.005	0.301	0.367
Cost per QALY gained (ICER)		-£808,425		£212,038	
Cost per Life-year gained		-£601,379		£287,115	

Table 30. Updated incremental results for abiraterone and enzalutamide.

	Cabazitaxel	Abiraterone	Difference	Enzalutamide	Difference
2nd line chemotherapy (includes administration, pre- & concomitant medication)					
Costs associated with treating Adverse events during 2nd line chemotherapy					
Total health care cost during 2nd line chemotherapy (=SD)					
Total health care cost during progressive disease (=PD)					
End-of-life costs					
Total life-time cost per patient	**£31,734**	**£56,466**	**-£24,731**	**£73,796**	**-£42,061**
QALYs	0.922	0.901	0.022	1.101	-0.179
Life-years	1.485	1.456	0.029	1.617	-0.132
Progression-free life years	0.817	0.793	0.024	1.316	-0.499
Post-progression survival	0.668	0.663	0.005	0.301	0.367
Cost per QALY gained (ICER)		-£1,147,038		£235,630	

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	Cabazitaxel	Abiraterone	Difference	Enzalutamide	Difference
Cost per Life-year gained		-£853,269		£319,060	

The total lifetime cost for patients in the abiraterone and enzalutamide arms is increased. In scenario analysis in section 5.11 we presented the deterministic ICERs for abiraterone and enzalutamide at modelled [redacted]% discounts. In this analysis cabazitaxel continued to dominate abiraterone at this discount (incremental cost = [redacted]) and whilst the point estimate for the ICER is still in the south west quadrant versus enzalutamide, the ICER is [redacted]. The updated analysis suggest the incremental cost versus abiraterone is much larger at and the ICER versus enzalutamide is[redacted] in the southwest quadrant (incremental cost of[redacted]). In other words, this correction improves the results for cabazitaxel, but the concerns expressed in the main submission about the relevance of these analyses still remain.

B15.Please clarify if the proportion of patients receiving best supportive care as post second line treatment should be varied in the probabilistic sensitivity analysis. Currently, this is varied, but only for enzalutamide. Please amend as appropriate.

Thank you for highlighting this issue. The formula required which points to the PSA sheet had not been replaced in cells E29:E32 on the 'Resource input' sheet in the model submitted to the ERG after final testing of the model. During this testing absolute values were included.

The PSA has been re-run to check that the results presented in the submission dossier remain substantively unchanged. The probabilistic results, after re-running the analysis versus mitoxantrone with the correct formula in cells E29:E32, are presented in the response to Question B4 above. Whilst there will always be slight differences in the figures obtained from each PSA run, these match the submitted results and do not change the interpretation.

B16.Please clarify why the value of body surface area used in the model (1.9, based on clinical opinion) has changed from the value used in TA255 (2.01 from the TROPIC trial).

The UK-specific base-case value for the body surface area (BSA) was estimated by UK clinical experts during advisory boards held at the time of TA255 to be 1.9 m^2. The average BSA of patients included in the TROPIC trial was 2.01 m^2, however, the TROPIC population was drawn from many different countries with varying average BSAs. Thus, in the base-case, it has since been deemed more appropriate to use am estimated UK-specific average BSA.

Sensitivity analysis is provided for BSA 2.01 m^2 in table 80 on page 188 of the submission document.

B17.Please clarify why the quality of life data (section 5.4, page 150) from the EAP is different to that reported in reference 12

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(http://www.ncbi.nlm.nih.gov/pubmed/25639506). Please confirm that the data used in the submission is the most up-to-date.

The quality of life data published in graphical form in the paper by Bahl(34) is described as the final cut of the data. However in the time since publication several more questionnaires have been returned and so the numbers of patients at each cycle have increased slightly and the utility values have changed marginally as a consequence. We were able to provide this more complete dataset for the analysis presented in the dossier. This was available to us in numerical form and included measures of variance.

Question B21 explores the effect of small differences in the utility values for the stable disease state and as can be seen there is no substantive difference to the ICER.

B18.Please clarify how secondary G-CSF use is implemented in the company's model (table 63, page 166).

Secondary G-CSF is implemented in the model separately to primary G-CSF prophylaxis. Table 63, page 166 refers to primary prophylaxis which is incorporated into the model as part of the total cost of pre-medication and concomitant drugs and is then included as part of the total cost of the SD state. Secondary G-CSF has been incorporated as part of treatment of adverse events because patients receiving secondary G-CSF experience higher rates of febrile neutropenia. Frequencies of neutropenia and febrile neutropenia for patients that did not receive any G-CSF as primary prophylaxis are then used in the model.

It is recommended that patients that experience febrile neutropenia should be treated with G-CSF as secondary prophylaxis in every remaining cycle after the event if they did not receive previously a primary prophylaxis. However, as this is a cohort model, the prophylaxis use cannot be modelled for each patient individually. Instead of modelling the proportion of patients in the cohort treated with G-CSF as secondary prophylaxis in each cycle, the proportion of patients treated with G-CSF as secondary prophylaxis or with curative intent was estimated by clinical experts and then used in the model.

On the 'Resource Input' tab in the Adverse Event section, the model includes drug treatment used for neutropenia and febrile neutropenia (as well as others). 50% of patients experiencing Neutropenia receive a total dose of 3 units of Filgastrim and 20% of patients experiencing Febrile Neutropenia receive a total dose of 0.9 units (as per expert opinion).

Although the ASCO guidelines advise that secondary prophylaxis is only recommended for patients who did not receive it as primary prophylaxis, the percentage of patients that received G-CSF as primary prophylaxis was not subtracted from the percentage of patients that received G-CSF as secondary prophylaxis. This approach was taken since the UK clinical expert panel estimated the proportion of patients receiving G-CSF as secondary

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prophylaxis or with curative intent irrespective of any known proportions of primary prophylaxis. This implies that the proportion of patients receiving G-CSF as secondary prophylaxis or with curative intent may be overestimated in the model, but this can be regarded as a conservative assumption.

B19.When adverse event treatment is costed in the Model, (tab 'AE Care') some grade 3+ events receive neither inpatient care nor drugs (for example, for neutropenia 2% require inpatient care and 50% receive filgastrim, so at least 48% receive neither). Please confirm that this is as intended and justify why.

The rates of drug use implemented in the base-case were validated with clinical experts at the time of the original submission.

We recognise that the face validity of these rates could be challenged and so have performed an extreme sensitivity analysis in which the rates of drug use for all adverse events are set to 1. This ensures all patients receive a therapeutic intervention. The incremental results from this analysis are presented in Table 31.

Table 31. Incremental analysis with rates of drug use set to 1 for all adverse event therapies.

	Cabazitaxel	Mitoxantrone	Difference
2nd line chemotherapy (includes administration, pre- & concomitant medication)	[redacted]		
Costs associated with treating Adverse events during 2nd line chemotherapy			
Total health care cost during 2nd line chemotherapy (=SD)			
Total health care cost during progressive disease (=PD)			
End-of-life costs			
Total life-time cost per patient	£29,639	£18,128	£11,511
QALYs	0.878	0.645	0.232
Life-years	1.541	1.203	0.338
Progression-free life years	0.361	0.234	0.127
Post-progression survival	1.180	0.969	0.211
Cost per QALY gained (ICER)	£49,587		
Cost per Life-year gained	£34,095		

The ICER is marginally increased from £49,327 in the base-case to £49,587. This is due to an increase of [redacted] in the cabazitaxel arm and [redacted] in the mitoxantrone arm for the cost of treating adverse events during 2nd line chemotherapy. A small increase only is expected given the limited impact of adverse events on the overall analysis.

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This represents the extreme case and it is expected that in real world practice, rates of therapeutic intervention would be lower.

B20.Please provide further details about the evidence used for the rates of drug use for adverse events.

Since drugs filed in the TROPIC database cannot easily be assigned to every AE, treatment of every specific AE was based on UK clinical expert opinion. This is described in the submission document in Section 5.3.4.

Extreme sensitivity analysis around the rates of drug use is provided above in question 19.

B21.The submission states (Table 61, page 161 - Utility in the stable disease state) that odd cycles are interpolated. Please provide details about how these interpolated values were derived, and justify this method over linear interpolation between cycles (for example, the cycle 3 value would be the mean of the values observed for cycles 2 and 4).

The odd cycle utilities were interpolated using the TREND function in excel. (Table 32).

Table 32. Interpolation method used to obtain utilities for the odd cycles.

Cycle	Utility Value from UK EAP	TREND function*	Trend result
Baseline	0.6821		
1		TREND(W11:W16,V11:V16,1)	0.703724
2	0.7284		
3		TREND(W11:W16,V11:V16,3)	0.728487
4	0.7495		
5		TREND(W11:W16,V11:V16,5)	0.75325
6	0.7518		
7		TREND(W11:W16,V11:V16,7)	0.778013
8	0.7892		
9		TREND(W11:W16,V11:V16,9)	0.802776
10	0.8185		

*The range W11:W16 refers to the range of utility values from the UK EAP and the range V11:V16 refers to the cycle number.

This method was chosen because it takes into account the entire dataset and not just adjacent values as would be the case by taking a simple average.

B22.Please provide information (with references) about the proportion of patients requiring each end-of-life resource component (Table 67 and 68, pages 172-175): Please also provide a cost (with reference) for a hospice home stay.

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Costs are higher towards the end of life, and based on advice from clinical experts, a separate 'end-of-life' cost is incorporated in the model to account for this. This is applied as a transition cost on death.
It was estimated by clinical experts that end-of-life care, defined as the time period from interruption of active treatment until death, has an average duration of 1 month.
In the model, it was assumed that patients do not receive any post-second line treatment mix or BSC during their last month of life.
All resources use that occurred during the last month of life was not available in the UK observational study. This was available, however, for hospitalisations. Expert opinion was used to provide estimates for other resource use items during the last month of life, including hospice care and palliative care at home. A summary of the estimates received from UK clinical experts and the UK observational study regarding end-of-life care is outlined in Table 33 below.

Table 33. Resource estimates for end-of-life care

Type of end-of-life care	Share of patients	Average number of episodes / visits per month	Average length of stay per episode	Source
Hospice home	0.2	2	5	UK clinical expert
Palliative care at home	0.5	6		UK clinical expert
Nurse visits	0.8			UK clinical expert
Physician (GP) visits	0.2			UK clinical expert
Palliative hospital outpatients visits	0.5	0.8		UK clinical expert
Palliative care - hospital inpatient	1	0.32	8	UK observational study

The cost for Hospice care comes from the National Audit Office, End of Life report from 2008 which can be found here: https://www.nao.org.uk/wp-content/uploads/2008/11/07081043.pdf). This figure has been inflated to 2013-14 costs using the GDP deflator which can be found here: https://www.gov.uk/government/statistics/gdp-deflators-at-market-prices-and-money-gdp-march-2015-quarterly-national-accounts

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Cabazitaxel for hormone-relapsed metastatic prostate cancer previously treated with a docetaxel-containing regimen (review of TA255) [ID889]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: [redacted]

Your position in the organisation: [redacted]

Brief description of the organisation: Prostate Cancer UK is the UK's leading charity for men with prostate cancer and prostate problems. We support men and provide information, find answers through funding research and lead change to raise awareness and improve care. The charity is committed to ensuring the voice of people affected by prostate disease is at the heart of all we do.

The following pharmaceutical companies sponsored and/or supported activities carried out by Prostate Cancer UK from April 2014 – March 2015:

- Astellas Pharma UK
- Lilly UK

Prostate Cancer UK has a policy that funding from pharmaceutical and medical device companies will not exceed 5% of its total annual income. During the financial year 2014/2015 donations from such organisations, expressed as a percentage of our total annual income, were less than 0.1%.

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Men with advanced prostate cancer tell us that they are often bed-ridden and unable to perform day-to-day activities, many experiencing significant pain and fatigue. Other symptoms associated with advanced disease include hypercalcaemia, urinary problems, swollen and uncomfortable lymph nodes and, occasionally, metastatic spinal cord compression causing weakness and numbness in the legs.

Living with prostate cancer can also have a strong emotional impact on the lives of men and those close to them. Men with prostate cancer have an

increased risk of depression and anxiety. Anxiety has been identified in 10–36% of short- and long-term prostate cancer survivors (1). Between 13% and 27% of prostate cancer patients are thought to have major depressive disorder or clinically significant levels of depression (2).

Men with prostate cancer can experience significant side effects following treatment. Depending on the treatment type, physiological side effects can include: osteoporosis, breast swelling and tenderness, chills/fever, nausea, headaches, hot flushes, difficulty having or maintaining an erection, infertility, loss of libido, muscle aches, pain, bowel and urinary incontinence, problems passing urine, fatigue, weight gain, and weight and muscle loss. Psychological side effects, such as anxiety and depression, have also been observed (3–6).

Many side effects are experienced by a high proportion of people living with prostate cancer. An English PROMs (Patient Reported Outcome Measures) study involving 866 prostate cancer patients found 58.4% of patients reported being unable to have an erection, 38.5% reported some degree of urinary leakage, and 12.9% reported difficulty controlling their bowels (7). Our own survey carried out with 610 men between October 2011 and January 2012 found 52% experienced anxiety as a side effect of treatment, 60% of whom rated this as bad or very bad. In addition to this, 67% experienced fatigue (59% of whom rated this bad or very bad) and 57% experienced problems passing urine (33% of whom rated this bad or very bad) (8).

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Our research shows that people affected by cancer place a high value on treatments that can prolong life. An opinion survey we commissioned with 412 people affected by cancer showed 98% of respondents placed a high value on treatments that can give people approaching the end of their lives extra time (9). Our most recent survey, conducted in 2014 with 267 people affected by prostate cancer on the availability of the enzalutamide, showed a large number of men living with prostate cancer place value on extending life as a

means to spend extra time with loved ones. Life extending treatments are also valued by some men as a means to achieve closure and to prepare for the end of life (10). Men see this as important, even when the extra time given is relatively short.

A part of this survey, we asked men and their loved ones to describe what life extension would mean to them (10):

> *"It is quite hard to imagine how much even two extra months can mean until you face being given or denied that time"* – man diagnosed with prostate cancer.

> *"Two months longer on your life is priceless; family moments are precious"* – family member of a man who has died from prostate cancer.

99% of respondents to our opinion survey also indicated that priority should also be given to the ability of a drug to improve quality of life (QOL) with the highest priority given to pain relief (9). One man said:

> *"Life is precious and if treatment can extend it while retaining a moderate quality of life this will be important to me and my dependents"* – man diagnosed with prostate cancer.

Other men place value on treatments that would enable them to continue to participate as a full member of society, while others highlighted personal fulfilment benefits to be gained from life extending treatment (10).

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

Men with advanced prostate cancer are currently able to access enzalutamide and abiraterone after chemotherapy routinely on the NHS. Both these drugs significantly increase overall survival when taken after chemotherapy (11,12). Cabazitaxel, currently available through the Cancer Drugs Fund (CDF) in England, offers an important additional option after chemotherapy for men with advanced prostate cancer, and has been shown to improve overall survival by 2.4 months in patients with hormone-relapsed prostate cancer

(13). Data published in September 2014 have also shown a 2.1 month increase in overall survival for patients with metastatic hormone-relapsed prostate cancer previously treated with docetaxel if they had cabazitaxel then abiraterone, compared to abiraterone then cabazitaxel (14). In addition to this, extended follow-up data from the TROPIC trial also demonstrated significantly reduced tumour-related pain for men treated with the drug (15). Findings from the UK Early Access Programme indicate cabazitaxel could improve QOL in men with metastatic hormone-relapsed prostate cancer (16).

Treatments that can extend life and improve QOL are of upmost importance to men living with prostate cancer and their loved ones (10). Clinicians should have the maximum number of treatments at their disposal so they can tailor the optimum treatment pathway for their individual patients. Cabazitaxel is regularly used to treat advanced prostate cancer and recent figures show 1270 men have accessed cabazitaxel through the CDF in the two years between April 2013 and March 2015 (17,18). This has been for use as a second line treatment following docetaxel chemotherapy, or a third line treatment following docetaxel and abiraterone.

A recent study conducted at the Institute of Cancer Research (ICR) indicated that, for some men, cabazitaxel was active when given after abiraterone or enzalutamide (19). The only other effective treatment that we are aware of at this point in the pathway is radium-223 dichloride. However, this is contraindicated in patients with liver metastases (20). Cabazitaxel could therefore be the only active treatment option for men whose prostate cancer has metastasised to the liver following endocrine treatment and docetaxel. Furthermore, radium-223 dichloride has been marked for delisting from the CDF on 4 November 2015 (21), which means that cabazitaxel will be the only active treatment option available to men in England whose prostate cancer has progressed following endocrine treatment and docetaxel.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

Improved overall survival is seen by people affected by prostate cancer as a major benefit of using cabazitaxel. In a survey we carried out in 2011 on the availability of cabazitaxel with 30 people affected by prostate cancer, 19 respondents identified that the possibility of extended life that cabazitaxel offers was its most important benefit, particularly when no other treatment options are available. The survival benefit was seen by some as an opportunity for these patients to be able to spend more time with family and friends. Comments from respondents suggested another benefit was the increase in hope the availability of such a drug could give, which would have a positive impact on QOL and potentially reduce distress (22).

In a recent survey conducted with 267 people affected by prostate cancer on the availability of enzalutamide, men described hope where treatments prolong life, and stressed how valuable it is to be able to spend extra time with loved ones. Patients have also highlighted the importance of treatment choice (10). The availability of cabazitaxel would mean more clinically effective options are available to men after chemotherapy, allowing men more options when deciding on the best treatment for them.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

Cabazitaxel is an important option for men whose prostate cancer has metastasised to the liver following novel endocrine treatments and docetaxel.

There is evidence that the use of cabazitaxel after docetaxel is becoming part of routine clinical practice. NHS England's National Chemotherapy Algorithm for advanced hormone-relapsed prostate cancer recommends cabazitaxel as an option for men whose cancer has progressed after docetaxel or after the use of abiraterone or enzalutamide and docetaxel (23). Between April 2013 and March 2015, 707 men accessed cabazitaxel as a third line treatment for advanced hormone-relapsed prostate cancer following docetaxel and abiraterone via the CDF. A further 563 accessed it as a second line treatment for advanced hormone-relapsed prostate cancer following a docetaxel based regimen (17,18).

Without cabazitaxel there are no active treatment options for men with advanced hormone-relapsed prostate cancer that has metastasised to the liver following novel endocrine treatments and docetaxel. Evidence that indicates cabazitaxel might still be active when used after enzalutamide and abiraterone (19) will therefore be important to patients as it suggests cabazitaxel can provide hope of extending life beyond what is possible with the treatments that are currently routinely available.

Evidence showing cabazitaxel can increase overall survival when used before abiraterone (14) also makes it an increasingly desirable treatment option for men as it again offers hope of extending life beyond what is possible with the treatments that are currently routinely available.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

None known.

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Many patients and their loved ones have concerns about the side effects of chemotherapy. Delaying or avoiding chemotherapy, or having a treatment option where chemotherapy is not an option, came through as a key theme in our previous survey (10).

Please list any concerns patients or carers have about the treatment being appraised.

Trial findings show the most common clinically significant grade 3 or higher adverse events associated with cabazitaxel were neutropenia and diarrhoea (13). Another study into the safety profile and QOL data for patients with metastatic hormone-relapsed prostate cancer treated with cabazitaxel found that the most frequent grade 3 or 4 treatment-emergent adverse events were fatigue, diarrhoea and neutropenic sepsis (16). These side effects will be a concern to some patients, depending on their own personal circumstances and attitudes to the effects of treatment. However, our survey on cabazitaxel found that many patients accept that all treatments have some side effects, and will want balanced information on the potential risks and benefits of a

treatment so they can make an informed decision themselves as to whether to have it (22).

Cabazitaxel is administered in combination with prednisone or prednisolone. These corticosteroids may be unsuitable for some patients due to the severity of associated side effects (24).

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

Most of the people affected by prostate cancer who we surveyed about cabazitaxel agreed that its main benefit was increased survival and that there were very few concerns about its side effects. Of the 30 respondents, only 1 thought that the disadvantages of the drug outweighed the advantages (22).

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Men with advanced, hormone-relapsed prostate cancer who have already had abiraterone or enzalutamide and docetaxel, and whose cancer has progressed, might benefit from the availability of this treatment (19) (see sections 3 and 4).

The only other treatment option at this stage is radium-223 dichloride. While radium-223 dichloride can be used following treatment with either abiraterone or enzalutamide and docetaxel, it is contraindicated in patients with liver metastases (20,25). Therefore, cabazitaxel may be the only active treatment option for men whose prostate cancer has metastasised to the liver following novel endocrine treatments and docetaxel. Furthermore, radium-223 dichloride has been marked for delisting from the CDF on 4 November 2015 (21), which means that cabazitaxel is set to become the only active treatment option available to men in England whose prostate cancer has progressed following endocrine treatment and docetaxel.

Cabazitaxel, therefore, addresses an important unmet need for a sub-population of patients who are not served by alternative active therapies.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

Cabazitaxel is administered in combination with prednisone or prednisolone. These corticosteroids may be unsuitable for some patients because of severe side effects (24).

Cabazitaxel is also unsuitable for patients with a low neutrophil count due to the chance it can cause further neutropenia (16,26).

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☒ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Unfortunately we have been unable to gather patient's real-world experience of using this treatment.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

The original TROPIC clinical trial captured overall survival and QOL data, measured by Present Pain Intensity (PPI) and analgesic score and ECOG PS (a measure of quality of life) (15). Cabazitaxel was shown to provide similar palliation of pain to mitoxantrone and ECOG PS deterioration was similar between treatment groups. However patients in the cabazitaxel group received a greater number of treatment cycles versus those in the mitoxantrone group (15).

The subsequent publication of QOL and safety data from metastatic hormone-relapsed prostate cancer patients treated with cabazitaxel in the UK EAP

included QOL data measured by the Visual Analogue Scale (VAS), which is a quantitative measure of health status, and EQ-5D-3L questionnaires. The study showed improvements in VAS and EQ-5D-3L pain scores as patients received more cycles of treatment. The UK EAP experience indicates that cabazitaxel might improve QOL in men with metastatic hormone-relapsed prostate cancer and represents a useful addition to the armamentarium of treatment for patients whose disease has progressed during or after docetaxel (16).

Overall, whilst the original trial was limited in its scope of measuring QOL, when taken with the UK EAP experience data we believe it gives a good picture of the outcomes that are important to patients (overall survival and QOL data).

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

N/A

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☒ Yes ☐ No

If yes, please provide references to the relevant studies.

1. Prostate Cancer UK. 'A survey of people affected by cancers' views on cabazitaxel becoming a treatment option for men with advanced prostate cancer'. 30 people responded to an online and paper survey. 90% of respondents had been diagnosed with prostate cancer (the others were relatives or friends of someone with the disease) and 33% of respondents had advanced cancer. None had any experience of cabazitaxel. Fieldwork was undertaken between 24th May and 3rd June 2011. 2011.

2. Prostate Cancer UK. 'A survey of the public's views on Xtandi® (enzalutamide) becoming a treatment option for men with advanced prostate cancer, who have not previously received chemotherapy'. Total sample size was 267 UK adults which included men with prostate cancer and friends/family of men with prostate cancer. Fieldwork was undertaken between 7th January and 1st February 2015. The survey was carried out online. 2015.

3. Prostate Cancer UK. Hampered by Hormones [Internet]. [cited 2013 Jun 21]. Available from: http://prostatecanceruk.org/media/49198/htcampaignreport.pdf

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8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

None.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

Cabazitaxel is administered in combination with prednisone or prednisolone.

These corticosteroids may be unsuitable for some patients because of severe side effects (24).

Cabazitaxel is also unsuitable for patients with a low neutrophil count due to the chance it can cause further neutropenia (16,26).

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes ☒ No

If yes, please explain what makes it significantly different from other treatments for the condition.

N/A

Are there any other issues that you would like the Appraisal Committee to consider?

None.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- People affected by prostate cancer place high value on treatments that can extend life. A large number of men living with prostate cancer place value on extending life as a means to spend extra time with loved ones. It is also valued by some men as a means to achieve closure and to prepare for the end of life (10). Men see this as important even when the extra time given is relatively short.

- Cabazitaxel has been shown to improve overall survival by 2.4 months in patients with hormone relapsed prostate cancer (13). Data published in September 2014 have also shown a 2.1 month increase in overall survival for patients with metastatic hormone-relapsed prostate cancer previously treated with docetaxel if they had cabazitaxel then abiraterone, compared to abiraterone then cabazitaxel (14).

- There is evidence that the use of cabazitaxel after chemotherapy is becoming part of routine clinical practice. NHS England's National Chemotherapy Algorithm for advanced hormone-relapsed prostate cancer recommends cabazitaxel as an option for men whose cancer has progressed after docetaxel or after the use of abiraterone or enzalutamide and docetaxel (23). Between April 2013 and March 2015, 1270 men accessed cabazitaxel through the Cancer Drugs Fund (17,18).

- Cabazitaxel has the potential to address an important unmet need for patients whose prostate cancer has progressed after novel endocrine treatments and docetaxel chemotherapy. A recent study conducted at the Institute of Cancer Research (ICR) suggested that cabazitaxel is active when given after docetaxel followed by abiraterone and enzalutamide (19).
- Without cabazitaxel there are no active treatment options for men with advanced hormone-relapsed prostate cancer that has metastasised to the liver following novel endocrine treatment and docetaxel.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Cabazitaxel for hormone-relapsed metastatic prostate cancer previously treated with a docetaxel-containing regimen (review of TA255) [ID889]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Tackle Prostate Cancer

Your position in the organisation: [redacted]

Brief description of the organisation: Tackle Prostate Cancer is the only patient led prostate cancer charity. It provides help, support and advice to individual prostate cancer support groups in the whole of the UK. It works hard to raise awareness of prostate cancer and runs a national 24/7 help line for anybody who needs help or advice.

We have some 7500 members plus partners and we rely donations from our members, private trusts and some Pharma Companies. The donations from Pharma Companies follow the strict guidelines set down by the industry and Tackle is a completely independent charity.

(For example: who funds the organisation? How many members does the organisation have?)

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Advanced prostate cancer is a progressive disease. For some years, life can carry on as normal. As the disease progresses, the patient is likely to suffer from bone pain, fractures immobility and eventually death. This causes problems for patients and carers both in practical ways and emotional and psychological ways as well.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these

are most important? If possible, please explain why.

As cabazitaxel has proven to perform much better in the clinical setting than in trials, both patients and carers would like to see:

• A decrease in levels of pain

• A longer survival time

• An increase of mobility due to the decrease in pain.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

At the moment, the end of life drugs being used are Abiraterone and Enzalutamide. Both are very successful, but both have a limited life. When either of these drugs stop working, there is very little else in the armoury to fight this disease and death will surely follow. Cabazitaxel is the final treatment which will give any hope of survival after the failure of Abiraterone or Enzalutamide. There are also patients for whom hormone treatment and docetaxel have not been very successful. Cabazitaxel has been shown to be remarkably successful within this group. In the clinical setting, it has been shown to be highly successful, much better than in trials, with few side affects. It is therefore of the utmost importance that it is recommended by NICE for use in the NHS

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)

- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

It would be realistic to expect a positive benefit on physical symptoms, less pain and increased mobility. A longer survival time and a general increase in the quality of life. Cabazitaxel has proven to be a very successful treatment for controlling advanced prostate cancer after Abiraterone or Enzalutamide have failed.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

At the moment, this is the final treatment which will help to control advanced prostate cancer, after all of the other treatments have failed. There is nothing else which can take its place and nothing to compare it with.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

None that I know of

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

This is a chemotherapy treatment with all of the rigours that this implies.

However, It seems that side affects are few and the quality of life whilst it is being given is good. Therefore, any disadvantages are far out weighed by the advantages.

Please list any concerns patients or carers have about the treatment being appraised.

None that I know of

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

None that I know of

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

None that I know of

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

None that I know of

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

x Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Cabazitaxel has been shown to far exceed the trial results. It has the endorsement of the leading oncologists in the country.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

The clinical trials did not demonstrate the full potential of this treatment

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Cabazitaxel is available from the CDF and is performing much better than the clinical trials would have suggested.

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ☐x No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

None

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

None

9. Other issues

Do you consider the treatment to be innovative?

☐X Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

There are no other treatments, This is the last treatment available which will keep patients not only alive, but alive with a good quality of life.

Are there any other issues that you would like the Appraisal Committee to consider?

No

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- This is the last available treatment to control advanced prostate cancer
- Cabazitaxel will reduce pain and increase mobility
- Cabazitaxel will increase survival time
- Cabazitaxel will give hope to patients and carers
- Cabazitaxel will enable patients to continue with a normal life and contribute to society, enjoy time with family and friends and in some cases, continue working.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

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

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation : British Uro-Oncology Group (BUG)

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? ***Yes***
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? ***Yes***
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? ***Executive Committee member and Trustee of British Uro-Oncology Group***
- other? (please specify)

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Single Technology Appraisal (STA)

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

What is the expected place of the technology in current practice?

How is thecondition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The condition under consideration is metastatic castration-resistant prostate cancer which is progressing post-docetaxel. National clinical guidelines are currently under development for prostate cancer. Local practice is governed by locally developed guidelines and local implementation of NICE guidance.
Current treatment options for management include:
1. Abiraterone or enzalutamide in the post-docetaxel setting if not already used in the patient in the pre-docetaxel setting (NICE approved)
2. Radium 223 in the appropriate patient with bone only metastases (NCDF in England)
3. Alternative chemotherapy regimens- paucity of evidence, based on local expertise
4. Best supportive care

Docetaxel is recommended by NICE for the treatment of metastatic hormone-refractory prostate cancer in men of KPS 60% and is widely used for this indication with no geographical variation.

Abiraterone acetate or enzalutamide is recommended by NICE for patients with metastatic castration resistant prostate cancer that has progressed after docetaxel-containing chemotherapy regimens.
Abiraterone and enzalutamide also have marketing authorisation for patients with metastatic castration resistant prostate cancer who are asymptomatic or mildly symptomatic in whom docetaxel chemotherapy is not yet indicated. However they are not approved by NICE for this indication. It is available in England through the Cancer Drugs Fund (CDF) but is not available in Wales. In England it is widely used for this indication with high uptake through the CDF. There is no significant geographic or clinical variation in this practice.

Best supportive care alone is not a relevant comparator as any patient who is fit for cabazitaxel would be keen on further treatment and there is a high likelihood of use of other chemotherapy regimens.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

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

As well as clear improvements in median overall survival in the reported randomised trial (TROPIC), the UK Expanded Access Programme showed a significant improvement in pain with treatment with cabazitaxel with no detriment to QOL of individuals treated with cabazitaxel.

In England, the uptake of cabazitaxel through NCDF shows the unmet need for this group of patients and the use is across the country with no significant geographical variation.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?
If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.
If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?
What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Cabazitaxel chemotherapy was given as part of the TROPIC trial which was done in 26 countries including UK. It reflects the 'real-life' setting of treating these patients. The most important outcome was improvement in overall survival which previous to this trial was never seen with any other intervention in this group.

The published evidence of the UK Expanded Access Programme shows the significant benefit in terms of pain control and no detriment to QOL with treatment with cabazitaxel.*(Final quality of life and safety data for patients with metastatic castration-resistant prostate cancer treated with cabazitaxel in the UK Early Access Programme (EAP) (NCT01254279).*

Bahl A, Masson S, Malik Z, Birtle AJ, Sundar S, Jones RJ, James ND, Mason MD, Kumar S, Bottomley D, Lydon A, Chowdhury S, Wylie J, de Bono JS.
BJU Int. 2015 Jan 30.

There are no robust randomised trials to address the optimum sequencing of treatments for mCRPC (metastatic castration resistant prostate cancer). The meta-analysis of 10 published sequencing studies shows that overall survival

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Single Technology Appraisal (STA)

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

is significantly better in patients with mCRPC who receive 3 agents (docetaxel, abiraterone and cabazitaxel) compared to those who receive 2 agents (docetaxel and abiraterone). (Maines F et al. ASCO GU 2015 (abstract 258)

Recent evidence indicates that Cabazitaxel is active in mCRPC in both AR-V7 positive and negative cases whilst abiraterone/enzalutamide are unlikely to be of benefit in AR-V7 positive MCRPC cases. *(Cabazitaxel Remains Active in Patients Progressing After Docetaxel Followed by Novel Androgen Receptor Pathway Targeted Therapies. Al Nakouzi N. Eur Urol. 2014 May 2)*

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

British Uro-oncology Group conducted a survey of specialist oncologists who treat prostate cancer to look at their views regarding the forthcoming developments in systemic therapy of prostate cancer. This has been submitted for publication to BJUI.

The views of British Ur-oncologists are similar to the European and St Gallen consensus guidelines which advocate cabazitaxel as an option for mCRPC cases post-docetaxel. This is also reflected in the NCCN guidelines.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within
3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

All chemotherapy units are equipped to provide chemotherapy. Cabazitaxel chemotherapy is already provided in established units through access to the drug from NCDF.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

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

Equality

Are there any issues that require special attention in light of the NICE's duties to have due regard to the need to eliminate unlawful discrimination and promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others?

No comment

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Cabazitaxel for hormone-relapsed metastatic prostate cancer previously treated with a docetaxel-containing regimen (review of TA255) [ID889]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: [redacted]

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Cabazitaxel for hormone-relapsed metastatic prostate cancer previously treated with a docetaxel-containing regimen (review of TA255) [ID889]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

For most men the main alternative to cabazitaxel will be Best Supportive Care (BSC), or in some cases, Radium-223. Not all patients with metastatic castration resistant prostate cancer (mCRPC; 'hormone-relapsing prostate cancer') are treated in the same way. Until 2010, docetaxel was only one proven life-prolonging therapy and in excess of 50% of patients were, for one reason or another, unsuitable. In addition to docetaxel we now have multiple life-prolonging options for these men including one of either abiraterone or enzalutamide, Radium-223 (for men with symptomatic bone-only disease) and cabazitaxel. Whilst most patients are suitable for at least one of these options, some men may be suitable for all of them, although there is no evidence to guide the optimal sequencing of these therapies. Increasingly, these men will have already received docetaxel prior to becoming castration resistant, and so docetaxel will not be a recognised option of these men when they relapse. In England, as in most other high-income countries, it is reasonably clear that the first treatment most men receive will be either abiraterone or enzalutamide, irrespective of whether or not they are suitable for chemotherapy in the future. On failure of this treatment it is likely that most men will receive docetaxel (if not previously given), Radium-223 (if symptomatic bone-only disease) or cabazitaxel (if previously given docetaxel). For those that are not suitable for any of these options, the only likely treatment will be Best Supportive Care. Although mitoxantrone has no marketing authorisation in UK, it is not a life-prolonging therapy and is now only rarely used as part of Best Supportive Care in patients who are symptomatic and who have no life-prolonging therapies available to them. There is no evidence to support the use of sequential abiraterone/enzalutamide therapy and, as these two drugs are highly cross-resistant, such sequential use is not generally permitted or desired, particularly if other life-prolonging therapies are available.

Within England there is little evidence of significant geographical variation in practice. Although there are differences of opinion, particularly with regards to the most appropriate timing of docetaxel (some advocate giving early in the course of the illness, others would not consider it until a patient becomes symptomatic), by and large most clinicians would offer abiraterone or enzalutamide as a first treatment at the point of diagnosis with mCRPC, the first manifestation of which is usually an asymptomatic rise in prostate-specific antigen (PSA).

By and large, most men who are being considered for cabazitaxel will, therefore, have had either abiraterone or enzalutamide before considering cabazitaxel, either before or after prior docetaxel. Only in very rare circumstances would a patient be considered for cabazitaxel in preference to one or other of these hormonal agents if they had no prior exposure to one of them. No clinician would routinely recommend cabazitaxel in preference to one or other of abiraterone or enzalutamide where the

patient had no prior exposure to one of these drugs. Therefore, the great majority (in excess of 90% by my estimate) of the men who are being considered of cabazitaxel will have previously had docetaxel and one of abiraterone or enzalutamide. As sequential enza/abi therapy is not considered, the only alternatives available to these men would be Radium-223 (where indicated) or Best Supportive Care (which, rarely, may include mitoxantrone). Best Supportive Care may also include radiotherapy, corticosteroids, palliative care measures, bisphosphonates and, occasionally, bone-seeking radioisotopes other than Radium.

The review should take into account that NICE guidance covers Wales, but that the CDF does not operate in Wales, hence patients do not receive pre-chemotherapy Aberaterone or Enzalutamide.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

There are no subgroups of patients who are specifically more likely to benefit from cabazitaxel as opposed to any alternative treatments. mCRPC covers a spectrum of disease, from men with slow-growing disease which may never cause problems in the remainder of that patient's life, to highly aggressive forms of the disease which rapidly causes debilitating symptoms and death. There are various factors which independently predict prognosis: these include baseline performance status, the presence of visceral disease and various biochemical and haematological parameters. Although patients with poor prognostic feature, by and large, gain less benefit from all systemic therapies, there are no widely accepted predictors of efficacy of cabazitaxel specifically. In particular there are no known markers which enable clinicians to choose between cytotoxics (such as cabazitaxel) and hormonal therapies (such as abiraterone and enzalutamide).

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

Cabazitaxel is only ever likely to be prescribed by specialist oncologists and administered in secondary care specialist clinics. These clinics are likely to be hospital based and will require input from specialist oncology nurses and oncology pharmacists. These facilities are no different from those required to give most commonly used intravenous cytotoxic drugs. In some cases, patients suffering from the acute toxicities of cabazitaxel, most notably complications of neutropenia such as sepsis will require emergency medical care as an inpatient.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Although uptake of cabazitaxel varies across the English NHS, this is assumed to be more due to variations in clinician preferences and experience rather than differences in the patient population. Within prostate cancer it is unlikely that it is being used outside of its licensed indication.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Among others, guidelines from the European Association of Urologists, the National Comprehensive Cancer Network, and the American Society for Clinical Oncology all recommend the use of cabazitaxel within its licensed indication. Although the specific methodologies employed by these organisations differ, the primary evidence is derived from the TROPIC trial (de Bono et al. Lancet 2010; 376: 1147–54) which was a phase III trial comparing predisone with either cabazitaxel or mitoxantrone in men with metastatic castration resistant prostate cancer who had had prior docetaxel. This trial demonstrated a significant survival advantage among the men receiving cabazitaxel. Subsequent retrospective studies suggest the activity of cabazitaxel is preserved in men who have also received prior abiraterone or enzalutamide (eg. Pezaro et al. Eur Urol. 2014 Sep;66(3):459–65).

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

As described previously, the main alternative to this technology is BSC, the nature and complexity of which will differ greatly from one patient to the next. The appropriate use of cabazitaxel has the potential to displace some of these BSC requirements, such as the requirement for complex analgesia or the use of external beam radiotherapy. Cabazitaxel does require resources for the administration of infusional chemotherapy and also requires the patient to attend a hospital-based infusion unit every 3 weeks during treatment. In addition it is advisable for the patient to have a full blood count on days 8 and 15 of the first cycle and prior to each cycle of treatment. In most areas, these blood tests can be delivered in conjunction with primary care, and so the patient need only attend their local surgery. If the patient is receiving Radium-223, the main alternative after BSC, then the patient would still require a blood test prior to each 4-weekly infusion which is infused in secondary care. Patients receiving BSC are unlikely to require regular blood tests. For patients receiving abiraterone (as outlined above, this is unlikely to be an alternative), blood tests are required every 15 days for the first 16 weeks and 4-weekly thereafter. For patients receiving enzalutamide (again, rarely an alternative to cabazitaxel), blood tests are not mandated. Both abiraterone and enzalutamide are usually prescribed in secondary care, although prescription intervals vary.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Cabazitaxel for hormone-relapsed metastatic prostate cancer previously treated with a docetaxel-containing regimen (review of TA255) [ID889]

Granulocyte colony stimulating factors (G-CSF) are recommended as secondary prophylaxis for prolonged or complicated neutropenia. These may be given daily, subcutaneously, for up to 10 days per cycle, or as a single dose of pegylated G-CSF on day 2. Some recommend the use of primary prophylactic G-CSF (ie. With the first dose of cabazitaxel without the 'need' to have observed prolonged or complicated neutropenia). Most patients requiring G-CSF would be able to self-administer, but sometimes community nurses are called upon to give them. G-CSF would not be required with any of the alternative treatments.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Patients would not commence cabazitaxel without evidence of disease progression on prior therapy. By and large this is indicated by a rising PSA blood test, but may include evidence from worsening bone and CT scans and / or symptoms. Cabazitaxel is given for a maximum of 10 3-weekly cycles, but should be discontinued prior to this if there is clear evidence of intolerance which cannot be managed without cessation of therapy, or disease progression. The former requires no specific testing, but the latter can be complex and the decision to stop treatment on the basis of disease progression will often be taken in the context of a rising PSA in combination with symptomatic progression and / or worsening disease on bone or CT scans. It is therefore good practice to perform one or both such scans prior to starting cabazitaxel. If one or both of these scans demonstrates metastatic disease at baseline, it is often necessary to repeat that / those scans to confirm disease progression (for example where the PSA is continuing to rise 12 weeks after commencing cabazitaxel). The precise number and nature of these scans will vary greatly from one patient to the next and between clinicians.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

I have prescribed cabazitaxel within its licensed indication to around 40 patients, mainly under clinical trial conditions, including participation in the TROPIC trial. In my experience, and in consultation with colleagues in England and elsewhere, patients are more carefully selected for cabazitaxel in routine practice than seemed to be the case in TROPIC such that the incidence of severe toxicity is lower in routine use than was observed in TROPIC.

The TROPIC trial was conducted globally but there were several UK centres involved, including that of the chief investigator (Royal Marsden / Institute of Cancer

Research). The findings have equal relevance in England as any other high income country.

There are two outcomes of major importance for men with mCRPC: first, overall survival and second, overall quality of life (QoL). Overall survival was robustly measured in TROPIC, but QoL was not. Improvement in pain control was assessed, but this is, in my opinion, only a week surrogate of QoL as it fails to encompass other symptoms of the disease or the toxicities of the treatment. Subsequent, non-randomized, prospective studies performed in the UK do suggest that QoL is at least maintained in patients receiving cabazitaxel (Sanofi, data on file).

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The most significant toxicity of cabazitaxel is neutropenia. Asymptomatic, uncomplicated neutropenia, even at high grade, is common but of no direct clinical significance and does not adversely affect the patient. Complicated neutropenia (neutropenic fever, neutropenic sepsis) is potentially life-threatening and requires hospitalisation, intravenous antibiotics and intensive monitoring with escalation of care if required. Patients suffering severe complications will suffer considerably and may not fully recover from the effects. Fortunately, with post marketing experience, such severe complications appear rare (probably due to better patient selection than was applied in the TROPIC trial along with judicious use of G-CSF). Other complications such as diarrhoea and cardiac dysrhythmias are also fortunately rare and usually occur simultaneously with complicated neutropenia. Clinically significant neuropathy is rare in patients who are appropriately managed with cabazitaxel in routine practice. The overall implications for QoL have not been formally assessed in TROPIC, but the non-randomized data available suggest that there is not an overall detrimental effect on QoL.

There are no major or significantly common adverse effects which have come to light post-marketing.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Bahl et al. BJU Int. 2015 Jan 30. UK prospective study of QoL (measured by EQ5D) among men receiving cabazitaxel within the expanded access programme. This

paper can be accessed by usual library sources. This suggested a trend towards improved QoL and lower incidence of neutropenic sepsis than seen in the TROPIC trial.

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

As cabazitaxel is currently available within its licensed indication on the Cancer Drugs Fund, it is unlikely that a NICE recommendation in favour of its use will significantly increase the amount of drug or other resources/facilities/equipment.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

I do not believe there are any equality issues.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Cabazitaxel for hormone-relapsed metastatic prostate cancer previously treated with a docetaxel-containing regimen (review of TA255) [ID889]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Cabazitaxel for treating hormone-relapsed metastatic prostate cancer after a docetaxel-containing regimen (review of TA255) [ID889]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the submission provided by **British Uro-Oncology Group** and consequently I will not be submitting a personal statement.

Name: .....Amit Bahl.....

Signed: .....  .....

Date: .....10th October 2015.....

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Cabazitaxel for treating hormone-relapsed metastatic prostate cancer after a docetaxel-containing regimen (review of TA255) [ID889]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Dr Zafar Malik.

Name of your organisation
The Clatterbridge Cancer Centre Liverpool

[redacted]

Are you (tick all that apply):

X a specialist in the treatment of people with the condition for which NICE is considering this technology?

X a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

X an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?

- other? (please specify)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How the condition is currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

How is the condition currently treated in the NHS?

Metastatic castrate resistant prostate cancer (mCRPC) is a heterogeneous disease. Currently the options available on diagnosis are LHRH therapy plus docetaxel or novel anti andogen therapy (abiraterone or enzalutamide) through the CDF. On relapse cabazitaxel is available through the CDF or for those patients who haven't received novel anti androgens in the chemo naïve setting. Abiraterone or enzalutamide are options available through the NICE adoption process.
The main advantage for cabazitaxel treatment is that it offers chance of response and survival benefit in a group of patients who have the most aggressive prostate cancer e.g. high tumour burden, visceral disease, poor response to hormonal therapy or docetaxel resistant disease. In these patients pursuing novel hormonal treatment offers no realistic prospect of response. Moreover it is likely to result in the patients' condition deteriorating and missing the window of opportunity where cabazitaxel may deliver clinical benefit.

Is there significant geographical variation in current practice?

It is difficult to comment on geographic variation, however within cancer centres variation does occur on treatments. This is dependent on patient characteristics: -

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

medical co morbidity, Performance Status, tumour characteristics, disease burden, Gleason grade, response to pervious hormonal therapy and biochemistry e.g. LDH, ALP N: L ratio, patient preference or indeed clinician choice. However, in the more aggressive prostate cancer patients mentioned above most clinicians would recommend chemotherapy treatment utilising cabazitaxel.

Are there differences of opinion between professionals as to what current practice should be?

Yes there are as no randomised data exists to guide optimal sequence for treatment. Also as this disease is heterogeneous in certain situations there may be advantages in pursuing further chemotherapy with cabazitaxel. Conversely in other settings for the aforementioned reasons there may be advantages for novel hormonal therapy.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

The alternative to cabazitaxel would be either abiraterone or enzalutamide treatment if this has not been administered in the chemo naive setting. The advantage of these treatments is that they are oral and often well tolerated. The main disadvantage is that for patients with aggressive prostate cancer who have responded poorly to previous hormonal treatment or those patients who have docetaxel resistant disease the chance of response to these hormonal treatments is extremely low.
Radium 223 treatment is an alternative available on the CDF for those patients who have nodal disease restricted to the pelvis and no evidence of visceral/ extra pelvic nodal disease. This represents a subgroup with relatively indolent metastatic disease in whom cabazitaxel would not be best treatment option

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?

Yes, as mentioned earlier metastatic castrate resistant prostate cancer is a heterogeneous disease. Treatment decisions are based on a whole range of factors including patient characteristics:- medical co morbidity, Performance Status, tumour characteristics, disease burden, Gleason grade, response to pervious hormonal therapy and biochemistry e.g. LDH,ALP N:L ratio, availability of medications on CDF and patient preference or indeed clinician choice.
All of these factors are considered by clinicians in making treatment recommendations. However no randomised controlled evidence exists to guide practice at present.

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

All the above treatments carry with them potential disadvantages and none of the treatment options offer 100% chance of response. However, in the more aggressive mCRPC cabazitaxel appears to offer therapeutic advantages especially if patients have responded poorly to prior hormonal treatment or have a significant disease burden.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?

This treatment can only be delivered in a special cancer centre /unit.

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

There is no extra provision required for this technology to be administered that is not already in place. Docetaxel chemotherapy treatment which is already approved by NICE has been offered for many years for metastatic prostate cancer and is available in all Cancer Centres throughout the UK. With this framework in place the necessary infrastructure exists to implement this technology as evidenced by usage within CDF.

If the technology is already available, is there variation in how it is being used in the NHS?

Is it always used within its licensed indications? If not, under what circumstances does this occur? Currently this technology is being utilised within its licence indication through the CDF. I do not see it being considered outside its current licence.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

This technology is a chemotherapy agent that offers survival benefits in patients with aggressive prostate cancer. In particular it offers a chance of response to treatment in patients that have responded poorly to previous hormonal or chemotherapy treatment. Often these patients have a poor prognosis and little chance of response to novel antiandrogen therapy and a narrow therapeutic window where the technology can be considered and applied.
This therapy has a side effect profile similar to docetaxel treatment which is NICE approved in the first line setting. With appropriate selection of patients and support this chemotherapy treatment can be safely delivered. It carries with it all the risks associated of chemotherapy treatment including febrile neutropenia and death.
As with all chemotherapy treatment 30 day mortality is collected and reported and this would be the case with this technology.
Many centres in the UK have undertaken audits and have reported a toxicity profile that is comparable with published registry data. However, one would expect further audits to be undertaken should this technology be approved to check that patients have received the treatment appropriately (starting and stopping treatment) and to monitor the toxicity profile.
In my clinical experience as well as published experience from other centres I have found that cabazitaxel is well tolerated in appropriately selected patients with a manageable side effect profile that is comparable with published data. Moreover it is no more difficult to use than NICE approved docetaxel treatment. In fact this regimen requires less steroid use and is better tolerated.
No randomised control trial evidence exists to show optimal sequencing of the available agents. No predictive biomarker tests are currently available to determine treatment recommendations in this mCRPC setting. None of the agents currently being prescribed in the mCRPC setting have directly been compared to each other in a trial setting.
mCRPC is an area of rapid change with many clinical trials being undertaken. This technology does have an important role to play in the mCRPC offering clinical benefit for patients where alternative treatment options are unlikely to be successful.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

This technology will not exclude or have any negative impact on any patients from the equality, diversity position.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

The recent STAMPEDE study in hormone sensitive prostate cancer showed that the utilisation of early chemotherapy significantly improved overall survival, ASCO 2015 LBA5001. The data are compelling and support finding from the CHAARTED study.

There is ongoing work to identify predictive biomarkers. However, currently none have been approved for clinical practice. Note the work published by Small in ASCO 2015. Abstract 5003.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Currently this technology is available for treatment on the CDF. Therefore all necessary support structures are in place to implement treatment should it receive positive NICE appraisal.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Cabazitaxel for treating hormone-relapsed metastatic prostate cancer after a docetaxel-containing regimen (review of TA255) [ID889]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted by TACKLE and consequently I will not be submitting a personal statement.

Name: .Hugh Gunn.....

Signed: .....

Date: 9/12/2015.....

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Cabazitaxel for treating hormone-relapsed metastatic prostate cancer after a docetaxel-containing regimen (review of TA255) [ID889]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: Allan Higgin
Name of your nominating organisation: Prostate Cancer Support Organisation (PCaSO)
Do you know if your nominating organisation has submitted a statement?

x Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

x Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

☐ Yes X No

- a carer of a patient with the condition?

☐ Yes X No

- a patient organisation employee or volunteer?
-

X Yes ☐ No

Do you have experience of the treatment being appraised?

☐ Yes X No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

I am prostate cancer patient who has been living with the disease for 6 years. I was on active surveillance for 3 years before electing to have a radical prostatectomy.

I am now involved with various PC charities, a member of PCUK's Grant Application Panel, involved in PSA testing across Dorset, including helping to run a counselling service. I am working with Surrey University on a mental health initiative aimed at PC suffers and I often lecture to various groups on prostate cancer awareness. Though these activities, I meet and talk to many men and their families who are living with the disease and it's varying symptoms and treatments.

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

A longer survival time

Increased quality of life

Reduction of pain and other side effects

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

It is very haphazard, the CDF creates unacceptable degrees of uncertainty. A sure knowledge that an agreed treatment regime will continue as long as necessary/effective is essential for both the patient and carer's mental wellbeing and quality of life.

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

None personally but others should benefit from a relief of physical symptoms and a more stable approach to mental welfare.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

I believe it is currently the final drug treatment available to sustain life after all other treatments have ceased to be effective,

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

None that I am aware of.

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)

- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

Some treatments only seem to be available to the few whilst others are rationed by CCG's.

Please list any concerns you have about the treatment being appraised.

Only those that would apply to any chemotherapy treatment and the possibility that unrealistic expectations may be assumed by the patient.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

None that I am aware of.

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

None that I am aware of.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

None that I am aware of.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐ Yes x No

If you answered 'no', please skip the rest of section 7 and move on to

section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

None

9. Other issues

Do you consider the treatment to be innovative?

x Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

It is the final treatment available to prolong a reasonable quality of life.

Is there anything else that you would like the Appraisal Committee to consider?

Nothing

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Men need to know it will continue to be available
- It's the last 'port-of-call' for those who have run out of options
- It will give hope to men, their families and carers
- It will enable men to live a longer 'normal' useful life
- It will reduce pain and other undesirable symptoms and increase and prolong a better quality of life

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

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
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Rider on responsibility for report

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

Abbreviations 6
1 SUMMARY 8
1.1 Critique of the decision problem in the company's submission 8
1.2 Summary of clinical effectiveness evidence submitted by the company 9
1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted 12
1.4 Summary of cost effectiveness submitted evidence by the company 13
1.5 Summary of the ERG's critique of cost effectiveness evidence submitted 13
1.6 ERG commentary on the robustness of evidence submitted by the company 14
1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG 15
2 BACKGROUND 17
2.1 Critique of the company's description of underlying health problem 17
2.2 Critique of the company's overview of current service provision 18
3 CRITIQUE OF THE COMPANY'S DEFINITION OF DECISION PROBLEM 23
3.1 Population 27
3.2 Intervention 27
3.3 Comparators 29
3.4 Outcomes 30
3.5 Other relevant factors 32
4 CLINICAL EFFECTIVENESS 34
4.1 Critique of the methods of review(s) 34
4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these) 42
4.3 Critique of trials identified and included in NMA 68
4.4 Critique of the NMA 80
4.5 Additional work on clinical effectiveness undertaken by the ERG 88
4.6 Conclusions of the clinical effectiveness section 91
5 COST EFFECTIVENESS 93
5.1 ERG comment on the company's review of cost-effectiveness evidence 93
5.2 ERG summary and critique of the company's submitted model and economic evaluation 96
5.3 Exploratory and sensitivity analyses undertaken by the ERG 119
5.4 Conclusions of the cost effectiveness section 121
6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG 122
7 END OF LIFE 128
8 OVERALL CONCLUSIONS 130
8.1 Implications for research 131
9 REFERENCES 132
10 APPENDICES 140
Appendix 1: Summary of TROPIC results (final analyses) as published by de Bono *et al.* 140
Appendix 2: Additional data on adverse events 142

LIST OF TABLES

Table 1: The company's decision problem (based on Table 5, p23-26, CS) 24
Table 2: Recommended dose modifications for adverse reactions in patients treated with cabazitaxel 28
Table 3: Inclusion/exclusion criteria used to select studies in the reviews conducted by the company (p56-58 and p88-90, CS) 37
Table 4: Characteristics of the TROPIC study (see CS, p64-74 and de Bono *et al.*) 44
Table 5: List of key ongoing studies of cabazitaxel for mCRPC post-docetaxel (p127 and Appendix 20, CS) 46
Table 6: Quality assessment results for the TROPIC study as assessed by the company 48
Table 7: Summary of OS in the TROPIC study - updated efficacy analysis 52

Table 8: Progression-free survival in the TROPIC study - updated efficacy analysis 53
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 55
Table 10: Treatment received and reasons for discontinuation in the TROPIC study 57
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). 59
Table 12: Deaths occurring within 30 days of last dose of study drug in the TROPIC trial 60
Table 13: Patient characteristics in TROPIC study and selected EAP/CUP reports (reproduced from CS, Table 33, p98) 63
Table 14: Efficacy and safety outcomes in TROPIC study and selected EAP/CUP reports (reproduced, with minor changes from CS, Table 36, p104-105) 64
Table 15: Studies examining cross resistance between abiraterone and enzalutamide (reproduced, with minor changes, from CS Tables 38 and 39, p 106) 67
Table 16: Overall survival for the TROPIC and ALSYMPCA (previous docetaxel use) populations. 69
Table 17: Characteristics of trials included in the NMA (adapted from Section 4.3 and appendices B (tables 1 and 2) of the CS) 71
Table 18: Characteristics of patients enrolled in the trials included in the NMA (reproduced from CS, Appendices B, Table 5) 74
Table 19: Definitions of progression-free survival in trials included in the NMA 78
Table 20: Quality (risk of bias) assessment for trials included in the NMA (based on data in the CS) 79
Table 21: Key results from the fixed effects NMA – ITT population, (reproduced, with minor changes, pg87, CS.) 83
Table 22: Table of adverse event data used in the company's economic model (based on company clarification response, Table 17) 85
Table 23: Adverse events leading to withdrawal or death in trials included in the NMA 87
Table 24: Key results from fixed effects NMAs of adverse events (summarised from Tables 18-27, company's clarification response to question B10) 88
Table 25: Results of NMA using random effects model, half-normal prior with variance 0.322 90
Table 26: Results of NMA using random effects model, half-normal prior with variance 0.222 90
Table 27: Key features of the company's *de novo* model. 96
Table 28: Goodness of fit data for the parametric models 100
Table 29: Utility values used in the economic model 103
Table 30: Adverse event data used in the economic model 104
Table 31: Direct treatment costs 107
Table 32: Additional treatment-dependent costs (base-case values per three weeks unless otherwise specified) 110
Table 33: Cost-effectiveness results comparing cabazitaxel with mitoxantrone 111
Table 34: Cost-effectiveness results comparing cabazitaxel with abiraterone and enzalutamide ... 113
Table 35: Overview of deterministic sensitivity analyses presented by the company 116
Table 36: Overview of ERG changes to the model 123
Table 37: Cost-effectiveness results comparing cabazitaxel with BSC, abiraterone and enzalutamide (ERG base-case assuming vial wastage) 125
Table 38: Cost-effectiveness results comparing cabazitaxel with BSC, abiraterone and enzalutamide (ERG base-case assuming no vial wastage) 126
Table 39: Summary of OS in the TROPIC study – final efficacy analysis 140
Table 40: Progression-free survival in the TROPIC study – final efficacy analysis 141
Table 41: Comparison of adverse events in trials included in the NMA 142

LIST OF FIGURES

Figure 1: Clinical pathways of care for mCRPC (reproduced from Figure 3, p40, CS)[a] 20
Figure 2: Simplified clinical pathway of care illustrating the comparators for cabazitaxel 22

Figure 3: Network diagrams for the included trials 77
Figure 4: Model schematic 97

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

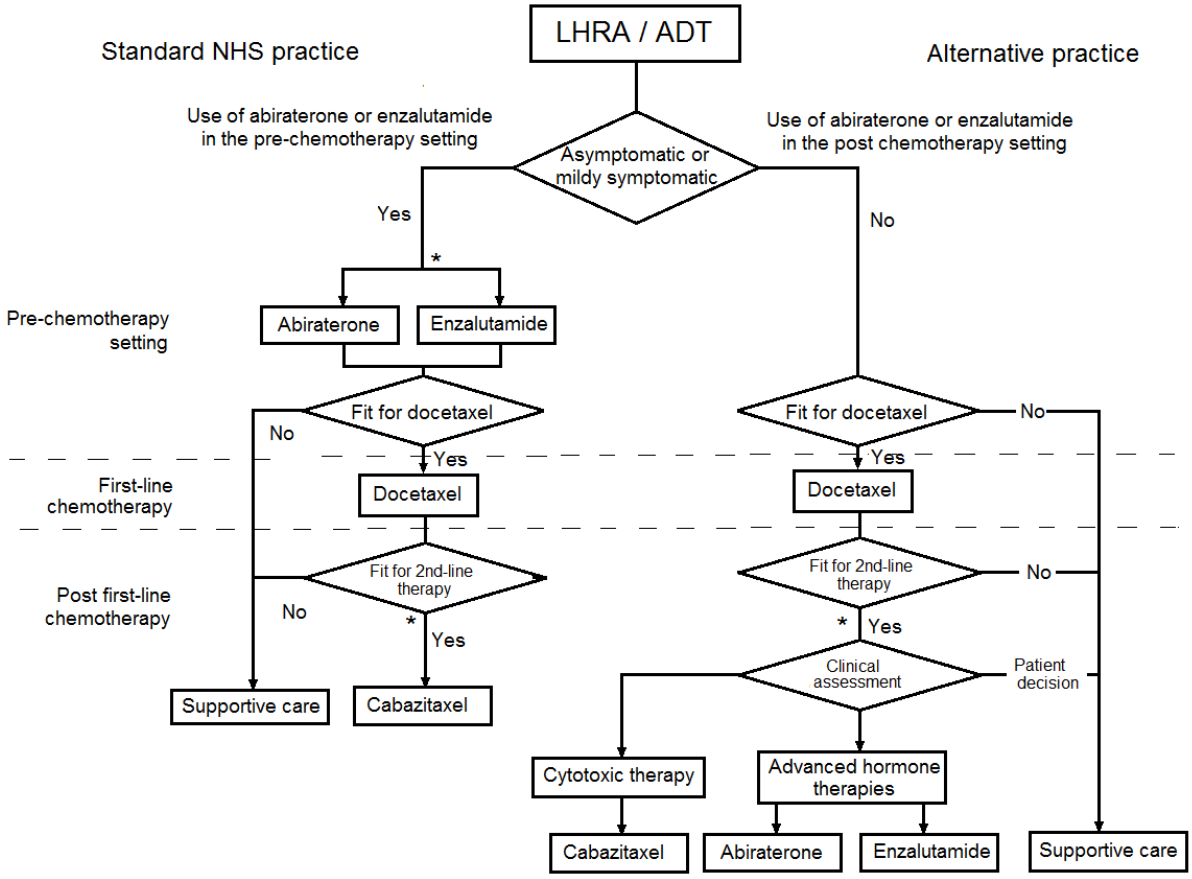
Figure 1) or post- chemotherapy (right-hand side). In both instances the chemotherapy was assumed to be docetaxel. At the time of the CS, use of either abiraterone or enzalutamide in the pre-chemotherapy setting was not approved by the National Institute for Health and Care Excellence (NICE), and was 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.

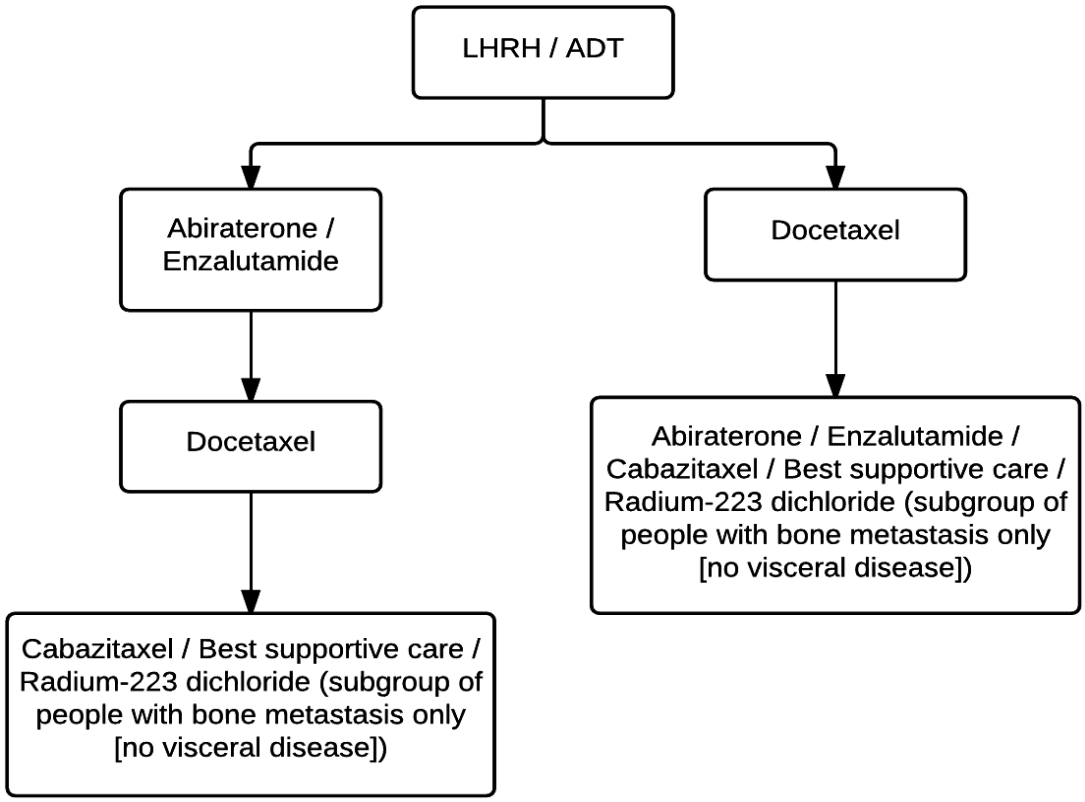
What is the role of radium-223 dichloride?
The company did not include radium-223 dichloride in their clinical pathways of care, nor did it include it in their economic evaluation. However, radium-223 dichloride was included in the final scope issued by NICE as a comparator. Radium-223 dichloride has 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:

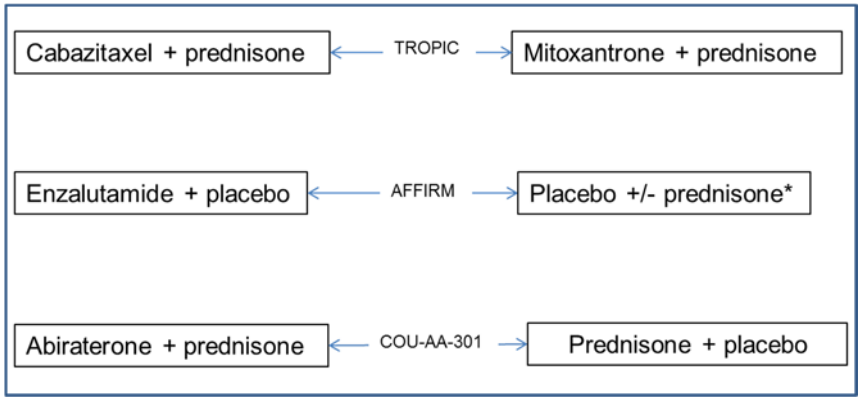
- prednisone was unlikely to affect overall or progression-free survival given that patients would have already received steroids and progressed on this treatment earlier in the course of the disease (ERG report TA316,[22] p82)
- median times for OS in the control groups were similar across the three 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

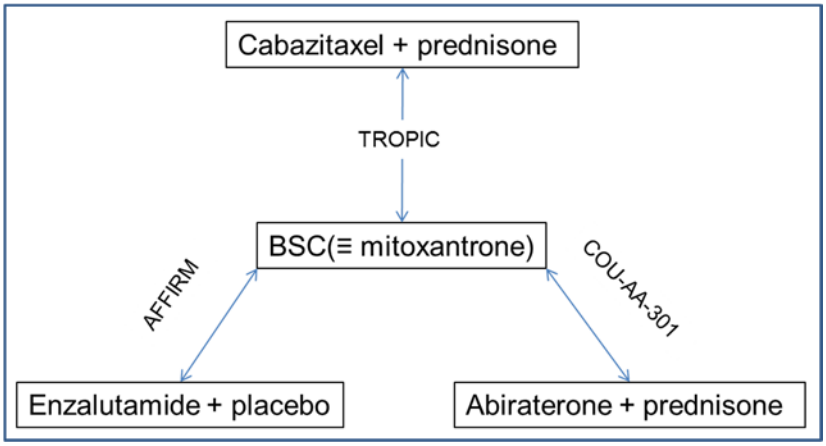


Table 19: Definitions of progression-free survival in trials included in the NMA

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.

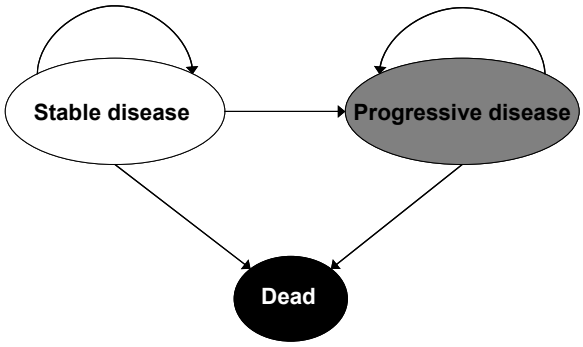
The ERG is satisfied that these are consistent with the NICE reference case.

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

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

Produced by School of Health and Related Research (ScHARR), The University of Sheffield

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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 £51,849.

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 £142,180 when vial wastage was modelled and £158,873 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 £107,604 when vial wastage was modelled and £86,888 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.

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 is 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

Table 1: 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	109 (29.4%)	50 (13.5%)
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, **Error! Reference source not found.**)

[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

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%), fatigue (27%) and diarrhoea (25%).

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 m^2 (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 m^2 was based on the clinical opinion of UK experts; the mean BSA observed in the TROPIC (2.01 m^2) 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 m^2 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 2. 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 2: Direct treatment costs based on list prices.

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. The PAS price is used for cabazitaxel in the main analyses. The PAS prices for abiraterone and enzalutamide are used in the confidential appendix.

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. The shorter pharmacist time required for cabazitaxel reflects the fact that cabazitaxel will be provided in prefilled bags with a tailored dose appropriate for specific patients. Hence no time is needed to make up the IV infusions. This additional time is required for mitoxantrone delivery.

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 2), along with administration costs and pre-medication costs were incurred for either ten cycles of treatment or until disease progression or death for cabazitaxel and mitoxantrone. Patients persist on treatment until 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 **Error! Reference source not found.**. Costs for treating AEs were based on

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 3).

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 both resource use estimates and the proportion receiving BSC taken 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)', and by setting the proportion receiving BSC for all treatments to be 0.80 (sheet 'Cost treatment').

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 utility 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 **Error! Reference source not found.** (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.

Table 3: 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 and proportion receiving BSC both from UK audit for all treatments.	[redacted]	[redacted]	[redacted]	[redacted]	11,353	0.232	48,908
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	[redacted]	[redacted]	[redacted]	[redacted]	9,347	0.137	68,168

based on lowest AIC value (no requirement 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]	11,823	0.230	51,308
ERG Probabilistic base-case 2 (changes A1 to A5)	[redacted]	[redacted]	[redacted]	[redacted]	12,133	0.234	51,849

BSC: Best supportive care. 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 £51,849 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 4 (assuming vial wastage) and Table 5 (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 4: 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]	£111,543 compared with best-supportive care
Abiraterone	[redacted]	[redacted]	Extendedly dominated by enzalutamide
Enzalutamide	[redacted]	[redacted]	£136,902 compared with cabazitaxel
Probabilistic sensitivity analysis results			
BSC	[redacted]	[redacted]	-
Cabazitaxel	[redacted]	[redacted]	£107,604 compared with best-supportive care
Abiraterone	[redacted]	[redacted]	Extendedly dominated by enzalutamide
Enzalutamide	[redacted]	[redacted]	£142,180 compared with cabazitaxel

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

Table 5: 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]	£85,934 compared with best-supportive care
Abiraterone	[redacted]	[redacted]	Extendedly dominated by enzalutamide
Enzalutamide	[redacted]	[redacted]	£152,914 compared with cabazitaxel
Probabilistic sensitivity analysis results			
BSC	[redacted]	[redacted]	-
Cabazitaxel	[redacted]	[redacted]	£86,888 compared with best-supportive care
Abiraterone	[redacted]	[redacted]	Extendedly dominated by enzalutamide
Enzalutamide	[redacted]	[redacted]	£158,873 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 £107,604 with vial wastage and £86,888 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 £142,180 with vial wastage and £158,873 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 **Error! Reference source not found.**. 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.

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 £51,849 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 £107,604 when vial wastage was modelled and £86,888 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 £142,180 when vial wastage was modelled and £158,873 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.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Cabazitaxel for treating hormone-relapsed metastatic prostate cancer after a docetaxel-containing regimen (review of TA255) [ID889]

You are asked to check the ERG report from the School of Health and Related Research (ScHARR) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, 15 December** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

	Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Issue 1	Page 11 paragraph 2 '*the AFFIRM study compared enzalutamide plus placebo with placebo with or without prednisone'* We believe the reader may be confused by, or misunderstand the two treatment arms	Suggested text change – include a comma after the first use of the word placebo: *'the AFFIRM study compared enzalutamide plus placebo**,** with placebo with or without prednisone'*	Clarity on the therapies used in the enzalutamide arm in the AFFIRM study	The ERG believe that it can be argued whether or not this represents a factual error. The ERG have not made any changes, the company can make this issue clear if necessary during the Appraisal Committee
	Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG response**
Issue 2	Page 17 paragraph 3 Footnote … '*The company's submission (CS) 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' a heterogeneous disease rather than 'can be' heterogeneous.	Suggested text change: *The company's submission (CS) provides an appropriate overview of prostate cancer noting that prostate cancer is heterogeneous with regards to both treatment response and the types of disease progression observed.*	As stated on page 16, paragraph 1 of the CS: *'…. prostate cancer tumours are in fact heterogeneous as they contain cells with a variety of malignant genetic changes.* It is important to highlight that prostate cancer is a heterogeneous disease.	The ERG has made the proposed change.
	Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG response**
Issue 3	Page 20 Figure 1	We apologise for the omission of this	The original figure was supplied without a footnote in error and was	No change required.

<table>
<tr><td></td><td>Footnote …'The CS does not provide a foot note for '*' in the figure'</td><td>footnote in the CS.
The footnote should read.
'* Radium-223 is licenced for patients with two or more bone metastases but no visceral metastases'</td><td>missed in final review. This footnote will be incorporated into the redacted version for the NICE website.
It is important to include this as we do recognise that radium-223 is a therapeutic option for some patients but have not included it in the analysis for the reasons given in the CS.</td><td></td></tr>
<tr><td></td><td>Description of problem</td><td colspan="2">Description of proposed amendment</td><td>Justification for amendment</td><td>ERG response</td></tr>
<tr><td>Issue 4</td><td>Page 57. Table 10, row 3.
The number of patients completing 10 cycles of treatment is not correct.</td><td colspan="2">Please change to:<table><tr><th></th><th>Cabazitaxel (n=378)</th><th>Mitoxantrone (n=377)</th></tr><tr><td>Number of patients completing planned 10 cycles of study treatment</td><td>109(29.4%)</td><td>50 (13.5%)</td></tr></table></td><td>Data is incorrectly reported.</td><td>Whilst this is not a factual error, the ERG has changed the number of patients completing 10 cycles of treatment to be now based on the more mature data, as requested.</td></tr>
<tr><td></td><td>Description of problem</td><td>Description of proposed amendment</td><td>Justification for amendment</td><td>ERG response</td></tr>
<tr><td>Issue 5</td><td>Page 84 paragraph 2
Diarrhoea is a key AE in ALSYMPCA and is missing from this list.</td><td>Suggested text change:

'The most common AEs in</td><td>Clarity on the key AEs in ALSYMPCA is important. Diarrhoea is a key AE and is missing from the</td><td>Whilst this is not a factual error, the ERG has made the</td></tr>
</table>

	Text … '*The most common AEs in ALSYMPCA in the relevant patient subgroup (those who had previously received docetaxel) were bone pain (53%), nausea (40%) and fatigue (27%).*	*ALSYMPCA in the relevant patient subgroup (those who had previously received docetaxel) were bone pain (53%), nausea (40%) fatigue (27%) and diarrhoea (25%)'*	list.	proposed change.
	Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG response**
Issue 6	Page 106 '*Stable disease*' paragraph. The body surface area of patients should include m^2 as the units: Text… '*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'*	Suggested changes incorporate the units: *'Within the submission the company assumed that the mean BSA was 1.9 m^2 (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 m^2 was based on the clinical opinion of UK experts; the mean BSA observed in the TROPIC (2.01 m^2) 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 m^2 is more likely to reflect values observed in the UK'*	Typographic amendment	Whilst this is not a factual error, the ERG has made the proposed change.

<table>
<tr><th></th><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr><td>Issue 7</td><td>Page 107 paragraph 1

Text… ‘it was assumed that mitoxantrone would require an hour of pharmacy time and cabazitaxel would require 15 minutes’.

Further clarification around the disparity in pharmacist time should be provided.</td><td>Suggest the text should include:
The shorter pharmacist time required for cabazitaxel reflects the fact that cabazitaxel will be provided in prefilled bags with a tailored dose appropriate for specific patients. Hence no time is needed to make up the IV infusions. This additional time is required for mitoxantrone delivery.</td><td>We provide an explanation for the difference in answer to question B3 at the clarification stage.</td><td>Whilst this is not a factual error, the ERG has made the proposed change.</td></tr>
</table>

	Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Issue 8	Page 106 paragraph 3 Text… ‘*The ERG further noted that in the company’s base-case there appeared to be no wastage assumed for either cabazitaxel or mitoxantrone.’* However this was not what was stated in the CS on page 165, table 63 which was: Active intervention: cabazitaxel | 47.50 mg per 3 weekly cycle plus daily 10 mg prednisolone | Based on dose of 25 mg/m^2, BSA of 1.9 m^2 assuming no wastage.	No amendment proposed.	For information: Correcting the model to reflect the use of vials for mitoxantrone as we had intended in our base-case leads to a deterministic ICER of £48,256. The probabilistic ICER is estimated to be £49,856 and the probability of being cost effective at a threshold	No change required.

	<table><tr><td>Comparator: mitoxantrone</td><td>1 or 2 vials of 20 mg plus daily 10 mg prednisolone</td><td>Based on dose of 12 mg/m^2, BSA of 1.9 m^2 and assumption of no vial sharing</td></tr></table> We thank the ERG for bringing this to our attention. It is an important clarification as this may affect the committees view on the cost effectiveness of cabazitaxel in the comparison with BSC. It was not our intention to present the analysis including mg of mitoxantrone in the base-case		willingness to pay of £50K is 51%. The disaggregated costs and method of calculation using the company model are shown in appendix A to this document (see below).	

	Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG response**
Issue 9	Page 107 Table 31 Value 4th column, row 3: £3696 £3696 is not the cost per 3 week cycle of cabazitaxel used in the model and does not reflect either the PAS price or the per mg dose. (Note the correct information should be redacted). Notwithstanding our comment in issue 8 above the footnote text does not reflect the actual vials used in the base-case for cabazitaxel. Footnote text… *'*Mitoxantrone and cabazitaxel are estimated by the company to require 1.73 and 1.00 vials per cycle, respectively.'*	The PAS cost of cabazitaxel per mg is provided in table 64 on page 167 of the CS and the number of mg used in the modelling is shown in on page 165, table 63. The product of these figures is the cost per patient per cycle of cabazitaxel. This cost should be redacted. Suggested change to the footnote text: *'*Mitoxantrone is estimated by the company to require 1.73 vials per cycle and 0.79 vials of cabazitaxel. NOTE The PAS adjusted cost is used for cabazitaxel.'*	The cost for cabazitaxel for each 3 weekly cycle is overstated in the table as the PAS price per mg is used in the base-case.	Whilst this is not a factual error, the ERG has changed the title of Table 31 to clarify that list prices are displayed. In addition, the following footnote has been added: "The PAS price is used for cabazitaxel in the main analyses. The PAS prices for abiraterone and enzalutamide are used in the confidential appendix.".

	Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG response**
Issue 10	Page 107 paragraph 3 Text…' *For patients with stable disease, the direct treatment costs (as detailed in* ***Error! Reference source not found.****), 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).'* The costs for mitoxantrone or cabazitaxel were incurred for 10 cycles, progression **or** death whichever comes first.	Suggest the text should include: *For patients with stable disease, the direct treatment costs (as detailed in* ***Error! Reference source not found.****), along with administration costs and pre-medication costs were incurred for either ten cycles of treatment or until disease progression or death for cabazitaxel and mitoxantrone. Patients persist on treatment until progression for abiraterone and enzalutamide.*	The text suggests that costs were incurred for all 10 cycles for the chemotherapy drugs. This is only the case for those patients who had not progressed during this time.	The ERG has made the proposed change. The ERG has also changed the last sentence in the proposed amendment to read: "Patients persist on treatment until progression or death for abiraterone and enzalutamide."
	Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG response**
Issue 11	Page 114 paragraph 3 Text…'*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).'*	No proposed amendment.	We agree that this was a typographical error in the CS	No change required.

	Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Issue 12	Page 118 paragraph 1 Text… '*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*.' The inclusion of the audit data is selective in this analysis.	We understand the rationale for the inclusion of the UK audit data in the ERG base-case. However the audit data comes in two parts. The post second line treatment mix was used in the ERG base-case but the proportions of patients to which post second line treatments are applied does not appear to have been used. If the both sets of information are used the ICER is decreased by 1% to provide a deterministic ICER of £48,908. The probabilistic ICER is estimated to be £48,819 and the probability of cabazitaxel being cost effective at a threshold willingness to pay of £50,000 is 50.3%. See Appendix B. A breakdown of how this affects the overall ERG base-case ICER is also provided below in Appendix C.	We believe that if the UK audit is to be used in the base-case then it should be implemented fully with both treatment mix and also proportion of patients considered. The company base-case including the post second line treatment mix and patient proportions derived from TROPIC provided a more conservative estimate of the ICER.	The ERG base-case ICER has been amended to also use the UK audit data for the proportion of patients to which post second line treatments are applied. This applies to all analyses involving the ERG base-case, in both the main report and the confidential appendix. In addition, analysis A4 in Table 36, and the text describing this on page 119 have been amended.
	Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG response**
Issue 13	Page 117 paragraph 2 Text… '*For the company's base-case analysis, OS and PFS were modelled*		For information we provide a revised estimate for the ERG base-case.	No change required.

	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.' The updated company model, which included the additional curve fits was not supplied to the ERG. This was our oversight.		In summary this includes • eMIT costs • No discontinuation • UK audit data for proportion and mix in second line treatment • Utility maintained until death in the PD state • Hybrid curve fits • Vials instead of mg for mitoxantrone The revised estimate for the ERG base-case which includes the updated curve fits and vials of mitoxantrone is £50,195. The probabilistic ICER is estimated to be £50,819. These results are shown in full Appendix D below.	
	Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG response**
Issue 14	Page 119 paragraph 8 Missing word ('utility') in the text…' *The value used in the base-case was 0.6266, based on data from the UK EAP.'*	Suggest the text should be amended to include the word 'utility': *The utility value used in the base-case was 0.6266, based on data from the UK EAP.'*	It is unclear what the value '*0.6266'* refers to.	Whilst this is not a factual error, the ERG has made the proposed change.

	Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Issue 15	Page 128 paragraph 4 Text…' *The company did not consider if cabazitaxel met this criteria when compared to other treatments.'* This does not precisely reflect the statement on page 21 of the CS. *'For patients previously treated with the advanced hormonal agents, or for those no-longer suitable for them, cabazitaxel represents a life-extending EoL therapy'* The statement in the ERG report suggests that we did not indicate that criterion 2 could be considered to be met. In the response to the scope, the decision problem meeting and in the CS we indicated that cabazitaxel meets this criterion where patients have BSC/mitoxantrone as their only option.	Text…' *The company considered that for patients previously treated with the advanced hormonal agents, or for those no-longer suitable for them, cabazitaxel represents a life-extending EoL therapy but did not consider if cabazitaxel met this criteria when compared to other treatments.'*	Given the uncertainty in the analysis versus abiraterone and enzalutamide we believe this comparison to be largely uninformative. The ERG concurred with this in the report on page 87… *'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. '* We also believe that the restrictions placed on the use of the advanced hormonal agents along with the expected (and established) place in therapy for cabazitaxel mean that the cabazitaxel patient is not directly comparable to the patient who might be treated with abiraterone or enzalutamide. We believe these issues should also extend to any comparison with radium-223.	The ERG believe that it can be argued whether or not this represents a factual error. The ERG have not made any changes, the company can make this issue clear if necessary during the Appraisal Committee

Appendix A. See Issue 8 Error in the Company model.

Updated base-case including vials of mitoxantrone rather than mg. This analysis is made possible by changing the contents of cell T20 on the 'Cost treatment' worksheet in the company model from:

=IF(CostCalcPerPatCabaChoice= "Price based on vial",VialMitox+MgPred,MgMitox+MgPred)

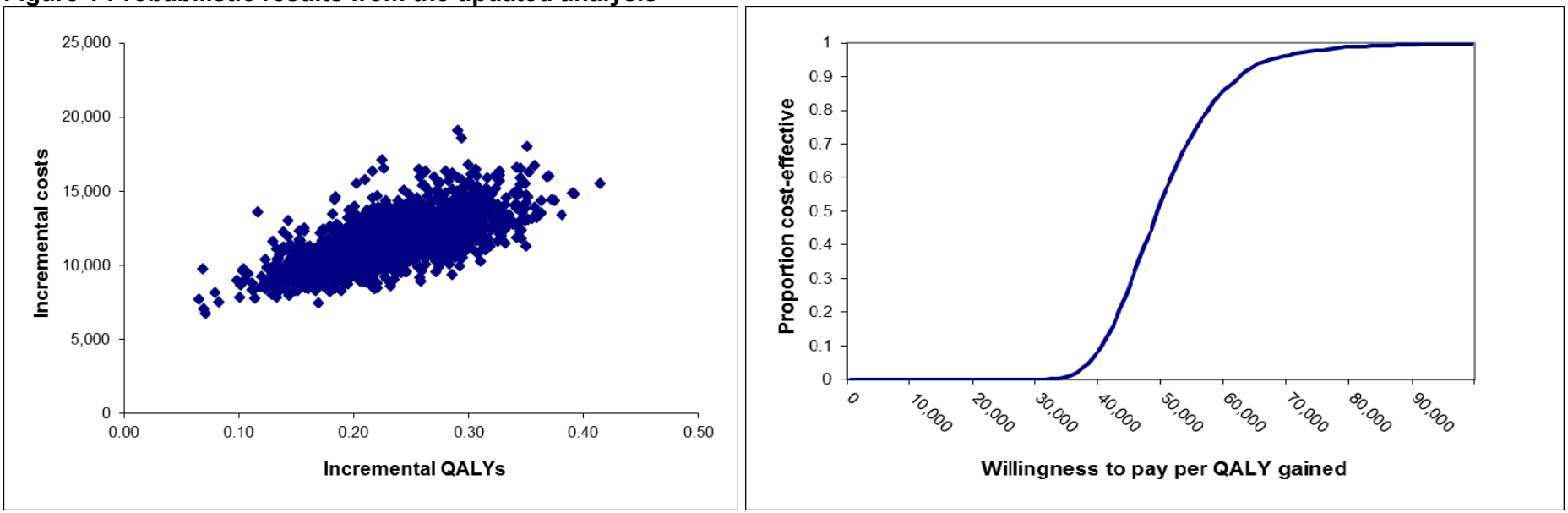
To

= VialMitox+MgPred

Table 1 Updated deterministic results

	Cabazitaxel	**Mitoxantrone**
Total costs (£)	[redacted]	[redacted]
Total LYG	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]
Incremental costs (£)	£11,202	
Incremental LYG	0.338	
Incremental QALYs	0.232	
ICER (£) versus baseline (QALYS)	£48,256	

Figure 1 Probabilistic results from the updated analysis



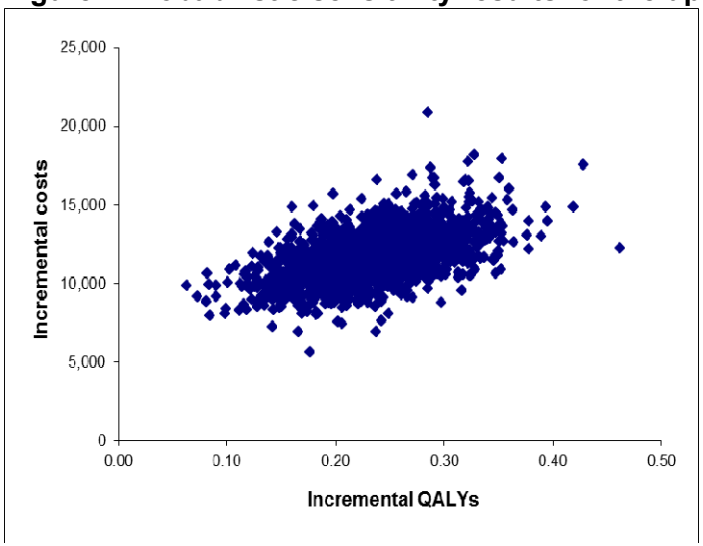
The probability of being cost-effective at a threshold willingness to pay of £50,000 is 51%

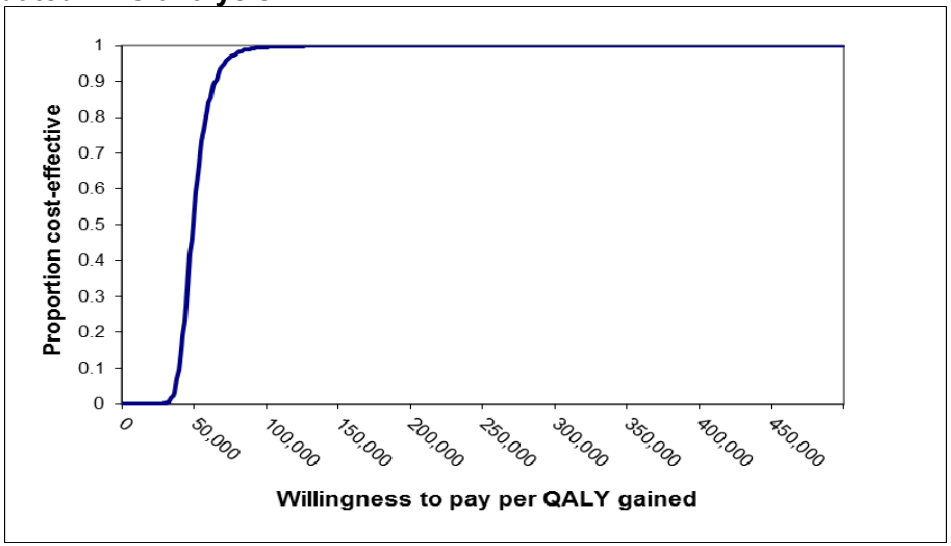
Appendix B See issue 12 Inclusion of the full UK audit data.

Table 2 Updated deterministic results

	Cabazitaxel	Mitoxantrone
Total costs (£)	[redacted]	[redacted]
Total LYG	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]
Incremental costs (£)	£11,353	
Incremental LYG	0.338	
Incremental QALYs	0.232	
ICER (£) versus baseline (QALYS)	£48,908	

Figure 2 Probabilistic sensitivity results for the updated ERG analysis A4





Appendix C. See issue 12 Inclusion of the full UK audit data.

Individual changes made at each step	Cabazitaxel		Mitoxantrone		Incremental values		Compound ICER (£)
	Total costs (£)	**Total QALYs**	**Total costs (£)**	**Total QALYs**	**Costs (£)**	**QALYS**	
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]	12,242	0.232	52,736
A3) Reduced disutility in the last 3 months of progressive disease not modelled	[redacted]	[redacted]	[redacted]	[redacted]	12,242	0.230	53,126
A4) Post-second line treatment resource use from UK audit for all treatments.	[redacted]	[redacted]	[redacted]	[redacted]	11,825	0.230	51,316
A5) Network meta-analysis results using a weakly informative prior (does not affect the comparison with mitoxantrone).	[redacted]	[redacted]	[redacted]	[redacted]	11,825	0.230	51,316

Appendix D. See issue 13. Updated ERG base-case including hybrid curve fit.

Table 3 Updated deterministic results including hybrid curve fit

	Cabazitaxel	Mitoxantrone
Total costs (£)	[redacted]	[redacted]
Total LYG	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]
Incremental costs (£)	£11,874	
Incremental LYG	0.347	
Incremental QALYs	0.237	
ICER (£) versus baseline (QALYS)	£50,195	

Figure 3 Probabilistic sensitivity results for the updated ERG base-case including hybrid curve fit